ORIGINAL ARTICLE

Trial of Prasinezumab in Early-Stage Parkinson's Disease

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ABSTRACT

BACKGROUND

Aggregated α-synuclein plays an important role in the pathogenesis of Parkinson's disease. The monoclonal antibody prasinezumab, directed at aggregated α-synuclein, is being studied for its effect on Parkinson's disease.

METHODS

In this phase 2 trial, we randomly assigned participants with early-stage Parkinson's disease in a 1:1:1 ratio to receive intravenous placebo or prasinezumab at a dose of 1500 mg or 4500 mg every 4 weeks for 52 weeks. The primary end point was the change from baseline to week 52 in the sum of scores on parts I, II, and III of the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS; range, 0 to 236, with higher scores indicating greater impairment). Secondary end points included the dopamine transporter levels in the putamen of the hemisphere ipsilateral to the clinically more affected side of the body, as measured by ^{123}I-ioflupane single-photon-emission computed tomography (SPECT).

RESULTS

A total of 316 participants were enrolled; 105 were assigned to receive placebo, 105 to receive 1500 mg of prasinezumab, and 106 to receive 4500 mg of prasinezumab. The baseline mean MDS-UPDRS scores were 32.0 in the placebo group, 31.5 in the 1500-mg group, and 30.8 in the 4500-mg group, and mean (±SE) changes from baseline to 52 weeks were 9.4±1.2 in the placebo group, 7.4±1.2 in the 1500-mg group (difference vs. placebo, –2.0; 80% confidence interval [CI], –4.2 to 0.2; P=0.24), and 8.8±1.2 in the 4500-mg group (difference vs. placebo, –0.6; 80% CI, –2.8 to 1.6; P=0.72). There was no substantial difference between the active-treatment groups and the placebo group in dopamine transporter levels on SPECT. The results for most clinical secondary end points were similar in the active-treatment groups and the placebo group. Serious adverse events occurred in 6.7% of the participants in the 1500-mg group and in 7.5% of those in the 4500-mg group; infusion reactions occurred in 19.0% and 34.0%, respectively.

CONCLUSIONS

Prasinezumab therapy had no meaningful effect on global or imaging measures of Parkinson's disease progression as compared with placebo and was associated with infusion reactions. (Funded by F. Hoffmann–La Roche and Prothena Biosciences; PASADENA ClinicalTrials.gov number, NCT03100149.)

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*The members of the PASADENA Investigators and Prasinezumab Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Aggregated α-synuclein is considered to be a main feature in the pathogenesis of Parkinson's disease.[1-4] Prasinezumab is a humanized monoclonal antibody that selectively binds aggregated α-synuclein at the C-terminal of the protein.[5-8] In mouse models of α-synucleinopathy, the murine form of prasinezumab reduced the accumulation of intraneuronal α-synuclein aggregates and synaptic loss, reversed astrogliosis and microgliosis, and improved functional performance in water-maze and horizontal-beam tests.[5-7] In phase 1 trials, prasinezumab showed brain penetration and resulted in dose-dependent reductions from baseline in free serum α-synuclein levels in healthy volunteers and persons with Parkinson's disease.[8,9]

The current Phase 2 Trial of Anti α-Synuclein Antibody in Early Parkinson's Disease (PASADENA) is a three-part, randomized trial assessing the efficacy and safety of low-dose (1500 mg) and high-dose (4500 mg) prasinezumab in persons with early-stage Parkinson's disease. Here, we report the results of the 52-week, double-blind, placebo-controlled part (part 1) and an exploratory additional 52-week blinded extension (part 2) in which all the participants received active treatment. Part 3 is an ongoing, 5-year open-label extension.

Methods

Trial Design and Oversight

The trial and recruitment materials were approved by institutional review boards or ethics committees at each trial site. The trial was conducted at 57 sites in Austria, France, Germany, Spain, and the United States. The trial was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All the participants provided written informed consent before undergoing any trial-specific screening tests or evaluations. The trial was sponsored by F. Hoffmann–La Roche, which managed the trial; provided the trial agents, medical monitoring, and drug-safety management; performed statistical, pharmacokinetic, and pharmacodynamic analyses; and funded professional medical writing. Individual author contributions and roles and responsibilities of F. Hoffmann–La Roche are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. There were confidentiality agreements in place between F. Hoffmann–La Roche and the authors.

Trial Procedures

Eligibility criteria were early-stage Parkinson's disease (stage 1 or 2 on the Hoehn and Yahr scale [stages range from 1 to 5, with higher stages indicating greater disease severity]), findings on dopamine transporter imaging with single-photon-emission computed tomography (SPECT) using the tracer ^{123}I-ioflupane that were consistent with Parkinson's disease, and no previous treatment for symptoms of Parkinson's disease. Participants who were receiving stable doses of a monoamine oxidase B (MAO-B) inhibitor could continue to do so.

In the 52-week randomized phase (part 1), participants were randomly assigned in a 1:1:1 ratio to receive placebo or prasinezumab at a dose of 1500 mg or 4500 mg (referred to as the 4500-mg group throughout, although participants with a body weight of <65 kg received just 3500 mg) intravenously every 4 weeks. In part 2 of the trial, participants who had received placebo were randomly assigned in a 1:1 ratio to receive prasinezumab at a dose of either 1500 mg or 4500 mg. Assessments were performed as indicated in the protocol, which was published previously[10] and is available at NEJM.org.

