ORIGINAL ARTICLE

Trial of Cinpanemab in Early Parkinson's Disease

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ABSTRACT

BACKGROUND

Aggregated α-synuclein plays an important role in Parkinson's disease pathogenesis. Cinpanemab, a human-derived monoclonal antibody that binds to α-synuclein, is being evaluated as a disease-modifying treatment for Parkinson's disease.

METHODS

In a 52-week, multicenter, double-blind, phase 2 trial, we randomly assigned, in a 2:1:2:2 ratio, participants with early Parkinson's disease to receive intravenous infusions of placebo (control) or cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg every 4 weeks, followed by an active-treatment dose-blinded extension period for up to 112 weeks. The primary end points were the changes from baseline in the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score (range, 0 to 236, with higher scores indicating worse performance) at weeks 52 and 72. Secondary end points included MDS-UPDRS subscale scores and striatal binding as assessed on dopamine transporter single-photon-emission computed tomography (DaT-SPECT).

RESULTS

Of the 357 enrolled participants, 100 were assigned to the control group, 55 to the 250-mg cinpanemab group, 102 to the 1250-mg group, and 100 to the 3500-mg group. The trial was stopped after the week 72 interim analysis owing to lack of efficacy. The change to week 52 in the MDS-UPDRS score was 10.8 points in the control group, 10.5 points in the 250-mg group, 11.3 points in the 1250-mg group, and 10.9 points in the 3500-mg group (adjusted mean difference vs. control, −0.3 points [95% confidence interval {CI}, −4.9 to 4.3], P=0.90; 0.5 points [95% CI, −3.3 to 4.3], P=0.80; and 0.1 point [95% CI, −3.8 to 4.0], P=0.97, respectively). The adjusted mean difference at 72 weeks between participants who received cinpanemab through 72 weeks and the pooled group of those who started cinpanemab at 52 weeks was −0.9 points (95% CI, −5.6 to 3.8) for the 250-mg dose, 0.6 points (95% CI, −3.3 to 4.4) for the 1250-mg dose, and −0.8 points (95% CI, −4.6 to 3.0) for the 3500-mg dose. Results for secondary end points were similar to those for the primary end points. DaT-SPECT imaging at week 52 showed no differences between the control group and any cinpanemab group. The most common adverse events with cinpanemab were headache, nasopharyngitis, and falls.

CONCLUSIONS

In participants with early Parkinson's disease, the effects of cinpanemab on clinical measures of disease progression and changes in DaT-SPECT imaging did not differ from those of placebo over a 52-week period. (Funded by Biogen; SPARK Clinical Trials.gov number, NCT03318523.)

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*A complete list of the investigators in the SPARK trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2022;387:408-20.
DOI: 10.1056/NEJMoa2203395

Parkinson's disease is the second most common neurodegenerative disorder and numerically the fastest growing neurologic disease, affecting approximately 1% of persons older than 60 years of age in high-income countries.[1,2] Although dopamine replacement has substantial benefit with regard to symptoms, it does not slow progression, and levodopa-resistant symptoms develop over time — findings that justify the exploration of disease-modifying therapies beyond currently existing ones. The pathology of Parkinson's disease has been linked with α-synuclein, a small, natively unfolded cytoplasmic protein that can misfold and form aggregated polymers, which are a major component of Lewy bodies and Lewy neurites. Rare genetic mutations of the *SNCA* gene encoding α-synuclein cause autosomal dominantly inherited Parkinson's disease.[3,4] In the brain, α-synuclein is highly expressed, and its roles include vesicular transport and neurotransmitter release, including the release of dopamine.[5] A proposed mechanism for the progressive nature of Parkinson's disease is that misfolded oligomeric α-synuclein spreads from cell to cell and induces misfolding of native α-synuclein in a prion-like fashion.[6] Targeting α-synuclein aggregates, including extracellular forms, has been proposed as a disease-modifying treatment of Parkinson's disease.[7,8]

Cinpanemab is a human-derived monoclonal antibody that binds preferentially to aggregated forms of extracellular α-synuclein.[9] After brain-tissue inoculation with preformed α-synuclein fibrils in a mouse model of Parkinson's disease, the administration of cinpanemab reduced the spread of α-synuclein, slowed motor impairment, and attenuated the loss of striatal dopamine-transporter density.[10] In a phase 1 study[9] involving healthy volunteers and participants with Parkinson's disease, cinpanemab concentrations in the serum and cerebrospinal fluid (CSF) increased in a dose-dependent manner, without evidence of the generation of anti-cinpanemab antibody. The finding of cinpanemab–α-synuclein complexes in the plasma has suggested dose-dependent biologic activity in persons with Parkinson's disease.[9] On the basis of these results, we conducted a phase 2 trial to assess the clinical effect, safety, pharmacokinetics, and pharmacodynamics of intravenously administered cinpanemab in persons with early-stage Parkinson's disease.

METHODS

TRIAL POPULATION

In this trial, we enrolled participants 40 to 80 years of age who had early-stage Parkinson's disease that had been diagnosed within the previous 3 years, who scored no more than 2.5 on the modified Hoehn and Yahr scale of Parkinson's disease progression (range, 1 [involvement on one side only] to 5 [wheelchair-bound or bedridden unless aided]), who had not received treatment previously (or had received no treatment for symptoms of Parkinson's disease within 12 weeks before day 1 of the trial and were not expected to start treatment for symptoms within 6 months after enrollment), and who had single-photon emission computed tomography (SPECT) imaging of the dopamine transporter (DaT) with ^{123}I-ioflupane (DaTScan, General Electric Healthcare) that showed evidence of striatal dopaminergic deficit that was consistent with Parkinson's disease.

