ORIGINAL ARTICLE

Trial of Lixisenatide in Early Parkinson's Disease

W.G. Meissner, P. Remy, C. Giordana, D. Maltête, P. Derkinderen, J.-L. Houéto, M. Anheim, I. Benatru, T. Boraud, C. Brefel-Courbon, N. Carrière, H. Catala, O. Colin, J.-C. Corvol, P. Damier, E. Dellapina, D. Devos, S. Drapier, M. Fabbri, V. Ferrier, A. Foubert-Samier, S. Frismand-Kryloff, A. Georget, C. Germain, S. Grimaldi, C. Hardy, L. Hopes, P. Krystkowiak, B. Laurens, R. Lefaucheur, L.-L. Mariani, A. Marques, C. Marse, F. Ory-Magne, V. Rigalleau, H. Salhi, A. Saubion, S.R.W. Stott, C. Thalamas, C. Thiriez, M. Tir, R.K. Wyse, A. Benard, and O. Rascol, for the LIXIPARK Study Group*

ABSTRACT

BACKGROUND

Lixisenatide, a glucagon-like peptide-1 receptor agonist used for the treatment of diabetes, has shown neuroprotective properties in a mouse model of Parkinson's disease.

METHODS

In this phase 2, double-blind, randomized, placebo-controlled trial, we assessed the effect of lixisenatide on the progression of motor disability in persons with Parkinson's disease. Participants in whom Parkinson's disease was diagnosed less than 3 years earlier, who were receiving a stable dose of medications to treat symptoms, and who did not have motor complications were randomly assigned in a 1:1 ratio to daily subcutaneous lixisenatide or placebo for 12 months, followed by a 2-month washout period. The primary end point was the change from baseline in scores on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (range, 0 to 132, with higher scores indicating greater motor disability), which was assessed in patients in the on-medication state at 12 months. Secondary end points included other MDS-UPDRS subscores at 6, 12, and 14 months and doses of levodopa equivalent.

RESULTS

A total of 156 persons were enrolled, with 78 assigned to each group. MDS-UPDRS part III scores at baseline were approximately 15 in both groups. At 12 months, scores on the MDS-UPDRS part III had changed by −0.04 points (indicating improvement) in the lixisenatide group and 3.04 points (indicating worsening disability) in the placebo group (difference, 3.08; 95% confidence interval, 0.86 to 5.30; P=0.007). At 14 months, after a 2-month washout period, the mean MDS-UPDRS motor scores in the off-medication state were 17.7 (95% CI, 15.7 to 19.7) with lixisenatide and 20.6 (95% CI, 18.5 to 22.8) with placebo. Other results relative to the secondary end points did not differ substantially between the groups. Nausea occurred in 46% of participants receiving lixisenatide, and vomiting occurred in 13%.

CONCLUSIONS

In participants with early Parkinson's disease, lixisenatide therapy resulted in less progression of motor disability than placebo at 12 months in a phase 2 trial but was associated with gastrointestinal side effects. Longer and larger trials are needed to determine the effects and safety of lixisenatide in persons with Parkinson's disease. (Funded by the French Ministry of Health and others; LIXIPARK ClinicalTrials.gov number, NCT03439943.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Rascol can be contacted at olivier.rascol@univ-tlse3.fr or at the Department of Clinical Pharmacology, Faculty of Medicine, 37 Allées Jules Guesde, 31000 Toulouse, France.

*The members of the LIXIPARK Study Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was updated on April 4, 2024, at NEJM.org.

N Engl J Med 2024;390:1176-85.
DOI: 10.1056/NEJMoa2312323

CME

Current treatments for Parkinson's disease are based primarily on dopaminergic replacement therapy to treat symptoms and have not convincingly shown an important effect on disease progression.[1] Some epidemiologic studies have shown an increased risk of Parkinson's disease among persons with type 2 diabetes mellitus as compared with persons without diabetes,[2] and there has been an association shown between α-synuclein aggregates, the pathologic hallmark of Parkinson's disease, and insulin resistance in the brain.[3] In addition, in some studies, the prevalence of Parkinson's disease was lower among patients with diabetes who were treated with glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 inhibitors, which increase GLP-1 levels, than among patients who received other diabetes medications.[4,5] GLP-1 receptor agonists increase glucose-level–dependent insulin secretion by pancreatic beta cells and inhibit secretion of glucagon from pancreatic alpha cells.[6] GLP-1 analogues reach measurable brain concentrations, and some preclinical evidence suggests that activation of GLP-1 receptors is protective against cytokine-mediated apoptosis and may stimulate neurogenesis.[7,8]

At least six GLP-1 receptor agonists have been or are being tested as potential treatments in persons with Parkinson's disease.[9] A small single-center, randomized, controlled trial of the GLP-1 receptor agonist exenatide showed positive effects on motor function during the period participants were not receiving medication for Parkinson's disease (the off-medication state); however, the positive effects on motor function, as well as positive effects associated with other end points, were not observed when participants were receiving medication (the on-medication state).[10] A phase 2 trial of NLY01, a pegylated analogue of exenatide, did not show benefits in participants with early Parkinson's disease who did not receive dopamine replacement therapy.[11]

Lixisenatide is a 44-amino-acid peptide that is used for the treatment of type 2 diabetes mellitus. Similar to exenatide, the formulation of lixisenatide is based on the naturally occurring GLP analogue exendin-4, and the affinity of lixisenatide for the GLP-1 receptor is up to four times greater than that of human GLP-1.[12] Neuroprotective actions of lixisenatide have been shown in animal models of Alzheimer's disease.[13,14] In one study that used the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease, lixisenatide (but not exendin-4) attenuated motor impairment and prevented the loss of dopamine neurons.[15] We performed a trial to assess the potential disease-modifying effect of lixisenatide in persons with early Parkinson's disease who had already begun receiving standard therapy.

