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Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

C.V.M. Verschuur, S.R. Suwijn, J.A. Boel, B. Post, B.R. Bloem, J.J. van Hilten, T. van Laar, G. Tissingh, A.G. Munts, G. Deuschl, A.E. Lang, M.G.W. Dijkgraaf, R.J. de Haan, and R.M.A. de Bie, for the LEAP Study Group*

ABSTRACT

BACKGROUND

Levodopa is the main treatment for symptoms of Parkinson's disease. Determining whether levodopa also has a disease-modifying effect could provide guidance as to when in the course of the disease the treatment with this drug should be initiated.

METHODS

In a multicenter, double-blind, placebo-controlled, delayed-start trial, we randomly assigned patients with early Parkinson's disease to receive levodopa (100 mg three times per day) in combination with carbidopa (25 mg three times per day) for 80 weeks (early-start group) or placebo for 40 weeks followed by levodopa in combination with carbidopa for 40 weeks (delayed-start group). The primary outcome was the between-group difference in the mean change from baseline to week 80 in the total score on the Unified Parkinson's Disease Rating Scale (UPDRS; scores range from 0 to 176, with higher scores signifying more severe disease). Secondary analyses included the progression of symptoms, as measured by the UPDRS score, between weeks 4 and 40 and the noninferiority of early initiation of treatment to delayed initiation between weeks 44 and 80, with a noninferiority margin of 0.055 points per week.

RESULTS

A total of 445 patients were randomly assigned: 222 to the early-start group and 223 to the delayed-start group. The mean (±SD) UPDRS score at baseline was 28.1±11.4 points in the early-start group and 29.3±12.1 points in the delayed-start group. The change in UPDRS score from baseline to week 80 was −1.0±13.1 points and −2.0±13.0 points, respectively (difference, 1.0 point; 95% confidence interval [CI], −1.5 to 3.5; P=0.44); this finding of no significant between-group difference at week 80 implies that levodopa had no disease-modifying effect. Between weeks 4 and 40, the rate of progression of symptoms, as measured in UPDRS points per week, was 0.04±0.23 in the early-start group and 0.06±0.34 in the delayed-start group (difference, −0.02; 95% CI, −0.07 to 0.03). The corresponding rates between weeks 44 and 80 were 0.10±0.25 and 0.03±0.28 (difference, 0.07; two-sided 90% CI, 0.03 to 0.10); the difference in the rate of progression between weeks 44 and 80 did not meet the criterion for noninferiority of early receipt of levodopa to delayed receipt. The rates of dyskinesia and levodopa-related fluctuations in motor response did not differ significantly between the two groups.

CONCLUSIONS

Among patients with early Parkinson's disease who were evaluated over the course of 80 weeks, treatment with levodopa in combination with carbidopa had no disease-modifying effect. (Funded by the Netherlands Organization for Health Research and Development and others; LEAP Current Controlled Trials number, ISRCTN30518857.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. de Bie at Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at r.m.debie@amc.uva.nl.

*A complete list of investigators in the LEAP Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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The main treatment for Parkinson's disease is the dopamine precursor levodopa. Physicians may delay initiation of levodopa for various reasons, including concern about the induction of dyskinesias.[1,2] However, almost all patients ultimately receive levodopa to control motor symptoms.[3] In the Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) trial, the results of which were reported previously in the *Journal*,[4] patients with early Parkinson's disease received levodopa or placebo, and after 40 weeks the trial regimen was stopped. Two weeks after cessation of the regimen, the condition of the patients who had received levodopa had not deteriorated to the same degree as that of the patients who had received placebo, which suggested either that levodopa had slowed the progression of Parkinson's disease or that the drug had had a prolonged effect on symptoms that was interpreted as ameliorating the underlying disease. In contrast to these clinical results, neuroimaging data from that trial suggested either that levodopa had the detrimental effect of accelerating the loss of dopamine nerve terminals or that it modified the striatal dopamine transporter.[4] Therefore, whether levodopa has an effect on the progression of Parkinson's disease beyond its immediate benefit with respect to symptoms remains unknown.

One method of separating a possible disease-modifying effect of levodopa from an effect on symptoms is by conducting a delayed-start trial in two phases. During phase 1, patients receive either the active drug or placebo. A difference between the groups at the end of this phase may be the result of an effect on symptoms, a disease-modifying effect, or both. During phase 2, both groups receive the active drug, and persistent differences between the groups at the end of this phase are presumed to be explained by a disease-modifying effect because the effects of the drug on symptoms at that time are the same in both groups.[5] Here, we report the results of the delayed-start trial Levodopa in Early Parkinson's Disease (LEAP), which evaluated whether levodopa has a disease-modifying effect on patients with early Parkinson's disease who had insufficient disability to warrant treatment with antiparkinson medication.

