ORIGINAL ARTICLE

# Trial of Deferiprone in Parkinson's Disease

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## ABSTRACT

### BACKGROUND

Iron content is increased in the substantia nigra of persons with Parkinson's disease and may contribute to the pathophysiology of the disorder. Early research suggests that the iron chelator deferiprone can reduce nigrostriatal iron content in persons with Parkinson's disease, but its effects on disease progression are unclear.

### METHODS

We conducted a multicenter, phase 2, randomized, double-blind trial involving participants with newly diagnosed Parkinson's disease who had never received levodopa. Participants were assigned (in a 1:1 ratio) to receive oral deferiprone at a dose of 15 mg per kilogram of body weight twice daily or matched placebo for 36 weeks. Dopaminergic therapy was withheld unless deemed necessary for symptom control. The primary outcome was the change in the total score on the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS; range, 0 to 260, with higher scores indicating more severe impairment) at 36 weeks. Secondary and exploratory clinical outcomes at up to 40 weeks included measures of motor and nonmotor disability. Brain iron content measured with the use of magnetic resonance imaging was also an exploratory outcome.

### RESULTS

A total of 372 participants were enrolled; 186 were assigned to receive deferiprone and 186 to receive placebo. Progression of symptoms led to the initiation of dopaminergic therapy in 22.0% of the participants in the deferiprone group and 2.7% of those in the placebo group. The mean MDS-UPDRS total score at baseline was 34.3 in the deferiprone group and 33.2 in the placebo group and increased (worsened) by 15.6 points and 6.3 points, respectively (difference, 9.3 points; 95% confidence interval, 6.3 to 12.2; P<0.001). Nigrostriatal iron content decreased more in the deferiprone group than in the placebo group. The main serious adverse events with deferiprone were agranulocytosis in 2 participants and neutropenia in 3 participants.

### CONCLUSIONS

In participants with early Parkinson's disease who had never received levodopa and in whom treatment with dopaminergic medications was not planned, deferiprone was associated with worse scores in measures of parkinsonism than those with placebo over a period of 36 weeks. (Funded by the European Union Horizon 2020 program; FAIRPARK-II ClinicalTrials.gov number, NCT02655315.)

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A Quick Take is available at NEJM.org

Parkinson's disease is a neurodegenerative disorder characterized by loss of dopamine neurons in the substantia nigra and widespread accumulation of misfolded α-synuclein and Lewy bodies in the central and peripheral autonomic nervous system.[1] Increased iron content in nigrostriatal neurons has been implicated in the pathophysiology of Parkinson's disease, although iron also has desired physiological effects as a cofactor for tyrosine hydroxylase activity. It is involved in dopamine synthesis, dopamine metabolism,[2-5] mitochondrial oxidative phosphorylation, and oxygen transport. Iron accumulation may also cause oxidative stress and initiate cell-death mechanisms.[6-8] Iron chelation inhibits cell death and is efficacious in models of Parkinson's disease.[2-5,9]

Deferiprone is an iron chelator used for transfusion-dependent thalassemia at daily doses of 100 mg per kilogram of body weight and is able to cross the blood–brain barrier.[9-11] Deferiprone at a conservative daily dose of 30 mg per kilogram has been tested for its effects on brain iron content in persons with Parkinson's disease receiving conventional dopaminergic symptomatic therapy. A small, placebo-controlled pilot trial with a delayed-start design showed that deferiprone reduced iron accumulation as measured by magnetic resonance imaging (MRI) and may have improved motor disability scores as compared with placebo.[9] Lower brain iron was also observed in a small proportion of participants in another pilot randomized, placebo-controlled trial of deferiprone, but there was no effect on Parkinson motor scores.[12]

We report the results of FAIRPARK-II, a phase 2 randomized, placebo-controlled trial that evaluated the efficacy and safety of deferiprone in persons with newly diagnosed Parkinson's disease who had not yet been treated with dopaminergic drugs.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

This was an investigator-initiated, multicenter, international trial conducted at 23 sites (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was supported by the European Union Horizon 2020 funding program, through the FAIR PARK II network (www.fairpark2.eu), with the support of the French NS-Park/FCRIN network (https://parkinson.network/en), in collaboration with ApoPharma and Chiesi, which provided deferiprone and placebo but otherwise had no role in the design of the trial, the analysis or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. The first and last authors were primarily responsible for writing the initial manuscript. An independent data and safety monitoring board reviewed safety data throughout the trial. Statistical analyses were independently performed by members of the Department of Biostatistics, Lille University Hospital, France (second and fifth authors). All the authors vouch for the completeness and accuracy of the data, the adherence of the trial to the protocol (available at NEJM.org), and the reporting of all adverse events.

The trial protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (https://www.spirit-statement.org/). The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. Ethics committees in each country approved the conduct of the trial. All the participants provided written informed consent before screening, including knowledge of the plan to withhold dopaminergic medication unless necessary.

