Prasinezumab slows motor progression in rapidly progressing early-stage Parkinson's disease

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Article

Keywords:

Posted Date: July 31st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3128098/v1

Additional Declarations: Yes there is potential Competing Interest. GP, KIT, AM, RD, PF, GAK, PB, TN and AB are employees and shareholders of F. Hoffmann-La Roche Ltd. RD is also employed by Genentech. PB has also ownership interests in Acousort AB, Enterin Inc, Axial Therapeutics and RYNE Bio. JAC and DT are employees of Roche Products Ltd. and shareholders of F. Hoffmann-La Roche Ltd. HS is an employee of Roche Diagnostics GmbH Deutschland and a shareholder of F. Hoffmann-La Roche. TS 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. TS 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, TS has received research funding from Amneal, Biogen, Neuroderm, Prevail, Roche, and UCB and is an investigator for NINDS, MJFF, Parkinson's Foundation. KM 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. RBP is a consultant for Biogen, Clinilabs, Curasen, Eisai, Inc., F. Hoffmann-La Roche Ltd., Merck, Takeda California, Inc., and Vaxxinity. NP reports participating in advisory boards for Britannia, Boston Scientific, Benevolent AI, Hoffmann-La Roche, inc., and Abbvie. NP 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, and Hoffmann-La Roche, inc. FS 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. KB is a consultant for F. Hoffmann-La Roche Ltd., Vanqua Bio, and the Michael J. Fox Foundation for Parkinson's Research.

Version of Record: A version of this preprint was published at Nature Medicine on April 15th, 2024. See the published version at https://doi.org/10.1038/s41591-024-02886-y.

Abstract

Background

Prasinezumab, a monoclonal antibody that binds aggregated alpha-synuclein, is currently being investigated as a potential disease-modifying therapy in early-stage Parkinson's disease (PD). In the PASADENA Phase II study, prasinezumab-treated individuals exhibited slower progression of motor signs than placebo-treated participants (MDS-UPDRS Part III). Here, we explore whether prasinezumab showed greater benefits on motor progression in rapidly compared with more slowly progressing subpopulations of PD.

Methods

Prasinezumab's effects on disease progression were assessed in pre-specified rapidly progressing and more slowly progressing subpopulations of PD during the double-blind phase of PASADENA (e.g., participants taking MAO-B inhibitors at baseline vs. treatment-naïve participants).

Results

In the rapidly progressing subpopulations of PASADENA, participants treated with prasinezumab showed less decline in MDS-UPDRS Part III compared with more slowly progressing subpopulations of PD.

Conclusion

Efficacy of prasinezumab was greater in individuals with early-stage PD with a more rapidly progressing clinical phenotype.

Main

Pathological alpha-synuclein is considered to be the hallmark of Parkinson's disease (PD) and several lines of evidence suggest a role for alpha-synuclein aggregates, and their propagation between neurons, in the pathogenesis of PD progression[1].

Prasinezumab is the first experimental therapeutic monoclonal antibody designed to bind aggregated alpha-synuclein[2,3]. The effect of prasinezumab was investigated in individuals with early-stage PD in the PASADENA Phase II study (NCT03100149)[4]. Part 1 of the study was double-blind and included 316 individuals with early-stage PD randomized 1:1:1 to intravenous infusions of placebo, prasinezumab 1500 mg, or prasinezumab 4500 mg every four weeks for 52 weeks. Participants were stratified for age at baseline (< 60 years vs. ≥60 years), sex at birth (male vs. female), and use of monoamine oxidase B (MAO-B) inhibitors at baseline (yes vs. no). Except for the use of MAO-B inhibitors, other symptomatic medications for PD, including levodopa and dopamine agonists, were not allowed at baseline, and their use was discouraged for the duration of the double-blind period of the study, unless absolutely necessary. In those cases, a prior-to-start of symptomatic treatment visit was performed to collect Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS[5]) scores before symptomatic medication was commenced.

Part 1 of PASADENA did not meet its primary endpoint (change from baseline in the sum of Parts I + II + III of the MDS-UPDRS[5])[4]. However, compared to participants treated with placebo, prasinezumab-treated individuals exhibited less progression on the secondary endpoint MDS-UPDRS Part III, while no differences were found for MDS-UPDRS Parts I and II[4]. MDS-UPDRS Parts I and II are unlikely to change over a 1-year period, as observed in the Parkinson's Progression Marker Initiative (PPMI), a larger observational study of PD natural progression; in fact, over 52 weeks, the PPMI cohort exhibited a clinically meaningful decline in MDS-UPDRS Part III scores, but minimal changes in MDS-UPDRS Parts II and I that fell below the thresholds for clinical meaningfulness[6–8]. These observations are consistent with the idea that a potential treatment effect on disease progression can only be demonstrated when patients progress sufficiently on the endpoint of interest.