A Quick Take is available at NEJM.org

METHODS

TRIAL CONDUCT AND PARTICIPANTS

The LIXIPARK trial was an investigator-initiated, phase 2, multicenter, double-blind, parallel-group, randomized, placebo-controlled trial that was conducted in France and was followed by a 2-month washout period. The trial was coordinated by the Clinical Investigation Center of Toulouse University Hospital. Funding was provided by the French Ministry of Health and Prevention and Cure Parkinson's. Sanofi provided the drug and placebo and advised investigators on the expected characteristics of the drug and potential safety issues associated with it but had no other role in the conduct of the trial, analysis of the data, or writing of the manuscript. Toulouse University Hospital provided medical-writing support for an earlier version of the manuscript.

A steering committee designed the trial. The first and last authors were primarily responsible for writing the initial manuscript. Statistical analyses were independently performed by members of the European Clinical Trials Platform and Development (EUCLID)–F-CRIN clinical trials platform (https://euclid-ctu.fr). All the authors vouch for the completeness and accuracy of the data, the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org), and the full and accurate reporting of adverse events.

The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation, the principles of the Declaration of Helsinki, and French law. The protocol was approved by the ethics committee of Ile de France VII. All the trial participants provided written informed consent.

Persons who were 40 to 75 years of age and had received a diagnosis of Parkinson's disease according to U.K. Brain Bank Criteria[16] within the past 3 years were recruited from 21 of 25

centers included in the French Clinical Research Network for Parkinson's Disease and Movement Disorders (NS-Park–F-CRIN).[17] Eligible participants were treated with an optimized stable dopaminergic medication regimen (dopamine agonist, levodopa, or monoamine oxidase B [MAO-B] inhibitor, or a combination of these), as determined by the site investigator, for at least 1 month before the baseline initiation of trial agents, with the expectation that the participants could continue the regimen for at least an additional 6 months.

Key exclusion criteria were a score of at least 3 on the Hoehn and Yahr scale (range, 1 to 5, with higher scores indicating worse disability), signifying at least mild-to-moderate bilateral motor involvement due to Parkinson's disease and some postural instability; the presence of motor fluctuations or dyskinesia (or both); atypical or secondary parkinsonism; a Montreal Cognitive Assessment (MoCA)[18] score of less than 26 (range, 0 to 30, with a score of 26 or higher indicating normal cognitive function), suggesting at least mild cognitive impairment; diabetes mellitus (types 1 and 2); and previous treatment with a GLP-1 receptor agonist. Persons with hyperthyroidism or uncontrolled hypothyroidism, severe renal insufficiency (creatinine clearance <30 ml per minute), active liver disease, severe depression, a history of drug or alcohol abuse, or a history of unexplained pancreatitis, chronic pancreatitis, or pancreatectomy were excluded, as were persons with a body-mass index (the weight in kilograms divided by the square of the height in meters) of less than 18.5, with malnutrition, or with a weight change of more than 5 kg within the 3 months before screening.

TRIAL DESIGN

Participants were randomly assigned in a 1:1 ratio to receive either subcutaneous lixisenatide or placebo as an add-on to their current Parkinson's disease medications for 12 months. Randomization, performed with the use of a Web-based system, was in unstratified blocks of 4 and 6. All the participants were trained in using pens for injecting themselves subcutaneously, and the trial drug or placebo was administered by the participants 15 minutes before dinner each night. Lixisenatide or an equivalent volume of placebo was administered at an initial dose of 10 μg per day for 14 days, after which the dose was increased to 20 μg per day for the remainder of the 12-month period.

Adherence to the assigned regimen was assessed by means of a participant diary and verified by the pharmacies at the trial sites. Participants in whom the higher target dose had adverse effects could continue to receive the assigned lixisenatide or placebo at a dose of 10 μg per day until the end of the trial. Participants continued their current Parkinson's disease medication regimen for at least the first 6 months of the trial and were encouraged to continue their same regimen for the entire trial unless the investigator deemed that a dose adjustment was appropriate.

Participants attended clinic visits at baseline, on day 15, and at months 1, 3, 6, 9, 12, and 14. Clinical assessments of Parkinson's disease were performed at baseline and at months 6 and 12; during the assessment visits, participants in an on-medication state (i.e., receiving a stable dose of dopaminergic medication to treat symptoms) were evaluated according to scores on the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I through IV,[19] the Parkinson's Disease Questionnaire summary index (PDQ-39; range, 0 to 100, with higher scores indicating worse health status),[20] and MoCA. In addition, at month 14, participants were assessed after a 2-month washout of the trial drug or placebo and an overnight washout of dopaminergic medication to treat symptoms (the practically defined off-medication state[21]). Fasting blood glucose and insulin concentrations were measured at baseline and at months 6 and 12. Adverse events and vital signs were recorded at each visit. The same investigator collected data regarding adverse events and assessed the scores on the MDS-UPDRS part III (motor subscale; range, 0 to 132, with higher scores indicating greater severity of impairment on a clinician-conducted motor examination) at each site.