### TRIAL PARTICIPANTS

The trial enrolled men and women 18 years of age or older, who had received a diagnosis of clinically probable Parkinson's disease according to the Movement Disorder Society Clinical Diagnostic Criteria[13] less than 18 months earlier. Participants had never received any dopaminergic therapy (e.g., levodopa, dopamine agonists, monoamine oxidase type B inhibitors, or anticholinergic agents). An inclusion criterion was that, on the basis of the investigators' judgment, participants were early enough in the disease and were affected mildly enough that they would be likely to complete the 9-month trial without symptomatic treatment. Exclusion criteria were cognitive impairment (Mini–Mental State Examination score of ≤24; range, 3 to 30, with lower scores indicating greater cognitive impairment), anemia, depression, a body weight

of more than 130 kg, and a known risk of agranulocytosis.

### TRIAL INTERVENTIONS AND PROCEDURES

Administration of deferiprone or placebo was centrally randomized with block randomization (block size of four) and stratified according to center in a 1:1 ratio from a list generated by the statistics department at Lille University Hospital. The randomization list was sent to an independent clinical research organization (Abplus, France) for allocation of deferiprone or placebo through an interactive Web-response system. The participants, caregivers, trial staff, investigators, and data analysts were unaware of the trial-group assignments.

The active molecule 3-hydroxy-1,2-dimethylpyridine-4-one (deferiprone) is a bidentate iron chelator that binds iron in a 3:1 molar ratio. Participants received 600-mg delayed-release tablets of deferiprone at a dose of 15 mg per kilogram twice daily or matching oral placebo twice daily for 36 weeks, followed by 4 weeks of monitoring after the treatment period.

Participants were evaluated at the time of screening, at baseline, and at 12, 24, 36, and 40 weeks. Three comprehensive examinations, with assessment of all primary and secondary outcomes, were performed at the randomization visit, week 36 (primary outcome), and week 40 (after completion of medication washout). At 12 and 24 weeks, we assessed the MDS-UPDRS total score and checked all safety criteria.

In a subgroup of participants from 10 selected centers that conducted quantitative MRI of the nigrostriatal pathway, iron content on T2* sequence and atrophy on three-dimensional T1 sequence were obtained at baseline and at 36 weeks.[9,12,14] The main results are given as milliseconds of relaxation time on the T2* sequence, with higher numbers reflecting a greater reduction in iron content. To monitor the effect of deferiprone on presynaptic dopaminergic neuronal density in the same subgroup, the density of dopamine transporter (DaT) was quantified with single-photon-emission computed tomographic (SPECT) DaT imaging.[15,16] The DaT binding potentials of $^{123}$I-ioflupane–labeled N-(3-fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl) nortropane ($^{123}$I-FP-CIT) were quantified at baseline and at 40 weeks (i.e., 4 weeks after deferipone or placebo was discontinued). This measurement was obtained after medication washout because of concerns that iron chelation could directly and acutely modulate DaT-1 levels.[15] Changes in the volume of brain structures were measured with the three-dimensional T1-weighted MRI sequence. A surrogate peripheral biomarker of iron was assessed in all the participants by measurement of serum ferritin levels with the Meso Scale Discovery R-PLEX Human Ferritin assay. To estimate the effects of both interventions on dopamine metabolism, we measured serum prolactin (a marker of inhibition of dopamine synthesis) with the use of a chemiluminescence immunoassay; this was an unplanned analysis, which was added in view of the clinical results. All MRI and SPECT DaT acquisition and reconstruction variables were harmonized with the use of the CATI (Centre pour l'Acquisition et le Traitement des Images) platform (https://cati-neuroimaging.com) and assessed systematically in the 10 selected trial sites, which together enrolled a minimum of 150 participants (see the Supplementary Appendix).

### OUTCOMES

The primary outcome was the change from baseline to week 36 in the MDS-UPDRS total score, a four-part score (parts I through IV) that includes subscales of mental function, activities of daily living, and motor function (total range, 0 to 260, with higher scores indicating more severe impairment).[17] Secondary efficacy outcomes were the changes in the score on MDS-UPDRS part II (motor aspects of experiences of daily living), the score on part III (motor symptoms), and the sum of scores on parts II and III between baseline and 36 weeks or 40 weeks. Exploratory clinical outcomes between baseline and 36 or 40 weeks included the change in the score on MDS-UPDRS part I (nonmotor symptoms); gait and balance, both examined with the timed stand–walk–sit test (7-m distance); the overall cognitive status, measured with the Montreal Cognitive Assessment (MoCA), version 7 (scores range from 3 to 30, with higher scores indicating better cognition)[18]; and disease-related quality of life as assessed by the 39-item Parkinson's Disease Questionnaire (PDQ-39; scores range from 0 to 100, with higher scores indicating a worse disease-related quality of life).[19]

Other exploratory outcomes included target engagement with iron by deferiprone in the sub-

stantia nigra and striatum (T2* sequence), changes in brain-structure volume (three-dimensional T1 sequence), serum ferritin levels, the density of DaT quantified with SPECT DaT, and serum prolactin levels (see the Supplementary Appendix). To assess safety, a complete blood count with absolute neutrophil count, hemoglobin, hematocrit, and red-cell count was measured weekly (±3 days) from the start of deferiprone or placebo for 24 weeks and then monthly until week 40.[20]

