Modelling PD Progression To Quantify Long-Term Treatment Effects

The Concept of `Time-Saved`: Insights From PPMI and PASADENA Open-Label Extension

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*Philippe B. Pierrillas affiliation at time of analysis.

Disclosures

- **Benjamin Ribba, Tania Nikolcheva, Philippe B. Pierrillas,* Cheikh Diack, Annabelle Monnet, Benedicte Ricci, Matthew May, Gennaro Pagano, Geoffrey A. Kerchner and Patrik Brundin:** Full-time employees and own shares of F. Hoffmann-La Roche Ltd

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It’s a question of Time

People with Parkinson’s are talking about Time

“If there was a cure found for Parkinson's now, it would give me back my future”

"I'm trying to buy myself as much time as I can, so I don't develop the negative side effects of dopaminergic treatment"

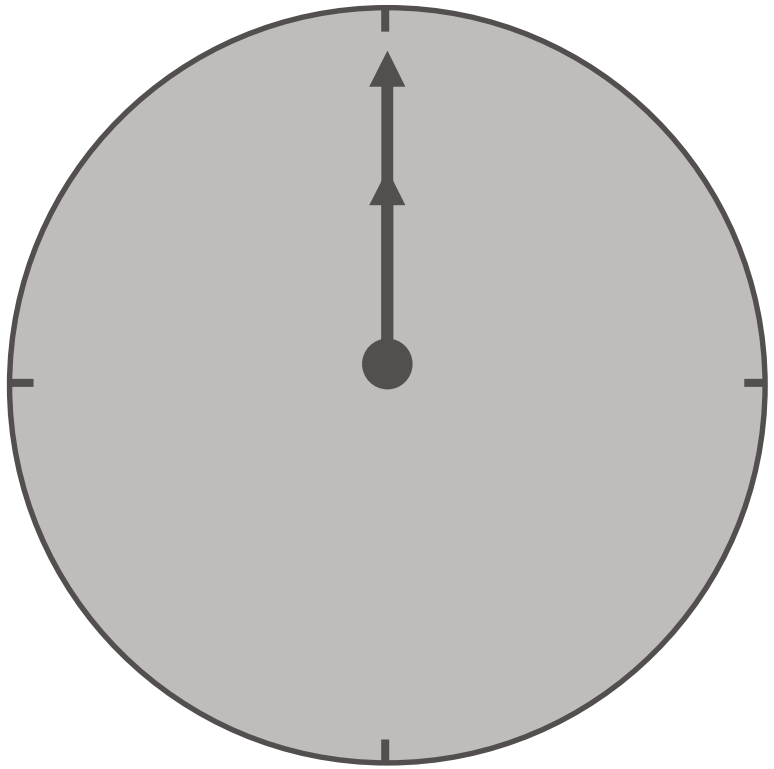
"3 months ago I was able to walk my dog, or wash my car, mow the lawn, now I can't"

"The biggest threat is time... There are things I can do today that might be taken from me tomorrow”

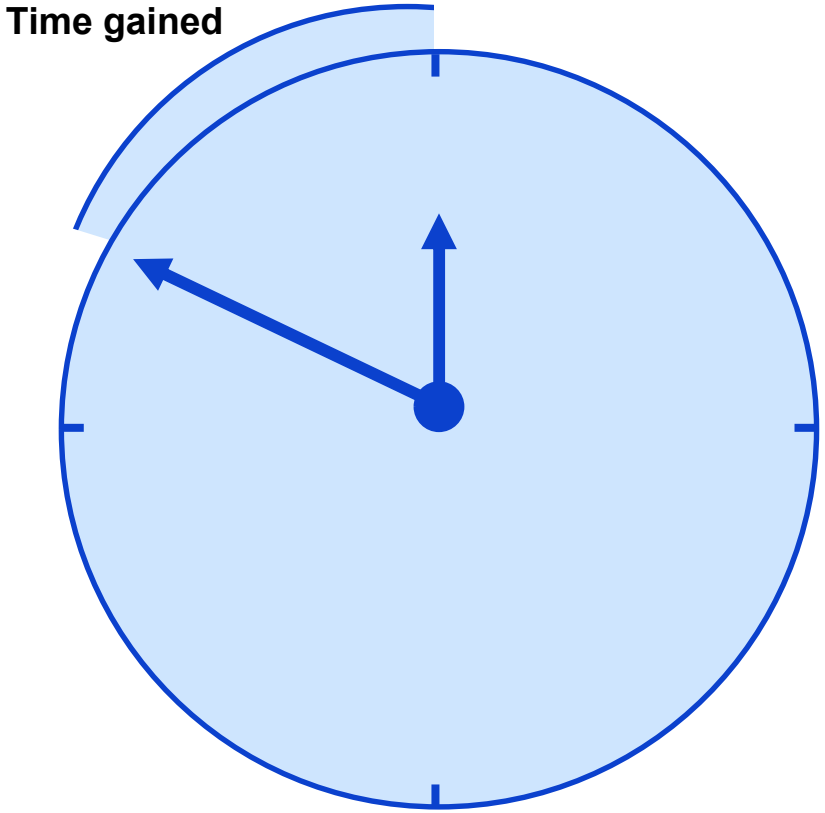
Quotations provided by the Michael J. Fox Foundation and Cure Parkinson’s.

The `Time Gained` Concept

Shifting the efficacy paradigm: From 'Points Change' to 'Time Gained'



Natural history / Placebo



Treatment

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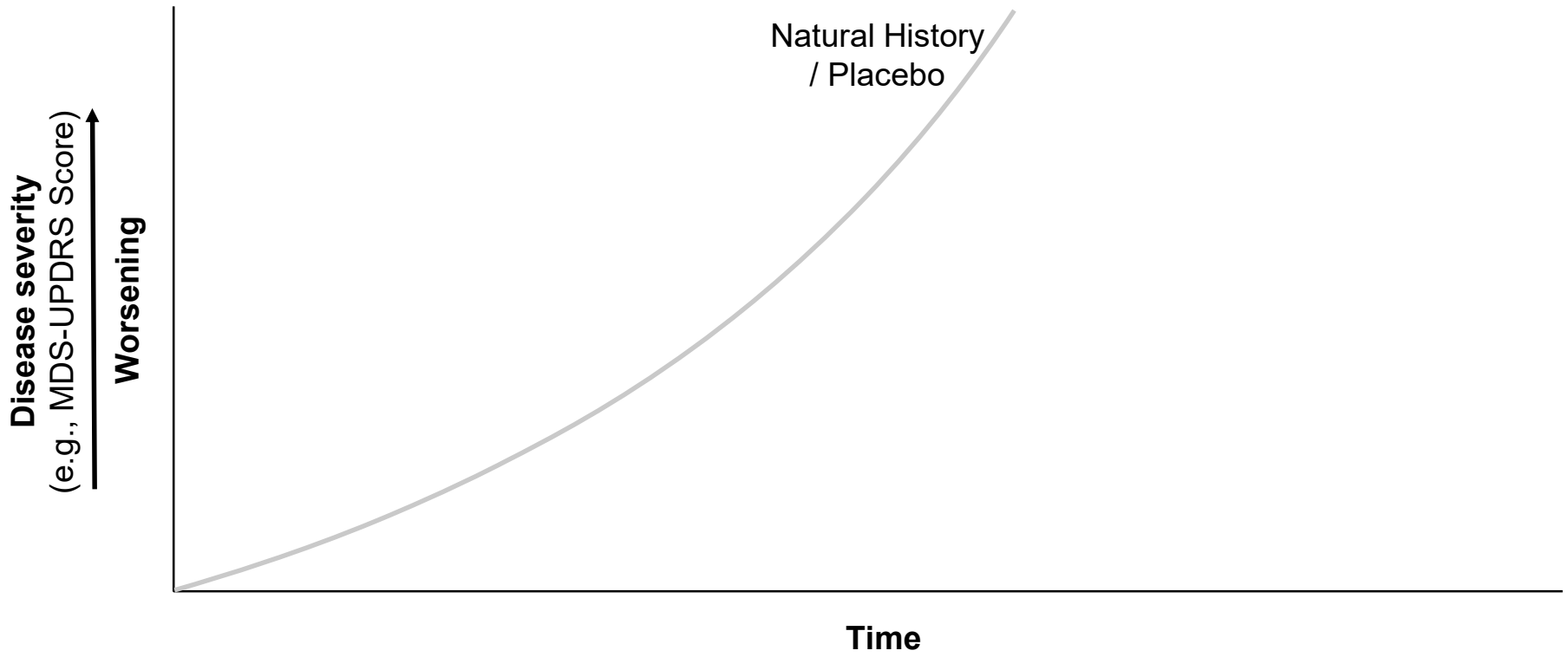

MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

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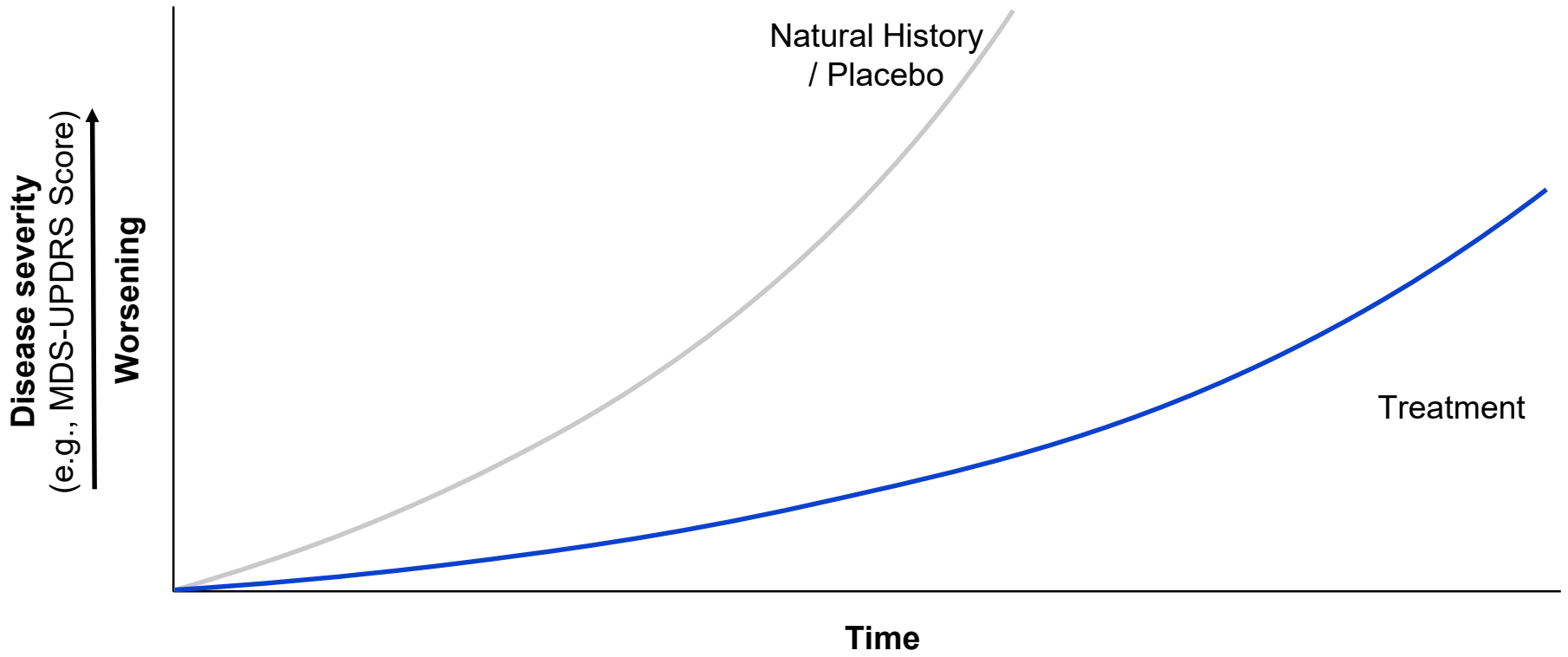

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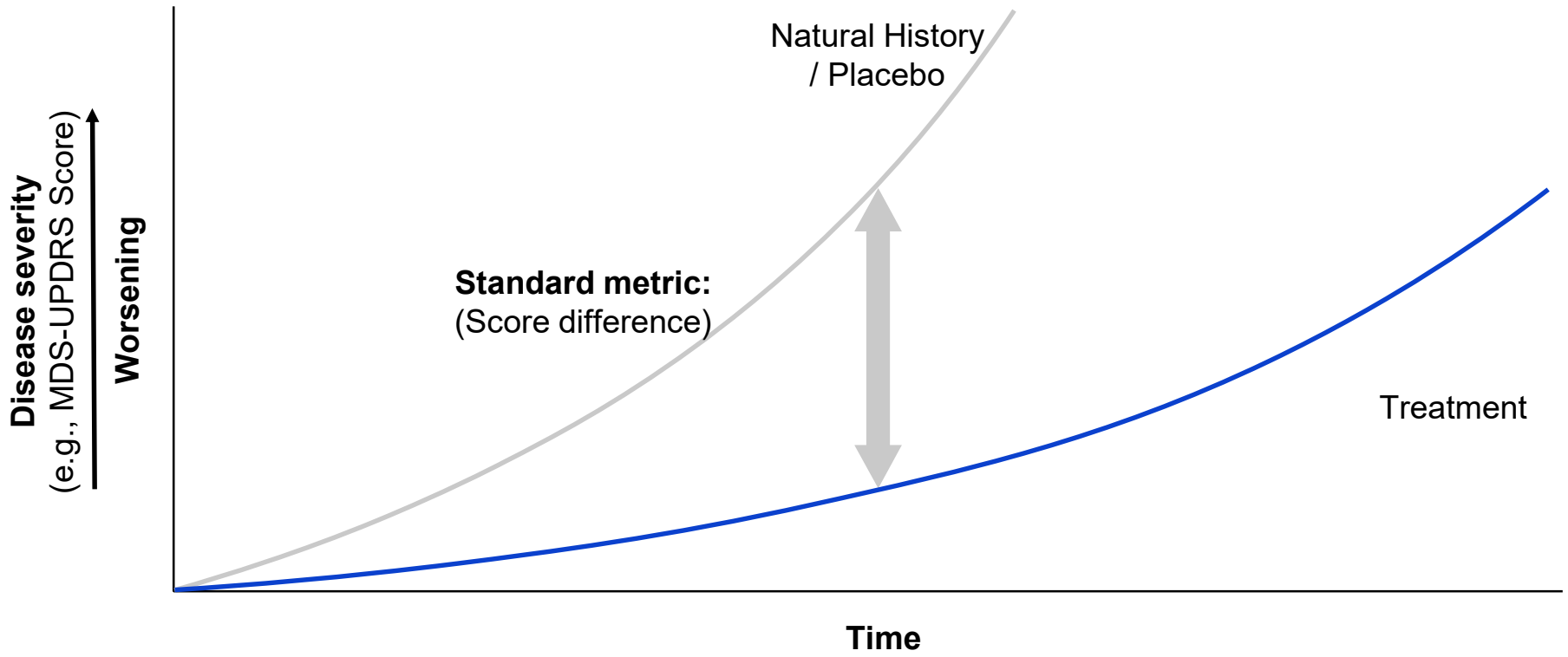