END POINTS

The primary efficacy end point was the change from baseline to month 12 in scores on the MDS-UPDRS part III as assessed in the on-medication state. Secondary efficacy end points that were based on MDS-UPDRS scores were the change from baseline to month 6 and month 12 in scores on MDS-UPDRS part I (nonmotor aspects

of daily living; range, 0 to 52, with higher scores indicating greater severity of impairment), part II (motor aspects of daily living; range, 0 to 52, with higher scores indicating greater severity of impairment), and part IV (motor complications; range, 0 to 24, with higher scores indicating more severe motor complications); change from baseline to month 12 in the total MDS-UPDRS scores (sum of scores on parts I, II, and III; range, 0 to 236, with higher totals indicating greater severity of impairment); and change from baseline to month 6 in part III scores. The effect of lixisenatide therapy on motor symptoms in the practically defined off-medication state[21] was assessed as the between-group difference in motor scores as assessed in patients in the off-medication state at month 14.

Although doses of Parkinson's disease medication were prespecified to remain stable for the first 6 months of the trial, dose changes were permitted during the second 6-month period and were considered to be an indicator of efficacy. A dose change was defined as a change from baseline to month 12 in the levodopa equivalent daily dose that was calculated using published conversion ratios.[22] Changes from baseline to month 12 in scores on the PDQ-39 summary index and MoCA were assessed as exploratory end points.

STATISTICAL ANALYSIS

On the basis of findings in a previous trial of exenatide in Parkinson's disease,[23] we estimated that a sample size of 158 participants (79 per group) would provide the trial with 80% power to detect a between-group difference of 4 in scores on the MDS-UPDRS part III. These calculations were based on a common standard deviation of 8, a dropout rate of 10%, and a two-sided type I error of 5%.

Efficacy and safety end points were assessed in the modified intention-to-treat population, excluding participants with missing data. After confirming a normal distribution and homogeneous variances, we assessed efficacy in the two groups using Student's t-test for quantitative variables. We planned to impute missing data with the use of multiple imputation. However, given the small number of patients with missing data, analyses were conducted on available data. Because there was no prespecified plan for adjustment of the widths of the confidence intervals of secondary end points for multiplicity, the intervals may not be used in place of hypothesis testing and no definite conclusions can be drawn from these results.

To assess any potential effects of fasting blood glucose levels and insulin concentrations at baseline on the primary end point, we performed linear regression analyses with the score on the MDS-UPDRS part III as the dependent variable, and glycemia or insulinemia and a term of interaction between glycemia or insulinemia and the trial group as explanatory variables. In addition, because results from the phase 2 trial of the GLP-1 receptor agonist NLY01 showed that age (<60 years vs. ≥60 years) may be a factor in response,[11] we performed post hoc subgroup analyses of MDS-UPDRS motor scores with respect to these ages.

RESULTS

TRIAL POPULATION

From February 2018 through March 2020, a total of 177 patients were screened at NS-PARK–F-CRIN sites. In March 2020, the steering committee decided to halt the recruitment at 156 participants (instead of the planned 158) to avoid delays caused by the coronavirus disease 2019 pandemic (see the Methods section in the Supplementary Appendix, available at NEJM.org) and owing to the low number of dropouts. A total of 157 participants (out of the 177 initially screened) were assessed for eligibility and 156 (78 per group) were enrolled; 1 participant did not undergo randomization because he had shingles. A total of 7 participants discontinued lixisenatide or placebo across both groups with no single reason as a common cause of early discontinuation; all but 4 of the participants who discontinued were followed until month 12 and their outcomes were included in the primary analysis (Fig. 1).

Overall, 28 participants (36%) in the lixisenatide group had unacceptable side effects when receiving the target dose of 20 μg per day and switched to the reduced dose of 10 μg per day. One participant in the lixisenatide group and 3 in the placebo group had missing data related to scores on the MDS-UPDRS part III at month 12; we did not perform imputation for the missing data, and these results were not included in the primary analysis. Three participants (4%) in the

placebo group had a dose reduction. Adherence to the administration of the assigned drug or placebo was greater than 92.2% at all visits.

The demographic and clinical characteristics of the participants at baseline were similar in the two groups and were typical of early disease (Table 1); the mean duration of disease from the time of diagnosis was 1.4 years in both groups. The mean (±SD) MDS-UPDRS motor score at baseline was 14.8±7.3 in the lixisenatide group and 15.5±7.8 in the placebo group. The representativeness of the trial population is shown in Table S1 in the Supplementary Appendix.

EFFICACY

At month 12, the mean score on the MDS-UPDRS part III in the on-medication state was 14.9 (95% CI, 13.3 to 16.6) in the lixisenatide group and 18.8 (95% CI, 16.6 to 21.0) in the placebo group. Scores in the lixisenatide group improved from baseline by −0.04 points (95% confidence interval [CI], −1.62 to 1.54) and in the placebo group worsened by 3.04 points (95% CI, 1.46 to 4.62), a difference of 3.08 (95% CI, 0.86 to 5.30; P=0.007) (Table 2 and Fig. S1). At month 14, after the 2-month washout period, the mean score on the MDS-UPDRS part III, as measured in the off-medication state, was 17.7 (95% CI, 15.7 to 19.7) in the lixisenatide group and 20.6 (95% CI, 18.5 to 22.8) in the placebo group.

Results for other secondary and exploratory efficacy measures were generally similar in the two groups at month 6 and month 12 (Table 2 and Table S2). Mean changes from baseline in the levodopa equivalent daily dosage were 35.8 mg per day (95% CI, 8.3 to 63.2) with lixisenatide and 31.3 mg per day (95% CI, 9.2 to 53.5) with placebo.

