Roche PD Mobile Application v2 Detects Slowing of Early Parkinson's Disease Progression under Prasinezumab: PASADENA Phase II Part 1 Results

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Disclosures

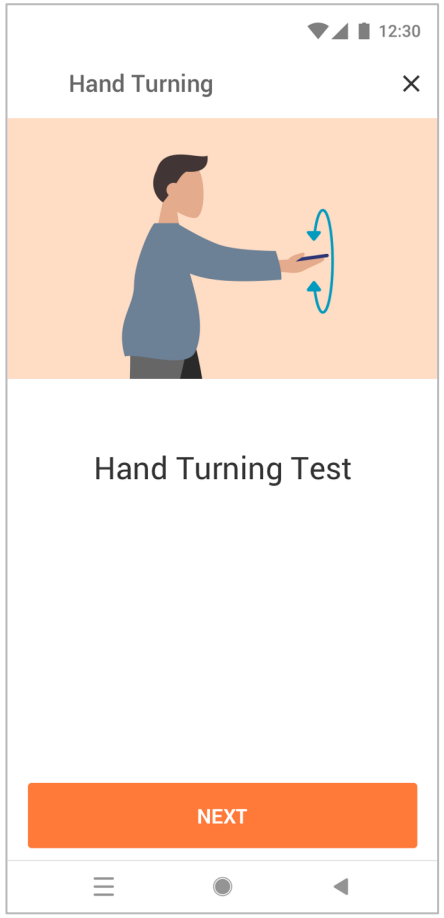
Kirsten I. Taylor is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd.

Introduction

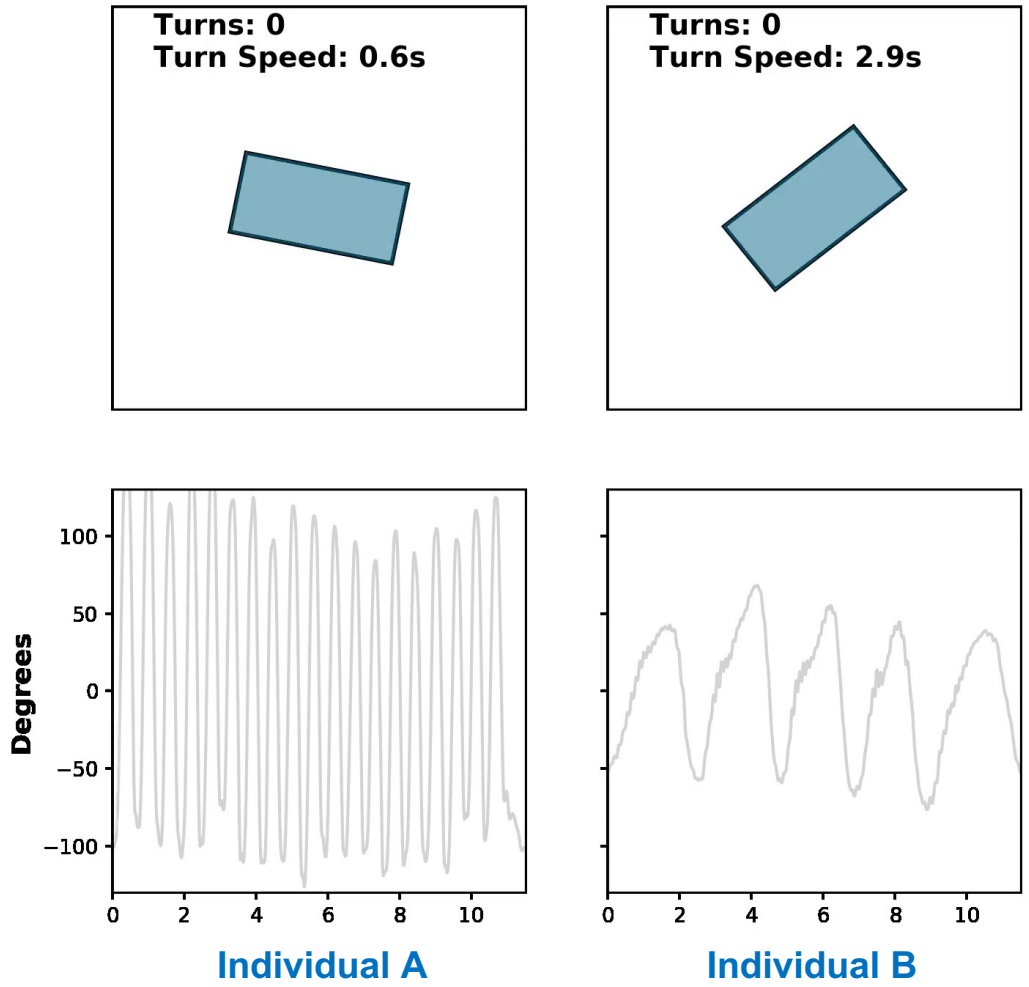
- The fluctuating nature of Parkinsonian symptoms make it difficult to measure potential treatment effects from infrequent clinic visit data.
- Digital Health Technology tools (DHTTs) enable remote and therefore frequent assessments
  - Ecological validity: in environments where individuals live and work
  - Sensors highly sensitive to motor manifestations

