Sustained effect of prasinezumab on Parkinson's disease motor progression in the open-label extension of the PASADENA trial, 5-year update

Fabiana Gullotta,[1] Gennaro Pagano,[1] Adriana Reyes,[1] Annabelle Monnet,[1] Tanya Simuni,[2] Ronald B. Postuma,[3] Nicola Pavese,[4] Fabrizio Stocchi,[5] Kathrin Brockmann,[6] Patrik Brundin,[1] Kenneth Marek,[7] Geoffrey A. Kerchner,[1] Tania Nikolcheva[1]

1. F. Hoffmann-La Roche Ltd, Basel, Switzerland; 2. Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 3. Department of Neurology, McGill University, and Montreal Neurological Institute, Montreal, Canada; 4. Clinical Ageing Research Unit, Newcastle University, Newcastle upon Tyne, United Kingdom; 5. University San Raffaele Roma and the Institute for Research and Medical Care, IRCCS San Raffaele Pisana, Rome, Italy; 6. Department of Neurodegeneration, Hertie-Institute for Clinical Brain Research, Tuebingen, Germany; 7. Institute for Neurodegenerative Disorders, New Haven, CT, USA

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What does this mean for the Parkinson's community?

This exploratory analysis suggests that targeting α-synuclein with prasinezumab may slow motor and functional decline. This may result in:

- Maintaining independence and quality of life for people with Parkinson's disease (PD) at early clinical stage
- Reducing burden on healthcare systems and care partners
- Potentially delaying the need for higher doses of symptomatic therapies

Conclusions

Durability of treatment effect: The effect of prasinezumab on slowing motor progression and functional decline is sustained for 5 years vs an external comparator.
Clinically Meaningful Impact: Relative differences in MDS-UPDRS Part III scores (–41% OFF and –95% ON) suggest a substantial shift in the disease trajectory.
Next Steps: These exploratory findings support continued exploration of prasinezumab's effect in randomised, placebo-controlled trials, such as the ongoing PARAISO study.

Background

- Prasinezumab is a humanised monoclonal antibody that binds aggregated α-synuclein to inhibit its neuron-to-neuron spread in PD
- In the Phase II PASADENA study (NCT03100149), a signal in slowing motor progression (MDS-UPDRS Part III) was observed, particularly in faster progressing subgroups, even though the primary endpoint was not met
- Previously published 4-year results compared the PASADENA open-label extension (OLE) to an external cohort from the Parkinson's Progression Markers Initiative (PPMI). This comparison demonstrated a sustained slowing of motor and functional decline in prasinezumab-treated participants compared to the weighted external comparator

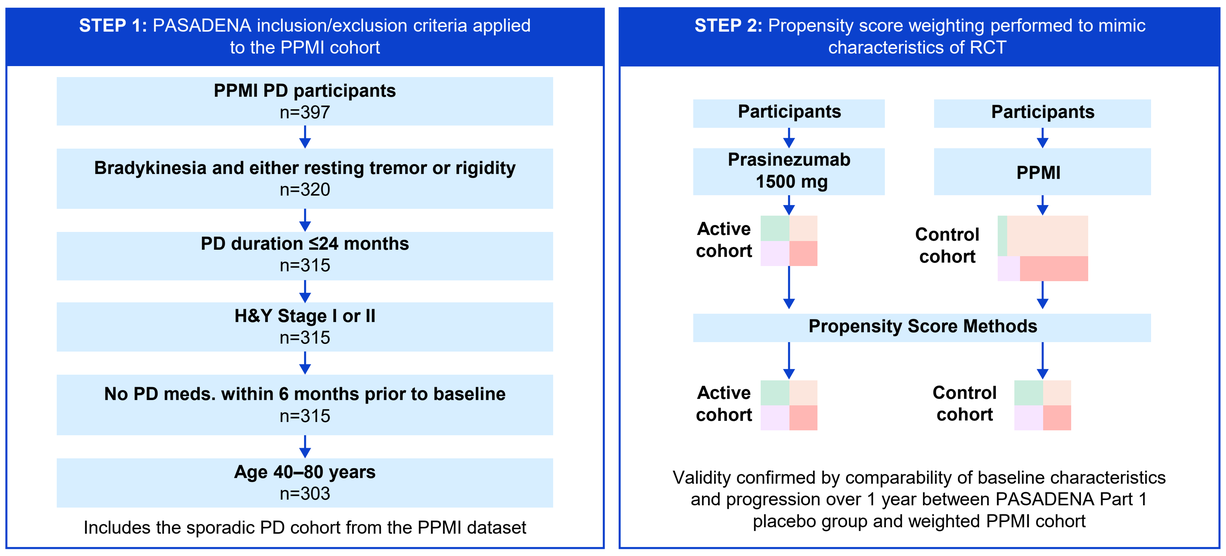
Objective

The current exploratory analysis extends this longitudinal comparison to 5 years.