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Key exclusion criteria were the presence of freezing of gait, a Montreal Cognitive Assessment score of less than 23 (on a scale from 0 to 30, with lower scores indicating greater cognitive impairment) or other evidence of cognitive impairment or clinical dementia, evidence of clinically relevant abnormality on magnetic resonance imaging (MRI) of the head, and previous participation in any active immunotherapy trial targeting α-synuclein. A complete listing of the inclusion and exclusion criteria is provided in the protocol (available with the full text of this article at NEJM.org).

TRIAL DESIGN

This 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 2 trial was followed by an active-treatment, dose-blinded extension period (for a total period of up to 112 weeks). The trial was conducted in Austria, Canada, France, Germany, Israel, Italy, Spain, the United Kingdom, and the United States. Participants were enrolled in two stages. First, there was a lead-in group (cohort A) in which participants were randomly assigned in a 1:1:1:1 ratio to receive placebo (control) or cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg, administered intravenously every 4 weeks. Participants in cohort A were assessed for 12 weeks, at which time an independent data and safety monitoring com-

mittee reviewed the safety and pharmacokinetic data. Participants in cohort B were randomly assigned in a 2:1:2:2 ratio to receive placebo or cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg, administered intravenously every 4 weeks (Fig. S1 in the Supplementary Appendix, available at NEJM.org). (The 250-mg dose of cinpanemab was the lowest dose that was anticipated to have efficacy, and fewer participants were assigned to this dose level in order for the researchers to maintain a reasonable sample size and to increase the power of the trial to detect effects at the other doses.) Cohort A was incorporated with cohort B in this 52-week, placebo-controlled portion of the trial.

At 52 weeks, participants who had received placebo started to receive cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg (randomization assigned at trial baseline in a 1:2:2 ratio). These participants were considered to be in the delayed-start cohort (pooled here as a control group for the analyses in the dose-blinded extension period). Participants who received cinpanemab in the placebo-controlled period continued with the same dose regimen in the dose-blinded extension period and were considered to be in the early-start cohort for the purposes of comparison with the delayed-start cohort at 72 weeks. All the investigators and participants remained unaware of the trial-group assignments and of the dose levels throughout the double-blind and extension periods.

TRIAL OVERSIGHT

This trial was performed in accordance with the principles outlined in the Declaration of Helsinki and with Good Clinical Practice guidelines. The protocol was approved by the ethics committee at each trial site, and all the participants provided written informed consent. The trial was designed by the sponsor (Biogen) and the academic authors. Biogen provided trial oversight, analyzed the data, provided cinpanemab, and paid for medical writing assistance; commercially available saline that was provided by the sites was used for placebo. All the authors reviewed the data and participated in writing or reviewing the manuscript. The persons who designed the trial, analyzed the data, and wrote the manuscript are listed in the Supplementary Appendix. There were confidentiality agreements in place between the sponsor and authors.

END POINTS

The two primary end points were the change from baseline in the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score at weeks 52 and 72. (The MDS-UPDRS total score is the sum of subscale parts I [nonmotor aspects of experiences of daily living; range, 0 to 52], II [motor aspect of experiences of daily living; range, 0 to 52], and III [motor examination; range, 0 to 132], with a range for the total score of 0 to 236, with higher scores indicating more severe symptoms.) The primary end point of the change in score at 72 weeks was assessed in the early-start cohort (original cinpanemab groups) and the delayed-start cohort (original placebo group). Participants who started receiving medications to treat symptoms of Parkinson's disease during the trial were requested to refrain from taking these medications for approximately 12 hours before each subsequent trial visit involving the MDS-UPDRS assessment so that they could be examined in the off-medication state, as confirmed by the examiner.

Secondary efficacy end points included the change from baseline in the MDS-UPDRS total score at week 96; the change from baseline in the scores on MDS-UPDRS subscale parts I, II, and III individually at weeks 52, 72, and 96; and the change from baseline to week 52 in the striatal binding ratios for the striatum, putamen, and caudate as measured by DaT-SPECT. Additional secondary end points included the pharmacokinetics of cinpanemab in serum, dose-related safety of cinpanemab as assessed by the incidence of adverse events and serious adverse events, and immunogenicity as assessed by the incidence and titer of anti-cinpanemab antibodies. Several measures (e.g., flexible visit windows and shortened visits) were implemented to minimize the disruption of the coronavirus disease 2019 (Covid-19) pandemic on the collection of trial data. Exploratory end points and measures, including scales of quality of life, are described in Section S3.

The methods and analysis of DaT-SPECT acquisition were harmonized across the trial sites. Images were processed at a central laboratory with a standardized reconstruction algorithm (Hermes Medical Solutions) and were qualitatively read by neuroradiologists who were unaware of the trial-

group assignments, before the automated quantitative analysis was conducted.[12] The presence of α-synuclein seeds in CSF was evaluated with the use of an α-synuclein seeding amplification assay.[13] Pharmacokinetic analyses are described in Section S4.