Methods

Trial Oversight

This was a multicenter, randomized, double-blind, placebo-controlled, delayed-start trial. Patients were recruited from 50 community hospitals and 7 academic hospitals in the Netherlands. The trial design has been published previously.[6] The protocol, which was approved by the ethics committee at the Amsterdam University Medical Centers in the Netherlands, is available with the full text of this article at NEJM.org. The trial was conducted in accordance with the principles of the Declaration of Helsinki. Trial monitoring and data management were performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. Combination tablets of levodopa (100 mg) and carbidopa (25 mg) and matching placebo tablets were manufactured by and delivered to the participating patients by ACE Pharmaceuticals (Zeewolde, the Netherlands), which did not have any other role in the trial, including in the design or conduct of the trial, the analysis of the data, or the preparation of the manuscript. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. All the patients provided written informed consent. There was no industry involvement in the trial.

Patients

Patients were eligible for enrollment if they had received a diagnosis of Parkinson's disease within the previous 2 years from an experienced neurologist who based the diagnosis on standard clinical criteria,[7] if they had insufficient disability to warrant treatment with antiparkinson medication, if they were 30 years of age or older, and if they had a life expectancy of more than 2 years. Patients who had been treated previously with antiparkinson medication (e.g., levodopa, dopamine agonists, monoamine oxidase B inhibitor, catechol O-methyltransferase inhibitor, or amantadine) were excluded. Patients were also excluded if their most prominent symptom was tremor, such as a severe resting tremor that was present almost continuously or resulted in disability; if they had dementia; and if they had features that indicated atypical or secondary parkinsonism.

TRIAL PROCEDURES

After a baseline assessment, patients were randomly assigned, in a 1:1 ratio by a central Web-based computer program, to receive oral levodopa (100 mg three times per day) in combination with oral carbidopa (25 mg three times per day) for 80 weeks (early-start group) or to receive placebo three times per day for 40 weeks followed by oral levodopa (100 mg three times per day) in combination with oral carbidopa (25 mg three times per day) for 40 weeks (delayed-start group). Randomization was stratified according to type of hospital (academic vs. community hospital), age (<65 vs. ≥65 years), and duration of symptoms (<0.5 vs. ≥0.5 years) and was performed with the use of variable permuted blocks, with block sizes ranging from two to eight patients. During phase 1, the first 40 weeks of the trial, patients received levodopa or placebo. During phase 2, the second 40 weeks, patients in both trial groups received levodopa. If a disability involving activities of daily living developed during the first 40 weeks and the clinician determined that treatment for the disability should be administered, the patient was switched from the blinded treatment of phase 1 (levodopa in the early-start group and placebo in the delayed-start group) to open-label levodopa for the remainder of phase 1. If such a scenario occurred in a patient in the early-start group, the patient continued to receive the same dose of levodopa. Masking of the initial treatment assignment was preserved for both the patient and the investigator. Assessments were performed by trained research nurses at baseline and at weeks 4, 22, 40, 44, 56, 68, and 80.

OUTCOMES

The primary outcome was the difference between the early-start group and the delayed-start group in the mean change from baseline to week 80 in the total score on the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS includes subscales of mental function, activities of daily living, and motor function; total scores on the scale range from 0 to 176, with higher scores indicating more severe disease.[8] The main secondary outcomes were the progression of symptoms between weeks 4 and 40 and between weeks 44 and 80, as measured by the score on the UPDRS. Additional secondary outcomes at 80 weeks were disability as assessed by the Academic Medical Center Linear Disability Score (ALDS; scores range from 0 to 100, with lower scores indicating greater disability),[9] cognitive impairment as assessed by the Mini–Mental State Examination (MMSE; scores range from 0 to 30, with lower scores indicating greater cognitive impairment),[10] depression as assessed by the Beck Depression Inventory II (BDI-II; scores range from 0 to 63, with higher scores indicating more severe depressive symptoms),[11] and disease-related quality of life as assessed by the Parkinson's Disease Questionnaire-39 (PDQ-39; scores range from 0 to 100, with higher scores indicating a lower disease-related quality of life).[12] Outcomes at other time points are described in the protocol. In addition, we assessed the number of patients who received additional antiparkinson medication, the number of patients who had treatment complications including dyskinesia and levodopa-related fluctuations in motor response, and the type, incidence, and duration of adverse events.