Quantifying bradykinesia with smartphone sensors

example: Hand-turning test



Accelerometer output during hand turning task in less (Individual A) and more (Individual B) affected individuals with PD

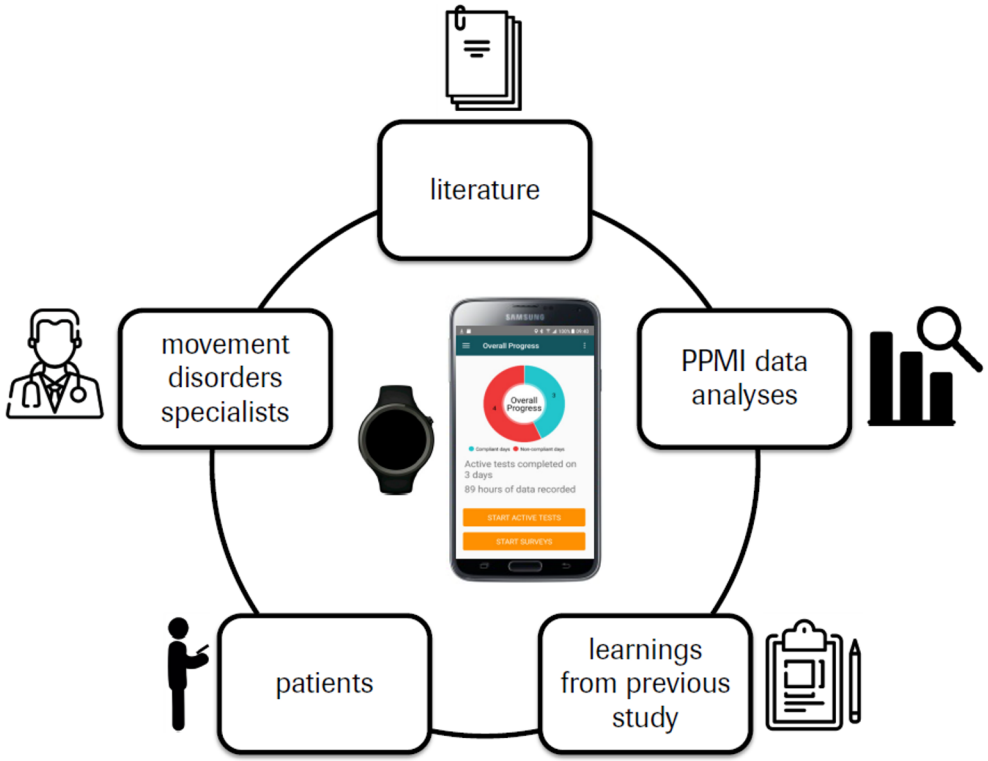


Introduction

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- **DHTTs may provide highly sensitive markers of disease progression and treatment response**