There were no apparent associations between baseline fasting blood glucose and insulin con-

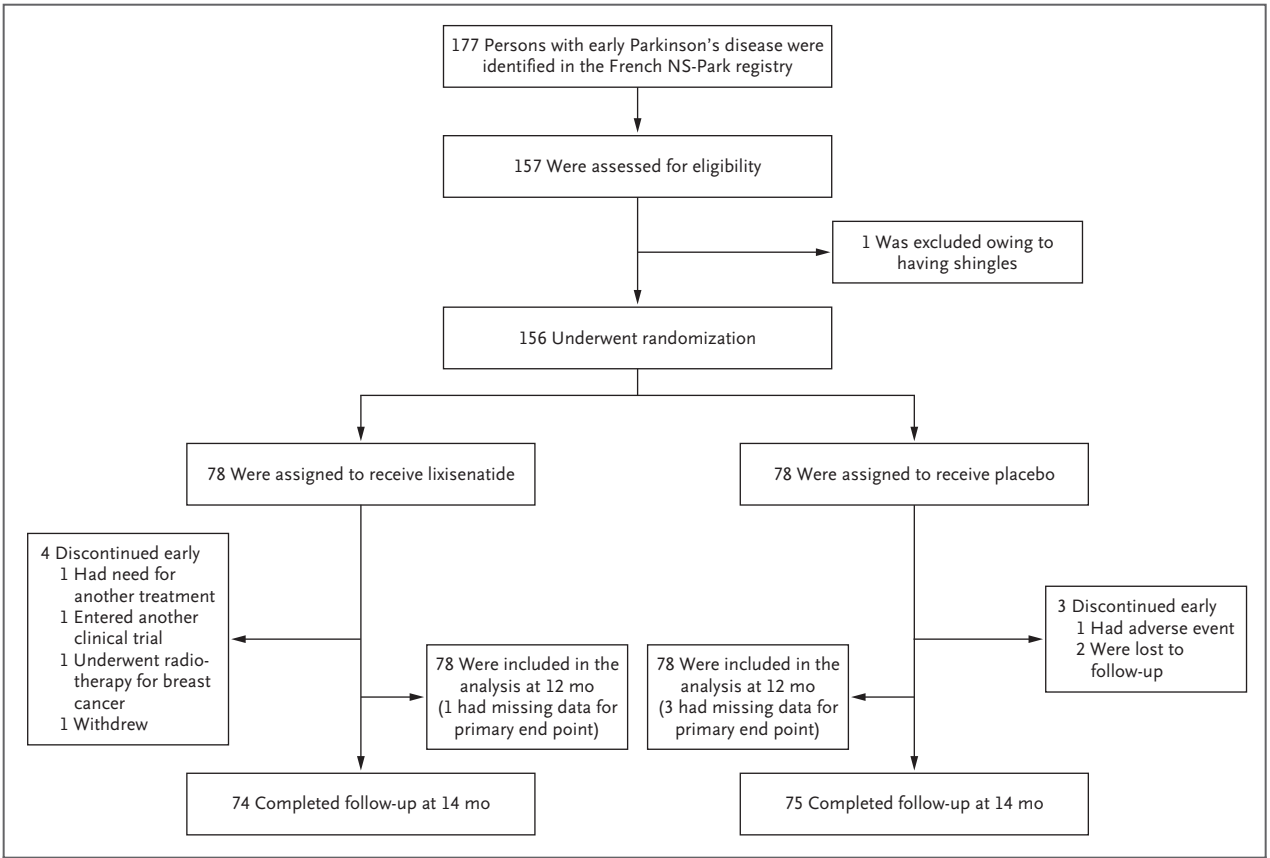

Figure 1. Trial Recruitment and Follow-up.

centrations and scores on the MDS-UPDRS part III at month 12 (Tables S3 and S4). Post hoc subgroup analysis, from which no conclusions can be drawn, showed that at month 12, lixisenatide had a numerically larger treatment effect in participants younger than 60 years of age than in those 60 years of age or older (difference in scores on the MDS-UPDRS part III, 5.22 [95% CI, 1.95 to 8.48] vs. 1.00 [95% CI, –2.01 to 4.03]) (Fig. S2).

ADVERSE EVENTS

At least one adverse event was reported in a majority of the participants (86% who received lixisenatide and 71% who received placebo) (Table 3). Gastrointestinal side effects were more common with lixisenatide than with placebo and included nausea (46% vs. 12%), vomiting (13% vs. 3%), and gastroesophageal reflux (8% vs. 1%). The incidence of serious adverse events was similar in the two groups (five participants in each group); only one serious adverse event in each group was considered by the investigators to be treatment-related (pancreatitis in the lixisenatide group and syncope in the placebo group). In the lixisenatide group, six participants reported weight loss as an adverse event; no such adverse events were reported in the placebo group. No between-group difference was observed in the mean weight at any visit (Table S5). One case of hypoglycemia was reported in the placebo group; there were no reports of hypoglycemia with lixisenatide. Post hoc analysis showed that the presence of nausea apparently did not affect the magnitude of effect with respect to the primary end point in the lixisenatide group, but no conclusions can be drawn from these results (Table S6).