Safety was assessed by the pharmacovigilance team of the sponsor. The team evaluated adverse events and serious adverse events, clinical laboratory abnormalities, vital-sign measurements, physical and neurologic examination findings, electrocardiogram readings, disease activity according to measures of MRI of the head, body weight, and the Columbia Suicide Severity Rating Scale score. The severity grading of adverse events was defined according to the Common Terminology Criteria for Adverse Events, version 5.0.

STATISTICAL ANALYSIS

Using a power analysis, we estimated that a sample size of 357 (with 101 participants in the control group, 54 in the 250-mg group, 101 in the 1250-mg group, and 101 in the 3500-mg group) would provide the trial with approximately 80% average power to detect dose–response curves over a 1-year treatment period, on the basis of a two-sided type I error of 0.05 for prespecified dose–response shapes or curves, assuming that 10% of the participants would withdraw by week 52. Models were constructed to detect potential dose–response shapes under a set of seven common dose–response curves[14] (linear, maximum effective dose [EMAX], exponential at two concavities, logistic, linear in log dose, and quadratic) at week 52 for the power calculation. Power for the week 72 analysis was calculated with the use of a similar approach. A multiplicity control procedure was prespecified for the overall type I error of the trial at an alpha level of 0.05 owing to the two primary end points (changes in scores at weeks 52 and 72). Details are provided in the statistical analysis plan, which is available with the protocol.

Demographic data were summarized descriptively, both overall and according to trial group. Efficacy analyses for the primary and secondary end points were performed in the modified intention-to-treat population, which included all the participants who underwent randomization and received at least one dose of cinpanemab or placebo. Safety was analyzed according to the receipt of cinpanemab or placebo and was summarized with the use of descriptive statistics (continuous variables) or numbers and percentages of participants with an adverse event (categorical variables).

Analysis of the primary efficacy end points used mixed-model repeated measures, a method that assumes that missing data are missing at random, conditional on observed data. Baseline values were defined as the most recent nonmissing measurement obtained before the receipt of the first dose of cinpanemab or placebo. For analyses to week 52, MDS-UPDRS data from visits that occurred after the start of medications to treat symptoms of Parkinson's disease, which were started at the discretion of the treating physicians (who were unaware of the trial-group assignments), were excluded from the primary analysis, and repeated measures were modeled with the use of random participant-level intercepts and slopes. For the analyses at week 72 and week 96, all the data that had been collected before the start of Parkinson's disease medications and those obtained after the start of Parkinson's disease medications while participants were in the off-medication state were included, and covariance among repeated measures was modeled with the use of an unstructured participant-level covariance matrix.

A delayed-start analysis that was conducted from baseline to week 72 compared the changes in the MDS-UPDRS total scores between participants who had initially been randomly assigned to a cinpanemab group (early-start cohort) and those who had been initially randomly assigned to receive placebo and crossed over to one of the three doses of cinpanemab (delayed-start cohort). A two-step dose–response, multiple comparison procedure and modeling (MCP-Mod) analysis across the three doses and placebo was planned at week 52 and week 72.

Because the statistical analysis plan did not include a provision for multiplicity correction of the widths of confidence intervals for the secondary or exploratory end points, results are reported as point estimates with 95% confidence intervals. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute). An interim analysis was planned at 72 weeks, and although there was not a formal stopping rule, the sponsor stopped the trial for lack of efficacy

after that point. Details of the statistical methods are provided in the protocol and in Section S2.

RESULTS

PARTICIPANTS

The trial was conducted from January 2018 to April 2021, including during the Covid-19 pandemic.[11] The overall trial-data loss due to the Covid-19 pandemic was less than 5%.

A total of 482 persons with Parkinson's disease were assessed for eligibility, of whom 357 (29 in cohort A and 328 in cohort B) were randomly assigned in the double-blind phase to the control group (100 participants), the 250-mg cinpanemab group (55), the 1250-mg group (102), and the 3500-mg group (100) (Fig. S2). The demographic and clinical characteristics of the participants at baseline were similar among the trial groups (Tables 1 and S2). Approximately 90% of the enrolled participants were White, a finding that reflected the locations of the centers involved in the trial. Screening failure due to DaT-SPECT imaging with no evidence of dopaminergic deficit occurred in 15 participants (4%).[12] Approximately 20% of the participants had taken some Parkinson's disease medication before trial entry. In a subgroup of 118 participants who underwent a CSF α-synuclein seeding amplification assay, the majority (110 participants) had a positive result, a finding that indicated the presence of aggregation-inducing α-synuclein species.

Of the 357 participants in the trial, 97% continued to be enrolled at week 52 and 94% at week 72. In the dose-blinded extension period, demographic characteristics were similar among the treatment groups (data not shown). Approximately 40% of the participants in each group (41% in the control group, 42% in the 250-mg group, 40% in the 1250-mg group, and 44% in the 3500-mg group) started Parkinson's disease medications by week 52, and as prespecified, their end-point data after the start of these medications were excluded from the primary analysis at week 52. However, these participants continued in the trial and were assessed at 72 weeks in the off-medication state (Fig. S3). The trial was stopped owing to lack of efficacy after the results of a prespecified interim analysis at 72 weeks were available.