### STATISTICAL ANALYSIS

On the basis of an expected mean difference of 3 points favoring deferiprone in the change in the MDS-UPDRS total score from baseline at 36 weeks (as reported in a trial of rasagiline involving persons with Parkinson's disease[21]), a standard deviation of 9.0, and a 23% dropout rate, we calculated that 372 participants in total (186 per group) would be sufficient to show superiority of deferiprone over placebo, with a statistical power of 80%. Efficacy analyses involved all randomly assigned participants in their assigned group according to the intention-to-treat principle with the use of a two-sided test with a significance level of 0.05. The results for the primary efficacy outcome in the deferiprone and placebo groups were compared with the use of the constrained longitudinal data analysis (cLDA) model (changed before the database was locked from analysis of covariance [ANCOVA] in the original protocol) including site as a random effect, from which the baseline-adjusted mean difference at 36 weeks was estimated with a 95% confidence interval as a measure of treatment effect.[22] All secondary and exploratory outcomes were also analyzed with the use of the cLDA model; in cases of deviation from normality and when logarithmic transformation could not be applied, the absolute changes between baseline and the follow-up time point of interest were calculated and compared between the two groups with the use of nonparametric ANCOVA adjusted for baseline values (standardized difference and 95% confidence interval).

For all clinical outcomes, primary efficacy analyses were performed after multiple imputation for missing values, including for participants who withdrew from the trial, with imputation under a missing-at-random assumption, with the use of trial group and the main baseline characteristics. Imputation was performed with the use of a regression-switching approach (chained equations, m=20 imputations), with a predictive mean matching method for quantitative variables and logistic-regression models (binomial, ordinal, or multinomial) for categorical variables.[23] Treatment-effect estimates that were obtained in multiple imputed datasets were to be combined with the use of Rubin's rules.[24,25] Two sensitivity analyses were performed, first by restricting the analysis to available data and second by imputing missing outcome values with the use of the last observation carried forward. For per-protocol analyses of the primary outcome, leave-one-out site analysis (an unplanned analysis to assess the site effect) and prespecified subgroup analyses were performed. An exploratory analysis was performed to estimate and compare the slope of evolution in MDS-UPDRS total scores with the use of a linear mixed model with random coefficients. For unplanned analyses, we estimated the cumulative incidence of adverse events and dropouts for aggravation of Parkinson's disease using the Kaplan–Meier method and comparing deferiprone with placebo by means of the Cox proportional-hazards model (hazard ratio) after checking the proportionality assumption using Schoenfeld residual plots. Details are provided in the statistical analysis plan, available with the protocol at NEJM.org. Because there was no plan for adjustment of the widths of confidence intervals for multiple comparisons of secondary outcomes, P values are not reported and no definite conclusions can be drawn from these results. Data were analyzed with the use of SAS software, release 9.4 (SAS Institute).

## RESULTS

### TRIAL PARTICIPANTS

From February 2016 through December 2019, a total of 411 persons with Parkinson's disease who had never received dopaminergic drugs were screened, of whom 372 were enrolled; 186 were assigned to receive deferiprone and 186 to receive placebo (Fig. 1). Participants had a median of 419 days (interquartile range, 266 to 631) since the first subjective motor symptom of Parkinson's disease and 102 days (interquartile range, 49 to 190) since formal diagnosis. A total of 118 (63.4%) of the participants in the deferi-

prone group and 165 (88.7%) in the placebo group completed the trial at week 36. One participant in the placebo group died by suicide. A total of 41 participants (22.0%) in the deferiprone group and 5 (2.7%) in the placebo group withdrew from the trial because of disease progression that warranted dopaminergic therapy. A total of 13 participants in the deferiprone group and 6 in the placebo group withdrew because of adverse events. Therefore, imputation of the primary-outcome result was required for 54 participants in the deferiprone group and 11 in the placebo group. The demographic and clinical characteristics of the participants at baseline were similar in the two trial groups except for a slightly longer disease duration in the deferiprone group (Table 1). The representativeness of the trial population with respect to the population of persons with Parkinson's disease is described in Table S8 in the Supplementary Appendix.