End Points

Part 1 (Baseline to Week 52)

The primary end point was the difference 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 Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS; range, 0 to 236, with higher scores indicating greater impairment).[11,12] Secondary end points included the change from baseline to week 52 in the scores on MDS-UPDRS part I (nonmotor aspects of daily living; range, 0 to 52), part II (motor aspects of daily living; range, 0 to 52), and part III (clinician-conducted motor examination; range, 0 to 132)[11]; ^{123}I-ioflupane mean binding in the putamen ipsilateral to the clinically most affected side (striatal binding ratio [SBR]); the score on the Montreal Cognitive Assessment (MoCA; range, 0 to 30, with higher scores indicating better performance); the score on the Clinical Global Impression–Improvement (CGI-I) scale (range, 1 to 7, with higher scores indicating greater severity of impairment); the score on the Patient Global Impression of Change

(PGI-C) scale (range, 1 to 7, with higher scores indicating greater severity of impairment); the score on the Schwab and England Activities of Daily Living (SE-ADL) scale (range, 0 to 100%, with higher scores indicating a greater level of independence); first occurrence of a 3-point increase from baseline in the score on MDS-UPDRS part I or II (time-to-event analysis); and start of dopaminergic (levodopa or dopamine agonist) treatment (time-to-event analysis). Efficacy end points were assessed by site investigators who were unaware of the trial-group assignments.

Exploratory end points included centralized MDS-UPDRS part III video-based ratings by independent raters (part 1 of the trial only) and assessments of motor function and activity from a smartphone and smartwatch application that are being analyzed separately (see the protocol). For participants who had started dopaminergic treatment, scores on MDS-UPDRS part III were obtained at site visits while participants were in a practically defined off-medication state, meaning that no levodopa or dopamine agonist treatment had been used since the evening before the clinic assessment. Participants who were receiving MAO-B inhibitors were not required to hold treatment before the assessments.

Part 2 (Weeks 56 to 104)

Prespecified exploratory analyses were conducted to compare the participants in the early-start cohort, who received prasinezumab at a dose of 1500 mg or 4500 mg for 104 weeks, with those in the delayed-start cohort, who received placebo for the first 52 weeks (in part 1) and prasinezumab at a dose of 1500 mg or 4500 mg from weeks 56 through 104 (in part 2). Participants in the delayed-start cohort did not receive any treatment between week 52 and week 56.

SAFETY

Safety findings are reported separately for part 1 and part 2. Safety assessments included the incidence and severity of adverse events, the incidence of infusion reactions, changes in electrocardiography, abnormalities in magnetic resonance imaging, blood pressure, and laboratory tests. Safety assessments were performed by site investigators who were not conducting the efficacy assessments and who were unaware of the trial-group assignments. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 22.1.

STATISTICAL ANALYSIS

A sample of 100 participants per trial group (placebo, prasinezumab at a dose of 1500 mg, and prasinezumab at a dose of 4500 mg) was calculated to detect a 3-point difference in the change from baseline to week 52 in the sum of scores on parts I, II, and III of the MDS-UPDRS (primary end point) for the pairwise comparison of each active-treatment group with the placebo group, under the assumption of an increase of 8 points per year in the placebo group at a two-sided alpha significance level of 20% (80% power). All randomly assigned participants who received prasinezumab or placebo were included in the part 1 efficacy analyses (intention-to-treat population). All data collected within the 52 weeks, regardless of the initiation of treatment for symptoms of Parkinson's disease, were used for safety, ^{123}I-ioflupane SPECT, MoCA, and SE-ADL analyses. All other end points, including MDS-UPDRS total scores and subscores and PGI-C and CGI-I ratings, were analyzed with data obtained up to the time of first treatment for symptoms of Parkinson's disease. Details of the analysis for each end point are provided in Section 2.5 in the Methods section in the Supplementary Appendix. These analyses were repeated with all data regardless of the start of therapy for symptoms as sensitivity analyses.

The MDS-UPDRS total scores and subscores were analyzed with the use of a mixed model for repeated measures, which used all data from every randomly assigned participant before the start of treatment for symptoms to account for missing data in the change-from-baseline model. All part 1 analyses tested for differences from baseline between the prasinezumab 1500-mg group and the placebo group and between the prasinezumab 4500-mg group and the placebo group with the use of the following stratification factors as covariates: age (<60 years vs. ≥60 years), sex (male vs. female), and MAO-B inhibitor treatment at baseline (yes vs. no), plus the additional covariates of the ^{123}I-ioflupane SPECT SBR in the putamen contralateral to the clinically most affected side and, for continuous variables, the baseline score for the end point. To check the robustness of the mixed-model-for-repeated-mea-

sures approach with respect to missing data, a post hoc analysis was performed with the use of multiple imputation on the basis of a Markov chain Monte Carlo method, under the assumption of multivariate normality.

The ^{123}I-ioflupane SPECT SBR in the putamen ipsilateral to the clinically most affected side, MoCA total score, and SE-ADL score were assessed with the use of analysis of covariance (including all data regardless of the start of therapy for symptoms), and CGI-I and PGI-C scores were analyzed with the use of logistic regression, with no explicit modeling of missing data; relative risks are reported to conform to *Journal* style. Time-to-event end points were analyzed with the use of a Cox proportional-hazards model with all data regardless of the start of therapy for symptoms. For end points not following the proportionality assumption, we performed a Wilcoxon test.

Because there was no provision for correcting the widths of the confidence intervals for multiple comparisons of secondary end points, results are reported as point estimates and 80% confidence intervals from which no definite conclusions can be drawn. An independent data monitoring committee reviewed safety data on two occasions during part 1 of the trial, soon after the first 30 participants and 60 participants had received their first three infusions or discontinued the trial prematurely. There was no evaluation of efficacy data by the independent data monitoring committee; therefore, no alpha was spent before the evaluation of the primary end point at week 52. All analyses were performed with the use of SAS software, version 9.4.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

A total of 443 participants were screened, and 316 were enrolled: 105 were assigned to the placebo group, 105 to the prasinezumab 1500-mg group, and 106 to the prasinezumab 4500-mg group (Fig. 1). The demographic and clinical characteristics of the participants at baseline are presented in Table 1, and Table S5 in the Supplementary Appendix. The number of participants who started or changed the dose or regimen of treatment for symptoms of Parkinson's disease by week 52 was 29 (27.6%) in the placebo group, 27 (25.7%) in the prasinezumab 1500-mg group, and 31 (29.2%) in the prasinezumab 4500-mg group.