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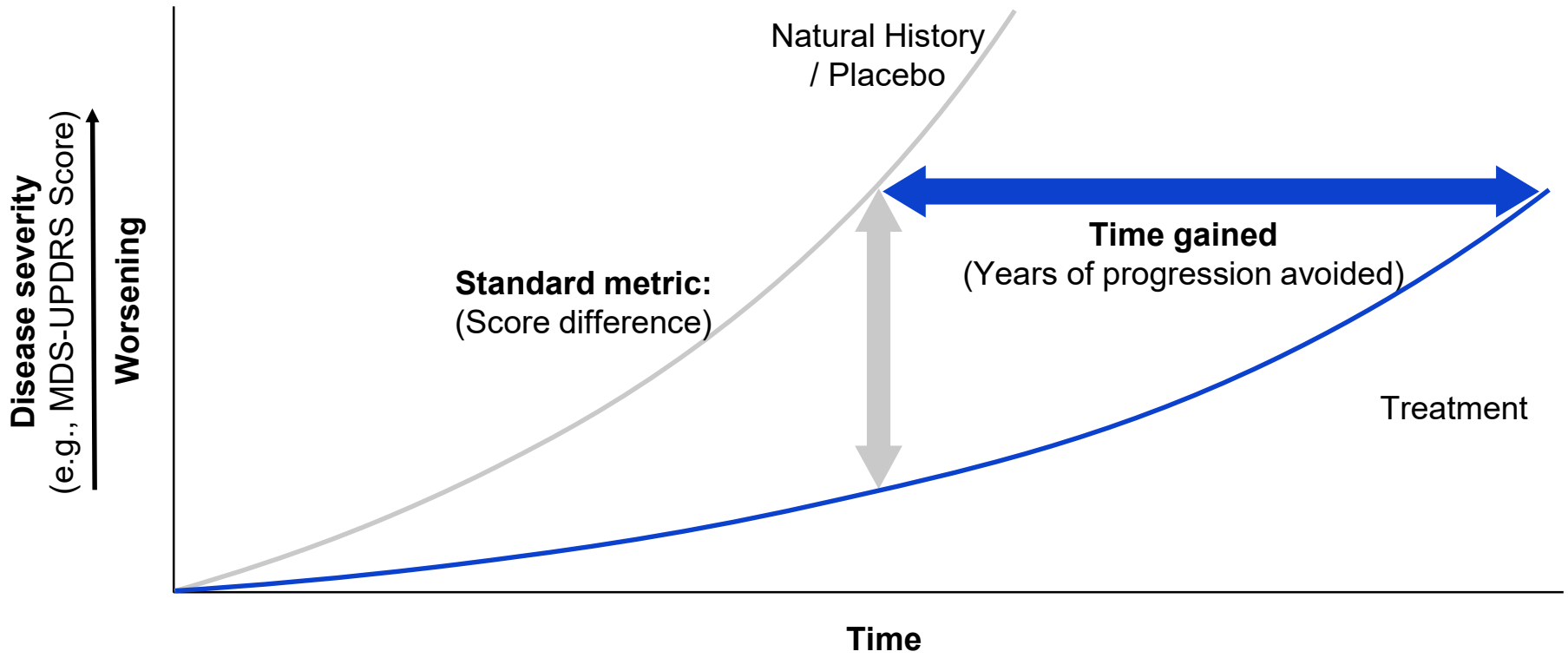

MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

The Challenge: Detecting signal in early-stage PD

Slow progression rates, symptomatics masking treatment effects, and variability in Parkinson's journey

Slowly progressing disease

Low signal:

- Low rate of change in early disease: patient-reported motor symptoms (MDS-UPDRS Part II) ~1 pt/year versus clinician-rated motor signs (MDS-UPDRS Part III) ~3 pts/year

High noise:

- Impact of symptomatic therapy on outcome measures can mask treatment effects
- High variability of Parkinson's journeys

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Limitations of current measurement tools

- Cannot detect early, very mild changes in ability to perform daily activities
- No suitable functional endpoints for registrational trials with disease-modifying treatments

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Without sensitive quantification, potentially effective drugs may not meet their primary endpoint and be discontinued

MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale, PD, Parkinson's disease; pt, patient.

The Feasibility Gap: Why we need modelling

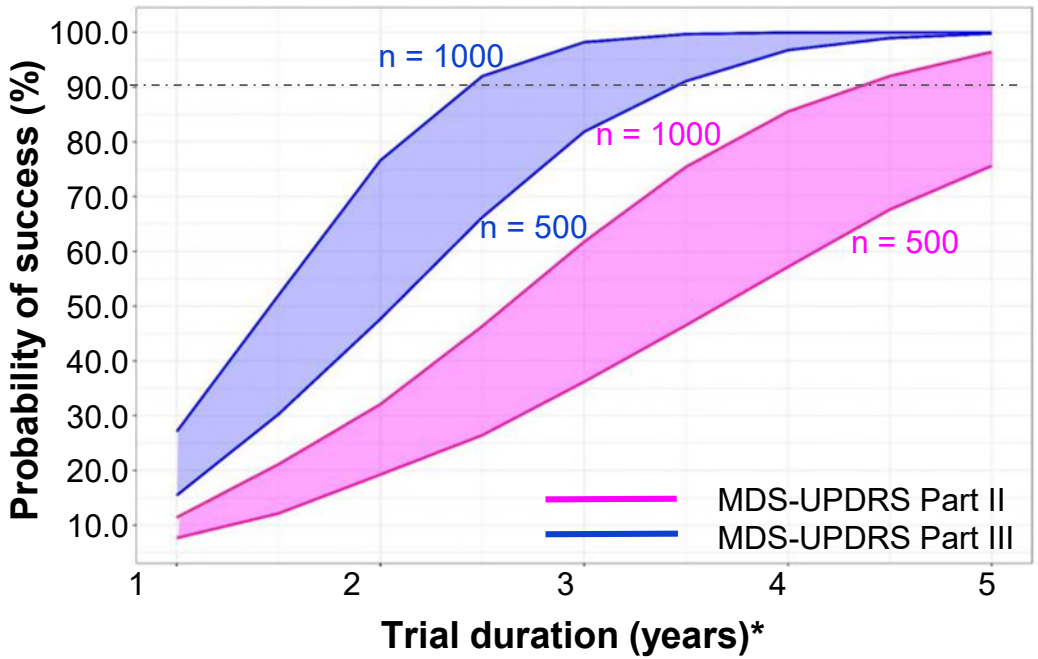
Clinical trial simulations suggest standard designs can hardly detect change in function

Endpoint selection = patient-relevant outcomes x capacity to detect a response in randomised clinical trials

Time (years) to 90% probability of study success as function of endpoint, efficacy level (reduction of progression) and sample size

	MDS-UPDRS Part II		MDS-UPDRS Part III	
Efficacy level	n=500	n=1000	n=500	n=1000
20%	>5	>5	>5	4.25
35%	>5	4.5	3.5	2.5
50%	4.25	3	2.5	1.75

Probability of study success by endpoints and sample size (35% efficacy level)

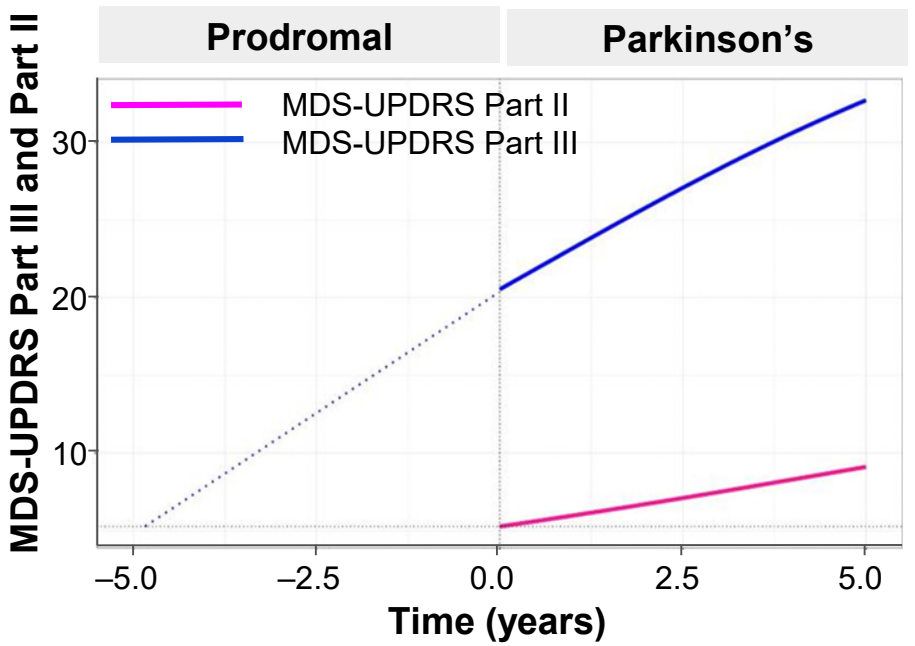


*For MDS-UPDRS Part II and Part III (a measure of motor aspects of experiences of daily living), trials of disease-modifying treatments are likely to require >5 years to detect effect.
MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.
Ribba B, et al. *J Parkinson Dis.* 2024;14:1225—35.