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Lixisenatide (N=78)	Placebo (N=78)
Age — yr	59.5±8.1	59.9±8.4
Male sex — no. (%)	44 (56)	48 (62)
Body-mass index	25.6±3.9	25.8±4.2
Time since diagnosis — yr	1.4±0.8	1.4±0.7
MDS-UPDRS score†		
Part I nm-EDL	6.1±4.0	6.4±4.2
Part II m-EDL	5.0±3.5	5.4±4.3
Part III motor	14.8±7.3	15.5±7.8
Total of parts I, II, and III	25.6±11.7	27.0±12.4
Part IV motor complications	0.3±1.3	0.2±0.8
MoCA score‡	27.8±1.4	28.1±1.4
PDQ-39 score§	17.4±10.9	16.8±13.0
Levodopa equivalent daily dose — mg	317±179	355±215
Parkinson's disease medication — no. (%)		
Levodopa	78 (100)	76 (97)
MAO-B inhibitor	35 (45)	32 (41)
Dopamine agonist	54 (69)	61 (78)

* Plus–minus values are means ±SD unless otherwise noted. No information on race or ethnic group was collected. MAO-B denotes monoamine oxidase B, m-EDL motor aspects of daily living, and nm-EDL nonmotor aspects of daily living.

† Scores on the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part I, range from 0 to 52, with higher scores indicating greater severity of impairment in nonmotor aspects of daily living; scores on part II range from 0 to 52, with higher scores indicating greater severity of impairment in motor aspects of daily living; scores on part III range from 0 to 132, with higher scores indicating greater severity of impairment on a clinician-conducted motor examination; scores on part IV range from 0 to 24, with higher scores indicating more severe motor complications; and the total (sum of scores on parts I, II, and III) range from 0 to 236, with higher sums indicating greater severity of impairment.

‡ Scores on the Montreal Cognitive Assessment (MoCA) range from 0 to 30, with higher scores indicating better cognitive function.

§ Scores on the Parkinson's Disease Questionnaire summary index (PDQ-39) range from 0 to 100, with higher scores indicating worse health status.

DISCUSSION

In this phase 2, randomized trial involving participants with early, treated Parkinson's disease in the on-medication state, the GLP-1 receptor agonist lixisenatide had a three-point beneficial effect, as compared with placebo, in the change over a 12-month period from a baseline value of approximately 15 points on a 132-point scale measuring motor disability. This difference was apparently driven by the increase in scores (indicating disease progression) in the placebo group, which was below but close to the 3.25 threshold on the motor scale that has been considered to be clinically important to the participants in other studies.[24] Most secondary end points did not support the primary analysis and had similar results in the two groups with regard to Parkinson's disease scales other than the primary end point. After a 2-month washout period and with participants in the off-medication state, there was a 3-point between-group difference in motor score favoring active treatment, a

Table 2. Efficacy Measures.

Efficacy Measure	Placebo (N=75)	Lixisenatide (N=77)	Difference
Primary end point — mean point estimate (95% CI)			
Change in score on MDS-UPDRS part III, on-medication state, 12 mo*	3.04 (1.46 to 4.62)	−0.04 (−1.62 to 1.54)	3.08 (0.86 to 5.30)
Secondary end points — mean point estimate (95% CI)			
MDS-UPDRS part III score, off-medication state after 2-month washout, 14 mo†‡	20.6 (18.5 to 22.8)	17.7 (15.7 to 19.7)	3.0 (0.1 to 5.8)
Change from baseline in MDS-UPDRS score, on-medication state			
Part III, 6 mo	1.66 (0.36 to 2.97)	0.54 (−0.93 to 2.00)	1.13 (−0.82 to 3.07)
Total, 12 mo	5.18 (2.90 to 7.45)	2.80 (0.29 to 5.31)	2.38 (−0.98 to 5.73)
Part I nm-EDL, 6 mo	0.69 (−0.10 to 1.48)	0.55 (−0.18 to 1.28)	0.14 (−0.93 to 1.21)
Part I nm-EDL, 12 mo	0.61 (−0.11 to 1.33)	1.25 (0.29 to 2.21)	−0.64 (−1.83 to 0.55)
Part II m-EDL, 6 mo	0.63 (0.03 to 1.23)	0.67 (−0.18 to 1.52)	−0.04 (−1.08 to 0.99)
Part II m-EDL, 12 mo	1.40 (0.65 to 2.15)	1.45 (0.58 to 2.33)	−0.05 (−1.19 to 1.09)
Part IV, 6 mo	0.2 (−0.2 to 0.6)	0.2 (0 to 0.5)	−0.03 (−0.50 to 0.44)
Part IV, 12 mo	0.2 (0 to 0.4)	0.2 (−0.1 to 0.6)	−0.06 (−0.44 to 0.33)
Change from baseline in levodopa equivalent daily dose at 12 mo — mg	31.3 (9.2 to 53.5)	35.8 (8.3 to 63.2)	−4.4 (−39.5 to 30.6)

* At month 12, scores on the MDS-UPDRS part III in the on-medication state were 14.9 (95% CI, 13.3 to 16.6) in the lixisenatide group and 18.8 (95% CI, 16.6 to 21.0) in the placebo group, with higher scores indicating greater motor disability. P=0.007 for the between-group difference.
† Analyses included 70 participants in the lixisenatide group and 74 participants in the placebo group.
‡ Participants were considered to be in an off-medication state if they had not received antiparkinsonian medications for at least 12 hours before evaluation.

result that was not adjusted for multiplicity and from which no conclusions can be drawn. Gastrointestinal side effects occurred in more than half the participants receiving lixisenatide, which frequently led to a decrease in dose from 20 μg per day to 10 μg per day in some participants; in a post hoc analysis, nausea did not apparently affect the magnitude of effect with regard to the primary end point. In addition to gastrointestinal side effects, weight loss was slightly more common in the lixisenatide group.

The worsening in scores on the MDS-UPDRS part III in the placebo group was smaller than that reported in recent trials of the monoclonal antibodies for Parkinson's disease, cinpanemab and prasinezumab, in persons with newly diagnosed Parkinson's disease who had not previously received drug therapy.[25,26] Participants in the current trial were already receiving stable dopaminergic therapy to treat symptoms, and this may explain the difference, but the trials cannot be compared owing to differences in design and patient populations.