Roche PD Mobile Application v2 is designed to measure core motor signs of PD





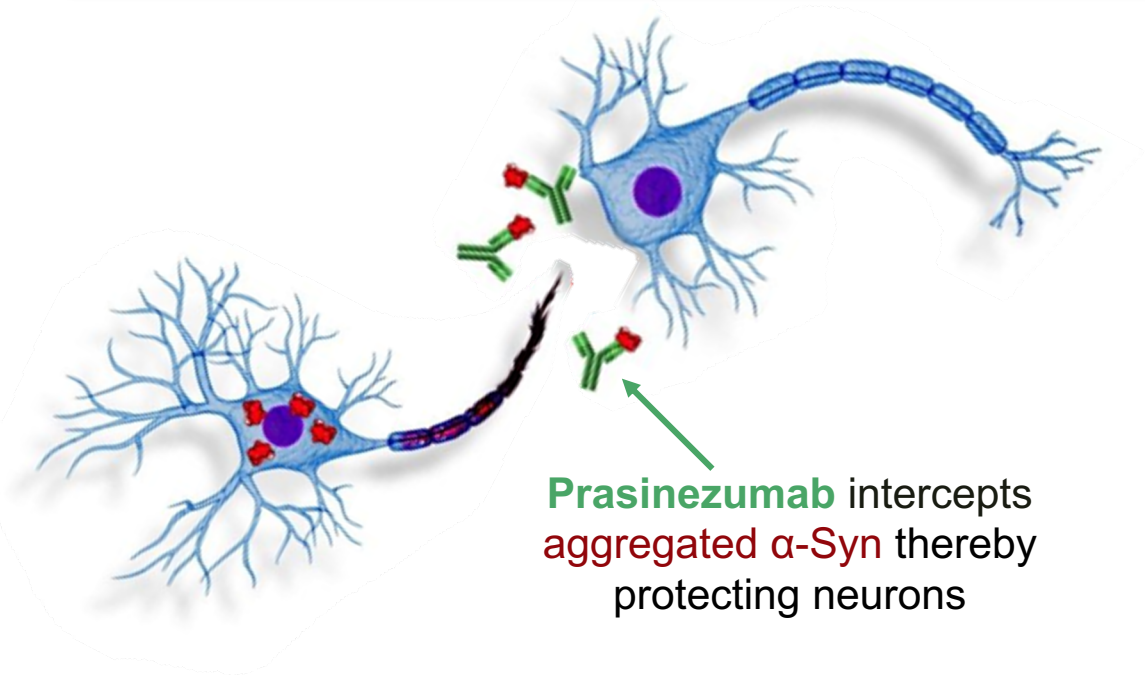
PASSIVE MONITORING		
Bradykinesia and Activities of Daily Living		
Gait	Armswing & Gesture	Mobility
Daily	Daily	Daily

ACTIVE TESTS									
Bradykinesia			*Tremor/Bradykinesia*	*Tremor*			*Rigidity/Postural Instability*		*Cognition*
Draw A Shape	Dexterity	Hand Turning	Speech	Phonation	Postural Tremor	Rest Tremor	Balance	U-Turn	Cognitive Test (SDMT)
Bradykinesia Days (Every 2nd Day)			Alternating		Tremor and Stability Days (Every 2nd Day)				Fortnightly

PPMI = Parkinson's Progression Markers Initiative

Prasinezumab is a humanized monoclonal antibody, designed to target aggregated α-Syn in PD

No treatments exist that can affect the underlying cause of PD[1–3]
Currently available treatments have powerful effects on symptoms but do not prevent or slow disease progression[2,3]