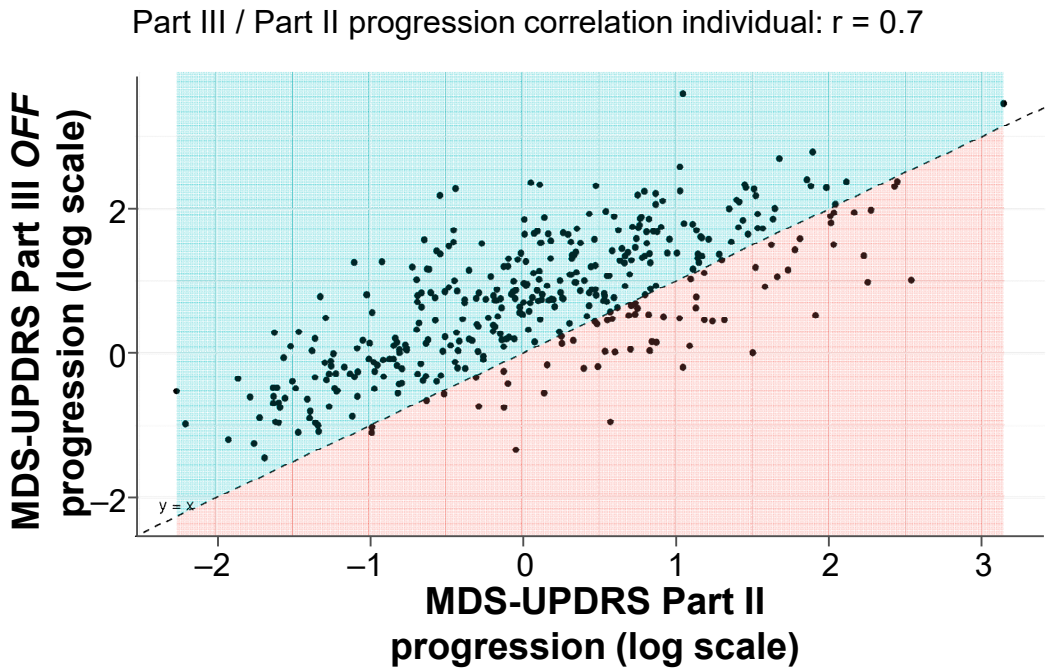
Clinician-assessed motor signs as leading indicator

Longitudinal modelling of natural history identifies progression of MDS-UPDRS Part III earlier and faster than Part II

Backward extrapolation of MDS-UPDRS Part III scores supported by PPMI data in the prodromal cohort (blue dotted line)



Modelled PPMI progression MDS-UPDRS Part III *OFF* faster than Part II for >80% of individuals (dots in the green area)



MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative.
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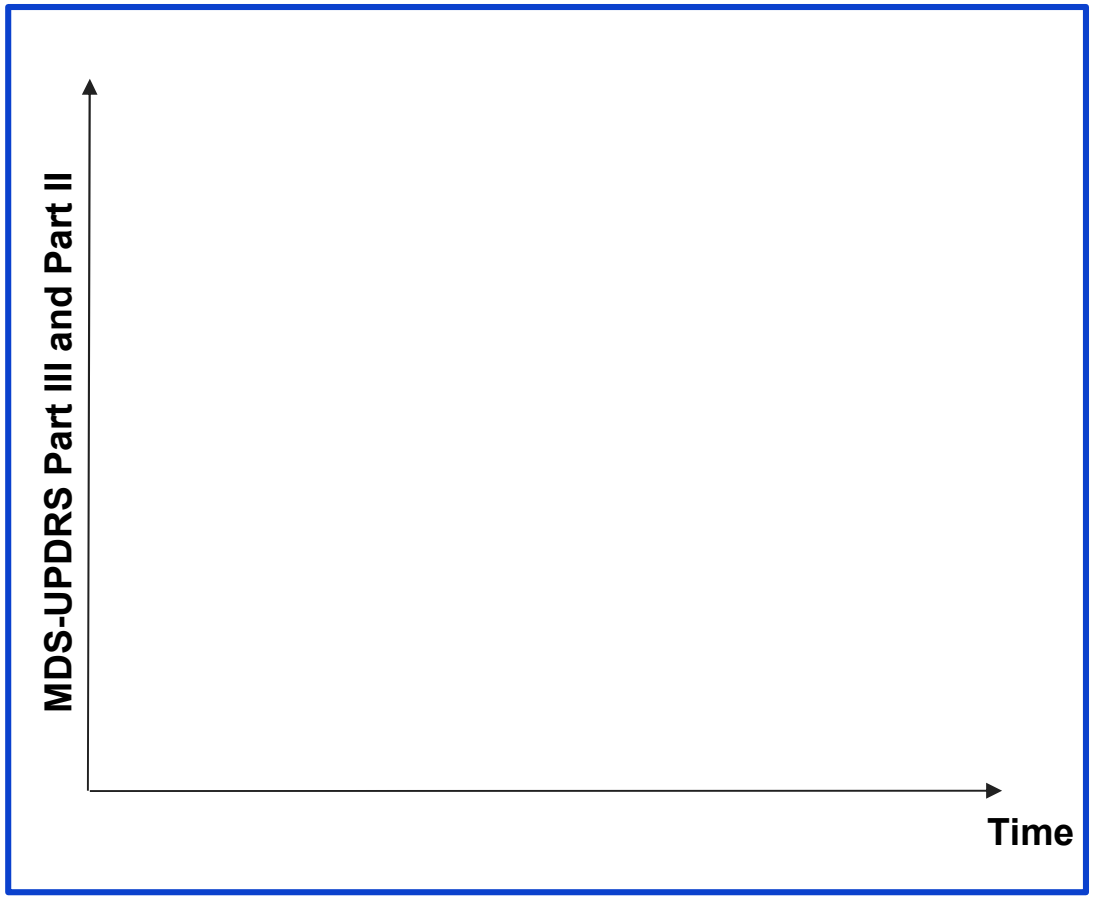
Slowing progression of motor signs could predict functional outcome