Similar to trials of the GLP-1 receptor agonists exenatide and NLY01[10,11] involving patients with Parkinson's disease, our trial did not show improvements in nonmotor symptoms with lixisenatide, a result that is in contrast to preliminary reports from a trial of the GLP-1 receptor agonist liraglutide.[27] Our results, similar to those in the phase 2 trial of NLY01,[11] show a potentially larger treatment effect in participants younger than 60 years of age, but these are post hoc analyses, and no conclusions can be drawn from them.

Although our findings suggest an effect on motor disability progression that is potentially related to a neuroprotective mechanism, as supported by the findings of lower scores on the MDS-UPDRS part III in patients in the off-medication state after the 2-month washout period, an effect of lixisenatide on symptoms cannot be

ruled out. Preclinical and clinical studies assessing the effect of the GLP-1 receptor agonist exenatide in addiction disorders suggested that the drug may enhance synaptic dopamine levels that could lead to benefit with respect to symptoms in Parkinson's disease.[28,29] Further studies are needed to determine the mechanisms of action of GLP-1 receptor agonists in Parkinson's disease.

A strength of our trial is the inclusion of participants with Parkinson's disease who were still early enough in the course of the disease to potentially benefit from a neuroprotective agent, were relatively easy to recruit, and already had had a positive response to dopaminergic medications, which enhanced the reliability of the Parkinson's disease diagnosis, as compared with patients with newly diagnosed Parkinson's disease who have not received drug therapy. Another advantage is that the participants in our trial were receiving stable doses of medications to treat symptoms at the time of enrollment, and dose adjustment was less likely to occur during the 12-month trial period. In contrast, in clinical trials that recruited patients with newly diagnosed Parkinson's disease who had not received drug therapy, approximately one third of the participants began receiving treatment for symptoms within the first year of follow-up, which introduced a confounding factor for interpretation of the results in those trials.[25,26,30]

However, our trial has several limitations. It was conducted over a period of 1 year and involved participants with early Parkinson's disease; it remains to be determined whether the apparent effect of the drug on motor scores persists with longer exposure and at other stages of Parkinson's disease. The secondary end points provide no definite support for the primary endpoint results, and longer washout periods may be necessary to determine whether lixisenatide therapy has a long-lasting effect. No imaging biomarkers (e.g., dopamine transporter imaging) were used to monitor disease progression and changes with drug administration. The trial was conducted in France, where the collection of data regarding race or ethnic group is prohibited by law without specific justification. Finally, we tested only one dose of lixisenatide, on the basis of recommendations for the treatment of diabetes mellitus, and other doses might have better or worse effects in persons with Parkinson's disease.

Table 3. Adverse Events.

Event	Lixisenatide (N=78)	Placebo (N=78)
	no. of participants (%)	
Any	67 (86)	55 (71)
Adverse event related or possibly related to lixisenatide or placebo*	55 (71)	25 (32)
Serious adverse event†	5 (6)	5 (6)
Serious adverse event related or possibly related to lixisenatide or placebo‡	1 (1)	1 (1)
Common adverse events§		
Nausea	36 (46)	9 (12)
Vomiting	10 (13)	2 (3)
Headache	7 (9)	5 (6)
Gastroesophageal reflux	6 (8)	1 (1)
Diarrhea	6 (8)	5 (6)
Fatigue	6 (8)	1 (1)
Weight loss	6 (8)	0
Urinary tract infection	5 (6)	2 (3)
Gastroenteritis	4 (5)	4 (5)
Dyspepsia	4 (5)	2 (3)
Pain in limb	2 (3)	5 (6)
Back pain	2 (3)	5 (6)
Sciatica	1 (1)	5 (6)

* The relationship of an adverse event to a trial drug or placebo was assessed by the investigator.
† Serious adverse events reported in the lixisenatide group were acute cholecystitis, spinal stenosis, peritonitis (in a participant with a history of gastric ulcer), breast cancer, and pancreatitis.
‡ The relationship of an adverse event to a trial drug or placebo was assessed by the investigator. The only serious adverse events considered by investigators to be treatment-related were one case of pancreatitis in the lixisenatide group and one case of syncope in the placebo group.
§ Common adverse events were those that occurred in at least four participants (≥5%) in either group.

In a 12-month phase 2 trial, the subcutaneously administered GLP-1 receptor agonist lixisenatide modestly reduced motor disability progression in patients with early Parkinson's disease as compared with placebo but had gastrointestinal side effects. Larger and longer trials are needed to determine the effect and safety of this agent in the treatment of Parkinson's disease.

Supported by grants from the French Ministry of Health (PHRC-N program, PHRC-16-0402) and Cure Parkinson's (in partnership with the Van Andel Institute).