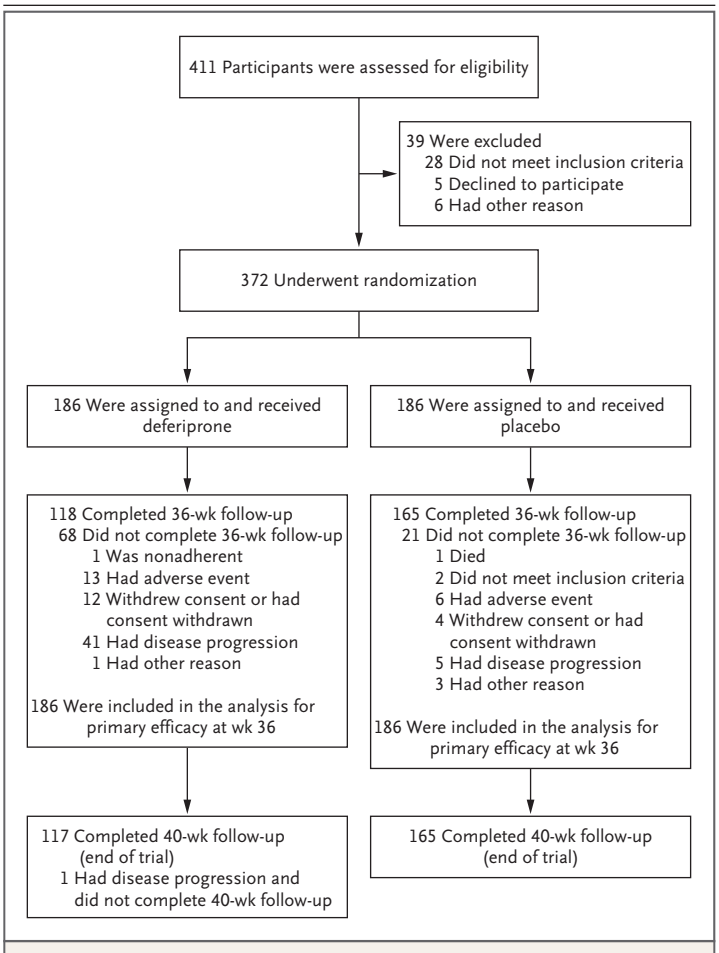


**Figure 1. Screening, Randomization, and Follow-up.**

### PRIMARY OUTCOME

The mean MDS-UPDRS total score increased (worsened) from baseline to week 36 by 15.6 points with deferiprone as compared with 6.3 points with placebo (difference, 9.3 points; 95% confidence interval, 6.3 to 12.2; P<0.001). The intention-to-treat analysis, available-data analysis, and per-protocol analysis yielded similar differences in favor of placebo at week 36 and at week 40 (Table 2; Tables S1, S2, and S3; and Fig. S1A). No effect according to trial site was observed (Fig. S2). There was no apparent influence of age, sex, total disability, or level of iron in the nigrostriatal pathway at baseline on these results (Fig. S3).

### SECONDARY AND EXPLORATORY CLINICAL OUTCOMES

Between-group differences for the change from baseline in the scores on MDS-UPDRS part I, II, and III, the sum of scores on parts II and III, and the PDQ-39 score were numerically higher (worse) in the deferiprone group than in the placebo group (Table 2 and Table S2). The results for the stand–walk–sit test and the MoCA were similar in the two groups (Table S4). After a 4-week washout period between weeks 36 and 40, the directions of differences between trial groups in primary or secondary outcome measures were generally similar to those in the primary analysis (Tables S3 and S4).

### EXPLORATORY IMAGING OUTCOMES

Levels of iron in the brain were analyzed by means of imaging in 78 participants in the deferiprone group and 70 in the placebo group. Brain MRI showed a greater decrease from baseline in iron content in the deferiprone group than in the placebo group, as reflected by a standardized difference of medians in the substantia nigras of 0.41 msec (right) and 0.23 msec (left). The results for the putamen and caudate nuclei are shown in Table 3. The median volumes of the left and right putamen and right caudate nucleus decreased with placebo but increased with deferiprone (Table 3, Table S5, and Fig. S4). No inverse correlation was observed between brain-structure volumes and iron content in the left and right putamen and caudate nucleus (unplanned analysis). Iron content or volume measured outside the nigrostriatal path-

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

| Characteristics | Deferiprone (N = 186) | Placebo (N = 186) |
|---|---|---|
| Age — yr | 62.0±10.1 | 62.9±9.2 |
| Sex — no. (%) | | |
| Male | 115 (61.8) | 119 (64.0) |
| Female | 71 (38.2) | 67 (36.0) |
| Median disease duration since first symptoms (IQR) — days† | 443 (268–663) | 390 (265–573) |
| Median disease duration since diagnosis (IQR) — days | 109.5 (53–187) | 101 (42–191) |
| MDS-UPDRS total score‡ | 34.3±14.0 | 33.2±12.9 |
| Score on MDS-UPDRS part I§ | 6.3±4.5 | 5.9±4.3 |
| Score on MDS-UPDRS part II¶ | 6.0±4.1 | 5.4±4.1 |
| Score on MDS-UPDRS part III‖ | 22.0±9.3 | 21.9±9.3 |
| Sum of scores on MDS-UPDRS parts II and III | 28.0±11.7 | 27.3±11.0 |
| Stand–walk–sit test** | | |
| Median time (IQR) — sec†† | 11.5 (9.5–14.0) | 11 (9.0–13.5) |
| Median no. of steps (IQR)‡‡ | 20 (14–22) | 18 (13–21) |
| PDQ-39 score§§ | 20.5±16.0 | 20.2±16.6 |
| MoCA score¶¶ | 27.0±2.7 | 27.0±2.7 |