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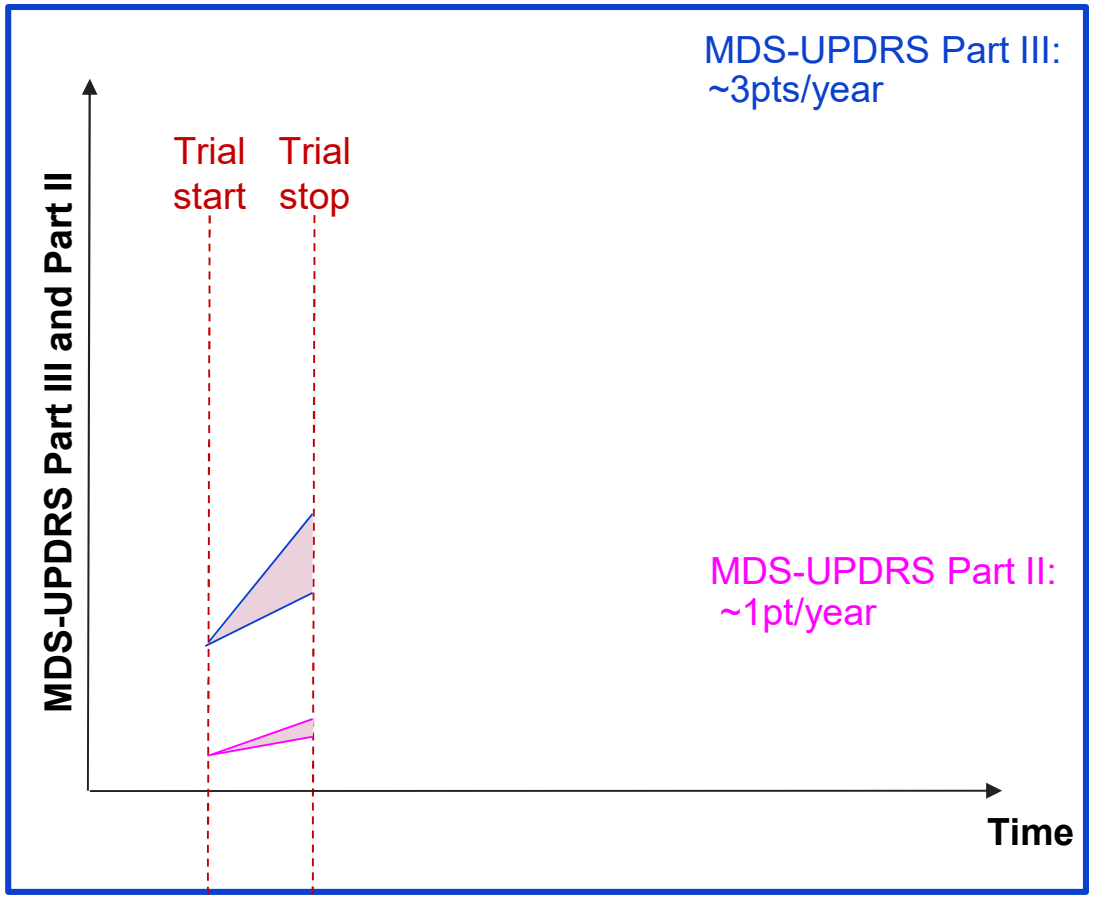

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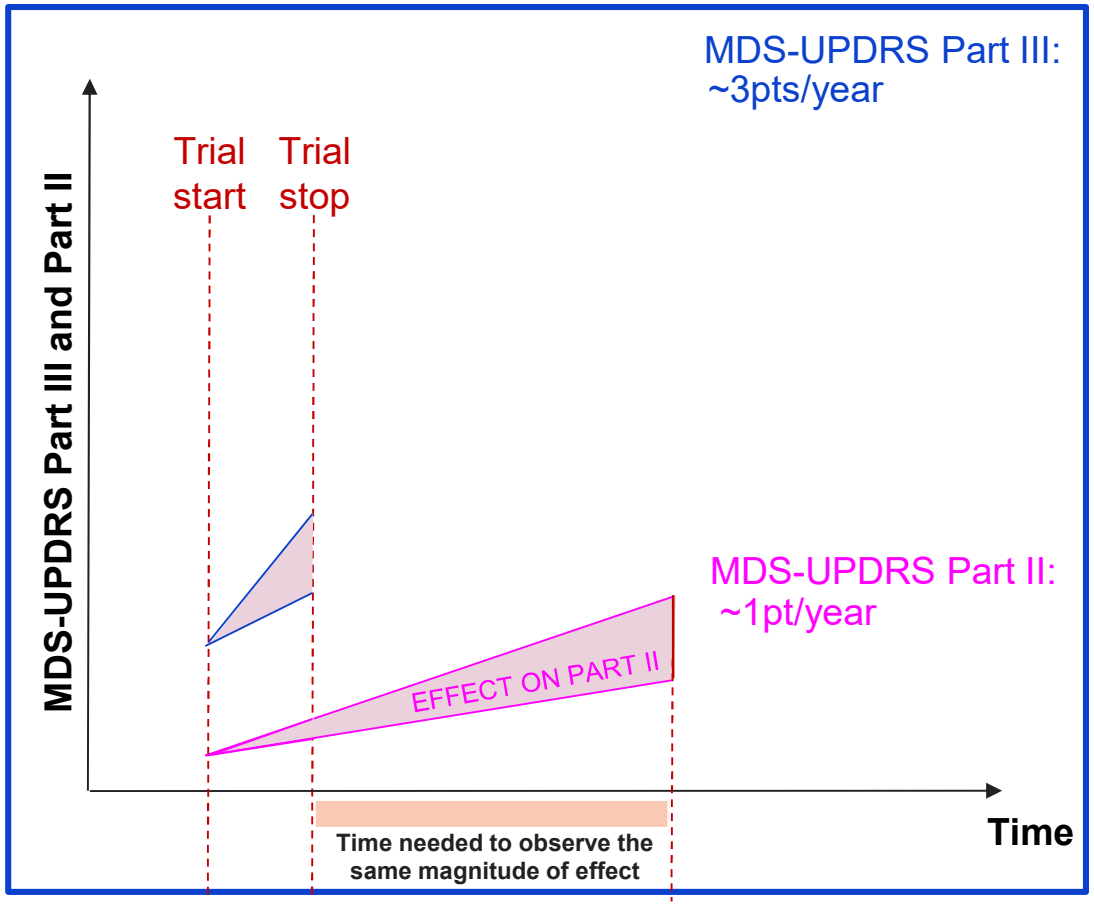

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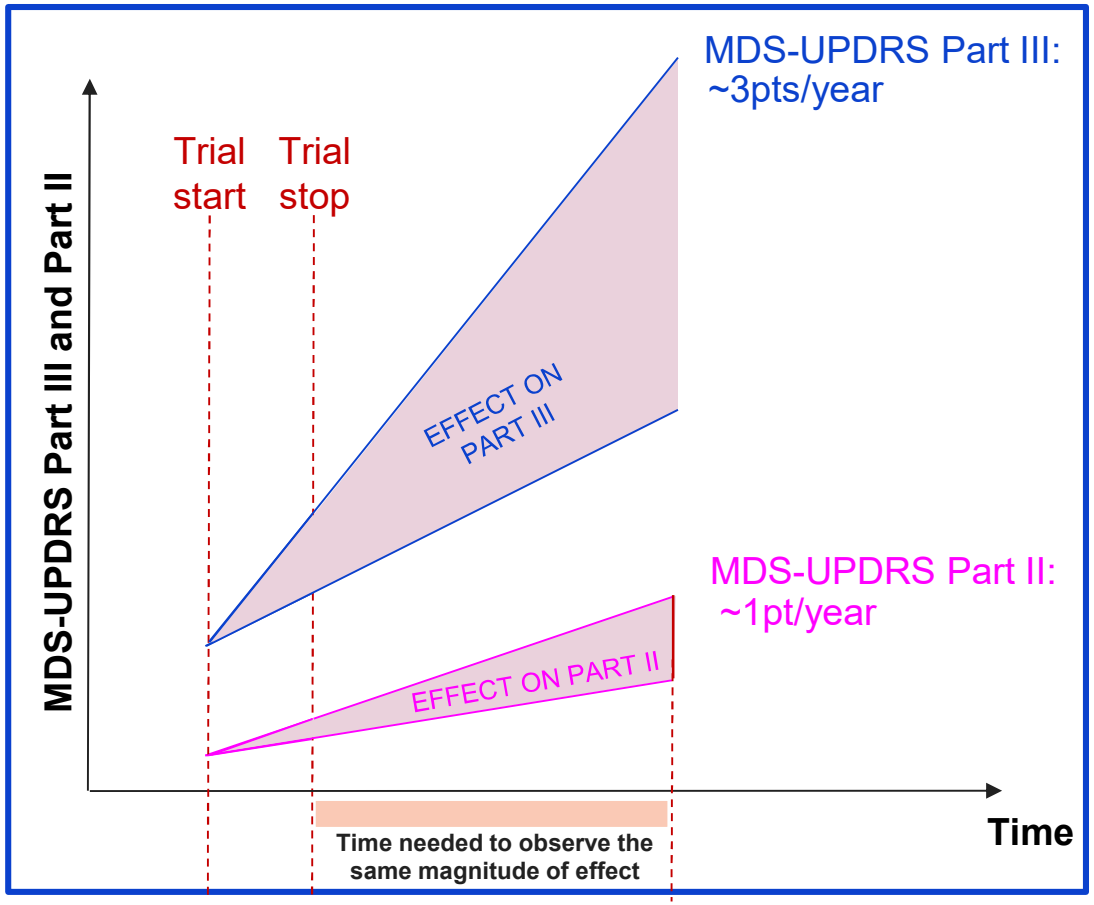