STATISTICAL ANALYSIS

On the basis of the results of the ELLDOPA trial, we anticipated a mean (±SD) difference between the groups of 4±13 points on the UPDRS in the primary outcome in favor of the early-start group.[4] This magnitude of difference has been considered to be clinically relevant.[13] We calculated that enrollment of 167 patients in each group would provide the trial with 80% power to detect a difference in the UPDRS mean score of 4 points, using Student's t-test at a two-sided alpha level of 0.05. Assuming a dropout rate of 25%,[4,14,15] we planned to include 223 patients in each trial group.

Data were analyzed according to the intention-to-treat principle. Patients who proceeded to receive the phase 2 treatment before week 40 as a result of the need for control of symptoms were included in the group to which they had been randomly assigned.

The main analysis was a comparison of the primary outcome between the two trial groups at week 80. First, the difference between the groups in the mean change from baseline to week 80 in the total UPDRS score was analyzed with the use

of Student's t-test. Second, the UPDRS scores at 80 weeks were assessed with the use of an analysis of covariance model, taking into account baseline UPDRS scores. We used linear mixed-model analysis, model-based multiple imputation, and per-protocol analyses to evaluate the robustness of the results and to address the issue of missing data. Patients were excluded from the per-protocol analyses if they had received additional antiparkinson medication (e.g., patients who received phase 2 treatment during the first 40 weeks of the trial), if they had not received the correct treatment or the correct dose of the treatment, or if they did not have assessments at baseline, week 4, week 40, week 44, or week 80.

The main secondary analysis was a comparison of the progression of symptoms between weeks 4 and 40 (phase 1) and between weeks 44 and 80 (phase 2); a random-effects model was used to account for the repeated measures within patients. Progression of symptoms was gauged on the basis of the weekly change in the mean UPDRS score. We used the measurements at weeks 4, 22, and 40 and the measurements at weeks 44, 56, 68, and 80 to estimate the difference in the rate of progression between the two trial groups. If progression was found to occur more rapidly in the delayed-start group than in the early-start group during phase 1, but noninferiority of the early-start group to the delayed-start group with respect to the rate of progression was not shown during phase 2, this finding was to be interpreted as showing the effect of levodopa only on symptoms, with no disease-modifying effect. We used noninferiority tests only for analyses of rates of progression during phase 2. A noninferiority margin of 0.055 points on the UPDRS, which represents 2 UPDRS points during a period of 36 weeks, was prespecified. Noninferiority for phase 2 was assessed with the use of two-sided 90% confidence intervals (95% one-sided confidence intervals). The rate of progression between weeks 4 and 40 and between weeks 44 and 80 was also analyzed with the use of a per-protocol approach with data from patients who had had UPDRS scores in the highest quartile of scores at baseline and who also were adherent to the trial protocol. There was no plan for correction for multiple comparisons of secondary outcomes; these results are presented as point estimates with unadjusted 95% confidence intervals, without P values.

We also analyzed the between-group difference in the mean score on the UPDRS at 80 weeks in prespecified subgroups defined according to type of hospital, age, and duration of disease. For comparisons of the other outcomes (ALDS, MMSE, BDI-II, and PDQ-39), we used the appropriate parametric and nonparametric statistics; details are provided in the Supplementary Appendix, available at NEJM.org. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed with the use of SPSS software, version 24.

RESULTS

PATIENTS

From August 2011 through May 2016, a total of 446 patients were enrolled. One patient withdrew from the trial before the baseline assessment. Thus, 445 patients underwent randomization: 222 patients were randomly assigned to the early-start group and 223 to the delayed-start group (Fig. 1). A total of 207 patients in the early-start group and 210 patients in the delayed-start group completed the 80-week trial. Because of a need for symptomatic relief, 87 patients in the delayed-start group proceeded to receive the phase 2 trial medication (levodopa) before week 40, and 24 patients in the early-start group proceeded to open-label treatment with the same dose of levodopa. The demographic and clinical characteristics of the two groups were similar at baseline, with a mean (±SD) UPDRS score of 28.1±11.4 in the early-start group and 29.3±12.1 in the delayed-start group (Table 1). Before evaluation for eligibility for enrollment, 98 patients (22%) had undergone imaging of the dopamine transporter, which confirmed degeneration of substantia nigra neurons.