Methodology

- All participants from the PASADENA Phase II trial who entered the OLE were included. The early- and delayed-start treatment arms were pooled for this analysis
- STEP 1: An external comparator was created by applying PASADENA inclusion criteria to the PPMI sporadic PD cohort
- STEP 2: Trial and comparator groups were balanced using inverse probability of treatment weighting based on key baseline covariates
- Longitudinal endpoints were evaluated using a mixed model for repeated measures (MMRM)

Figure 1. Conceptual framework.

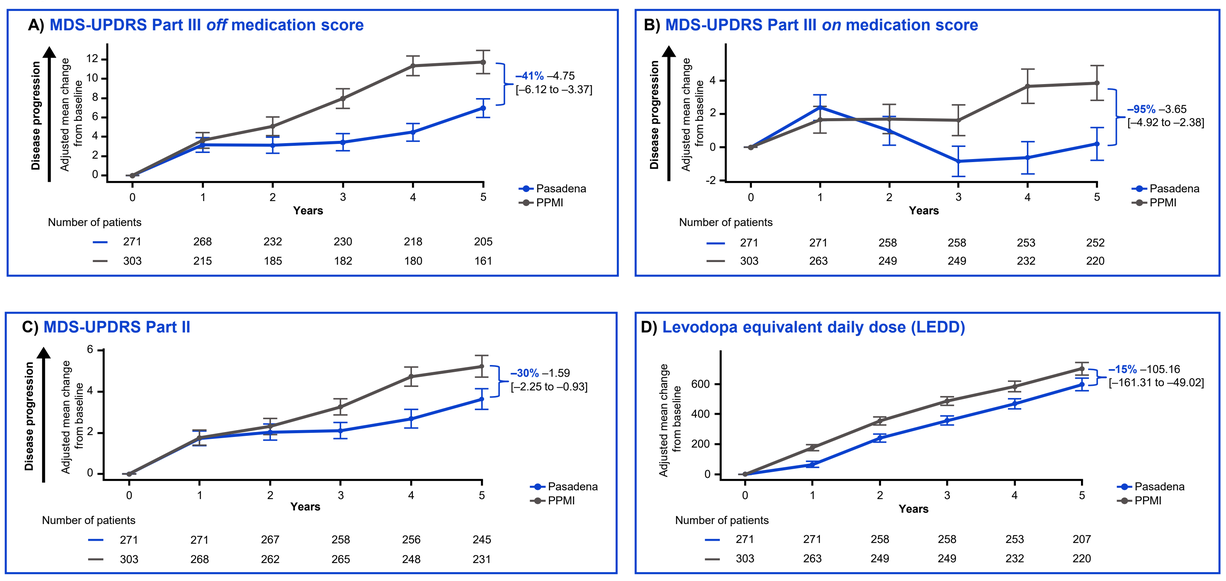


H&Y, modified Hoehn and Yahr stage; PD, Parkinson's disease; PPMI, Parkinson Progression Marker Initiative.

Results

This analysis included 271 PASADENA and 303 PPMI participants.

Figure 2. Adjusted mean change from baseline.



At Year 5, the combined PASADENA arm (early- and delayed-start groups) exhibited a sustained reduction in motor and functional decline compared to the weighted PPMI cohort (reported as mean difference in points with 80% confidence interval [CI]).

The use of symptomatic therapies was generally higher in the PPMI cohort compared to the PASADENA arm. The average LEDD remained approximately 100 mg higher in the PPMI group through Year 5.

Table 1. Study retention.

Cohort	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
PASADENA	271 (100%)	271 (100%)	271 (100%)	269 (99%)	263 (97%)	253 (93%)
PPMI	303 (100%)	297 (98%)	290 (96%)	285 (94%)	273 (90%)	260 (86%)

Study withdrawal summaries over the 5-year period showed that the PASADENA cohort exhibited higher retention than the propensity score-weighted PPMI cohort, with 18 total discontinuations in PASADENA compared to 43 in the PPMI group.

Discussion

- **Sustained Treatment Effect:** This exploratory analysis suggests that the effect of prasinezumab in slowing motor progression and functional decline in PD is sustained over the 5-year period compared to an external comparator
- **Meaningful Impact:** The gradually increasing separation of the motor and functional curves is consistent with a disease modifying effect with a substantial shift in the disease trajectory
- **Study Limitations:** Considering the lack of a placebo arm, a potential placebo effect cannot be ruled out. Furthermore, differences in clinic visit frequency and potential selection bias inherent to retrospective external comparators must be considered. Interpretation may be influenced by missing data, differential attrition and evolving treatment imbalances over time
- **Confirmation needed:** These exploratory findings support continued exploration of prasinezumab's effect in placebo-control trials, such as the ongoing PARAISO Phase III study

PARAISO Phase III Study

Further information

- Ongoing Research: The PASADENA OLE is planned to continue for up to 10 years to evaluate long-term safety and efficacy

References

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Disclosures

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