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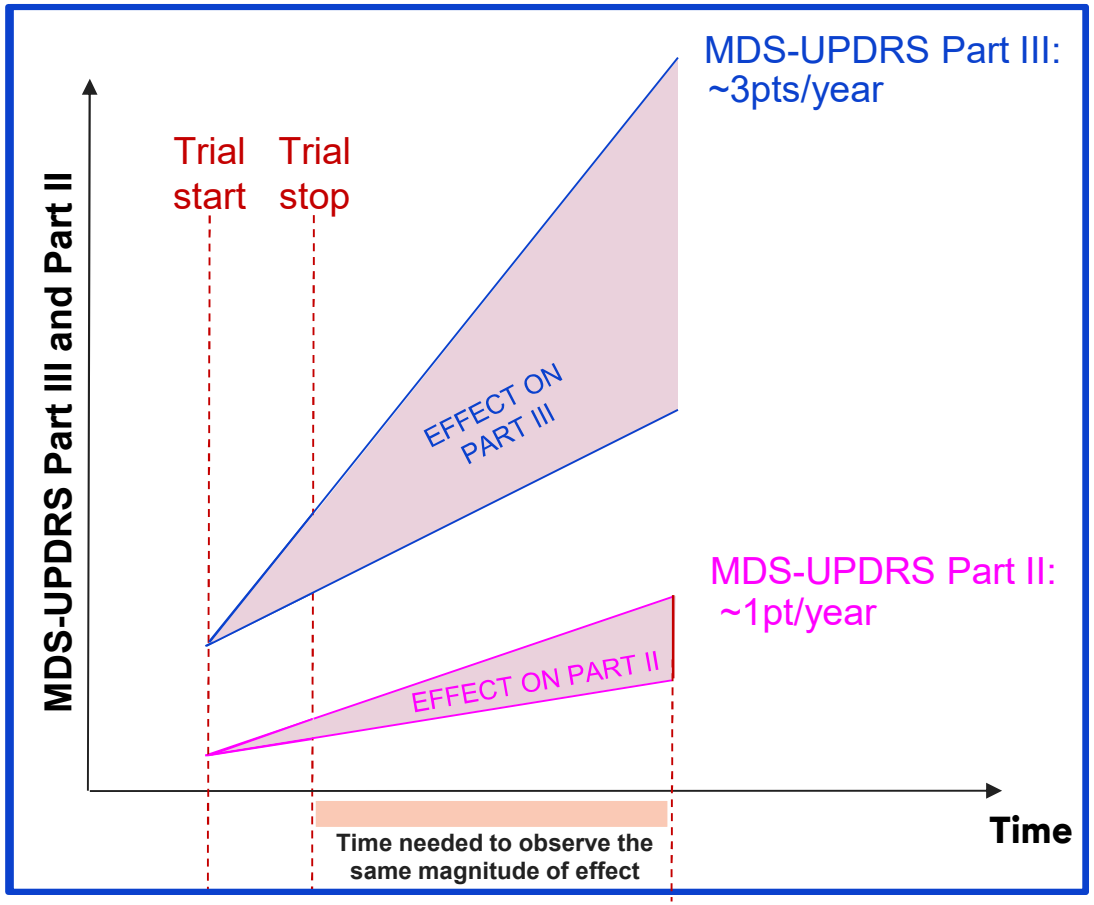

Comparison to PASADENA OLE data with PPMI-based model predictions supports the hypothesis that effect on signs precedes effect on symptoms

	MDS-UPDRS Part III (motor signs)	MDS-UPDRS Part II (motor symptoms)
Time of significant separation of PASADENA data from PPMI-based predictions	Year 2	Year 3–4

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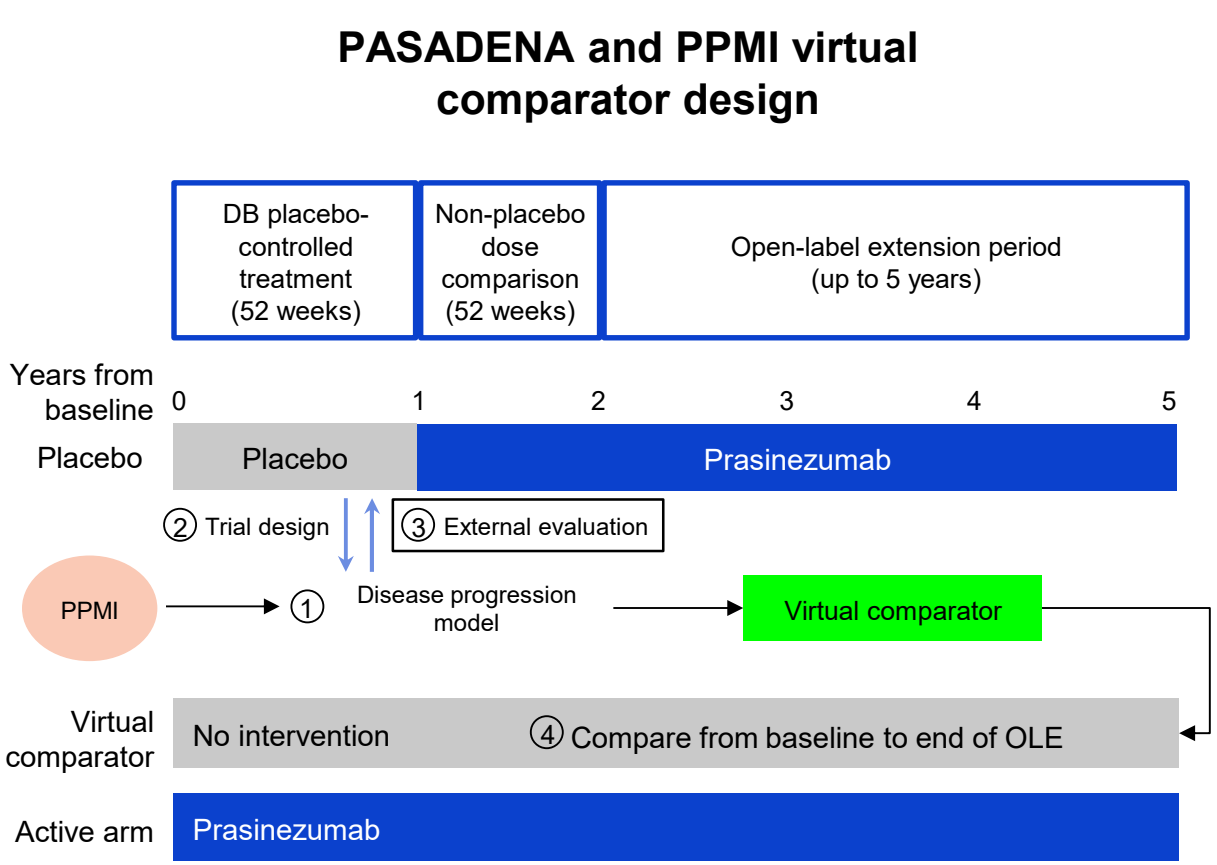
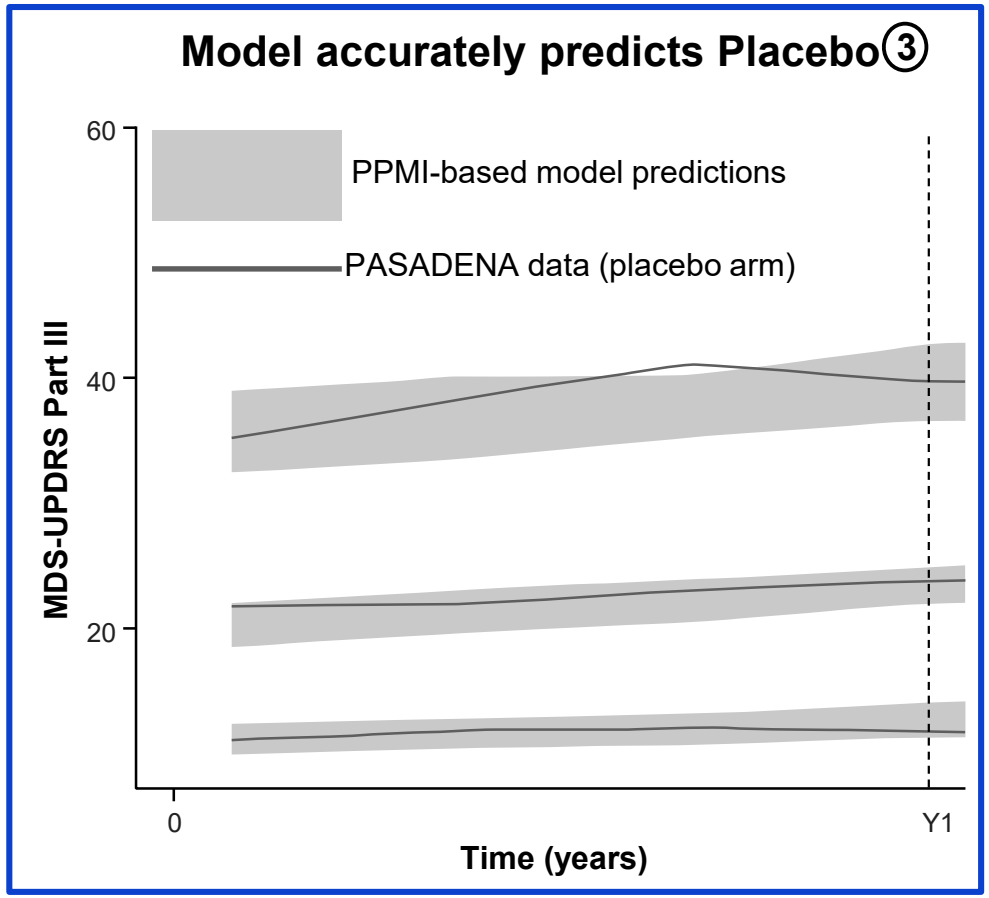
Constructing a virtual comparator