We therefore hypothesized that prasinezumab may show a greater effect in subpopulations with rapidly progressing disease, compared with more slowly progressing subpopulations. The initial PASADENA protocol included six pre-specified primary subpopulations and nine pre-specified exploratory subpopulations, defined by factors known to be associated with faster progression. The six primary subpopulations comprised: i) participants taking MAO-B inhibitors at baseline vs. participants who were treatment-naïve; ii) participants with Hoehn & Yahr stage 2 vs. Hoehn & Yahr stage 1; iii) participants with rapid eye movement sleep behavior disorder (RBD) vs. participants without RBD; iv) participants with diffuse malignant vs. non-diffuse malignant subphenotypes; v) participants with vs. without alpha-synuclein skin (staining by IHC on skin biopsy sections at baseline); and vi) participants with dopamine transporter-single-photon emission computed tomography striatal binding ratio (DaT-SPECT SBR; putamen-ipsilateral) very abnormal vs. abnormal (defined on the baseline data with a validated cutoff of 0.6). The nine exploratory subpopulations comprised: i) participants with age at

baseline < 60 years vs. ≥60 years; ii) male vs. female participants; iii) participants with disease duration < 12 months vs. >12 months; iv) participants with age at diagnosis < 60 years vs. ≥60 years; v) participants with vs. without atrophy in the nucleus basalis of Meynert; vi) participants with Montreal Cognitive Assessment (MoCA) total score < 22 vs. >22; vii) participants with vs. without *GBA* mutation; viii) participants with akinetic-rigid vs. tremor-dominant motor subphenotypes; and ix) participants with postural instability gait dysfunction (PIGD) vs. tremor-dominant motor subphenotypes[9].

We focused on the hypothesis that prasinezumab may show a greater effect in subpopulations with rapidly progressing disease because, firstly, greater progression (with comparable variability of progression) is expected to increase the signal-to-noise ratio (i.e., degree of change over time) and the likelihood of showing a potential treatment effect, and, secondly, more rapid progression may be associated with greater levels of aggregated alpha-synuclein[10], the target of prasinezumab.

In this report, we describe the effect of prasinezumab on disease progression as quantified by the MDS-UPDRS Parts I, II and III scores, focusing on (a) the subpopulation taking stable doses of MAO-B inhibitors at baseline, and (b) those with the above listed pre-specified indicators of possible rapid progression.

Results

Baseline characteristics of the participants

Only subpopulations containing at least 20% of patients from the modified intention-to-treat (mITT) population at baseline were included in the final analyses presented in this article. Of the six primary subpopulations that were initially defined, four were included in the final analyses: i) MAO-B inhibitors at baseline (yes vs. no); ii) Hoehn & Yahr stage (1 vs. 2); iii) RBD (yes vs. no); and iv) data-driven subphenotypes (diffuse malignant vs. non-diffuse malignant). Similarly, of the nine exploratory subpopulations, six were included in the final analyses: i) age at baseline (< 60 vs. ≥60 years); ii) sex (male vs. female); iii) disease duration (< 12 vs. >12 months); iv) age at diagnosis (< 60 vs. ≥60 years); v) motor subphenotypes tremor dominant vs. akinetic-rigid; and vi) motor subphenotypes tremor dominant vs. PIGD. Baseline demographic and clinical characteristics of the placebo and prasinezumab groups were comparable in the subpopulations of patients who received MAO-B inhibitors at baseline vs. those who were treatment-naïve (Table 1), and in the other primary and exploratory subpopulations included in the analyses (Supplementary Table S1).

Table 1
Baseline demographic and clinical characteristics of the whole study population, participants taking MAO-B inhibitors at baseline and those who were treatment-naïve at baseline

	Whole population		MAO-B inhibitors		Treatment-naïve	
	Placebo (n = 105)	Prasinezumab pooled (n = 211)	Placebo (n = 38)	Prasinezumab pooled (n = 77)	Placebo (n = 67)	Prasinezumab pooled (n = 134)
Age (years), mean (SD)	59.9 (8.7)	59.9 (9.3)	58.3 (8.4)	58.2 (9.4)	60.8 (8.8)	60.9 (9.2)
Sex (male), n (%)	71 (67.6)	142 (67.3)	24 (63.2)	50 (64.9)	47 (70.1)	92 (68.7)
Time since diagnosis (months), mean (SD)	9.95 (6.79)	10.19 (6.37)	11.93 (6.37)	11.98 (5.99)	8.83 (6.81)	9.17 (6.37)
Time since diagnosis ≤ 12 months, n (%)	72 (68.6)	147 (69.7)	22 (57.9)	47 (61.0)	50 (74.6)	100 (74.6)
Hoehn and Yahr Stage, n (%)	20 (19.0)	58 (27.5)	7 (18.4)	25 (32.5)	13 (19.4)	33 (24.6)
Stage I	85 (81.0)	153 (72.5)	31 (81.6)	52 (67.5)	54 (80.6)	101 (75.4)
Stage II						
MDS-UPDRS Total (Sum of Parts I, II and III), mean (SD)	32.01 (12.98)	31.11 (12.70)	32.16 (12.01)	29.25 (11.90)	31.93 (13.58)	32.19 (13.06)
MDS-UPDRS Part I, mean (SD)	4.91 (3.71)	4.45 (3.88)	5.08 (3.82)	4.19 (3.15)	4.82 (3.67)	4.60 (4.25)
MDS-UPDRS Part II, mean (SD)	5.55 (4.09)	5.22 (4.03)	5.84 (4.25)	4.87 (3.69)	5.39 (4.01)	5.43 (4.21)
MDS-UPDRS Part III, mean (SD)	21.54 (9.11)	21.44 (8.97)	21.24 (8.77)	20.18 (8.87)	21.72 (9.36)	22.16 (8.98)
DaT-SPECT SBR*, mean (SD)	1.06 (0.30)	1.06 (0.34)	1.03 (0.30)	1.02 (0.31)	1.09 (0.29)	1.09 (0.35)

n represents number of participants contributing to summary statistics. Percentages are based on n.