- **α-Syn** is genetically and neuropathologically validated as a **key target in PD[4]**
- **Prasinezumab binds aggregated α-Syn at the C-terminus[5–7]**
  - The targeted epitope results in higher selectivity for aggregated α-Syn, as well as consistently high levels of efficacy across several preclinical models
- **Prasinezumab demonstrated efficacy in multiple *in vivo* and cellular α-synucleinopathy models:[5–9]**
  - Reducing build-up of intracellular α-Syn pathology and protecting neurons
  - Blocking cell-to-cell transmission of α-Syn
  - Protecting synapses and reduceing gliosis
  - Ameliorating motor and cognitive behavioral deficits

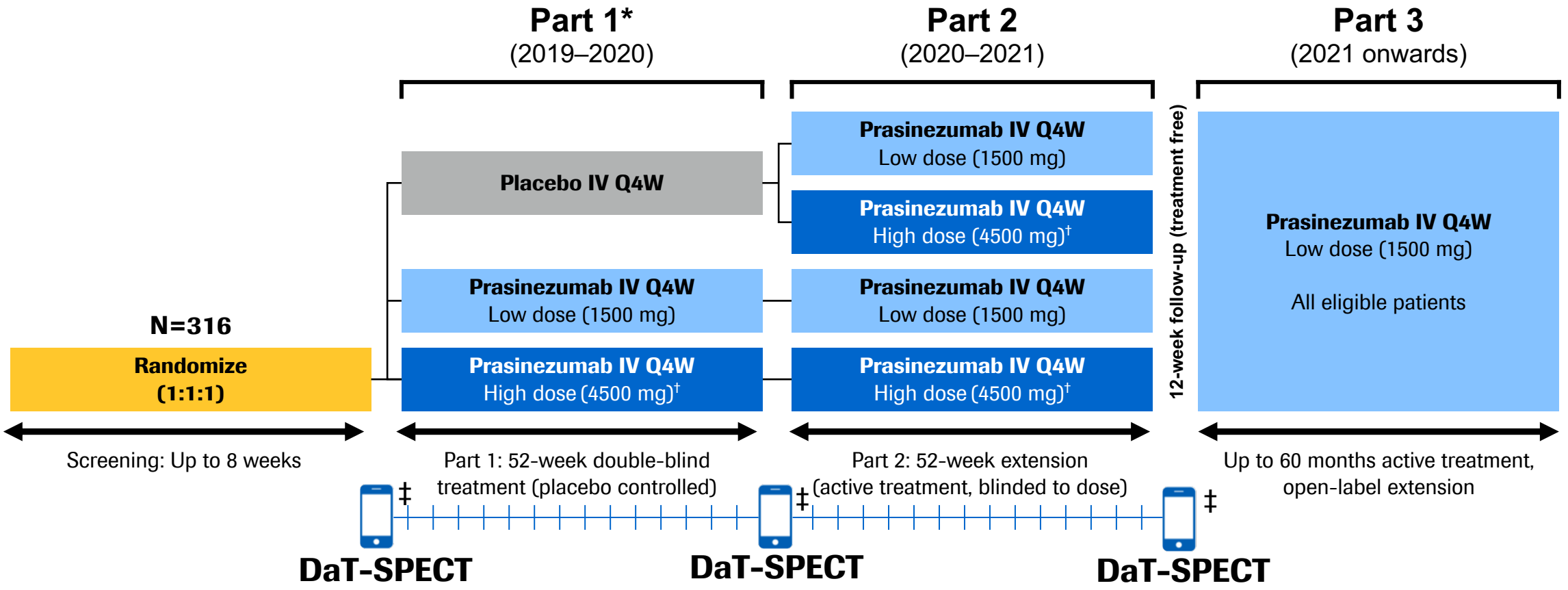
Prasinezumab has the potential to slow disease progression by protecting neurons from toxic α-Syn species

α-Syn, alpha-synuclein; PD, Parkinson's disease.