OUTCOMES

The difference between the groups in the mean change from baseline to week 80 in the total score on the UPDRS, the primary outcome, was not significant. The mean change was –1.0±13.1 points in the early-start group and –2.0±13.0 points in the delayed-start group, with a decrease

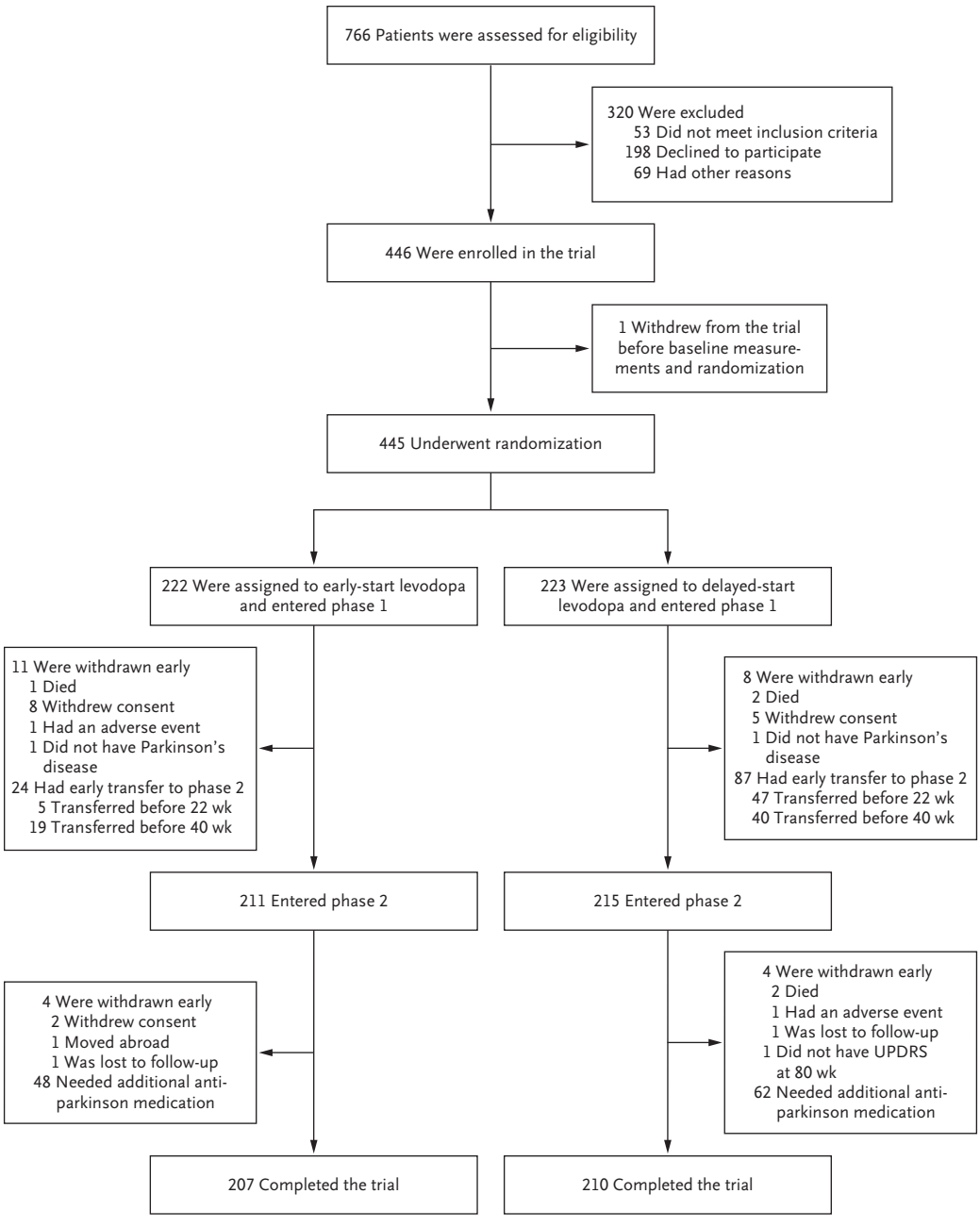

Figure 1. Enrollment and Randomization.