*Putamen-ipsilateral.

DAT-SPECT, dopamine transporter-single-photon emission computed tomography; MAO-B, monoamine oxidase-B; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SD, standard deviation, SBR, striatal binding ratio.

Responses to prasinezumab treatment in participants taking MAO-B-inhibitors at baseline and those who were treatment-naïve

Analyses were performed using two estimand strategies: the 'hypothetical strategy' assumes a scenario in which the events of start of symptomatic therapy or change in MAO-B inhibitor dose did not occur (performed for the mITT population), and the 'treatment policy strategy' in which the treatment effect is estimated irrespective of symptomatic treatment start or changes in MAO-B inhibitor treatment (performed for the ITT population) (see Methods for further details). With the hypothetical strategy, the mean (standard error [SE]) change from baseline to Week 52 in MDS-UPDRS Part III score in the entire PASADENA placebo population was 5.57 (0.90) points (Table 2). The corresponding mean (SE) change in the placebo group of the subpopulation of participants taking MAO-B inhibitors at baseline was 6.82 (1.37) points, compared with 5.04 (1.16) points in the placebo group of the treatment-naïve subpopulation (Table 2 and Fig. 1A). The differences in adjusted means from baseline at Week 52 in the prasinezumab group vs. placebo were − 2.66 points (80% confidence interval [CI], − 4.87, − 0.45; relative reduction, − 39.0%) in the subpopulation of participants taking MAO-B inhibitors at baseline and − 0.87 points (80% CI, − 2.69, 0.94; relative reduction, − 17.3%) in the subpopulation of participants who were treatment-naïve (Table 2 and Fig. 1A).

Table 2
Change from baseline at Week 52 in the subpopulations of participants taking MAO-B inhibitors at baseline and those who were treatment-naïve at baseline

	Placebo			Prasinezumab pooled					
	MAO-B (n = 38)	Treatment-naïve (n = 67)	All (n = 105)	MAO-B (n = 77)			Treatment-naïve (n = 134)		
	Adjusted mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	Difference in adjusted means (SE)	80% CI	%RR	Difference in adjusted means (SE)	80% CI	%RR
MDS-UPDRS Part III									
Hypothetical strategy*	6.82 (1.371) n = 28	5.04 (1.163) n = 48	5.57 (0.897) n = 76	−2.66 (1.713) n = 55	−4.87, −0.45	−39.0	−0.87 (1.411) n = 92	−2.69, 0.94	−17.3
Treatment policy OFF#	4.79 (1.214) n = 36	3.10 (1.048) n = 65	3.56 (0.800) n = 101	−2.60 (1.476) n = 76	−4.51, −0.70	−54.3	0.53 (1.267) n = 125	−1.10, 2.16	+17.1
Treatment policy ON#	4.18 (1.248) n = 38	2.01 (1.109) n = 67	2.66 (0.840) n = 105	−2.60 (1.532) n = 76	−4.57, −0.63	−62.2	0.32 (1.340) n = 130	−1.40, 2.04	+15.9
MDS-UPDRS Part II									
Hypothetical strategy*	2.40 (0.635) n = 28	2.89 (0.467) n = 48	2.75 (0.373) n = 76	0.20 (0.773) n = 55	−0.80, 1.20	+8.3	0.10 (0.567) n = 92	−0.63, 0.83	+3.5
Treatment policy#	1.21 (0.592) n = 38	1.63 (0.438) n = 67	1.47 (0.353) n = 105	0.22 (0.721) n = 76	−0.71, 1.15	+18.2	0.25 (0.531) n = 129	−0.43, 0.93	+15.3
MDS-UPDRS Part I									
Hypothetical strategy*	1.28 (0.466) n = 28	0.38 (0.371) n = 48	0.77 (0.295) n = 76	−0.44 (0.567) n = 55	−1.17, 0.29	−34.4	0.30 (0.447) n = 92	−0.27, 0.88	+78.9
Treatment policy#	0.50 (0.452) n = 37	0.10 (0.375) n = 67	0.20 (0.292) n = 104	0.03 (0.549) n = 76	−0.68, 0.73	+6.0	0.65 (0.453) n = 125	0.06, 1.23	+650.0

* 'Hypothetical strategy' assumes a scenario in which the events of start of symptomatic therapy or change in MAO-B inhibitor dose did not occur (performed for the mITT population)

'Treatment policy strategy' in which the treatment effect is estimated irrespective of symptomatic treatment start or changes in MAO-B inhibitor treatment (performed for the ITT population)

CI, confidence interval; ITT, intention-to-treat; MAO-B, monoamine oxidase-B; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; mITT, modified intention-to-treat; %RR, percent relative reduction; SE, standard error.