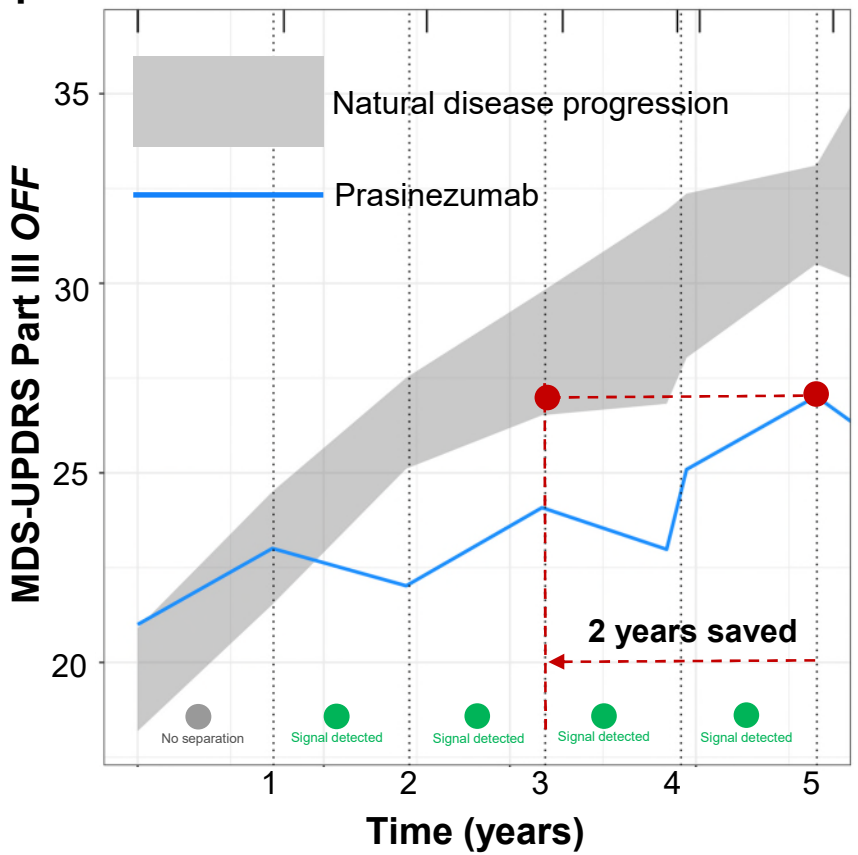


MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; OLE, open-label extension; PPMI, Parkinson's Progression Markers Initiative.

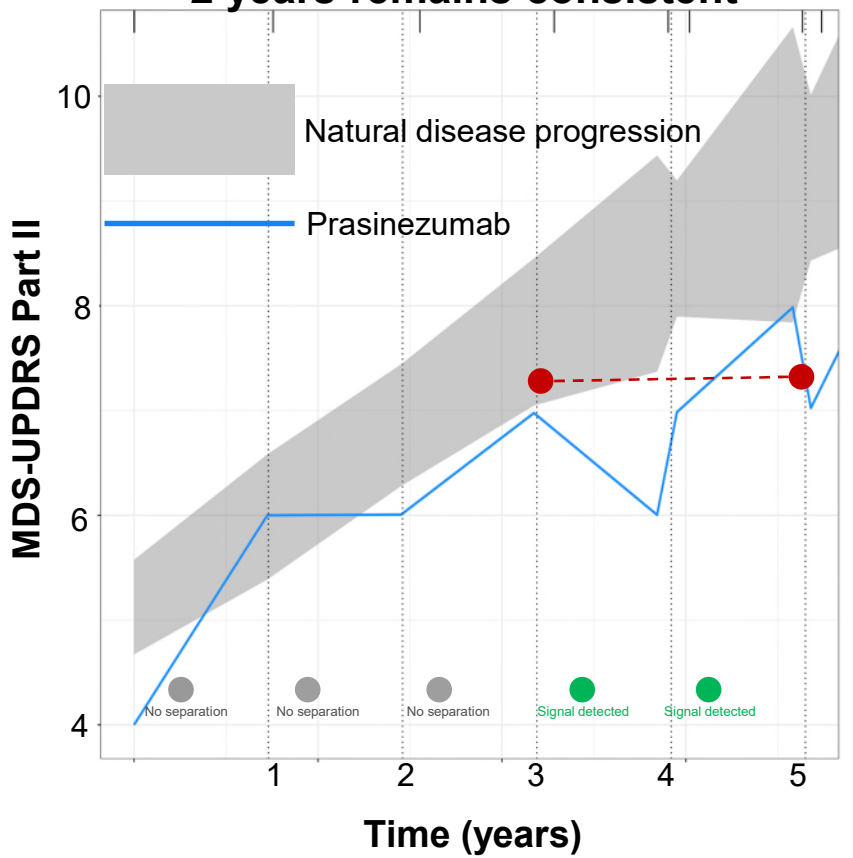
Prasinezumab delays progression by ~2 years over 5 years of treatment

Consistent ~2 years of 'Time Gained' across motor and functional domains

Disease modelling suggests an average of ~2 years saved over 5 years of prasinezumab treatment in PASADENA



Slower progression compresses the vertical signal but the time saved of 2 years remains consistent