For one patient in the delayed-start group who completed the trial, the Unified Parkinson's Disease Rating Scale (UPDRS) score was not available at 80 weeks.

in points signifying improvement; the between-group difference was 1.0 point (95% confidence interval [CI], –1.5 to 3.5; P=0.44). An analysis adjusted for baseline scores on the UPDRS also showed no significant difference between the groups at 80 weeks (difference, 0.6 points; 95%

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Early-Start Group (N=222)	Delayed-Start Group (N=223)
Age — yr	64.8±8.7	65.5±8.8
Age ≥65 yr — no. (%)	129 (58.1)	129 (57.8)
Male sex — no. (%)	157 (70.7)	154 (69.1)
Recruited from academic hospital — no. (%)	62 (27.9)	67 (30.0)
Duration of symptoms <0.5 yr — no. (%)	22 (9.9)	26 (11.7)
First symptom — no. (%)†		
Tremor	131 (59.0)	130 (58.3)
Bradykinesia	85 (38.3)	76 (34.1)
Rigidity	75 (33.8)	75 (33.6)
Pain	20 (9.0)	21 (9.4)
UPDRS score‡		
Total	28.1±11.4	29.3±12.1
Part I	2.4±1.4	2.3±1.2
Part II	7.3±3.6	7.4±3.7
Part III	18.4±8.7	19.5±9.4
Median ALDS score (IQR)§	89.5 (89.0–89.5)	89.5 (89.0–89.5)
Median MMSE score (IQR)¶	29.0 (28.0–30.0)	29.0 (28.0–30.0)
Median BDI-II score (IQR)‖	7.0 (3.0–10.0)	6.0 (4.0–10.0)
Median PDQ-39 score (IQR)**	10.3 (5.8–16.7)	9.0 (5.1–15.4)

* Plus–minus values are means ±SD. Baseline variables were compared between the two groups with the use of a two-group t-test, Mann–Whitney tests, and chi-square tests; P values ranged between 0.19 and 0.96. IQR denotes interquartile range.
† Patients could have had more than one first symptom.
‡ Scores on the Unified Parkinson's Disease Rating Scale (UPDRS) range from 0 to 176, with higher scores indicating more severe disease; the scale includes subscales of mental function (Part I), activities of daily living (Part II), and motor function (Part III).
§ Disability was assessed with the use of the Academic Medical Center Linear Disability Score (ALDS), which ranges from 0 to 100, with lower scores indicate greater disability.
¶ Cognitive impairment was assessed with the use of the Mini–Mental State Examination (MMSE); scores range from 0 to 30, with lower scores indicating greater cognitive impairment.
‖ Depression was assessed with the use of the Beck Depression Inventory II (BDI-II); scores range from 0 to 63, with higher scores indicating more severe depressive symptoms.
** Disease-related quality of life was assessed with the use of the Parkinson's Disease Questionnaire-39 (PDQ-39); scores range from 0 to 100, with higher scores indicating a lower disease-related quality of life.

CI, –1.8 to 3.0; P=0.60). The change in the UPDRS score from baseline to week 40 was –3.1±10.2 in the early-start group and 2.0±12.3 in the delayed-start group (difference, –5.1 points; 95% CI, –7.2 to –2.9), favoring the early-start group and reflecting the effect of levodopa on symptoms of the disease. The estimates of the rate of progression of symptoms (the mean change per week in the total UPDRS score) between weeks 4 and 40 (phase 1) showed no significant difference between the early-start group (0.04±0.23 points per week) and the delayed-start group (0.06±0.34 points per week) (estimated difference, –0.02 points; 95% CI, –0.07 to 0.03). The estimates of the rate of change between weeks 44 and 80 (phase 2) were 0.10±0.25 points per week in the early-start group as compared with 0.03±0.28 points per week in the delayed-start group (estimated difference, 0.07 points; 90% CI, 0.03 to 0.10), which did not meet the criterion for noninferiority of early receipt of levodopa to delayed receipt. The results of the per-protocol analyses showed a pattern that was similar to that of the intention-to-treat analyses (Tables S3 and S4 in the Supplementary Appendix). At 80 weeks, the point estimates and confidence intervals suggested no significant differences between the two groups in ALDS, MMSE, BDI-II, and PDQ-39 scores (Table 2). Figure 2 shows the UPDRS and PDQ-39 scores of both groups over the course of the trial.

During the first 40 weeks of the trial, the incidence of nausea was higher in the early-start group than in the delayed start-group (23.0% vs. 14.3%, P=0.02) (Table 3). At 80 weeks, the percentage of patients with motor complications, including dyskinesias and fluctuations in motor response, did not differ significantly between the two groups (Table S5 in the Supplementary Appendix). The results of the other secondary outcomes are shown in the Supplementary Appendix.