1. Verschuur CVM, et al. *N Engl J Med*. 2019; 380:315–324; 2. Lang AE & Espay AJ. *Mov Disord*. 2018; 33:660–677; 3. Cheng H, et al. *Ann Neurol*. 2010; 67: 715–725; 4. Dehay B, et al. *Lancet* Neurol. 2015; 14:855–866; 5. Masliah E, et al. *Neuron*. 2005; 46:857–868; 6. Masliah E, et al. *PLoS ONE*. 2011; 6:e19338; 7. Games D, et al. *J Neurosci*. 2014; 34:9441–9454; 8. Spencer B, et al. *Acta Neuropathol Commun*. 2017; 5:7; 9. Jankovic J et al. *JAMA Neurol*. 2018; 75:1206–1214.

PASADENA Phase II study in individuals with early PD

A 52-week multicenter, randomized, double-blind, placebo-controlled study



Signal-detection study designed to include ~100 patients/arm, resulting in 80% power and two-sided alpha of 0.20, to detect a 37.5% relative change in MDS-UPDRS Total score between groups from baseline to Week 52

*COVID-19 did not affect assessments during PASADENA Part 1 as these were completed before the pandemic. †High dose = 4500 mg for ≥65 kg; 3500 mg for <65 kg. ‡Digital biomarkers (smartphone and wrist-worn wearable assessments). COVID-19, coronavirus disease 2019; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; IV, intravenous; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; PD, Parkinson's disease; Q4W, every month. ClinicalTrials.gov. NCT03100149. (Accessed February 2021).

The mentioned compounds and their use are investigational and have not yet received regulatory approval in any country.

Baseline characteristics are generally well balanced among treatment arms

For further details, see Pagano et al., ADPD 2021

	Placebo (n=105)*	Prasinezumab 1500 mg (n=105)*	Prasinezumab 4500 mg† (n=106)*	All patients (N=316)
Age, years Mean (SD)	59.9 (8.7)	60.3 (8.8)	59.4 (9.8)	59.9 (9.1)
Gender, Male N (%)	71 (67.6)	71 (67.6)	71 (67.0)	213 (67.4)
Time from diagnosis Mean (SD)	9.9 (6.8)	10.2 (6.3)	10.1 (6.5)	10.1 (6.5)
MAO-B inhibitor				
Yes	38 (36.2)	38 (36.2)	39 (36.8)	115 (36.4)
No	67 (63.8)	67 (63.8)	67 (63.2)	201 (63.6)
Sub-phenotypes				
Diffuse malignant	15 (14.3)	21 (20.0)	23 (21.7)	59 (18.7)
Mild motor predominant	39 (37.1)	28 (26.7)	39 (36.8)	106 (33.5)
Intermediate	51 (48.6)	56 (53.3)	44 (41.5)	151 (47.8)
MDS-UPDRS Total Mean (SD)	32.01 (12.98)	31.49 (13.32)	30.75 (12.10)	31.41 (12.78)
MDS-UPDRS Part III Mean (SD)	21.54 (9.11)	21.90 (9.14)	20.97 (8.81)	21.47 (9.00)
MDS-UPDRS Part II Mean (SD)	5.55 (4.09)	4.94 (3.99)	5.50 (4.07)	5.33 (4.04)
MDS-UPDRS Part I Mean (SD)	4.91 (3.71)	4.64 (4.16)	4.27 (3.57)	4.61 (3.83)
H&Y Stage category				
I (%)	20 (19.0)	29 (27.6)	29 (27.4)	78 (24.7)
II (%)	85 (81.0)	76 (72.4)	77 (72.6)	238 (75.3)
Patients with evaluable data at Week 52‡	76 (72.4)	75 (73.5)	73 (70.9)	224 (70.9)

*n represents number of participants contributing to summary statistics. Percentages are based on n. †3500 mg for <65 kg. ‡Visits are time windowed. Non-evaluable data are considered as patient starting symptomatic PD treatment, an increase on MAO-B inhibitor (if the patient was on MAO-B inhibitor at baseline), or withdrawal from the study.

H&Y, Hoehn and Yahr; MAO-B, monoamine oxidase B; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; PD, Parkinson's disease; SD, standard deviation.