END POINTS

The change in the MDS-UPDRS total score from baseline to week 52 (one of the primary end points; higher values indicate worse performance) was 10.8 points in the control group, 10.5 points in the 250-mg group (difference vs. control, −0.3 points; 95% confidence interval [CI], −4.9 to 4.3; P=0.90), 11.3 points in the 1250-mg group (difference, 0.5 points; 95% CI, −3.3 to 4.3; P=0.80), and 10.9 points in the 3500-mg group (difference, 0.1 point; 95% CI, −3.8 to 4.0; P=0.97) (Table 2 and Fig. 1A). These end-point results excluded data after participants started taking medications to control symptoms. A dose–response MCP-Mod analysis across the three doses and placebo was conducted at week 52, and no dose–response relation was detected; the week 72 MCP-Mod analysis was not conducted owing to lack of efficacy.

For the other primary end point, the change in MDS-UPDRS total score from baseline to week 72, in which participants were assessed in the off-medication state and for which results were not censored if a participant had started treatment to control symptoms, the adjusted mean differences between the early-start cohort and the pooled delayed-start cohort were as follows: −0.9 points (95% CI, −5.6 to 3.8) for the 250-mg dose of cinpanemab, 0.6 points (95% CI, −3.3 to 4.4) for the 1250-mg dose, and −0.8 points (95% CI, −4.6 to 3.0) for the 3500-mg dose (Table 2 and Fig. 1B). The absence of differences between active treatment and control was observed through week 96 on the basis of visual inspection of Figure 1B; results of the formal analysis are not presented here.

There was no substantial difference in the change from baseline in the secondary end points of scores on the MDS-UPDRS subscale parts I, II, or III at week 52 or week 72 on the basis of the inclusion of zero in the confidence intervals for the differences between the active-treatment groups and the control group (Table 2 and Fig. S4). Similarly, there was no evidence of an effect of cinpanemab on other secondary end points at week 52 (Tables 2 and S3) or at weeks 72 or 96 on the scores for the Physical Activity Scale for the Elderly or in the Schwab and England Activities of Daily Living Scale (Figs. S5 and S6). There was no evidence of a benefit with cinpanemab throughout the trial across other

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

Characteristic	Control (N=100)	Cinpanemab, 250 mg (N=55)	Cinpanemab, 1250 mg (N=102)	Cinpanemab, 3500 mg (N=100)	Total (N=357)
Age — yr	61.0±8.4	61.3±9.2	59.2±8.5	59.3±9.9	60.1±9.0
Male sex — no. (%)	72 (72)	39 (71)	73 (72)	66 (66)	250 (70)
White race — no. (%)†	96 (96)	53 (96)	92 (90)	84 (84)	325 (91)
Time since onset of Parkinson's disease — yr	2.0±2.0	2.2±2.4	1.7±1.2	2.0±1.6	1.9±1.8
Interquartile range	0.9–2.2	1.1–2.6	0.9–2.2	1.0–2.5	1.0–2.3
Time since diagnosis — yr	0.7±0.6	0.7±0.6	0.6±0.6	0.7±0.7	0.7±0.6
Interquartile range	0.2–1.0	0.2–0.9	0.2–0.8	0.2–1.0	0.2–0.9
MDS-UPDRS scores‡					
Total score	31.9±12.4	31.9±12.2	32.9±12.6	32.6±13.5	32.4±12.7
Part I score	4.3±3.5	3.3±2.7	4.8±4.0	4.3±3.6	4.3±3.6
Part II score	5.4±3.9	5.0±3.3	5.3±3.7	5.5±4.3	5.3±3.8
Part III score	22.2±9.3	23.5±9.4	22.8±8.7	22.9±8.9	22.8±9.0
Hoehn and Yahr stage§					
Stage 1	29 (29)	12 (22)	23 (23)	22 (22)	86 (24)
Stage 1.5	3 (3)	4 (7)	9 (9)	5 (5)	21 (6)
Stage 2	64 (64)	37 (67)	64 (63)	68 (68)	233 (65)
Stage 2.5	3 (3)	1 (2)	6 (6)	5 (5)	15 (4)
Stage 3	1 (1)	1 (1)	0	0	2 (1)
Montreal Cognitive Assessment total score¶	27.1±2.0	27.5±1.9	27.6±1.8	27.5±1.9	27.4±1.9
Schwab and England Activities of Daily Living Scale total score‖	92.3±6.2	93.3±6.1	91.4±7.3	92.3±8.9	92.2±7.3
Physical Activity Scale for the Elderly total score**	165.3±92.6	182.4±88.1	170.7±86.4	164.5±82.1	169.2±87.1
Epworth Sleepiness Scale total score††	4.9±3.7	4.9±3.7	4.6±3.2	4.8±3.6	4.8±3.5
EQ-5D summary index score‡‡	0.897±0.092	0.903±0.096	0.874±0.108	0.868±0.121	0.883±0.106