DISCUSSION

This randomized trial showed an effect of levodopa on symptoms of Parkinson's disease in the first 40 weeks of the trial (the placebo-controlled phase of the trial) but no significant difference in the UPDRS score at week 80 (with all patients receiving active treatment from week 40 on), which indicates that the severity of parkinsonian symptoms at the end of the trial did not differ significantly between patients who received

Table 2. Primary and Secondary Outcomes.*

Outcome	Early-Start Group (N=207)	Delayed-Start Group (N=210)	Difference between Mean Scores (95% CI)	P Value
Primary outcome: change from baseline to week 80 in UPDRS score				
Baseline	28.0±11.2	29.0±11.8		
Week 80	27.0±14.8	27.0±14.3		
Difference	−1.0±13.1	−2.0±13.0	1.0 (−1.5 to 3.5)	0.44†
Secondary outcome measures‡				
Progression of symptoms, as evaluated by an increase in UPDRS score per week				
Between wk 4 and wk 40	0.04±0.23	0.06±0.34	−0.02 (−0.07 to 0.03)§	
Between wk 44 and wk 80	0.10±0.25	0.03±0.28	0.07 (0.03 to 0.10)¶	
Median disability score at 80 wk, as assessed with the ALDS (IQR)	89.5 (88.7 to 89.5)	89.5 (88.7 to 89.5)	0.10 (−1.21 to 1.41)‖	
Median global cognitive functioning score at 80 wk, as assessed with the MMSE (IQR)	29.0 (28.0 to 30.0)	29.0 (28.0 to 30.0)	0.12 (−0.21 to 0.45)‖	
Median depression score at 80 wk, as assessed with the BDI-II (IQR)	6.0 (3.0 to 10.0)	6.0 (3.0 to 10.0)	0.18 (−0.78 to 1.10)‖	
Median disease-related quality of life at 80 wk, as assessed with the PDQ-39 (IQR)	7.7 (3.2 to 14.7)	8.3 (3.8 to 14.7)	−0.39 (−2.09 to 1.27)‖	

* Plus–minus values are means ±SD.
† The P value was calculated with the use of a two-group t-test.
‡ Because of the lack of a plan for adjustment for multiplicity, the secondary outcomes are presented as point estimates with unadjusted 95% confidence intervals and cannot be used for clinical inferences.
§ The 95% confidence intervals are based on a linear mixed model that included trial group, time (4, 22, and 40 weeks), and an interaction between these two variables. Dependency of repeated measures was taken into account by including a random intercept for each patient, and maximum likelihood was used as the estimation method.
¶ The prespecified noninferiority margin was 0.055 points on the UPDRS. Because of the use of noninferiority testing, a two-sided 90% confidence interval is reported (95% one-sided confidence interval). The confidence interval is based on a linear mixed model that included trial group, time (44, 56, 68, and 80 weeks), and an interaction between these two variables. Dependency of repeated measures was taken into account by including a random intercept for each patient, and maximum likelihood was used as the estimation method.
‖ Values were calculated with the use of the bootstrap method (information on bootstrapping specifications can be found in the Supplementary Appendix).

early initiation of the drug and those who received delayed initiation. These findings imply that levodopa had no disease-modifying effect on Parkinson's disease over the period of the trial. The prespecified analysis of the rate of progression of symptoms in the second part of the trial, which did not show the noninferiority of early initiation to delayed initiation, supports this conclusion. During the first 40 weeks of the trial, nausea was more common among the patients who were receiving levodopa than among those who were receiving placebo, but the incidence of the other adverse events, particularly dyskinesias and levodopa-related motor fluctuations, did not differ significantly between the two groups.

One interpretation of the outcome of the noninferiority analysis during phase 2 of the trial, during which both groups were exposed to levodopa and during which the rate of change in the UPDRS score was faster in the early-start group than in the delayed-start group, is that disease progression was more rapid in the early-start group. However, the lack of a between-group difference at week 80 makes it more likely that the rate of progression differed because the effect of the drug on symptoms of the disease had not yet fully accrued in the delayed-start group at week 44. The slope of UPDRS progression was similar in the two groups from week 56 onward (Fig. 2), which also supports the latter hypothesis.