All 105 participants in the placebo group continued from part 1 to part 2 of the trial and underwent randomization again to receive prasinezumab at a dose of either 1500 mg or 4500 mg (Fig. 1). The number of participants who started or changed the dose or regimen of treatment for symptoms of Parkinson's disease by week 104 was 74 of 105 (70.5%) in the delayed-start cohort and 140 of 204 (68.6%) in the early-start cohort. All participant data contributed to the analysis until the participant either started or changed the dose or regimen of treatment for symptoms of Parkinson's disease, and data were censored for the main analyses at that point. Accordingly, 76 participants in the placebo group, 74 in the prasinezumab 1500-mg group, and 73 in the prasinezumab 4500-mg group were included in the primary analysis at week 52. For the same reason, data for 27 participants in the delayed-start cohort and 55 in the early-start cohort were not censored and were included in the analysis at week 104.

PRIMARY END POINT

The mean (±SE) increase (indicative of worsening) from baseline at week 52 in the sum of scores on parts I, II, and III of the MDS-UPDRS was 9.4±1.2 points in the placebo group, 7.4±1.2 points in the prasinezumab 1500-mg group, and 8.8±1.2 points in the prasinezumab 4500-mg group. The adjusted mean differences in change from baseline at week 52 as compared with placebo with censoring of data for participants who started treatment for symptoms were −2.0 points (80% confidence interval [CI], −4.2 to 0.2; P=0.24) for prasinezumab at a dose of 1500 mg and −0.6 points (80% CI, −2.8 to 1.6; P=0.72) for prasinezumab at a dose of 4500 mg (Table 2 and Fig. 2A). A sensitivity analysis of the primary end point that included all the participants at 52 weeks, regardless of the start of treatment for symptoms, showed differences between the prasinezumab 1500-mg group and the placebo group of −0.1 (80% CI, −2.1 to 1.9) and between the prasinezumab 4500-mg group and the placebo group of 0.1 (80% CI, −1.9 to 2.1), findings that affirmed the null result of the primary analysis (Table S8A).

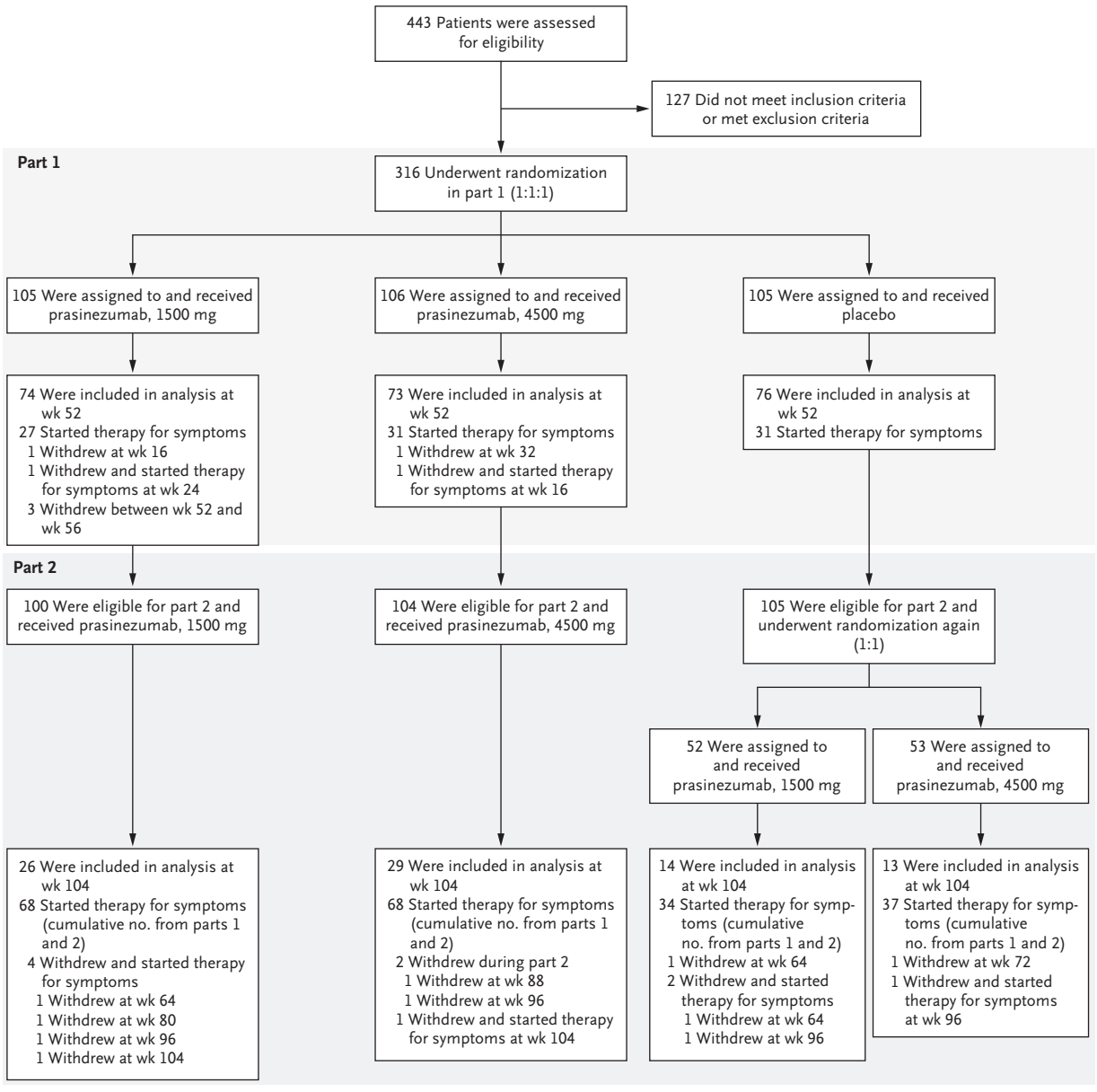

Figure 1. Screening, Randomization, and Follow-up in Parts 1 and 2.