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Data were missing for 2 participants in the deferiprone group.
‡ Total scores on the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS, parts I through IV) range from 0 to 260, with higher scores indicating more severe impairment.
§ Scores on MDS-UPDRS part I range from 0 to 52, with higher scores indicating more severe impairment in nonmotor aspects of daily living.
¶ Scores on MDS-UPDRS part II range from 0 to 52, with higher scores indicating more severe impairment in motor aspects of daily living.
‖ Scores on MDS-UPDRS part III range from 0 to 132, with higher scores indicating more severe impairment on a clinician-conducted motor examination.
** The test involves standing from a seated position, walking 7 meters, and returning to sit down.
†† Data were missing for 9 participants in the deferiprone group and 13 in the placebo group.
‡‡ Data were missing for 15 participants in the deferiprone group and 16 in the placebo group.
§§ Scores on the 39-item Parkinson's Disease Questionnaire (PDQ-39) range from 0 to 100, with higher scores indicating a lower disease-related quality of life. Data were missing for 9 participants in the deferiprone group and 10 in the placebo group.
¶¶ Scores on the Montreal Cognitive Assessment (MoCA) range from 3 to 30, with higher scores indicating better cognition.

way was similar in the two trial groups (Table S6). At week 40, no meaningful between-group difference was observed in the change in the DaT binding potentials in the posterior putamen and in the anterior putamen and caudate nucleus (Table 3 and Table S7). Plasma ferritin levels decreased more with deferiprone than with placebo, whereas plasma prolactin levels increased more with deferiprone than with placebo (Table 3).

### SAFETY

A total of 9.7% of the participants in the deferiprone group and 4.8% of those in the placebo group had serious adverse events, including agranulocytosis in 2 participants and neutropenia in 3 participants in the deferiprone group (Table 4). A total of 87.1% of the participants in the deferiprone group and 80.1% of those in the placebo group reported one or more adverse events during the trial. Adverse events unrelated to Parkinson's disease, with an incidence of 5.0% or more in either group, were generally similar in frequency in the two groups. However, general disorders (including fatigue) and psychiatric disorders were more frequently reported with deferiprone than with placebo, whereas musculoskeletal disorders were numerically fewer with deferiprone than with placebo. Two cases of transient anemia were reported in the deferiprone group, one related to thalassemia minor and the

**Table 2. Primary, Secondary, and Exploratory Clinical Outcomes (Intention-to-Treat Population).***

| Outcome | Deferiprone (N=186) | Placebo (N=186) | Mean Adjusted Difference (95% CI)† |
|---|---|---|---|
| **Primary outcome** | | | |
| MDS-UPDRS total score | | | |
| Value at wk 36 | 50.7±23.4 | 39.6±17.7 | |
| Change from baseline (95% CI) | 15.6 (13.5 to 17.6)† | 6.3 (4.2 to 8.4)† | 9.3 (6.3 to 12.2)‡ |
| **Secondary outcomes§** | | | |
| Score on MDS-UPDRS part III | | | |
| Value at wk 36 | 31.8±14.0 | 25.9±11.7 | |
| Change from baseline (95% CI) | 9.8 (8.2 to 11.3)† | 4.0 (2.7 to 5.3)† | 5.8 (3.8 to 7.7) |
| Score on MDS-UPDRS part II | | | |
| Value at wk 36 | 10.2±7.7 | 7.1±5.4 | |
| Change from baseline (95% CI) | 4.2 (3.4 to 5.1)† | 1.8 (1.0 to 2.6)† | 2.5 (1.3 to 3.6) |
| Sum of scores on MDS-UPDRS parts II and III | | | |
| Value at wk 36 | 42.2±18.8 | 33.1±15.0 | |
| Change from baseline (95% CI) | 14.2 (12.2 to 16.1)† | 5.9 (4.1 to 7.6)† | 8.3 (5.7 to 10.8) |
| **Exploratory clinical outcome§** | | | |
| Score on MDS-UPDRS part I | | | |
| Value at wk 36 | 8.2±5.9 | 6.2±4.6 | |
| Change from baseline (95% CI) | 2.0 (1.3 to 2.7)† | 0.2 (–0.4 to 0.9)† | 1.8 (0.8 to 2.8) |

* Plus–minus values are means ±SD. Higher total scores on the MDS-UPDRS and higher scores on MDS-UPDRS parts I, II, and III indicate worse performance. CI denotes confidence interval.
† Adjusted means and 95% confidence intervals were estimated from the constrained longitudinal data analysis (cLDA) model with the use of baseline, 12-week, 24-week, 36-week, and 40-week values and with site included as a random effect, after missing values were handled by means of multiple imputation.
‡ P<0.001.
§ Because there was no plan for correction of the widths of confidence intervals for multiple comparisons, no definite inferences can be made from these results.

other related to upper gastrointestinal hemorrhage. Transient and mild neutropenia was reported in 3.2% of the participants in the deferiprone group and in 3.8% of those in the placebo group.

Progression of Parkinson's disease was reported as a serious adverse event in two participants in the deferiprone group. Progression of Parkinson's disease was reported as an adverse event in 45 participants (24.2%) in the deferiprone group and 13 (7.0%) in the placebo group (Table 4 and Fig. S1B).