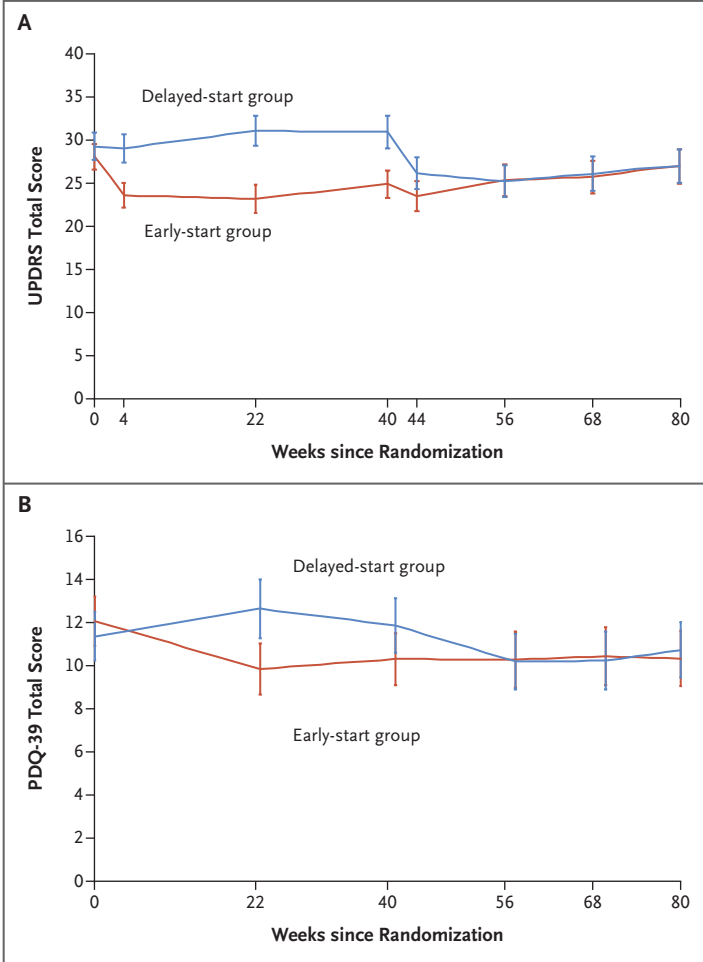

Figure 2. Unified Parkinson's Disease Rating Scale and Parkinson's Disease Questionnaire-39 Scores during the Trial.

The analyses were based on the intention-to-treat population. Mean Unified Parkinson's Disease Rating Scale (UPDRS) total scores (Panel A) and Parkinson's Disease Questionnaire-39 (PDQ-39) scores (Panel B) for each trial group are shown. UPDRS scores range from 0 to 176, with higher scores indicating more severe disease; the scale includes subscales of mental function, activities of daily living, and motor function. PDQ-39 scores range from 0 to 100, with higher scores indicating a lower disease-related quality of life. I bars denote 95% confidence intervals.

The dose of levodopa (100 mg three times per day) in combination with carbidopa (25 mg three times per day) that was used in the trial was chosen as a compromise between higher doses, which are associated with a greater risk of side effects, and lower, less effective doses. In the ELLDOPA trial, levodopa at a dose of 100 mg three times per day in combination with carbidopa at a dose of 25 mg three times per day was in the middle of the range of three doses tested.[4] The choice of 40 weeks as the duration of each phase was the result of two considerations. First, phase 1 had to be long enough to allow any disease-modifying effect of the active drug to become apparent later in the trial. In previous placebo-controlled, delayed-start trials that evaluated early Parkinson's disease, the duration of phase 1 was 26 to 40 weeks.[14-16] Second, the duration of phase 2 had to be long enough for treatment to fully exert an effect on symptoms in the delayed-start group but could not be so long that most patients would be expected to need additional treatment for symptoms.

During phase 1 of the trial (the first 40 weeks), 39% of the patients in the delayed-start group proceeded to receive the phase 2 trial medication (levodopa), and 11% in the early-start group proceeded to open-label treatment with the same dose of levodopa. This resulted in a comparatively shorter mean time that treatment with levodopa could exert a possible disease-modifying effect in the early-start group than in the delayed-start group. However, the results of the per-protocol analyses, which took the switch to levodopa into account, were similar to the results of the intention-to-treat analysis.

In patients with early Parkinson's disease, the clinical diagnosis may be incorrect in up to 15% of patients.[4,17] Confirmatory neuroimaging of the dopamine transporter was not a prerequisite for participation in the trial. However, 22% of the entire cohort had undergone imaging of the dopamine transporter, which confirmed degeneration of substantia nigra neurons, before evaluation for eligibility.

We conclude that treatment with levodopa at a dose of 100 mg three times per day in combination with carbidopa at a dose of 25 mg three times per day had no disease-modifying effect, either beneficial or detrimental, on early Parkinson's disease among patients who were evaluated over the course of 80 weeks. Whether higher doses of the drug, longer periods of administration, or initiation of the drug at later stages of the disease could alter the course of Parkinson's disease warrants evaluation in future trials.