In part 1 of the trial, participants were randomly assigned in a 1:1:1 ratio to receive intravenous placebo or prasinezumab at a dose of 1500 mg or 4500 mg (referred to as the 4500-mg group throughout, although participants with a body weight of <65 kg received just 3500 mg) every 4 weeks for 52 weeks. In part 2, participants who had been assigned to receive placebo underwent randomization again in a 1:1 ratio to receive prasinezumab at a dose of either 1500 mg or 4500 mg, whereas prasinezumab groups received the same blinded dose as during part 1 for an additional 52 weeks. Participants and investigators were aware that all the participants would receive prasinezumab in part 2 and remained unaware of the trial agent received and dose allocation in both part 1 and part 2. Randomization in part 1 was stratified according to age (<60 years vs. ≥60 years), sex, and baseline therapy with monoamine oxidase B (MAO-B) inhibitors (yes vs. no). In part 2, randomization was stratified according to age (<60 years vs. ≥60 years), baseline therapy with MAO-B inhibitors (yes vs. no), and dopaminergic therapy at the beginning of part 2 (yes vs. no). Participants with nonevaluable data are defined as those who started therapy for symptoms of Parkinson's disease, those who had an increase in the dose of an MAO-B inhibitor (if the participant was receiving an MAO-B inhibitor at baseline), and those who withdrew from the trial. In part 1, of 31 participants in the placebo group who started therapy for symptoms, 2 did so after their week 52 assessment and contributed data to part 1 analyses.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Placebo (N=105)	Prasinezumab, 1500 mg (N=105)	Prasinezumab, 4500 mg (N=106)†
Age — yr	59.9±8.7	60.3±8.8	59.4±9.8
Male sex — no. (%)	71 (67.6)	71 (67.6)	71 (67.0)
Time since diagnosis — mo	10.0±6.8	10.3±6.3	10.1±6.5
Hoehn and Yahr stage — no. (%)‡			
Stage 1	20 (19.0)	29 (27.6)	29 (27.4)
Stage 2	85 (81.0)	76 (72.4)	77 (72.6)
Treatment with MAO-B inhibitor — no. (%)	38 (36.2)	38 (36.2)	39 (36.8)
Sum of scores on MDS-UPDRS parts I, II, and III§	32.0±13.0	31.5±13.3	30.8±12.1
Score on MDS-UPDRS part I¶	4.9±3.7	4.6±4.2	4.3±3.6
Score on MDS-UPDRS part II¶	5.6±4.1	4.9±4.0	5.5±4.1
Score on MDS-UPDRS part III‖	21.5±9.1	21.9±9.1	21.0±8.8

* Plus–minus values are means ±SD. MAO-B denotes monoamine oxidase B.
† Participants with a body weight of less than 65 kg received 3500 mg. For simplicity, participants who received 3500 mg or 4500 mg are referred to collectively as the 4500-mg group.
‡ Stages range from 1 to 5, with higher stages indicating greater disease severity.
§ The sum of scores on parts I, II, and III of the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) ranges from 0 to 236, with higher sums indicating greater severity of impairment.
¶ Scores on parts I and II of the MDS-UPDRS range from 0 to 52, with higher scores indicating greater severity of impairment in nonmotor aspects of daily living (part I) or motor aspects of daily living (part II).
‖ Scores on part III of the MDS-UPDRS range from 0 to 132, with higher scores indicating greater severity of impairment on a clinician-conducted motor examination.

SECONDARY END POINTS

For each of the three MDS-UPDRS parts (I, II, and III), the 80% confidence intervals for differences between the active-treatment groups and the placebo group to week 52 included zero for both doses, with the exception of the 1500-mg dose for MDS-UPDRS part III (Tables 2 and S7 and Figs. 2B and S2). This result was not adjusted for multiple comparisons, so no conclusion can be drawn from this finding. The results of the MDS-UPDRS part III centralized video ratings are shown in Figure S3 and Table S11, and the results of the MDS-UPDRS part III site rating sensitivity analyses that included all the participants irrespective of the start of treatment for symptoms are provided in Table S8A and S8B. The mean (±SE) change from baseline to week 52 in the ^{123}I-ioflupane SPECT SBR in the putamen ipsilateral to the clinically most affected side was −0.08±0.02 in the placebo group, −0.10±0.02 in the prasinezumab 1500-mg group, and −0.11±0.02 in the prasinezumab 4500-mg group (Table 2). The adjusted mean differences in the change in ^{123}I-ioflupane SPECT SBR from baseline to week 52, as compared with the placebo group, were −0.02 (80% CI, −0.05 to 0.01) in the prasinezumab 1500-mg group and −0.03 (80% CI, −0.06 to −0.0003) in the prasinezumab 4500-mg group. The exploratory PASADENA Digital Motor Score changes from baseline to week 52 are shown in Figure S4 and Table S11.