* Plus–minus values are means ±SD.
† Race was reported by the participant.
‡ Total scores on the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) range from 0 to 236, with higher scores indicating worse performance. The total score is the sum of subscale parts I (nonmotor aspects of experiences of daily living; range, 0 to 52), II (motor aspect of experiences of daily living; range, 0 to 52), and III (motor examination; range, 0 to 132).
§ The modified Hoehn and Yahr disability scale of Parkinson's disease progression ranges from 1 (involvement on one side only) to 5 (wheelchair-bound or bedridden unless aided). Participants with stage 3 disability were assessed as having protocol deviations.
¶ Total scores on the Montreal Cognitive Assessment range from 0 to 30, with higher scores indicating better cognitive function.
‖ Total scores on the Schwab and England Activities of Daily Living Scale range from 0 to 100 (with a score of 100 indicating normal function). A score above 70 indicates complete independence in activities of daily living, whereas a score of 70 or less indicates that caregiver help is necessary.
** The Physical Activity Scale for the Elderly assesses activities that are typical in older adults (walking, recreational activities, exercise, housework, yard work, and caring for others). Scores are based on frequency, duration, and intensity level of activity during the previous week and range from 0 to 793, with higher scores indicating greater physical activity.
†† Total scores on the Epworth Sleepiness Scale range from 0.0 to 24.0, with higher scores indicating more daytime sleepiness.
‡‡ Summary index scores on the European Quality of Life 5-Dimension (EQ-5D) questionnaire range from –0.285 to 1, with higher scores indicating better outcomes.

Table 2. Primary End Points at Weeks 52 and 72 and Secondary End Points at Week 52.*

End Point	Control (N=100)		Cinpanemab, 250 mg (N=55)			Cinpanemab, 1250 mg (N=102)			Cinpanemab, 3500 mg (N=100)		
	Adjusted Mean Change		Adjusted Mean Change	Difference (95% CI)	P Value	Adjusted Mean Change	Difference (95% CI)	P Value	Adjusted Mean Change	Difference (95% CI)	P Value
Primary end point: change in MDS-UPDRS total score†											
At 52 wk											
No. of participants	53		29			57			51		
Score change (95% CI)	10.8 (7.9 to 13.7)		10.5 (6.6 to 14.3)	−0.3 (−4.9 to 4.3)	0.90	11.3 (8.4 to 14.1)	0.5 (−3.3 to 4.3)	0.80	10.9 (7.9 to 13.8)	0.1 (−3.8 to 4.0)	0.97
At 72 wk											
No. of participants	68		32			62			65		
Score change (95% CI)	7.0 (4.1 to 9.8)		6.0 (2.1 to 10.0)	−0.9 (−5.6 to 3.8)	0.70	7.5 (4.6 to 10.4)	0.6 (−3.3 to 4.4)	0.78	6.2 (3.3 to 9.1)	−0.8 (−4.6 to 3.0)	0.70
Secondary end points at 52 wk‖											
Change in MDS-UPDRS I score†‡											
No. of participants	53		29			57			51		
Score change (95% CI)	1.4 (0.6 to 2.3)		0.9 (−0.2 to 2.0)	−0.5 (−1.8 to 0.8)		1.6 (0.7 to 2.4)	0.1 (−1.0 to 1.2)		1.7 (0.8 to 2.5)	0.2 (−0.9 to 1.3)	
Change in MDS-UPDRS II score†‡											
No. of participants	54		29			58			51		
Score change (95% CI)	3.2 (2.2 to 4.1)		2.7 (1.5 to 4.0)	−0.4 (−1.9 to 1.0)		3.2 (2.3 to 4.1)	0.0 (−1.2 to 1.2)		3.0 (2.1 to 4.0)	−0.2 (−1.4 to 1.1)	

Change in MDS-UPDRS III score†								
No. of participants	53	29		58		51		
Score change (95% CI)	6.1 (4.0 to 8.2)	6.7 (3.9 to 9.5)	0.6 (−2.7 to 3.9)	6.8 (4.7 to 8.8)	0.7 (−2.1 to 3.4)	6.2 (4.0 to 8.4)	0.1 (−2.7 to 2.9)	
Striatal binding ratios‡								
No. of participants	93	53		97		85		
Total striatum (95% CI)	−0.08 (−0.11 to −0.05)	−0.09 (−0.13 to −0.06)	−0.01 (−0.06 to 0.04)	−0.08 (−0.11 to −0.05)	0.00 (−0.04 to 0.04)	−0.11 (−0.14 to −0.08)	−0.03 (−0.07 to 0.01)	
Total putamen (95% CI)	−0.09 (−0.12 to −0.06)	−0.10 (−0.14 to −0.06)	−0.01 (−0.05 to 0.04)	−0.10 (−0.13 to −0.07)	−0.01 (−0.05 to 0.03)	−0.13 (−0.16 to −0.10)	−0.03 (−0.07 to 0.01)	
Total caudate (95% CI)	−0.07 (−0.10 to −0.04)	−0.08 (−0.12 to −0.04)	−0.01 (−0.06 to 0.05)	−0.06 (−0.09 to −0.03)	0.01 (−0.04 to 0.05)	−0.09 (−0.12 to −0.06)	−0.02 (−0.07 to 0.02)	

* Participants in the control group received placebo until week 52; at that point, they received cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg (randomization assigned at trial baseline in a 1:2:2 ratio) but are shown here as a pooled control group (delayed-start cohort). Differences from placebo (control) were based on a mixed model for repeated measures. Higher scores on the MDS-UPDRS indicate worse performance.

† Denominators differ from the initial randomization numbers because data after the initiation of medications to treat symptoms of Parkinson's disease were not included in the primary analysis for week 52 but were included in the week 72 analysis if the participants were assessed in the "off" state.