Similar results were observed when MAO-B inhibitor subpopulation MDS-UPDRS Part III data were analyzed with the treatment policy strategy, both in OFF state (difference in adjusted means, − 2.60 points; 80% CI, − 4.51, − 0.70; relative reduction, − 54.3%; Table 2; Fig. 1B) and in ON state (difference in adjusted means, − 2.60 points; 80% CI, − 4.57, − 0.63; relative reduction, − 62.2%; Table 2; Fig. 1C).

Mean (SE) changes (with the hypothetical strategy) from baseline to Week 52 in MDS-UPDRS Parts II and I scores in the entire PASADENA placebo population were 2.75 (0.37) and 0.77 (0.30) points, respectively (Table 2). The mean (SE) changes from baseline to Week 52 in MDS-UPDRS Part II score in the placebo subpopulations who were treated with MAO-B inhibitors and treatment-naïve at

baseline were 2.40 (0.64) and 2.89 (0.47) points, respectively, and the corresponding values for MDS-UPDRS Part I score were and 1.28 (0.47) and 0.38 (0.37) points, respectively (Table 2). No differences were found between the prasinezumab and the placebo groups on MDS-UPDRS Part II and Part I, using either the hypothetical or treatment policy strategies (Table 2).

Responses to prasinezumab treatment in subpopulations with rapidly progressing disease

The placebo groups in each pre-specified rapidly progressing subpopulation declined faster than their non-rapidly progressing counterparts on MDS-UPDRS Part III, as expected (Fig. 2; Supplementary Figure S1); for example, mean (SE) changes (with the hypothetical strategy) from baseline to Week 52 were 12.29 (3.45) points in the diffuse malignant subpopulation, 8.40 (1.59) points in those with the motor subphenotype of PIGD, 7.76 (2.01) points in those with Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ) score ≥ 5, 6.82 (1.37) points in those taking MAO-B inhibitors at baseline, and 6.34 (1.04) points in those with Hoehn & Yahr stage 2 (Fig. 2; Table 2; Supplementary Figure S1; Supplementary Table S2).

A greater beneficial effect for prasinezumab vs. placebo was shown in pre-specified subpopulations with more rapidly progressing disease compared with their non-rapidly progressing counterparts; for example, the differences in adjusted means in MDS-UPDRS Part III scores (with the hypothetical strategy) for prasinezumab vs. placebo in the diffuse malignant and the non-diffuse malignant subpopulations were − 7.86 points (80% CI, − 12.90, − 2.82; relative reduction, − 64.0%) and − 0.77 points (80% CI, − 2.20, 0.66; relative reduction, − 16.2%), respectively (Fig. 2; see Supplementary Table S2 for further details).

Discussion

In this pre-specified exploratory analysis of the PASADENA study, participants in rapidly progressing subpopulations treated with prasinezumab showed less increase (worsening) in MDS-UPDRS Part III compared with participants treated with placebo. These findings suggest that prasinezumab may slow the progression of motor signs in individuals with characteristics usually associated with more rapid progression. These findings also expand upon those of the original PASADENA study, in which the overall population of prasinezumab-treated individuals exhibited less progression on MDS-UPDRS Part III than those treated with placebo[4].

In the original PASADENA study, prasinezumab failed to meet the primary endpoint (change from baseline in MDS-UPDRS sum of Parts I + II + III)[4]. The MDS-UPDRS sum of Parts I + II + III is a global measure of PD, including motor signs rated by the clinicians (Part III), and motor (Part II) and non-motor (Part I) symptoms reported by the patients[5].

For a disease-modifying treatment to be able to exhibit a significant effect (i.e., a slowing of progression), a meaningful degree of disease progression in the placebo group is necessary during the study period. Importantly, the PASADENA participants (both placebo- and active-treated) progressed minimally on the MDS-UPDRS Part I (< 1 point) and Part II (< 3 points) over the 52-week double-blind treatment period. Minimal changes in the progression of MDS-UPDRS Parts I or II (i.e., changes below what is considered clinically meaningful) were also observed in other studies that included participants with early-stage PD, such as the PPMI study[6–8] and the De Novo Parkinson (DeNoPa) study[11]. On average, MDS-UPDRS Parts I and Part II declined 0.9 − 1.2 points and 1.0 − 1.6 points, respectively, at Week 52 in the PPMI cohort[6–8], which was similar to participants in the DeNoPa and PASADENA studies[4,11]. In contrast, both the prasinezumab- and placebo-treated PASADENA participants progressed on average by ~ 5 points on the MDS-UPDRS Part III, which was more than the minimum threshold for a clinically meaningful change (previously defined as 4.63 points)[8]. Based on the PASADENA original finding that prasinezumab-treated individuals exhibited a numerically reduced clinical decline in MDS-UPDRS Part III scores relative to placebo[4], we explored here the hypothesis that prasinezumab shows greater effects in pre-specified subpopulations that were expected to decline more rapidly in motor function. We focused on this hypothesis because, firstly, greater progression (with comparable variability of progression) is expected to increase the signal-to-noise ratio and the likelihood of showing a potential treatment effect in MDS-UPDRS Part III, and, secondly, more rapid progression may be associated with greater levels of aggregated alpha-synuclein[10] the target of prasinezumab.