Continuous data over 52 weeks enabled testing of divergence of *slopes* of motor sign progression



- A total of 17 pre-specified sensor features*, one per task/side and from passive monitoring
- Sensor features aggregated (median) over all data points within each two-week (fortnight) window** over entire 52 weeks of study
- Data censored at the start of symptomatic PD treatment
- Prasinezumab treatment groups combined (“pooled”)
- **Linear mixed effect (LME) model with random slope** (fortnights) of change from baseline
  - Covariates: baseline MAO-Bi therapy Yes/No; Age; Sex; baseline DaT-SPECT Specific Binding Ratio in ipsilateral putamen
  - Alpha = 0.2, beta = 0.8; multiple comparison correct = 15% False Discovery Rate (FDR)
  - Non-normally distributed residuals, report **Mixed Models with Repeated Measures (MMRM)**
  - **Effect of interest: interaction of fortnight by treatment group**

*median gesture power of passively monitored gestures, median turn speed in U-turn test and passively monitored gait, jerk in balance test, mel frequency cepstrum 2 in speech test, voice jitter in sustained phonation, number correct in Symbol Digit Modalities Test; for least and most affected sides separately: speeded tapping variability, maximum speed of hand-turning, spiral celerity in draw-a-shape task, median squared energy in rest and postural tremor tasks.
** If <3 data points per fortnight, then missing

Prasinezumab treatment associated with decreased progression of upper limb bradykinesia

category	Source	Feature	Result
Bradykinesia	Speeded tapping test	Variability, L	
		Variability, M	
	Hand turning test	Maximum speed, L	
		Maximum speed, M	
	Passive gestures	Power	
	Draw-a-shape	Spiral celerity, L	
		Spiral celerity, M	
Gait, balance	U-turn test	Median turn speed	
	Passive turning	Median turn speed	
	Balance test	Jerk	
Tremor	Postural tremor test	Median squared energy, L	
		Median squared energy, M	
	Rest tremor test	Median squared energy, L	
		Median squared energy, M	
Speech	Free speech test	Mel frequency cepstrum 2	
	Sustained phonation test	Voice jitter	
Cognition	SDMT	Number correct	

	Effect favors prasinezumab
	No effect
	Effect favors placebo

L = less affected side; M = most affected side
Celerity = accuracy / speed

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	Hand turning test	Maximum speed, L	
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	Passive gestures	***Power**	
	Draw-a-shape	Spiral celerity, L	
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	Balance test	Jerk	
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		Median squared energy, M	
	Rest tremor test	Median squared energy, L	
		Median squared energy, M	
Speech	Free speech test	Mel frequency cepstrum 2	
	Sustained phonation test	Voice jitter	
Cognition	SDMT	Number correct	

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***FDR <= 0.2**

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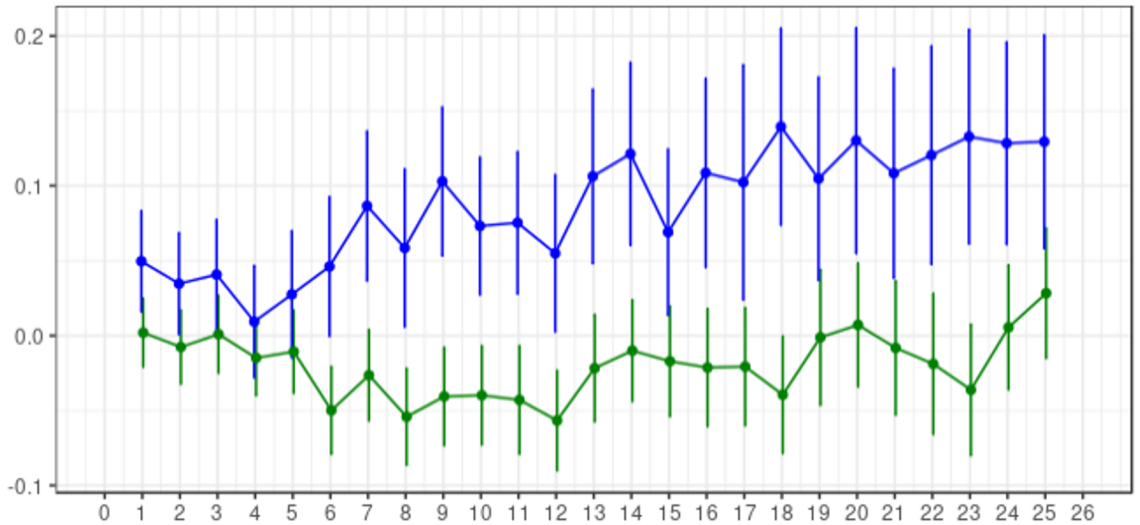
Less bradykinesia progression in treatment group