EXPLORATORY DELAYED-START ANALYSES

The mean change from baseline to week 104 in the sum of scores on parts I, II, and III of the MDS-UPDRS was 15.5±1.3 points in the early-start cohort and 17.3±1.8 points in the delayed-start cohort (Fig. 2C and Table S6). The mean change from baseline to week 104 in MDS-UPDRS part III scores was 8.4±1.0 points in the early-start cohort and 10.6±1.4 points in the delayed-start cohort (Fig. 2D and Table S6); a post hoc multiple-imputation analysis of MDS-UPDRS part III scores at week 104 showed similar null results (Table S13). The mean change from baseline to week 104 in the ^{123}I-ioflupane SPECT SBR in the putamen ipsilateral to the clinically most affected side was −0.20±0.01 in the early-start

Table 2. Primary and Secondary End Points in Part 1 of the Trial (to Week 52).*

End Point	Placebo (N=105)	Prasinezumab, 1500 mg (N=105)	Prasinezumab, 4500 mg (N=106)†
Primary end point			
Sum of scores on MDS-UPDRS parts I, II, and III‡			
Adjusted mean change from baseline	9.4±1.2	7.4±1.2	8.8±1.2
Difference in adjusted means vs. placebo (80% CI)	—	−2.0 (−4.2 to 0.2)	−0.6 (−2.8 to 1.6)
P value vs. placebo	—	0.24	0.72
Secondary end points§			
Score on MDS-UPDRS part I‡			
Adjusted mean change from baseline	0.8±0.3	0.6±0.3	0.9±0.3
Difference in adjusted means vs. placebo (80% CI)	—	−0.2 (−0.7 to 0.3)	0.1 (−0.4 to 0.7)
Score on MDS-UPDRS part II‡			
Adjusted mean change from baseline	2.8±0.4	3.1±0.4	2.7±0.4
Difference in adjusted means vs. placebo (80% CI)	—	0.3 (−0.3 to 1.0)	−0.1 (−0.7 to 0.6)
Score on MDS-UPDRS part III‡			
Adjusted mean change from baseline	5.6±0.9	3.7±0.9	4.6±0.9
Difference in adjusted means vs. placebo (80% CI)	—	−1.9 (−3.5 to −0.3)	−1.0 (−2.6 to 0.6)
^{123}I-ioflupane SPECT SBR in the putamen ipsilateral to the clinically most affected side¶			
Adjusted mean change from baseline	−0.08±0.02	−0.10±0.02	−0.11±0.02
Difference in adjusted means vs. placebo (80% CI)	—	−0.02 (−0.05 to 0.01)	−0.03 (−0.06 to 0.00)
MoCA score¶‖			
Adjusted mean change from baseline	0.07±0.18	0.30±0.18	0.51±0.18
Difference in adjusted means vs. placebo (80% CI)	—	0.22 (−0.09 to 0.54)	0.44 (0.13 to 0.75)
CGI-I score**			
Score of 5, 6, or 7 — no./total no. (%)	43/76 (56.6)	36/72 (50.0)	35/72 (48.6)
Relative risk (80% CI)	—	0.89 (0.70 to 1.07)	0.88 (0.69 to 1.06)
PGI-C score**			
Score of 5, 6, or 7 — no./total no. (%)	43/74 (58.1)	37/73 (50.7)	38/71 (53.5)
Relative risk (80% CI)	—	0.88 (0.69 to 1.06)	0.95 (0.76 to 1.12)
SE-ADL score at wk 52¶††			
Adjusted mean change from baseline	−1.83±0.64	−2.56±0.65	−2.50±0.65
Difference in adjusted means vs. placebo (80% CI)	—	−0.73 (−1.87 to 0.41)	−0.67 (−1.81 to 0.47)
First occurrence of ≥3-point increase from baseline in MDS-UPDRS part I or II score: hazard ratio vs. placebo (80% CI)¶	—	1.15 (0.94 to 1.42)	1.25 (1.02 to 1.53)
Start of dopaminergic treatment: hazard ratio vs. placebo (80% CI)¶	—	1.01 (0.77 to 1.33)	0.84 (0.63 to 1.13)

* Plus–minus values are means ±SE. SBR denotes striatal binding ratio, and SPECT single-photon-emission computed tomography.
† Participants with a body weight of less than 65 kg received 3500 mg. For simplicity, participants who received 3500 mg or 4500 mg are referred to collectively as the 4500-mg group.
‡ The end point was analyzed with the use of a hypothetical estimand strategy (regardless of the start of treatment for symptoms of Parkinson's disease).
§ For the secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.
¶ The end point was analyzed with the use of all data regardless of treatment for symptoms of Parkinson's disease.
‖ Scores on the Montreal Cognitive Assessment (MoCA) range from 0 to 30, with lower scores indicating greater severity of impairment.
** Scores on the Clinical Global Impression–Improvement (CGI-I) scale and the Patient Global Impression of Change (PGI-C) scale range from 0 to 7, with higher scores indicating greater severity of impairment. Participants with a score of 5, 6, or 7 were rated as being "minimally worse," "much worse," or "very much worse," respectively.
†† Scores on the Schwab and England Activities of Daily Living (SE-ADL) scale range from 0 to 100%, with higher scores indicating a greater level of independence.