‡ Striatal binding ratios were determined on the basis of single-photon emission computed tomography imaging of the dopamine transporter with ^{123}I-ioflupane. The analysis included data after the initiation of medications to treat symptoms of Parkinson's disease.

§ The widths of confidence intervals for secondary end points have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

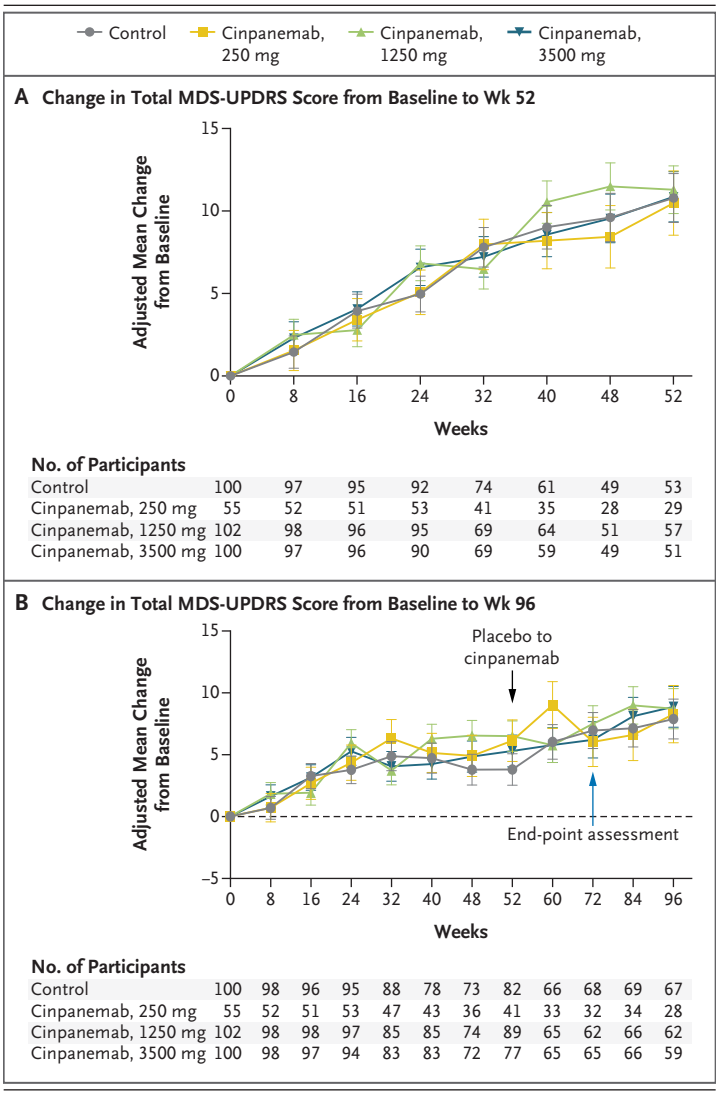


Figure 1. Adjusted Mean MDS-UPDRS Total Scores to Week 52 and Week 96.

Shown are the adjusted mean Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total scores to week 52 (one of two primary end points) (Panel A). Total scores range from 0 to 236, with higher scores indicating worse performance. MDS-UPDRS data from visits that occurred after the start of medications to treat symptoms of Parkinson's disease were excluded from the primary analysis. I bars indicate the standard error. Participants in the control group received placebo until week 52; at that point (Panel B, black arrow), they received cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg (randomization assigned at trial baseline in a 1:2:2 ratio) but are shown here as a pooled control group (delayed-start cohort). For scores to week 72 (Panel B, blue arrow), data after the initiation of Parkinson's disease medications were included in the analyses but only included assessments in the off-medication state if participants were assessed in that state. The modified intention-to-treat population included all the participants who underwent randomization and received at least one dose of cinpanemab or placebo. The mixed model for repeated measures included fixed effects of trial group, baseline MDS-UPDRS total score, geographic region, Parkinson's disease subtype (postural instability with gait difficulty, tremor dominant, or indeterminate disease), baseline dopamine transporter single-photon emission computed tomography (DaT-SPECT) striatal binding ratio values for the striatum, visit, and the interaction terms between trial group and visit, between baseline MDS-UPDRS total score and visit, and between baseline DaT-SPECT striatal binding ratio values for the striatum and visit. The heights of the I bars have not been adjusted for multiplicity and cannot be used to infer treatment effects.

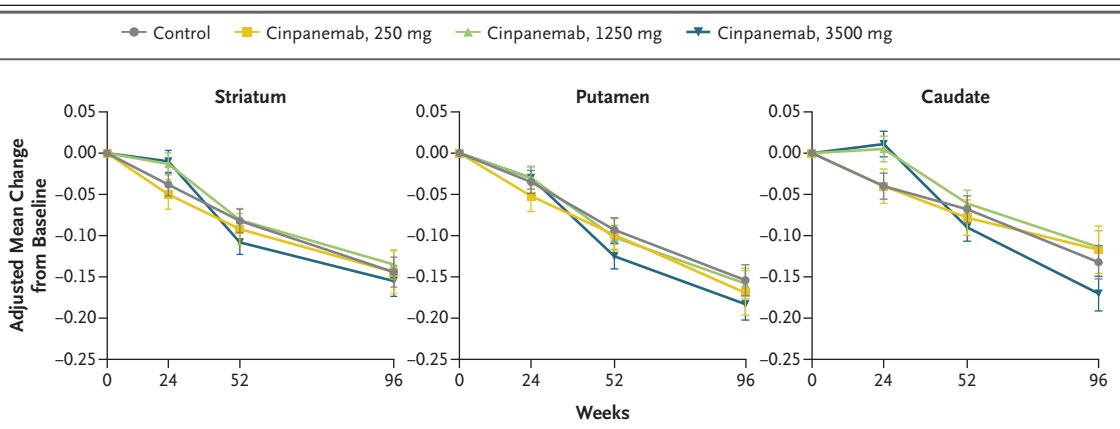
measures of quality of life on the basis of confidence intervals for differences or on indicators of cognition, sleep, balance, or autonomic symptoms (Figs. S7 and S8).