We confirmed faster declines in the subpopulations expected to progress more rapidly on motor signs (as measured by a larger increase in MDS-UPDRS Part III). All rapidly progressing subpopulations consistently showed numerically greater prasinezumab effect compared with their non-rapidly progressing counterparts. Moreover, we demonstrated that the prasinezumab effect size was related to the speed of progression in the placebo group. For example, the diffuse malignant subpopulation showed an increase (worsening) of 12.29 points on MDS-UPDRS Part III in the placebo group, and a 64.0% relative reduction of worsening in prasinezumab vs. placebo-treated

participants. In contrast, the non-diffuse malignant subpopulation showed an increase (worsening) of 4.76 points on MDS-UPDRS Part III in the placebo group, and a 16.2% relative reduction in worsening in prasinezumab vs. placebo.

Notably, the subpopulations that progressed faster on MDS-UPDRS Part III did not progress faster on MDS-UPDRS Parts II and I. This may suggest that the progression of motor signs (MDS-UPDRS Part III) precedes significant changes in both motor and non-motor symptoms (MDS-UPDRS Parts II and I). A difference in clinical rating of motor signs vs. a patient-self-ratings/awareness of motor symptoms can also explain the differences in progression between MDS-UPDRS Part III and MDS-UPDRS Parts II and I[12]. Much longer studies may be required to test the effect of potential disease-modifying treatments, such as prasinezumab, on progression of patient-reported motor symptoms, functional activity of daily living, and progression of non-motor symptoms. Moreover, it confirms that motor symptoms remain the most reliable biomarker of disease progression in early-stage PD, as also shown in other studies on prodromal PD[13].

The results of these analyses should be interpreted with caution, given the small sample sizes of most of the subpopulations and the lack of correction for multiple comparisons. However, the subpopulation of people treated with MAO-B inhibitors represents approximately 40% of the whole population, and the use of MAO-B inhibitors at baseline was included as a stratification factor at randomization. A further limitation of the study is that it cannot be excluded that the use of MAO-B inhibitors might reflect the treating clinician's/site's preferred approach to managing recently diagnosed patients, rather than representing an indicator of rapid progression in all patients. Three non-mutually exclusive explanations may account for the potentially greater effect of prasinezumab in subpopulations with faster progression. Firstly, the effect of prasinezumab might be more detectable in the faster-progressing subpopulation due to an increased signal-to-noise ratio (i.e., degree of change over time) on clinician-rated scale assessments of motor signs progression. Secondly, prasinezumab might exert a synergistic effect in people taking symptomatic therapy, such as MAO-B inhibitors. Evidence from multiple laboratory models suggests that alpha-synuclein aggregates induce both pre- and postsynaptic defects prior to promoting degeneration of the dopaminergic nigrostriatal pathway[14]. These findings suggest that removal of aggregates might induce relatively rapid restoration of neuronal function, which could translate into benefits on motor functions in PD, and that the benefits would be particularly evident when other pharmacotherapies that directly promote dopaminergic neurotransmission are used concomitantly (e.g., MAO-B inhibitors). This may explain why the treatment effect is larger in the treatment-policy analysis of MDS-UPDRS Part III, both in OFF and ON states, when measures of MDS-UPDRS Part III of people who started levodopa or dopamine agonists *during* the study are included in the analysis (Fig. 1B and 1C). Thirdly, those subpopulations that progressed faster on motor signs may have a larger amount or more widely distributed pathological aggregated alpha-synuclein in the brain at baseline and thus might have responded more to prasinezumab[10]. However, without a validated quantitative biomarker of *in vivo* pathological alpha-synuclein in the brain, this hypothesis cannot be tested.

Another clinical trial (the SPARK study; NCT03318523) explored the potential efficacy of cinpanemab in early-stage treatment-naïve PD populations, another monoclonal anti-alpha synuclein antibody[15]. In that trial, cinpanemab showed no effect on either the primary (MDS-UPDRS Parts I + II + III) or secondary (MDS-UPDRS Part III) endpoint[15]. Prasinezumab and the PASADENA study have three unique features compared with cinpanemab and the SPARK study: (1) prasinezumab binds to a C-terminal epitope of alpha-synuclein; (2) prasinezumab targets aggregated, monomeric, and intermediate oligomeric alpha-synuclein proteospecies[16]; and (3) the PASADENA study included both participants taking MAO-B inhibitors at baseline and participants who were treatment-naïve. The results in the treatment-naïve subpopulation in the PASADENA study are not dissimilar to those from the SPARK study. Cinpanemab binds to an N-terminal epitope of alpha-synuclein and only to aggregated alpha-synuclein, and, unlike prasinezumab, not to monomeric or oligomeric proteospecies[15].

In conclusion, prasinezumab showed a consistent numerical effect on slowing motor progression in subpopulations of individuals with rapidly progressing disease. A new Phase IIb study (PADOVA; NCT04777331) will test the effect of prasinezumab on slowing motor progression in early-stage PD populations on stable treatment with MAO-B inhibitors or levodopa.