Features with FDR≤0.2

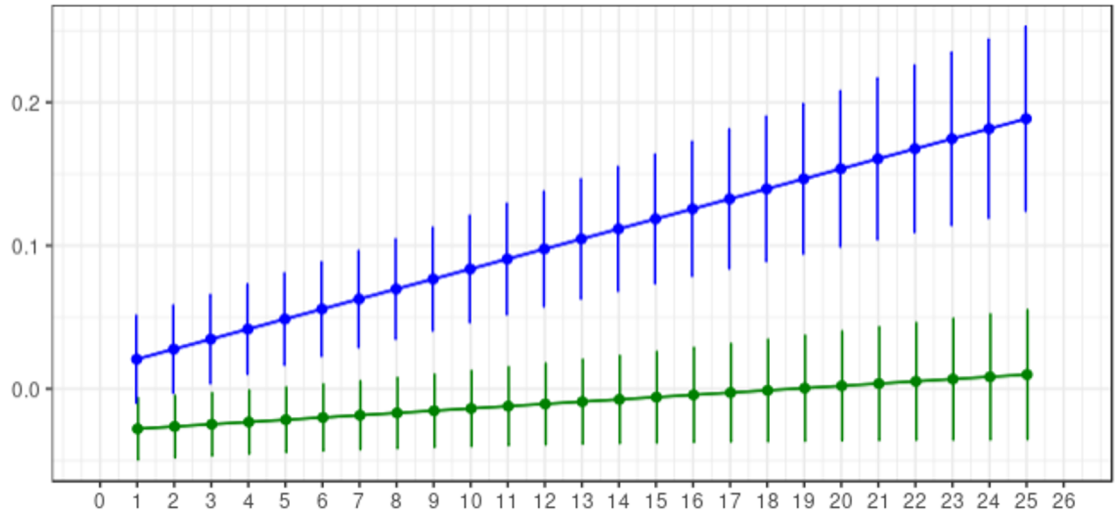
Placebo Pooled prasinezumab

Speeded tapping variability, less affected side

Raw change from baseline (80% CI)