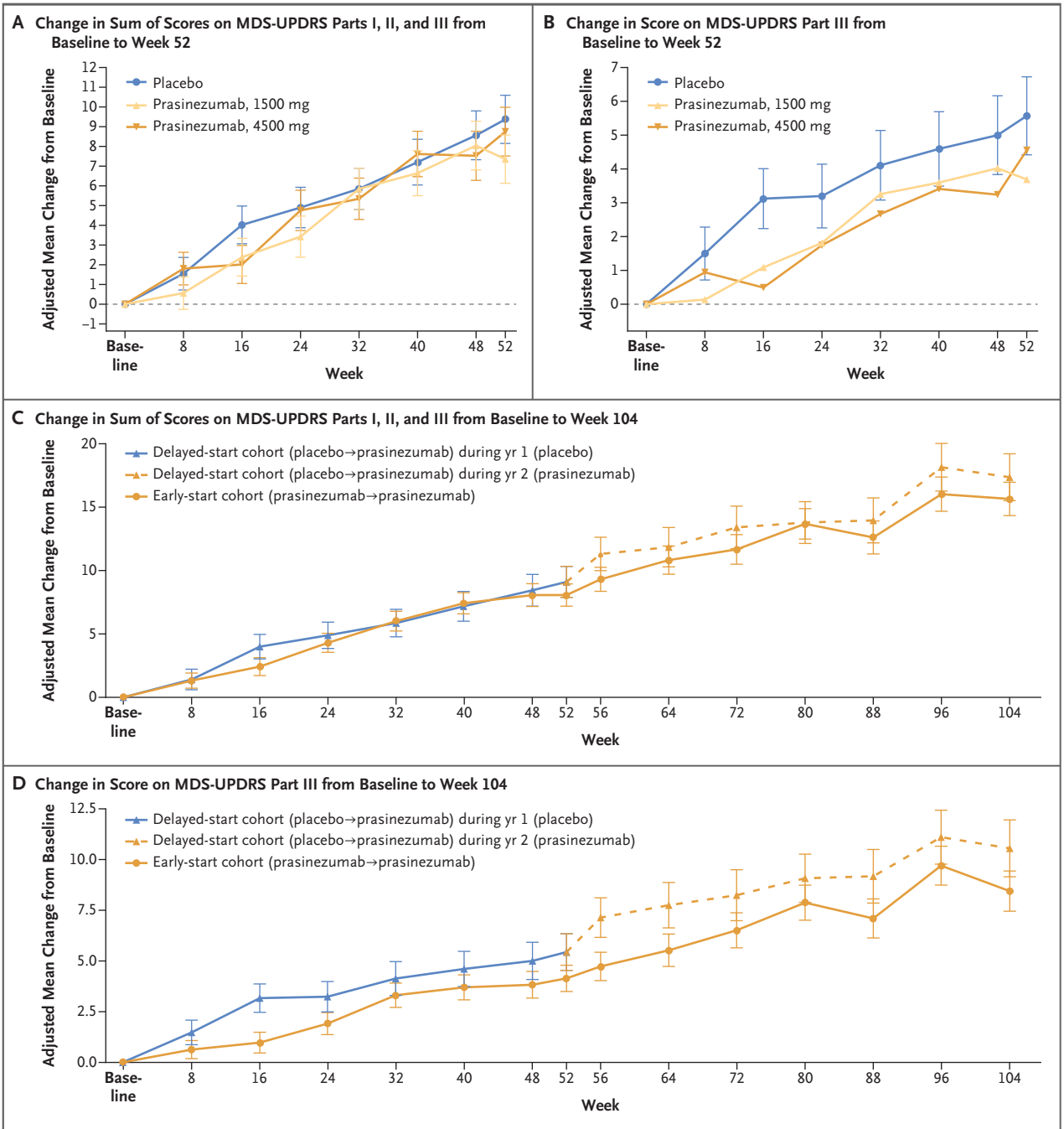

Figure 2. Change in MDS-UPDRS Scores over Time.

The sum of scores on parts I, II, and III of the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Panels A and C) ranges from 0 to 236, with higher scores indicating greater impairment. Scores on MDS-UPDRS part III (Panels B and D) range from 0 to 132, with higher scores indicating greater impairment on a clinician-conducted motor examination. Means are least-squares means, with estimates based on mixed models for repeated measures that used the following fixed covariates: MAO-B inhibitor treatment (yes vs. no), trial group, week, age (<60 years vs. ≥60 years), sex (male vs. female), the ^{123}I-ioflupane single-photon-emission computed tomographic striatal binding ratio in the putamen contralateral to the clinically most affected side, the baseline value of the corresponding end point, and the interaction between trial group and week. Participants who started therapy for symptoms of Parkinson's disease contributed data until the last visit before such therapy was started. The I bars represent standard errors.

Table 3. Overview of Adverse Events.

Adverse Event	Placebo (N=105)	Prasinezumab, 1500 mg (N=105)	Prasinezumab, 4500 mg (N=106)*
Any adverse event — no. (%)	87 (82.9)	98 (93.3)	97 (91.5)
Serious adverse event — no. (%)†	5 (4.8)	7 (6.7)	8 (7.5)
Adverse event related to prasinezumab or placebo — no. (%)‡	28 (26.7)	26 (24.8)	41 (38.7)
Adverse event leading to discontinuation of prasinezumab or placebo — no. (%)	0	1 (1.0)	0
Adverse event resulting in death — no.	0	0	0
Total no. of adverse events§	411	428	549

* Participants with a body weight of less than 65 kg received 3500 mg. For simplicity, participants who received 3500 mg or 4500 mg are referred to collectively as the 4500-mg group.
† Details on serious adverse events are provided in Table S9.
‡ An adverse event was considered to be related to the trial agent (prasinezumab or placebo) by the investigator if there was a reasonable possibility that the event may have been caused by the agent under investigation.
§ For frequency counts of the total number of adverse events, multiple occurrences of the same adverse event in an individual participant were counted separately.

cohort and −0.17±0.02 in the delayed-start cohort (Table S6).

SAFETY

Part 1 (Baseline to Week 52)

Overall, 282 participants (89.2%) had at least one adverse event with an onset at the time of or after the receipt of the first trial dose (Table 3). The percentage of participants with adverse events was higher in the prasinezumab 1500-mg group and 4500-mg group than in the placebo group (Figs. S5 and S6). Adverse events occurring in 10% or more of the participants in any dose group, irrespective of relationship to the trial agent (prasinezumab or placebo), were infusion reactions, nasopharyngitis, back pain, and headache (Table 4 and Figs. S7 and S8).

A total of 20 participants (6.3%) had 22 serious adverse events: 7 (6.7%) in the prasinezumab 1500-mg group, 8 (7.5%) in the prasinezumab 4500-mg group, and 5 (4.8%) in the placebo group (Tables 3 and S9). Two adverse events led to treatment discontinuation in 1 participant in the 1500-mg group (grade 3 basal-cell carcinoma and grade 3 malignant melanoma). No deaths occurred in part 1 (Table 3).