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 staff of Sanofi for providing the trial medication and placebo and for advice regarding the expected characteristics of lixisenatide and potential safety issues; the members of the NS-Park–F-CRIN network, the Toulouse Clinical Investigation Center (CIC1436), and the Bordeaux EUCLID–F-CRIN platform for assistance with regard to trial management; the participants, care partners, and staff; Cédrick Wallet, Florence Allais, and Isabelle Perrot for statistical support; and Anita Chadha-Patel (of ACP Clinical Communications) for writing support with an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: Wassilios G. Meissner, M.D., Ph.D., Philippe Remy, M.D., Ph.D., Caroline Giordana, M.D., David Maltête, M.D., Pascal Derkinderen, M.D., Ph.D., Jean-Luc Houéto, M.D., Mathieu Anheim, M.D., Ph.D., Isabelle Benatru, M.D., Thomas Boraud, M.D., Ph.D., Christine Brefel-Courbon, M.D., Nicolas Carrière, M.D., Hélène Catala, M.D., Olivier Colin, M.D., Jean-Christophe Corvol, M.D., Ph.D., Philippe Damier, M.D., Estelle Dellapina, Ph.D., David Devos, M.D., Ph.D., Sophie Drapier, M.D., Margherita Fabbri, M.D., Ph.D., Vanessa Ferrier, M.D., Alexandra Foubert-Samier, M.D., Ph.D., Solène Frismand-Kryloff, M.D., Aurore Georget, M.Sc., Christine Germain, M.Sc., Stéphane Grimaldi, M.D., Ph.D., Clémence Hardy, M.D., Lucie Hopes, M.D., Pierre Krystkowiak, M.D., Ph.D., Brice Laurens, M.D., Romain Lefaucheur, M.D., Louise-Laure Mariani, M.D., Ph.D., Ana Marques, M.D., Ph.D., Claire Marse, M.D., Fabienne Ory-Magne, M.D., Vincent Rigalleau, M.D., Ph.D., Hayet Salhi, M.D., Amandine Saubion, M.Sc., Simon R. W. Stott, Ph.D., Claire Thalamas, M.D., Claire Thiriez, M.D., Mélissa Tir, M.D., Ph.D., Richard K. Wyse, M.D., Ph.D., Antoine Benard, M.D., Ph.D., and Olivier Rascol, M.D., Ph.D.

The authors' affiliations are as follows: the French Clinical Research Network (F-CRIN) for Parkinson's Disease and Movement Disorders (NS-Park–F-CRIN) (W.G.M., P.R., C. Giordana, D.M., P. Derkinderen, J.-L.H., M.A., I.B., T.B., C.B.-C., N.C., O.C., J.-C.C., P. Damier, E.D., D.D., S.D., M.F., V.F., A.F.-S., S.F.-K., S.G., C.H., L.H., P.K., B.L., R.L., L.-L.M., A.M., C.M., F.O.-M., H.S., C. Thiriez, M.T., O.R.), Centre d'Investigation Clinique (CIC) 1436 and the Departments of Clinical Pharmacology and Neurosciences, Centre Expert Parkinson, University Hospital of Toulouse, INSERM, University of Toulouse 3 (C.B.-C., H.C., M.F., F.O.-M., C. Thalamas, O.R.), and CIC 1436, INSERM (E.D., A.S.), Toulouse, Service de Neurologie des Maladies Neurodégénératives, Centre Expert Parkinson, Institut des Maladies Neurodégénératives (IMN) Clinique (W.G.M., T.B., A.F.-S., B.L.), and Service d'Information Médicale, Unité de Soutien Méthodologique à la Recherche (USMR) (A.G., C. Germain, A.B.), Centre Hospitalier Universitaire (CHU) Bordeaux, Unité Mixte de Recherche (UMR) 5293, Université de Bordeaux, Centre National de la Recherche Scientifique (CNRS), IMN, Unité Mixte de Recherche (UMR) 5293 (W.G.M., T.B., A.F.-S.), and the European Clinical Trials Platform and Development–F-CRIN, CIC–Clinical Epidemiology Unit 1401, University of Bordeaux, INSERM, Institut Bergonié, CHU Bordeaux (A.G., C. Germain, A.B.), Bordeaux, the Department of Neurology, Centre Expert Parkinson, Equipe 01-Neuropsychologie Interventionnelle L'Institut Mondor de Recherches Biomédicales, CHU Henri Mondor, INSERM et Faculté de Santé, Université Paris-Est Créteil, Créteil (P.R., H.S.), the Department of Neurology, Centre Expert Parkinson, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice (C. Giordana, V.F., C.M.), the Department of Neurology, Centre Expert Parkinson, Laboratory of Neuronal and Neuroendocrine Differentiation and Communication, UMR 1239, Rouen University Hospital, University of Rouen, INSERM, Mont-Saint-Aignan (D.M.), and the Department of Neurology, Centre Expert Parkinson, Rouen University Hospital and University of Rouen (C.H., R.L.), Rouen, the Department of Neurology, Centre Expert Parkinson, CIC 1413, CHU Nantes, INSERM, Nantes (P. Derkinderen, P. Damier), Service de Neurologie, Centre Expert Parkinson, CIC 1402, CHU Limoges, CHU Poitiers INSERM, Limoges (J.-L.H., I.B., O.C.), the Department of Neurology, Centre Expert Parkinson, Strasbourg University Hospital, and Strasbourg Federation of Translational Medicine, Strasbourg University, Strasbourg (M.A.), the Institute of Genetics and Cellular and Molecular Biology, INSERM Unité 964, CNRS–UMR 7104, University of Strasbourg, Illkirch-Graffenstaden (M.A.), the Department of Medical Pharmacology INSERM Unité 1172, Lille Neurosciences and Cognition, Centre Hospitalier Régional Universitaire, University of Lille, Lille (N.C., D.D.), the Department of Neurology, CIC Neurosciences, Sorbonne Université, Paris Brain Institute, Assistance Publique–Hôpitaux de Paris, INSERM, CNRS, Pitié–Salpêtrière Hospital, Paris (J.-C.C., L.-L.M.), the Department of Neurology, Centre Expert Parkinson, CIC 1414, CHU Pontchaillou de Rennes, INSERM, Rennes (S.D.), the Department of Neurology, Centre Expert Parkinson, CHU de Nancy, Hôpital Central, Nancy (S.F.-K., L.H.), the Department of Neurology, Centre Expert Parkinson, University Hospital La Timone, Marseille (S.G.), the Department of Neurology, Centre Expert Parkinson, University Hospital of Amiens, Amiens (P.K., M.T.), the Department of Neurology, CHU Clermont-Ferrand, Université Clermont-Auvergne, CNRS, Image Guided Clinical Neuroscience and Connectomics, Institut Pascal, Clermont-Ferrand (A.M.), the Department of Nutrition–Diabetology, CHU de Bordeaux, Hôpital Haut-Lévêque, Pessac (V.R.), and the Department of Neurology, Centre Expert Parkinson, CHU de Caen, Caen (C. Thiriez) — all in France; the Department of Medicine, University of Otago, Christchurch, and the New Zealand Brain Research Institute — both in Christchurch, New Zealand (W.G.M.); Specialized Rehabilitation Hospital, Capital Health, Abu Dhabi, United Arab Emirates (P.K.); and Cure Parkinson's, London (S.R.W.S., R.K.W.).