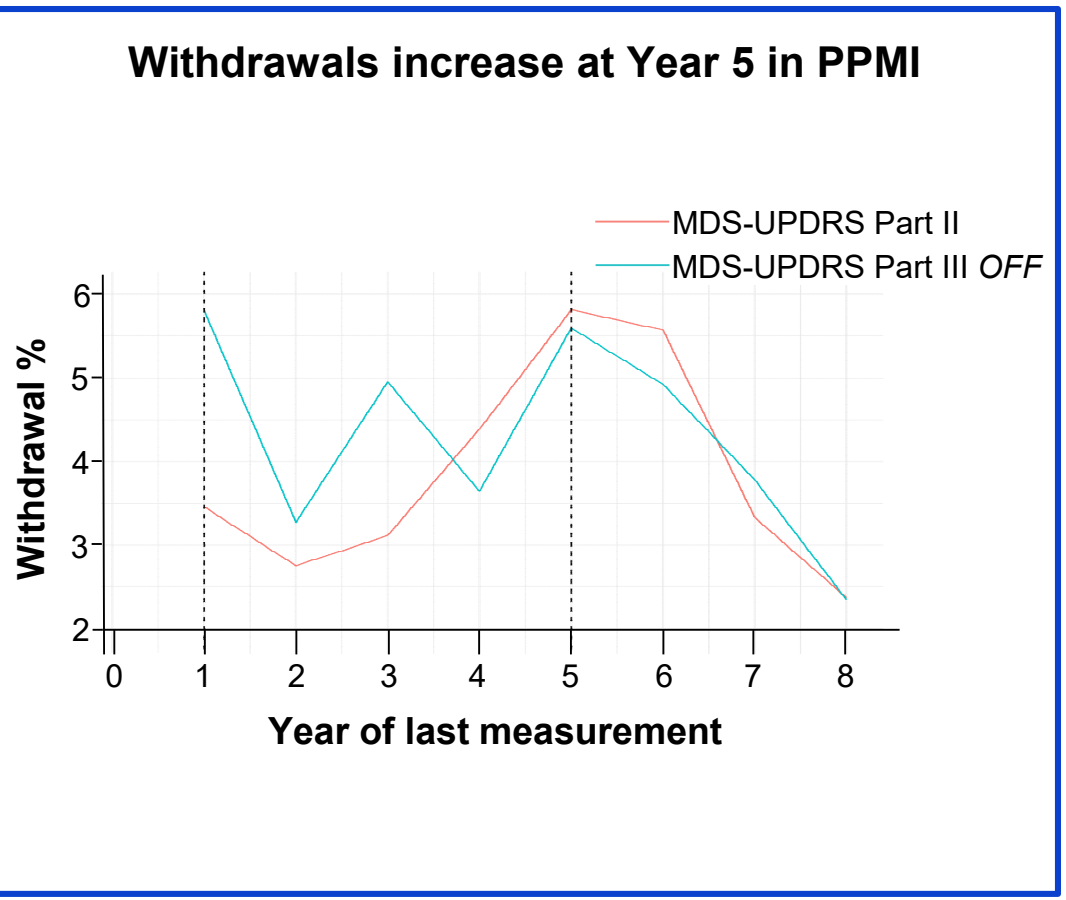
Sustained Effect of Prasinezumab on Parkinson's Disease Motor Progression in the Open-label Extension of the PASADENA Trial 5-year Update
Gullotta F, et al.
Poster Hall, 17–19 Mar

Prasinezumab in Early-stage Parkinson's Disease: Additional Data From the PADOVA Study
Nikolcheva T, et al.
Sat 21 Mar, 12:25PM, Auditorium 10+11

MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

Potential for additional ‘time gained’ beyond 2 years

Interpreting the structural impact of 'Missing Not At Random' attrition



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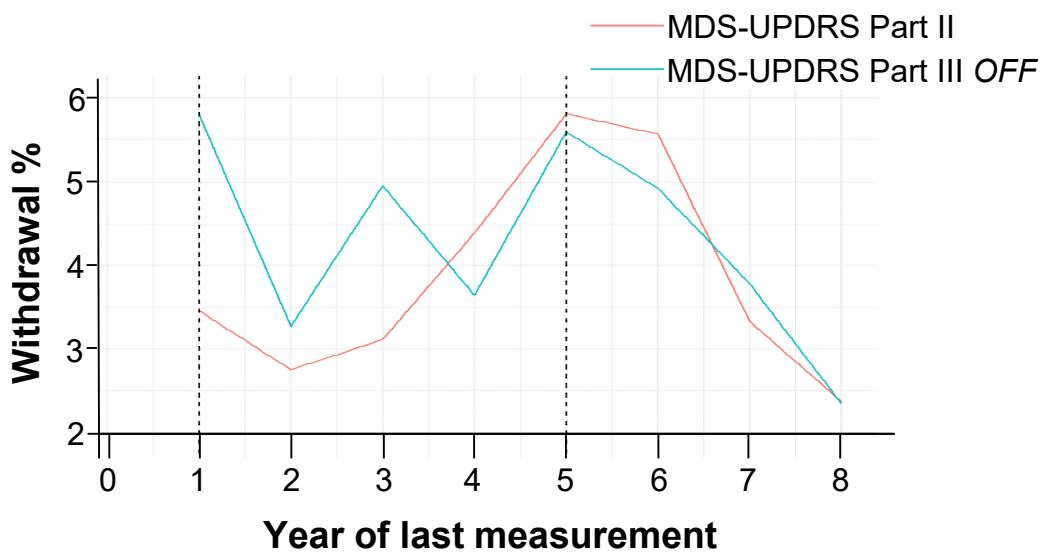
Potential for gaining even more time beyond 2 years

Interpreting the structural impact of 'Missing Not At Random' attrition

Withdrawals increase at Year 5 in PPMI



Baseline characteristics: All participants vs withdrawn in PPMI

	All participants (n=376)	Withdrawn participants (n=109)
Baseline Hoehn and Yahr Stage 2	57.0%	67.0%
Baseline MDS-UPDRS Part III	20.89	22.83

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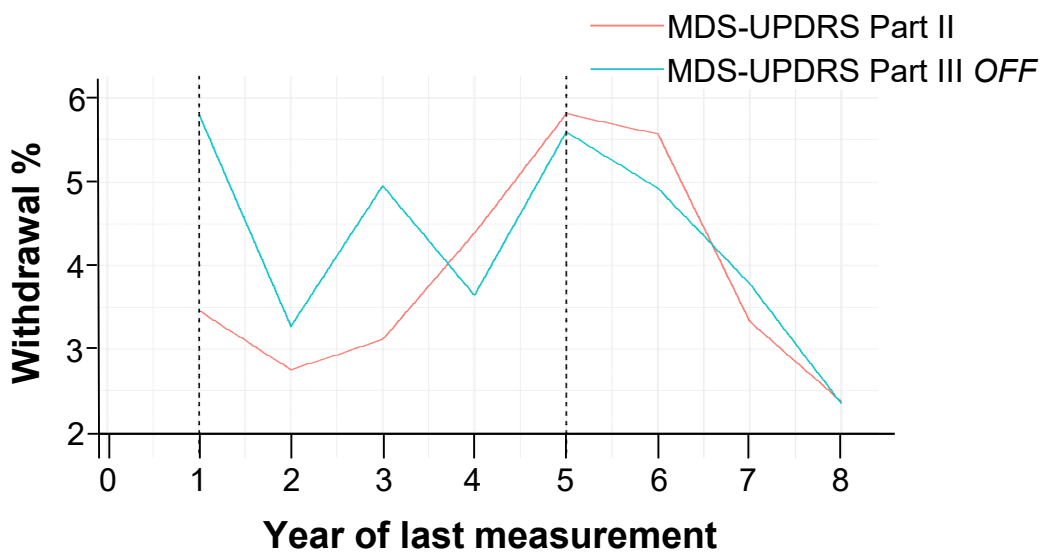

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Observation: PPMI Attrition

Withdrawals increase at Year 5

Hypothesis: Survivor bias

Fast progressors may drop out. Comparator likely with slower progressing participants

Consequence: Conservative benchmark

Comparator curve is flatter than what it should be

Conclusion

Attribution bias may potentially underestimate the progression rate in the comparator arm

MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative.

Summary

Quantifying long-term value through modelling

- Modelling establishes Motor Signs (MDS-UPDRS Part III *OFF*) as a robust **“Leading Indicator”** for future functional decline (MDS-UPDRS Part II)

- This metric **translates complex clinical data into tangible measures**

- Prasinezumab treatment resulted in **~2 years of Time Gained after 5 years** compared to virtual natural history

MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

Acknowledgements

We thank all the study participants and their families, and investigators and site staff, for their time and commitment to the prasinezumab clinical development programme

https://go.roche.link/xxlh74