Infusion reactions occurred in 19.0% of the participants in the prasinezumab 1500-mg group, in 34.0% of those in the prasinezumab 4500-mg group, and in 16.2% of those in the placebo group (Table 4). The most frequently reported infusion-reaction symptoms in part 1 (occurring in ≥3 participants) were nausea, headache, and rash in the 1500-mg group; nausea, headache, rash, urticaria, and pruritus in the 4500-mg group; and nausea and headache in the placebo group (Table S12). Additional details about common adverse events in part 1 and about adverse events that were deemed by the investigator to be related to the trial agent are included in Section 3.2 in the Results section in the Supplementary Appendix.

Part 2 (Weeks 56 to 104)

Overall, 237 of 309 participants (76.7%) had at least one adverse event between week 56 and week 104 (Table S10A). The percentage of participants with serious adverse events was higher in the prasinezumab 4500-mg delayed-start cohort than in the prasinezumab 4500-mg early-start cohort (Fig. S12), whereas there was no substantial difference in the percentage of patients with such events between the prasinezumab 1500-mg delayed-start cohort and the prasinezumab 1500-mg early-start cohort (Fig. S11). A total of 19 participants (6.1%) had 24 serious adverse events: 7 of 152 participants (4.6%) in the prasinezumab 1500-mg group and 12 of 157 (7.6%) in the prasinezumab 4500-mg group (Table S9).

In part 2, two adverse events led to treatment discontinuation in two participants in the 1500-mg group (one grade 3 bladder cancer and one grade 3 metastatic prostate cancer), and two adverse

Table 4. Individual Adverse Events (>3% Occurrence in Any Trial Group).*

MedDRA System Organ Class and Preferred Term	Placebo (N=105)	Prasinezumab, 1500 mg (N=105)	Prasinezumab, 4500 mg (N=106)†
		number (percent)	
Ear and labyrinth disorders: vertigo	4 (3.8)	0	1 (0.9)
Gastrointestinal disorders			
Constipation	6 (5.7)	8 (7.6)	10 (9.4)
Nausea	9 (8.6)	5 (4.8)	9 (8.5)
Diarrhea	4 (3.8)	2 (1.9)	4 (3.8)
Abdominal pain	1 (1.0)	4 (3.8)	1 (0.9)
General disorders and administration-site conditions: asthenia	4 (3.8)	1 (1.0)	2 (1.9)
Infections and infestations			
Nasopharyngitis	15 (14.3)	20 (19.0)	13 (12.3)
Upper respiratory infection	9 (8.6)	4 (3.8)	9 (8.5)
Urinary tract infection	3 (2.9)	5 (4.8)	4 (3.8)
Bronchitis	4 (3.8)	3 (2.9)	2 (1.9)
Gastroenteritis	4 (3.8)	1 (1.0)	3 (2.8)
Rhinitis	0	2 (1.9)	4 (3.8)
Injury, poisoning, and procedural complications			
Infusion reactions	17 (16.2)	20 (19.0)	36 (34.0)
Fall	5 (4.8)	5 (4.8)	10 (9.4)
Arthropod sting	0	4 (3.8)	0
Musculoskeletal and connective-tissue disorders			
Back pain	8 (7.6)	8 (7.6)	11 (10.4)
Arthralgia	8 (7.6)	7 (6.7)	4 (3.8)
Pain in arm or leg	2 (1.9)	6 (5.7)	5 (4.7)
Muscle spasms	5 (4.8)	2 (1.9)	4 (3.8)
Myalgia	3 (2.9)	1 (1.0)	4 (3.8)
Tendonitis	2 (1.9)	1 (1.0)	4 (3.8)
Neck pain	0	2 (1.9)	4 (3.8)
Musculoskeletal pain	4 (3.8)	1 (1.0)	3 (2.8)
Nervous system disorders			
Headache	10 (9.5)	10 (9.5)	12 (11.3)
Tremor	4 (3.8)	5 (4.8)	3 (2.8)
Dizziness	3 (2.9)	4 (3.8)	2 (1.9)
Psychiatric disorders			
Anxiety	3 (2.9)	2 (1.9)	7 (6.6)
Insomnia	5 (4.8)	3 (2.9)	8 (7.5)
Respiratory, thoracic, and mediastinal disorder: oropharyngeal pain	4 (3.8)	4 (3.8)	5 (4.7)
Skin and subcutaneous-tissue disorders			
Dermatitis, contact	6 (5.7)	1 (1.0)	3 (2.8)
Rash	2 (1.9)	2 (1.9)	5 (4.7)
Pruritus	4 (3.8)	1 (1.0)	2 (1.9)
Alopecia	0	4 (3.8)	1 (0.9)
Vascular disorders: hypertension	5 (4.8)	4 (3.8)	5 (4.7)

* For frequency counts according to the preferred term in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.1, multiple occurrences of the same adverse event in an individual participant were counted only once.
† Participants with a body weight of less than 65 kg received 3500 mg. For simplicity, participants who received 3500 mg or 4500 mg are referred to collectively as the 4500-mg group.

events led to treatment discontinuation in two participants in the 4500-mg group (one grade 1 infusion reaction and one grade 3 colon cancer [stage 4]) (Table S10A). One death (suicide) occurred 26 days after the first dose of 1500-mg prasinezumab in part 2; the participant had received placebo in part 1 of the trial. Additional details about common adverse events in part 2 and about adverse events that were deemed by the investigator to be related to the trial drug are included in Section 3.3 in the Results section in the Supplementary Appendix.

Immunogenicity

Of the 209 participants who started treatment with prasinezumab in part 1 and the 103 who started treatment with prasinezumab in part 2 who could be evaluated for immunogenicity analysis, 4 had antidrug antibodies that emerged during the treatment period. These findings of antidrug antibodies were single events and of low titer, with no apparent effect on safety.