DAT-SPECT IMAGING

Across the striatal binding ratios of the striatum, putamen, and caudate, DaT-SPECT imaging showed no substantial differences between the control (placebo) group and any cinpanemab group at week 52 and no dose-dependent responses (Table 2). The lack of evidence of a treatment effect was apparent at week 96 across all active-treatment groups, given the inclusion of zero in the confidence intervals for differences between each active-treatment group and the control group (delayed-start cohort) and on visual inspection of Figure 2.

SAFETY

During the placebo-controlled period (to week 52), a total of 211 of 257 participants (82%) who received cinpanemab and 80 of 100 participants (80%) who received placebo reported one or more adverse events. The most common adverse events with cinpanemab (occurring in >10% of the participants who received the drug) were headache, nasopharyngitis, and falls, with most of the adverse events being assessed as mild to moderate in severity (Table 3). Adverse events that were related to infusion reactions were reported in less than 5% of the cinpanemab-



No. of Participants												
Control	96	94	93	72	96	94	93	72	96	94	93	72
Cinpanemab, 250 mg	55	54	53	34	55	54	53	34	55	55	53	34
Cinpanemab, 1250 mg	100	99	97	73	100	99	97	73	100	99	97	73
Cinpanemab, 3500 mg	98	97	85	66	98	97	85	66	98	97	85	66

Figure 2. Adjusted Mean Change from Baseline to Week 96 in the DaT-SPECT Striatal Binding Ratio (Pooled Delayed Start).

The mixed model for repeated measures included a fixed effect of treatment group, baseline MDS-UPDRS total score values, geographic region, Parkinson's disease subtype, baseline DaT-SPECT striatal binding ratio values for the striatum, visit, and the interaction terms between treatment and visit, between the baseline MDS-UPDRS total score and visit, and between baseline DaT-SPECT striatal binding ratio values for the striatum and visit. Participants in the control group received placebo until week 52; at that point, they received cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg (randomization assigned at trial baseline in a 1:2:2 ratio) but are shown here as a pooled control group (delayed-start cohort). I bars indicate the standard error. The heights of the I bars have not been adjusted for multiplicity and cannot be used to infer treatment effects.

treated participants. Serious adverse events occurred in 21 participants overall (in 7 [7%] receiving placebo and in 14 [5%] receiving cinpanemab) and were most often single events.

In the double-blind and active-treatment, dose-blinded extension periods combined, 305 of 353 cinpanemab-treated participants (86%) reported one or more adverse events (Table S4). The most common adverse events (occurring in >10% of the participants) were headache, falls, back pain, arthralgia, and nasopharyngitis. Most participants reported that these adverse events were mild to moderate in severity. Adverse events that were related to infusion reactions were reported in less than 5% of cinpanemab-treated participants.

A total of 35 participants (10%) who received cinpanemab reported one or more serious adverse events. The most common serious adverse events according to preferred term (in ≥2 participants) were transient ischemic attack (in 4 [1%]) and Covid-19–related pneumonia, depression, fall, osteoarthritis, prostate cancer, and rotator cuff syndrome (in 2 [1%] each). All the other serious adverse events were single events. There were no serious adverse events involving infusion reactions. One death, due to myocardial infarction, occurred in the early-start cohort of participants who received the 3500-mg dose of cinpanemab and was assessed by the site investigator as not being related to the drug.

Pharmacokinetic data are summarized in Figure S9. Biomarkers in CSF, which reflect target engagement of the drug, could not be analyzed owing to the lack of adequate measures. Antidrug antibodies appeared in one cinpanemab-treated participant at week 4. No participants who received cinpanemab had antidrug antibodies at weeks 52, 72, or 96.

DISCUSSION

This trial that included previously untreated participants with early-stage Parkinson's disease, as well as confirmation of aggregation-inducing α-synuclein species in the CSF in a subgroup of participants, showed that cinpanemab, at the doses studied, did not lead to differences as compared