Table 3. Adverse Events, According to Phase and Trial Group.*

Event	Phase 1		Phase 2	
	Early-Start Group, Levodopa (N=222)	Delayed-Start Group, Placebo (N=223)	Early-Start Group, Levodopa (N=211)	Delayed-Start Group, Levodopa (N=215)
Adverse event — no. (%)†				
Nausea	51 (23.0)	32 (14.3)	26 (12.3)	40 (18.6)
Constipation	8 (3.6)	8 (3.6)	5 (2.4)	11 (5.1)
Light-headedness when standing	17 (7.7)	21 (9.4)	12 (5.7)	14 (6.5)
Daytime sleepiness	1 (0.5)	3 (1.3)	4 (1.9)	1 (0.5)
Impulse control disorder	1 (0.5)	0	2 (0.9)	0
Hallucinations	10 (4.5)	14 (6.3)	11 (5.2)	12 (5.6)
Dizziness	33 (14.9)	32 (14.3)	18 (8.5)	22 (10.2)
Tiredness	10 (4.5)	17 (7.6)	10 (4.7)	12 (5.6)
Worsening of parkinsonism	31 (14.0)	41 (18.4)	43 (20.4)	41 (19.1)
Depression	4 (1.8)	3 (1.3)	7 (3.3)	5 (2.3)
Pain	9 (4.1)	2 (0.9)	7 (3.3)	5 (2.3)
Falls	7 (3.2)	6 (2.7)	7 (3.3)	8 (3.7)
Greasy skin	23 (10.4)	23 (10.3)	15 (7.1)	12 (5.6)
Headache	3 (1.4)	9 (4.0)	4 (1.9)	8 (3.7)
Upper respiratory tract infection	3 (1.4)	8 (3.6)	8 (3.8)	5 (2.3)
Serious adverse event — no. of events‡				
Nausea	1	0	1	0
Orthostatic hypotension	0	1	1	0
Hallucinations	0	0	0	1
Falls	0	0	0	2
Falls with bone fracture	0	2	1	1
Cardiac arrhythmia	2	0	1	2
Myocardial infarction	1	1	1	1
Transient ischemic attack or stroke	1	3	1	3
Cancer other than melanoma	1	0	1	2
Melanoma	0	0	0	1
Surgery not related to Parkinson's disease (e.g., knee or cataract surgery)	5	8	6	4
Infection (e.g., urinary tract infection or pneumonia)	0	1	0	1
Pulmonary embolism	0	1	0	1

* For patients who proceeded to receive the trial regimen of phase 2 before week 40, adverse events that occurred before the switch were included in phase 1 for the analysis; adverse events that occurred after the switch were included in phase 2. Variables were compared between the two groups for the same phase with the use of chi-square tests; P values ranged between 0.02 and 0.99. The only significant difference observed between the early-start group (levodopa) and the delayed-start group (placebo) was the incidence of nausea during phase 1 (P=0.02).

† Included are adverse events that occurred in more than 3% of the patients in either group in either phase of the trial and adverse events of special interest (e.g., daytime sleepiness or impulse control disorder).

‡ An adverse event was categorized as a serious adverse event if it resulted in a visit to the emergency department, hospitalization, or persistent disability or death.

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

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APPENDIX

The authors' full names and academic degrees are as follows: Constant V.M. Verschuur, M.D., Sven R. Suwijn, M.D., Judith A. Boel, Ph.D., Bart Post, M.D., Ph.D., Bas R. Bloem, M.D., Ph.D., Johannes J. van Hilten, M.D., Ph.D., Teus van Laar, M.D., Ph.D., Gerrit Tissingh, M.D., Ph.D., Alexander G. Munts, M.D., Ph.D., Guenther Deuschl, M.D., Anthony E. Lang, M.D., Marcel G.W. Dijkgraaf, Ph.D., Rob J. de Haan, Ph.D., and Rob M.A. de Bie, M.D., Ph.D.

The authors' affiliations are as follows: the Department of Neurology, Amsterdam Neuroscience (C.V.M.V., S.R.S., J.A.B., R.M.A.B.), Clinical Epidemiology, Biostatistics, and Bioinformatics (M.G.W.D.), and the Clinical Research Unit (R.J.H.), Amsterdam UMC, University of Amsterdam, AMC, Amsterdam, the Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Nijmegen (B.P., B.R.B.), the Department of Neurology, Leiden University Medical Center, Leiden (J.J.H.), the Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen (T.L.), the Department of Neurology, Zuyderland Medical Center, Heerlen (G.T.), and the Department of Neurology, Spaarne Gasthuis, Haarlem (A.G.M.) — all in the Netherlands; the Department of Neurology, University Medical Center Schleswig-Holstein, Kiel, Germany (G.D.); and the Edmond J. Safra Program in Parkinson's Disease and Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University of Toronto, Toronto (A.E.L.).

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