DISCUSSION

In this randomized phase 2 trial, prasinezumab therapy showed no significant difference from placebo in 1-year progression of the sum of scores on parts I, II, and III of the MDS-UPDRS. Infusion reactions were the most frequently reported adverse event. We used the broad composite measure of the sum of scores on parts I, II, and III of the MDS-UPDRS as the primary end point in this trial.[13,14] Most of the progression between baseline and week 52 in the sum of scores on MDS-UPDRS parts I, II, and III was accounted for by the change in the MDS-UPDRS part III score (a clinician-rated score of the severity of motor sign), a finding similar to those in persons with early-stage Parkinson's disease in the Parkinson's Progression Markers Initiative (PPMI) study.[15] The MDS-UPDRS total scores or subscores did not improve in participants in the placebo group who were reassigned to prasinezumab in part 2 (delayed-start cohort) as compared with the early-start cohort, which suggests that an effect on symptoms with prasinezumab therapy for an additional 48 weeks is unlikely.

Treatment with prasinezumab had no appreciable effect on ^{123}I-ioflupane SPECT imaging. The lack of an effect may indicate no effect of prasinezumab on degeneration of nigrostriatal terminals. However, the SPECT binding ratio decreased less in participants in the PASADENA trial than in a similar population in the PPMI study.[15] Future studies might explore the potential relationship and temporal delay between removal of aggregated α-synuclein and neuronal sparing. As reported elsewhere in this issue of the *Journal*, treatment with cinpanemab — another monoclonal antibody directed at α-synuclein — did not affect clinical or imaging progression in patients with early Parkinson's disease over a period of 52 weeks.[16] Prasinezumab recognizes the C-terminal of α-synuclein and binds well to aggregated and monomeric protein, whereas cinpanemab recognizes the N-terminal and has a low binding affinity to monomeric α-synuclein.[17]

The limitations of our trial include the planned censoring of data from participants when they started treatment for symptoms of Parkinson's disease and their omission from the primary analysis. A total of 312 participants completed part 1 and 297 completed part 2 of the trial, and approximately 30% started medication for symptoms; data for participants who started such medication were censored for the primary end point at week 52. For the same reason, data for approximately 70% of the participants were censored for the analysis at week 104. However, a sensitivity analysis that included all the participants showed the same null results as the primary analysis. The trial population was not entirely representative of the wider population of persons with Parkinson's disease in that there was an underrepresentation of non-White and non-U.S. or non-European populations owing to the countries in which the trial was conducted (Table S4). Finally, we did not incorporate testing for target engagement because such tests are not well developed.

In this placebo-controlled trial, treatment with prasinezumab, a humanized monoclonal antibody targeting aggregated α-synuclein, had no meaningful effect on global clinical or imaging measures of Parkinson's disease progression. Infusion reactions were the most frequent adverse events.

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APPENDIX

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REFERENCES

1. Lang AE, Espay AJ. Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. Mov Disord 2018;33:660-77.
2. Nakamori M, Junn E, Mochizuki H, Mouradian MM. Nucleic acid-based therapeutics for Parkinson's disease. Neurotherapeutics 2019;16:287-98.
3. Stefanis L. α-Synuclein in Parkinson's disease. Cold Spring Harb Perspect Med 2012;2:a009399.
4. Dehay B, Vila M, Bezard E, Brundin P, Kordower JH. Alpha-synuclein propagation: new insights from animal models. Mov Disord 2016;31:161-8.
5. Masliah E, Rockenstein E, Mante M, et al. Passive immunization reduces behavioral and neuropathological deficits in an alpha-synuclein transgenic model of Lewy body disease. PLoS One 2011;6(4):e19338.
6. Games D, Valera E, Spencer B, et al. Reducing C-terminal-truncated alpha-synuclein by immunotherapy attenuates neurodegeneration and propagation in Parkinson's disease-like models. J Neurosci 2014;34:9441-54.
7. Masliah E, Rockenstein E, Adame A, et al. Effects of alpha-synuclein immunization in a mouse model of Parkinson's disease. Neuron 2005;46:857-68.
8. Jankovic J, Goodman I, Safirstein B, et al. Safety and tolerability of multiple ascending doses of PRX002/RG7935, an anti-α-synuclein monoclonal antibody, in patients with Parkinson disease: a randomized clinical trial. JAMA Neurol 2018;75:1206-14.
9. Schenk DB, Koller M, Ness DK, et al. First-in-human assessment of PRX002, an anti-α-synuclein monoclonal antibody, in healthy volunteers. Mov Disord 2017;32:211-8.
10. Pagano G, Boess FG, Taylor KI, et al. A phase II study to evaluate the safety and efficacy of prasinezumab in early Parkinson's disease (PASADENA): rationale, design and baseline data. Front Neurol 2021;12:705407.
11. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-70.
12. Holden SK, Finseth T, Sillau SH, Berman BD. Progression of MDS-UPDRS scores over five years in de novo Parkinson disease from the Parkinson's Progression Markers Initiative cohort. Mov Disord Clin Pract 2018;5:47-53.
13. Chaudhuri KR, Schrag A, Weintraub D, et al. The Movement Disorder Society Nonmotor Rating Scale: initial validation study. Mov Disord 2020;35:116-33.
14. Regnault A, Boroojerdi B, Meunier J, Bani M, Morel T, Cano S. Does the MDS-UPDRS provide the precision to assess progression in early Parkinson's disease? Learnings from the Parkinson's Progression Marker Initiative cohort. J Neurol 2019;266:1927-36.
15. Simuni T, Siderowf A, Lasch S, et al. Longitudinal change of clinical and biological measures in early Parkinson's disease: Parkinson's Progression Markers Initiative cohort. Mov Disord 2018;33:771-82.
16. Lang AE, Siderowf AD, Macklin EA, et al. Trial of cinpanemab in early Parkinson's disease. N Engl J Med 2022;387:408-20.
17. Rogers MB. For α-synuclein immunotherapy, is going later the key? Alzforum, April 4, 2021 (https://www.alzforum.org/news/conference-coverage/synuclein-immunotherapy-going-later-key).