## DISCUSSION

This 36-week phase 2, randomized, placebo-controlled trial showed that deferiprone did not slow the progression of Parkinson's disease in participants who had never received levodopa. To the contrary, deferiprone was associated with worsening of motor and nonmotor symptoms over a period of 36 weeks. Neuroimaging findings in a subgroup of participants showed target engagement of deferiprone with a greater reduction of iron content in nigrostriatal pathways, and particularly in the substantia nigras, than with placebo. These findings were paradoxically associated with decreased basal ganglia volume in the placebo group and increased volume in the deferiprone group and a lack of between-group differences on DaT imaging.

The apparent detrimental clinical effects of deferiprone on symptoms of Parkinson's disease became evident as more participants in the deferiprone group than in the placebo group discontinued the trial agent and wished to start dopaminergic therapy owing to disease progression, and by the visual inspection of graphs of MDS-UPDRS scores at the first scheduled visit at

**Table 3. MRI, Dopamine Transporter (DaT) Imaging, and Biologic Exploratory Outcomes.**

| Variable | Deferiprone (N=70) | Placebo (N=78) | Difference in Change from Baseline (95% CI)* |
|---|---|---|---|
| Median change from baseline to wk 36 on T2*-weighted MRI sequences (IQR) — msec | | | |
| Right putamen | 0.7 (–0.4 to 1.6) | 0.1 (–0.9 to 1.0) | 0.47 (0.15 to 0.79) |
| Left putamen | 0.5 (–0.2 to 1.4) | –0.1 (–0.9 to 0.7) | 0.60 (0.29 to 0.92) |
| Right caudate nucleus | 0.6 (–0.3 to 1.1) | –0.1 (–1.0 to 0.9) | 0.34 (0.03 to 0.65) |
| Left caudate nucleus | 0.6 (–0.7 to 1.6) | –0.3 (–1.4 to 1.3) | 0.35 (0.06 to 0.63) |
| Right substantia nigra | 1.8 (0.2 to 3.6) | 0.0 (–2.1 to 2.6) | 0.41 (0.10 to 0.72) |
| Left substantia nigra | 1.1 (–0.9 to 2.9) | 0.6 (–1.4 to 2.4) | 0.23 (–0.08 to 0.54) |
| Median change from baseline to wk 36 in MRI volumes (IQR) — $mm^3$ | | | |
| Right putamen | 29.8 (3.5 to 56.1) | –15.6 (–40.5 to 9.3) | 45.4 (9.1 to 81.8) |
| Left putamen | 36.3 (10.0 to 62.5) | –13.0 (–37.9 to 11.8) | 49.3 (13.2 to 85.4) |
| Right caudate nucleus | 17.2 (–5.9 to 40.4) | –29.0 (–51.0 to –7.2) | 46.2 (14.3 to 78.2) |
| Left caudate nucleus | 3.6 (–19.0 to 26.3) | –20.2 (–41.6 to 1.3) | 23.8 (–7.4 to 55.0) |
| Right substantia nigra | 2.0 (–0.3 to 4.3) | –0.1 (–2.3 to 2.1) | 2.08 (–1.03 to 5.18) |
| Left substantia nigra | 1.4 (–1.3 to 4.2) | 2.5 (–1.0 to 5.1) | –1.05 (–4.75 to 2.65) |
| Median change from baseline to wk 40 in DaT binding potentials (IQR) | | | |
| Right posterior putamen | –0.01 (–0.09 to 0.07) | –0.03 (–0.11 to 0.04) | 0.03 (–0.08 to 0.13) |
| Left posterior putamen | –0.10 (–0.17 to –0.03) | –0.07 (–0.13 to –0.01) | –0.03 (–0.12 to 0.07) |
| Right anterior putamen | –0.20 (–0.35 to –0.07) | –0.12 (–0.25 to 0.01) | –0.08 (–0.27 to 0.11) |
| Left anterior putamen | –0.02 (–0.14 to 0.09) | –0.07 (–0.18 to 0.03) | 0.05 (–0.10 to 0.20) |
| Right caudate nucleus | –0.05 (–0.13 to 0.04) | –0.04 (–0.12 to 0.04) | 0.00 (–0.11 to 0.11) |
| Left caudate nucleus | –0.10 (–0.22 to 0.02) | –0.04 (–0.16 to 0.07) | –0.05 (–0.21 to 0.11) |
| Median change from baseline to wk 36 in blood ferritin level (IQR) — ng/ml | –0.65 (–0.76 to –0.55) | –0.17 (–0.28 to –0.06) | –0.48 (–0.63 to –0.33) |
| Mean change from baseline to wk 36 in blood prolactin level (95% CI) — ng/ml† | 1.41 (1.25 to 1.58) | 1.09 (0.97 to 1.23) | 1.29 (1.10 to 1.52) |

* Differences were adjusted for baseline value. Standardized differences and 95% confidence intervals are shown for the MRI variables; these values were calculated on the basis of rank-transformed data. Adjusted mean differences and 95% confidence intervals are shown for the other variables; these values were estimated from the cLDA model with the use of baseline and follow-up values (at 36 or 40 weeks, according to the trial variable) and with site included as a random effect."