Online methods

Study design

Full details of the study design and results are published elsewhere[4,9]. The multicenter and multinational study was powered to assess a difference of 3 points between the prasinezumab and placebo groups in the change from baseline to Week 52 in the sum of scores on Parts I, II, and III of the MDS-UPDRS.

Endpoints

The results of the subpopulations analyses of the following secondary endpoints in PASADENA Part 1 (randomized controlled part of the study) are reported: MDS-UPDRS Parts I, II and III. Following the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 (R1) addendum, analyses were performed using two estimand strategies to handle the post-randomization event of start or increase of symptomatic treatment: (1) 'hypothetical strategy', the estimated treatment effect assumes a scenario in which the events of start of symptomatic therapy or change in MAO-B inhibitor dose did not occur (performed for the mITT population), and (2) 'treatment policy', an assessment of treatment effect irrespective of symptomatic treatment start or changes in MAO-B inhibitor treatment (performed for the ITT population). The hypothetical strategy implies that the data following the first dose of symptomatic treatment or change in MAO-B inhibitor dose are excluded from the analysis; instead, the treatment effect from these participants is estimated through the covariance matrix of the mixed models for repeated measures (MMRM) model. For the treatment policy analysis of MDS-UPDRS Part III, all the data are included in the analysis, regardless of symptomatic treatment intake. Two scenarios are considered in this case: (1) measurements in practically-defined OFF state (i.e., 12 hours after withdrawal of levodopa), and (2) ON state (after taking levodopa).

Description of subpopulations

A subpopulation analysis was performed if there were at least 20% of patients from the mITT in the subpopulation at baseline. The following primary subpopulations were defined *apriori* in the Statistical Analysis Plan: MAO-B inhibitors at baseline (yes vs. no); Hoehn & Yahr stage at baseline (1 vs. 2); RBDSQ score at baseline (≥ 5 vs. <5); data-driven subphenotypes (diffuse malignant vs. mild motor-predominant vs. intermediate) at baseline; alpha-synuclein skin (positive vs. negative; confirmed by IHC staining on skin biopsy sections at baseline); and DaT-SPECT of ipsilateral putamen (very abnormal vs. abnormal). In addition, the following exploratory subpopulations were defined: age at baseline (< 60 vs. ≥60 years); sex (male vs. female); disease duration (< 12 months vs. >12 months); age at diagnosis of PD (< 60 years vs. ≥60 years); atrophy in the nucleus basalis of Meynert (yes vs. no); MoCA total score (< 22 vs. >22); *GBA* mutation (yes vs. no); and motor subphenotypes (tremor dominant vs. akinetic-rigid vs. intermediate; tremor dominant vs. PIGD vs. indeterminate). To derive the PIGD and tremor-dominant motor subphenotypes, the following definitions were used: tremor score was defined as the mean of the MDS-UPDRS items 2.10 tremor, 3.15a (postural tremor – right hand), 3.15b (postural tremor – left hand), 3.16a (kinetic tremor – right hand), 3.16b (kinetic tremor – left hand), 3.17a (rest tremor amplitude – RUE), 3.17b (rest tremor amplitude – LUE), 3.17c (rest tremor amplitude – RLE), 3.17d (rest tremor amplitude – LLE), 3.17e (rest tremor amplitude – lip/jaw), and 3.18 (constancy of rest tremor). PIGD score was defined as sum of an individual's baseline falling, walking, freezing, gait, and postural stability scores (3.11 and 3.12), divided by 5. The ratio of tremor score to PIGD score was calculated; a subject was defined as 'tremor dominant' if the ratio was ≥ 1.15 OR the PIGD score was 0 and the tremor score was > 0; a subject was defined as having PIGD if the ratio was ≤ 0.9; and a subject was defined as being 'intermediate' if the ratio was > 0.9 and < 1.15, OR if the tremor score and PIGD score were 0.

For the derivation of the akinetic-rigid motor subphenotype, the akinetic-rigid score was calculated as the average of the items of bradykinesia, rigidity and axial symptoms. The ratio of mean tremor-dominant score/mean akinetic-rigid score was then calculated. Subjects were classified as having the 'akinetic-rigid subphenotype' if they had a ratio < 0.8, 'tremor-dominant subphenotype' if they had a ratio ≥ 1.0, and 'intermediate' if they had a ratio between 0.8 and 1.

To derive the data-driven subphenotypes (i.e., diffuse malignant), scales were classified into 'motor' and 'non-motor'. The motor scales were MDS-UPDRS Part II (motor symptoms) and MDS-UPDRS Part III (motor signs). The non-motor scales were the Scale for Outcomes in PD for Autonomic symptoms (SCOPA-AUT) (autonomic dysfunction), RBDSQ (sleep problems) and MoCA (cognitive impairment). The 'diffuse malignant' subpopulation was defined as either motor score (MDS-UPDRS Part II or MDS-UPDRS Part III) greater than the 75th percentile AND at least one non-motor score (autonomic dysfunction, sleep problems or cognitive impairment) greater than the 75th percentile OR all three non-motor scores greater than the 75th percentile. The 'non-diffuse malignant' subpopulation was defined as all the remaining participants not being classified as diffuse malignant. The definition of cut-off for DaT-SPECT striatal binding ratio (SBR) in percentiles was a *post-hoc* analysis.