REFERENCES

1. Vijiaratnam N, Simuni T, Bandmann O, Morris HR, Foltynie T. Progress towards therapies for disease modification in Parkinson's disease. Lancet Neurol 2021;20:559-72.
2. Cullinane PW, de Pablo Fernandez E, König A, Outeiro TF, Jaunmuktane Z, Warner TT. Type 2 diabetes and Parkinson's disease: a focused review of current concepts. Mov Disord 2023;38:162-77.
3. Bassil F, Delamarre A, Canron M-H, et al. Impaired brain insulin signalling in Parkinson's disease. Neuropathol Appl Neurobiol 2022;48(1):e12760.
4. Brauer R, Wei L, Ma T, et al. Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes. Brain 2020;143:3067-76.
5. Svenningsson P, Wirdefeldt K, Yin L, et al. Reduced incidence of Parkinson's disease after dipeptidyl peptidase-4 inhibitors — a nationwide case-control study. Mov Disord 2016;31:1422-3.
6. Cornell S. A review of GLP-1 receptor agonists in type 2 diabetes: a focus on the mechanism of action of once-weekly agents. J Clin Pharm Ther 2020;45:Suppl 1:17-27.
7. Bassil F, Fernagut P-O, Bezard E, Meissner WG. Insulin, IGF-1 and GLP-1 signaling in neurodegenerative disorders: targets for disease modification? Prog Neurobiol 2014;118:1-18.
8. Yun SP, Kam T-I, Panicker N, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. Nat Med 2018;24:931-8.

9. McFarthing K, Rafaloff G, Baptista M, et al. Parkinson's disease drug therapies in the clinical trial pipeline: 2022 update. J Parkinsons Dis 2022;12:1073-82.
10. Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:1664-75.
11. McGarry A, Rosanbalm S, Leinonen M, et al. Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2024; 23:37-45.
12. Leon N, LaCoursiere R, Yarosh D, Patel RS. Lixisenatide (Adlyxin): a once-daily incretin mimetic injection for type-2 diabetes. P T 2017;42:676-711.
13. Cai H-Y, Hölscher C, Yue X-H, et al. Lixisenatide rescues spatial memory and synaptic plasticity from amyloid β protein-induced impairments in rats. Neuroscience 2014;277:6-13.
14. McClean PL, Hölscher C. Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer's disease. Neuropharmacology 2014;86:241-58.
15. Liu W, Jalewa J, Sharma M, Li G, Li L, Hölscher C. Neuroprotective effects of lixisenatide and liraglutide in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. Neuroscience 2015;303:42-50.
16. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.
17. Mariani L-L, Doulazmi M, Chaigneau V, et al. Descriptive analysis of the French NS-Park registry: towards a nation-wide Parkinson's disease cohort? Parkinsonism Relat Disord 2019;64:226-34.
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. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-70.
20. 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.
21. Defer GL, Widner H, Marié RM, Rémy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 1999;14:572-84.
22. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25: 2649-53.
23. Aviles-Olmos I, Dickson J, Kefalopoulou Z, et al. Exenatide and the treatment of patients with Parkinson's disease. J Clin Invest 2013;123:2730-6.
24. Horváth K, Aschermann Z, Ács P, et al. Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. Parkinsonism Relat Disord 2015;21:1421-6.
25. Pagano G, Taylor KI, Anzures-Cabrera J, et al. Trial of prasinezumab in early-stage Parkinson's disease. N Engl J Med 2022;387:421-32.
26. Lang AE, Siderowf AD, Macklin EA, et al. Trial of cinpanemab in early Parkinson's disease. N Engl J Med 2022;387: 408-20.
27. Hogg E, Wu T, Bresee C, et al. A phase II, randomized, double-blinded, placebo-controlled trial of liraglutide in Parkinson's disease. September 12, 2022 (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4212371). preprint.
28. Klausen MK, Jensen ME, Møller M, et al. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. JCI Insight 2022;7(19):e159863.
29. Zhu C, Li H, Kong X, Wang Y, Sun T, Wang F. Possible mechanisms underlying the effects of glucagon-like peptide-1 receptor agonist on cocaine use disorder. Front Pharmacol 2022;13:819470.
30. McGhee DJM, Ritchie CW, Zajicek JP, Counsell CE. A review of clinical trial designs used to detect a disease-modifying effect of drug therapy in Alzheimer's disease and Parkinson's disease. BMC Neurol 2016;16:92.