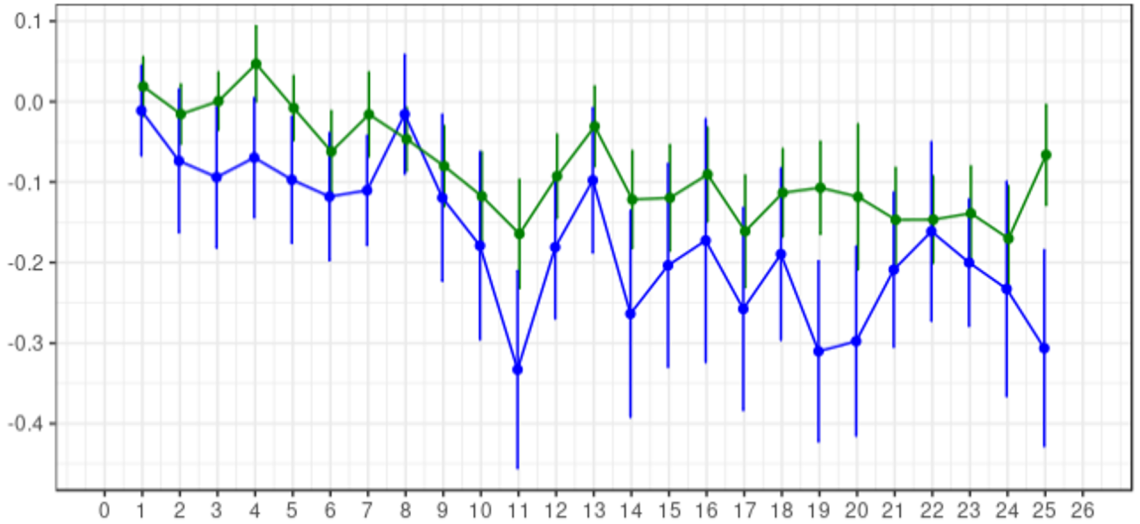


Results of Linear Mixed Effect model (80% CI)



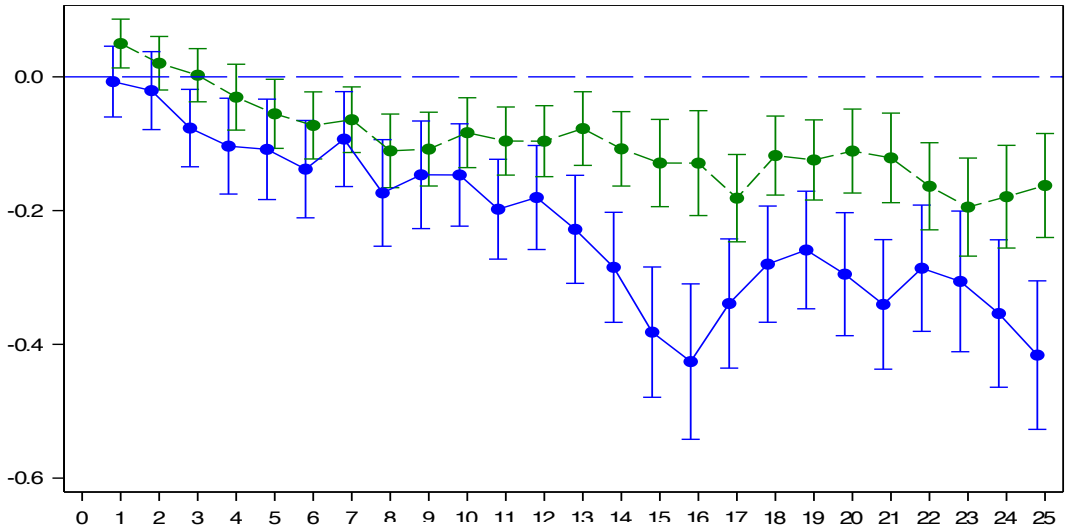
Passively monitored hand gesture power

Raw change from baseline (80% CI)



Fortnight (2-week period)

Result of Mixed Model with Repeated Measures (80% CI)



Fortnight (2-week period)

Summary and outlook

- DHTT measurements of the core signs of PD **remotely, continuously and objectively** enable the modelling of **slopes of motor sign progression**
- Daily quantification via the Roche PD Mobile Application in early-stage PD demonstrated a **divergence of slopes in bradykinesia progression**
- These results are consistent with a potential effect of prasinezumab in slowing PD progression
    - In line with PASADENA part 1 results (see ADPD presentation from Pagano et al, 2021)

Outlook:

- **Digital endpoints** for use in drug development decision-making (e.g. Taylor et al., 2020)
- **Data sharing** initiatives important to facilitate progress (e.g. Critical Path for Parkinson's Disease, Michael J. Fox Foundation)

Taylor KI, Staunton H, Lipsmeier F, Nobbs D, Lindemann M. Outcome measures based on digital health technology sensor data: data- and patient-centric approaches. npj Digit Med. 2020 Dec;3(1):97. https://doi.org/10.1038/s41746-020-0305-8; Pagano et al. ADPD 2021. A Phase II study to evaluate the safety and efficacy of prasinezumab in early Parkinson's disease (PASADENA): Results from Part 1 Week 52.

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