The subpopulations included in the current analysis (i.e., those with at least 20% of patients from the mITT population at baseline) are listed below. Primary subpopulations included were: MAO-B inhibitors at baseline (yes vs. no); Hoehn & Yahr stage (1 vs. 2); RBDSQ score (≥ 5 vs. <5); and data-driven subphenotypes (diffuse malignant vs. non-diffuse malignant). The exploratory subpopulations included were: age at baseline (< 60 years vs. ≥60); sex (male vs. female); disease duration (< 12 months vs. >12 months); age at diagnosis (< 60 years vs. ≥60 years); and motor subphenotypes (tremor dominant vs. akinetic-rigid; tremor dominant vs. PIGD).

Statistical analyses

The endpoints were analyzed by MMRM, using as covariates the stratification factors age at baseline (< 60 years vs. ≥60 years), sex at birth (male vs. female), MAO-B inhibitor treatment at baseline (yes vs. no), and the DaT-SPECT SBR in the putamen contralateral to the clinically most affected side (see also Pagano et al. 2022[4]). For subpopulations described by a covariate, the corresponding covariate was removed from the analyses. Primary analyses tested for differences in change from baseline between prasinezumab vs. placebo, for each subpopulation separately. In this analysis, the prasinezumab 1500 mg and 4500 mg groups were pooled as no dose-response was previously found[4]. Relative reductions were calculated as the ratio between the difference in estimated mean change from the baseline of the pooled prasinezumab group and the placebo group, divided by the estimated mean change from the baseline in the placebo group.

Declarations

Funding statement

The authors declare that F. Hoffmann-La Roche Ltd was the sponsor and sole funder of the study. F. Hoffmann-La Roche Ltd was involved in the study design, collection, analysis, interpretation of data, the writing of this article and the decision to submit it for publication.

Data availability

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Acknowledgements

The study is sponsored by F. Hoffmann-La Roche Ltd. We thank the patients and their families who participated in the study and the clinical investigators. Editorial assistance for this manuscript was provided by m*X*m Medical Communications funded by F. Hoffmann-La Roche Ltd.

Author contributions

Concept and design: GP, KIT, and JAC. Acquisition, analysis or interpretation of data: GP, KIT, JAC, TS, KM, RBP, NP, FS, KB, HS, DT, AM, RD, PF, GAK, PB, TN, and AB. Drafting of the manuscript: GP, KIT, and JAC. Critical revision and final approval of the manuscript: GP, KIT, JAC, TS, KM, RBP, NP, FS, KB, HS, DT, AM, RD, PF, GAK, PB, TN, and AB.

Competing interests

GP, KIT, AM, RD, PF, GAK, PB, TN and AB are employees and shareholders of F. Hoffmann-La Roche Ltd. RD is also employed by Genentech. PB has also ownership interests in Acousort AB, Enterin Inc, Axial Therapeutics and RYNE Bio. JAC and DT are employees of Roche Products Ltd. and shareholders of F. Hoffmann-La Roche Ltd. HS is an employee of Roche Diagnostics GmbH Deutschland and a shareholder of F. Hoffmann-La Roche. TS 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. TS 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, TS has received research funding from Amneal, Biogen, Neuroderm, Prevail, Roche, and UCB and is an investigator for NINDS, MJFF, Parkinson's Foundation. KM 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. RBP is a consultant for Biogen, Clinilabs, Curasen, Eisai, Inc., F. Hoffmann-La Roche Ltd., Merck, Takeda California, Inc., and Vaxxinity. NP reports participating in advisory boards for Britannia, Boston Scientific, Benevolent AI, Hoffmann-La Roche, inc., and Abbvie. NP 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, and Hoffmann-La Roche, inc. FS 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. KB is a consultant for F. Hoffmann-La Roche Ltd., Vanqua Bio, and the Michael J. Fox Foundation for Parkinson's Research.