Table 3. Adverse Events during the Placebo-Controlled Period (to Week 52).*

Event	Control (N=100)	Cinpanemab, 250 mg (N=55)	Cinpanemab, 1250 mg (N=102)	Cinpanemab, 3500 mg (N=100)	Cinpanemab, Total (N=257)
	number of participants with event (percent)				
Any adverse event	80 (80)	42 (76)	83 (81)	86 (86)	211 (82)
Adverse event according to maximum severity†					
Mild or moderate	77 (77)	40 (73)	77 (75)	78 (78)	195 (76)
Severe or life-threatening	3 (3)	2 (4)	6 (6)	8 (8)	16 (6)
Serious adverse event	7 (7)	4 (7)	4 (4)	6 (6)	14 (5)
Adverse event leading to trial discontinuation	1 (1)	0	2 (2)	0	2 (1)
Adverse events occurring in ≥5% of participants‡					
Headache	18 (18)	6 (11)	19 (19)	21 (21)	46 (18)
Nasopharyngitis	12 (12)	10 (18)	10 (10)	13 (13)	33 (13)
Fall	5 (5)	5 (9)	6 (6)	15 (15)	26 (10)
Back pain	9 (9)	3 (5)	8 (8)	13 (13)	24 (9)
Dizziness	3 (3)	4 (7)	9 (9)	7 (7)	20 (8)
Parkinson's disease§	1 (1)	4 (7)	8 (8)	8 (8)	20 (8)
Arthralgia	4 (4)	5 (9)	6 (6)	8 (8)	19 (7)
Fatigue	5 (5)	2 (4)	4 (4)	11 (11)	17 (7)
Diarrhea	4 (4)	5 (9)	5 (5)	6 (6)	16 (6)
Upper respiratory tract infection	3 (3)	2 (4)	6 (6)	7 (7)	15 (6)
Anxiety	3 (3)	0	9 (9)	5 (5)	14 (5)
Constipation	5 (5)	3 (5)	5 (5)	6 (6)	14 (5)
Nausea	6 (6)	1 (2)	6 (6)	6 (6)	13 (5)
Pain in arm or leg	3 (3)	4 (7)	5 (5)	1 (1)	10 (4)
Depression	3 (3)	3 (5)	3 (3)	3 (3)	9 (4)
Influenza	3 (3)	1 (2)	7 (7)	1 (1)	9 (4)
Rash	3 (3)	1 (2)	0	5 (5)	6 (2)

* Shown are adverse events through week 52; during this period, participants in the control group received placebo.
† Each participant was counted once at the maximum severity of adverse event.
‡ Participants were counted only once within each preferred term (*Medical Dictionary for Regulatory Activities*, version 23.0).
§ This adverse event was defined as worsening of Parkinson's disease beyond what would be expected on the basis of natural progression.

with placebo in the progression of motor function, nonmotor function, activities of daily living, quality of life, or imaging biomarkers at 52 weeks. The lack of an effect was also evident in the absence of a difference in the delayed-start analysis at 72 weeks, as well as in the start of treatment for symptoms of Parkinson's disease, two methods that have been used to evaluate potential disease modification in previous trials.[15,16] A limitation of the trial is that approximately 40% of the participants had data for the 52-week primary end point censored as a result of starting medications for Parkinson's disease symptoms; however, an analysis that included all the participants tested in the off-medication state showed no substantial difference between those who

continued cinpanemab through 72 weeks and those who switched from placebo to cinpanemab at 52 weeks.

The most common adverse events that were reported in cinpanemab-treated participants during the double-blind and active treatment, dose-blinded extension periods were headache, falls, back pain, arthralgia, and nasopharyngitis. Most of these adverse events in cinpanemab-treated participants were mild to moderate in severity. The incidence of infusion reactions among cinpanemab-treated participants was low, in contrast to the type of inflammatory reaction that can occur with an antiamyloid monoclonal antibody.

The timing of therapeutic intervention in degenerative neurologic diseases may be a factor in the failure of agents targeted to a misfolded protein. In persons with Parkinson's disease, the entrance of α-synuclein oligomers into cells may be an early event that progresses slowly to cellular dysfunction, as suggested by autopsy results in persons who have undergone cell transplantation.[17] If this is the case, the testing of treatments in preclinical or prodromal stages of Parkinson's disease may be valuable.

As with the findings reported in our trial, no evidence of a treatment benefit with prasinezumab on the MDS-UPDRS total score at week 52 was observed in the Phase 2 Trial of Anti α-Synuclein Antibody in Early Parkinson's Disease (PASADENA).[18] The changes on DaT-SPECT in the placebo group and the cinpanemab groups in our trial were lower than have been reported in natural history studies[19] or in studies of levodopa treatment.[20] Although these findings are variable across studies, PASADENA, which assessed the α-synuclein antibody prasinezumab, also showed no change with regard to this imaging biomarker.[18] Prasinezumab recognizes the C-terminal of α-synuclein and binds well to monomeric protein, whereas cinpanemab recognizes the N-terminal and has a low binding affinity to monomeric α-synuclein.[21]

Several methods of interference with the production or function of α-synuclein have been proposed.[8] The results of our trial suggest that targeting extracellular α-synuclein with an N-terminal–directed antibody as monotherapy may be insufficient to slow the progression of disease. However, a limitation of the trial is that we were unable to measure target engagement of the drug to verify clearance of α-synuclein.

In this trial involving participants with early Parkinson's disease, treatment with cinpanemab, a monoclonal antibody directed at α-synuclein, showed no evidence of benefit as compared with placebo with regard to clinical, imaging, or quality-of-life measures.

Supported by Biogen.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial coordinators, staff, and participants for their contributions to the trial; patient advocate Michael Byrne for providing trial input; and Linda Wagner and Cara Dickinson, of Excel Scientific Solutions, for writing and editorial support with an earlier version of the manuscript.

APPENDIX

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