† Values were calculated after a back-transformation was applied on log-transformed values. As the T2* value decreases, the iron load increases.

month 3, but no formal analysis of this time course was carried out. We speculate that the early separation of curves in favor of the placebo group may be consistent with a negative symptomatic effect of deferiprone rather than an accelerating effect on underlying disease progression. This conjecture is based on chelation of brain iron by deferiprone that presumably reduced activity of tyrosine hydroxylase, the rate-limiting enzyme for dopamine production, which is consistent with the increased levels of plasma prolactin, an inhibitor of which is dopamine. Had there been a reduction in the difference in outcomes between the two trial groups after discontinuation of deferiprone between weeks 36 and 40, a putative negative symptomatic effect would have been supported, but this was not observed, possibly because it takes more than 4 weeks to recharge the nigrostriatal pathway with iron as a compensatory mechanism to ensure dopamine synthesis.

Hematologic risks of deferiprone at the low

**Table 4. Summary of Adverse Events That Occurred during the 40-Week Trial Period.***

| Variables | Deferiprone (N=186) | Placebo (N=186) |
|---|---|---|
| No. of distinct events: adverse events and serious adverse events | 602 | 543 |
| ≥1 Adverse event — no. (%) | 162 (87.1) | 149 (80.1) |
| ≥1 Serious adverse event — no. (%) | 18 (9.7) | 9 (4.8) |
| Serious adverse events — no. (%) | | |
| Death by suicide | 0 | 1 (0.5) |
| Blood and lymphatic disorders | 5 (2.7) | 1 (0.5) |
| Agranulocytosis | 2 (1.1) | 0 |
| Neutropenia | 3 (1.6) | 1 (0.5) |
| Cardiac disorders | 0 | 1 (0.5) |
| Gastrointestinal disorders | 2 (1.1) | 1 (0.5) |
| Injury, poisoning, and procedural complications | 1 (0.5) | 1 (0.5) |
| Musculoskeletal and connective-tissue disorders | 1 (0.5) | 0 |
| Neoplasms: benign, malignant, and unspecified | 2 (1.1) | 0 |
| Psychiatric disorders, except suicide | 3 (1.6) | 1 (0.5) |
| Renal and urinary disorders | 0 | 2 (1.1) |
| Respiratory, thoracic, and mediastinal disorders | 1 (0.5) | 0 |
| Surgical and medical procedures | 2 (1.1) | 2 (1.1) |
| Adverse events with 5% incidence in either group — no. (%) | | |
| General disorders and administration-site conditions | 59 (31.7) | 36 (19.4) |
| Fatigue | 46 (24.7) | 21 (11.3) |
| Infections and infestations† | 46 (24.7) | 46 (24.7) |
| Nervous system disorders, except Parkinson's disease | 44 (23.7) | 46 (24.7) |
| Gastrointestinal disorders | 43 (23.1) | 40 (21.5) |
| Psychiatric disorders | 39 (21.0) | 30 (16.1) |
| Musculoskeletal and connective-tissue disorders | 38 (20.4) | 56 (30.1) |
| Injury, poisoning, and procedural complications | 22 (11.8) | 21 (11.3) |
| Investigations‡ | 18 (9.7) | 11 (5.9) |
| Skin and subcutaneous-tissue disorders | 16 (8.6) | 11 (5.9) |
| Respiratory, thoracic, and mediastinal disorders | 15 (8.1) | 16 (8.6) |
| Blood and lymphatic disorders | 11 (5.9) | 8 (4.3) |
| Neutropenia | 6 (3.2) | 7 (3.8) |
| Anemia | 2 (1.1)§ | 0 |
| Eye disorders | 10 (5.4) | 8 (4.3) |
| Progression of Parkinson's disease — no. (%) | | |
| Worsening of Parkinson's disease as serious adverse event | 2 (1.1) | 0 |
| Worsening of Parkinson's disease as adverse event | 45 (24.2) | 13 (7.0) |
| Worsening of tremor as adverse event | 17 (9.1) | 14 (7.5) |
| Discontinuation of deferiprone or placebo owing to disease progression — no. (%) | 42 (22.6) | 5 (2.7) |
| Delay of <60 days | 6 (3.2) | 0 |
| Delay of 60–275 days: during 9-mo treatment period | 36 (19.4) | 5 (2.7) |
| Delay of >275 days: after treatment period | 0 | 0 |

* Details on the management of serious adverse events and adverse events are provided in the Supplementary Appendix.
† Infections and infestations included nasopharyngitis, bronchitis, urinary infections, influenzae, and gastroenteritis.
‡ Examples are laboratory tests and radiologic studies.
§ One case was related to thalassemia minor, and the other case was related to upper digestive hemorrhage.

doses used in the trial were evident in 5% or fewer of the participants. Normal iron levels in red cells (i.e., mild reduction of the iron-storage marker ferritin without anemia) and iron levels that were reduced only in the nigro-striatal pathway showed conservation of systemic iron despite chelation.[9-11]

This trial has limitations. The results and their interpretation should be viewed in the context of our hypothesis that deferiprone would be superior to placebo in clinical outcomes, and we found the opposite. There was also a need for imputation of a large amount of clinical outcome data owing to participant dropout, particularly in the deferiprone group, and a lack of racial diversity. Whether participants receiving dopaminergic therapy would have a different outcome remains unclear, but in trials of deferiprone involving a total of approximately 240 participants who were receiving dopaminergic therapy, no worsening in scores of Parkinson's disease activity was observed with this agent, and some participants even had improvement in such scores.