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Figures

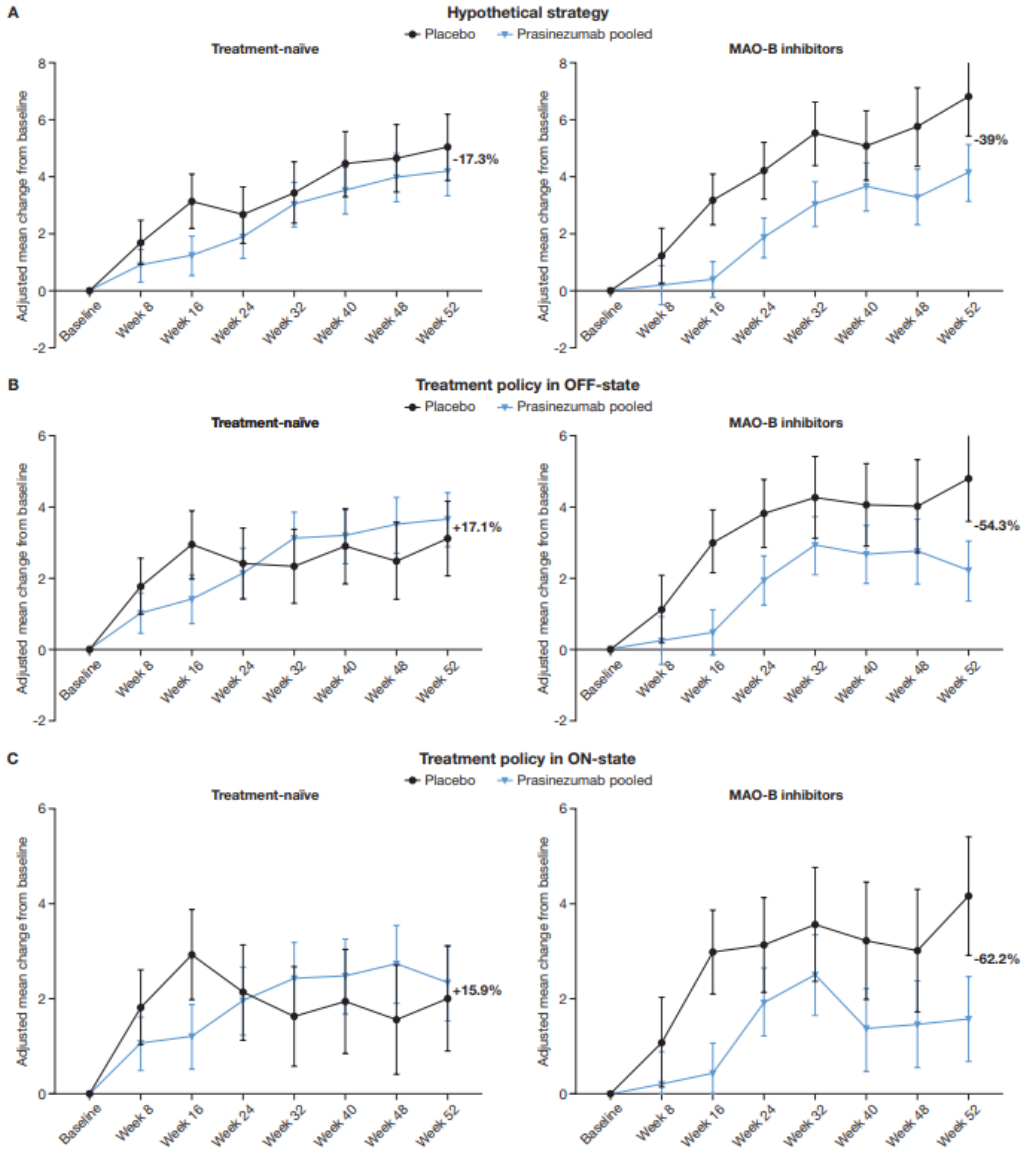

Figure 1

Prasinezumab effect on motor signs progression assessed using MDS-UPDRS Part III in participants taking MAO-B inhibitors at baseline and those who were treatment-naïve at baseline: (A) Hypothetical strategy; (B) Treatment policy in OFF-state; (C) Treatment policy in ON-state. The MDS-UPDRS endpoints were analyzed using mixed models for repeated measures (MMRM). MAO-B, monoamine oxidase B; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale

Category	Subgroup	Total n	Placebo adj. mean	Prasinezumab pool adj. mean	Adj. mean difference	80% CI	Relative difference
MAO-B inhibitor	Yes	115	6.82	4.15	-2.66	(-4.87, -0.45)	-39.0%
	No	201	5.04	4.18	-0.87	(-2.69, 0.94)	-17.3%
Hoehn & Yahr stage	2	238	6.34	3.76	-2.55	(-4.19, -0.90)	-40.2%
	1	78	2.17	5.23	3.14	(0.32, 5.95)	144.7%
RBDSQ	≥5	85	7.76	5.00	-2.76	(-5.78, 0.25)	-35.6%
	<5	230	4.98	3.95	-1.03	(-2.63, 0.57)	-20.7%
Data-driven subphenotype	Diffuse malignant	59	12.29	4.39	-7.86	(-12.90, -2.82)	-64.0%
	Non-diffuse malignant	257	4.76	3.99	-0.77	(-2.20, 0.66)	-16.2%

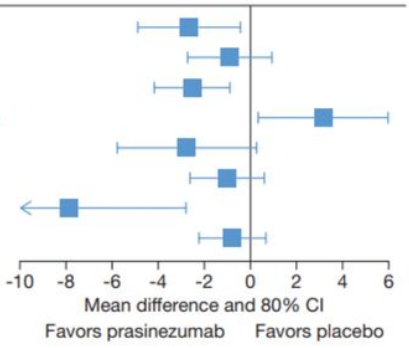

Figure 2

Forest plot of prasinezumab effects on motor progression as measured by the MDS-UPDRS Part III (hypothetical strategy) across the primary pre-specified subpopulations. Adj., adjusted; CI, confidence interval; MAO-B, monoamine oxidase B; RBDSQ, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PaganoPrasinezumabMAOBSupplementaryinformationFINAL30.06.23.docx