Despite evidence of target engagement of iron reduction in the substantia nigra of participants with Parkinson's disease who had never received levodopa and in whom treatment with a dopamine agonist was not planned, deferiprone was not associated with benefit as compared with placebo in measures of the progression of Parkinson's disease, and there was evidence of clinical worsening. Deferiprone was associated with adverse events.

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## APPENDIX

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## REFERENCES

**1.** Rocca WA. The burden of Parkinson's disease: a worldwide perspective. Lancet Neurol 2018;17:928-9.
**2.** Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L. The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol 2014;13:1045-60.
**3.** Moreau C, Duce JA, Rascol O, et al. Iron as a therapeutic target for Parkinson's disease. Mov Disord 2018;33:568-74.
**4.** Masaldan S, Bush AI, Devos D, Rolland AS, Moreau C. Striking while the iron is hot: iron metabolism and ferroptosis in neurodegeneration. Free Radic Biol Med 2019;133:221-33.
**5.** Devos D, Cabantchik ZI, Moreau C, et al. Conservative iron chelation for neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis. J Neural Transm (Vienna) 2020;127:189-203.
**6.** Do Van B, Gouel F, Jonneaux A, et al. Ferroptosis, a newly characterized form of cell death in Parkinson's disease that is regulated by PKC. Neurobiol Dis 2016;94:169-78.
**7.** Mahoney-Sánchez L, Bouchaoui H, Ayton S, Devos D, Duce JA, Devedjian J-C. Ferroptosis and its potential role in the physiopathology of Parkinson's disease. Prog Neurobiol 2021;196:101890.
**8.** Duce JA, Wong BX, Durham H, Devedjian J-C, Smith DP, Devos D. Post translational changes to $\alpha$-synuclein control iron and dopamine trafficking: a concept for neuron vulnerability in Parkinson's disease. Mol Neurodegener 2017;12:45.
**9.** Devos D, Moreau C, Devedjian JC, et al. Targeting chelatable iron as a therapeutic modality in Parkinson's disease. Antioxid Redox Signal 2014;21:195-210.
**10.** Cabantchik ZI, Munnich A, Youdim MB, Devos D. Regional siderosis: a new challenge for iron chelation therapy. Front Pharmacol 2013;4:167.
**11.** Crichton RR, Ward RJ, Hider RC. The efficacy of iron chelators for removing iron from specific brain regions and the pituitary-ironing out the brain. Pharmaceuticals (Basel) 2019;12:138.
**12.** Martin-Bastida A, Ward RJ, Newbould R, et al. Brain iron chelation by deferiprone in a phase 2 randomised double-blinded placebo controlled clinical trial in Parkinson's disease. Sci Rep 2017;7:1398.
**13.** Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591-601.
**14.** Hopes L, Grolez G, Moreau C, et al. Magnetic resonance imaging features of the nigrostriatal system: biomarkers of Parkinson's disease stages? PLoS One 2016;11(4):e0147947.
**15.** Wiesinger JA, Buwen JP, Cifelli CJ, Unger EL, Jones BC, Beard JL. Down-regulation of dopamine transporter by iron chelation in vitro is mediated by altered trafficking, not synthesis. J Neurochem 2007;100:167-79.
**16.** Morrish PK. How valid is dopamine transporter imaging as a surrogate marker in research trials in Parkinson's disease? Mov Disord 2003;18:Suppl 7:S63-S70.
**17.** Goetz CG, Fahn S, Martinez-Martin P, et al. Movement disorder society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. Mov Disord 2007;22:41-7.
**18.** Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-9.
**19.** Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 1997;26:353-7.
**20.** Cohen AR, Galanello R, Piga A, Dipalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol 2000;108:305-12.
**21.** Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med 2009;361:1268-78.
**22.** Liu GF, Lu K, Mogg R, Mallick M, Mehrotra DV. Should baseline be a covariate or dependent variable in analyses of change from baseline in clinical trials? Stat Med 2009;28:2509-30.
**23.** Van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1-67.
**24.** Rubin DB. Multiple Imputation for nonresponse in surveys. New York: John Wiley, 1987.
**25.** Li K-H, Meng X-L, Raghunathan TE, Rubin DB. Significance levels from repeated p-values with multiply-imputed data. Stat Sin 1991;1:65-92 (http://www.jstor.org/stable/24303994).