

Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial



Nirosen Vijaratnam, Christine Girges, Grace Auld, Rachel McComish, Alexa King, Simon S Skene, Steve Hibbert, Alan Wong, Sabina Melander, Rachel Gibson, Helen Matthews, John Dickson, Camille Carroll, Abigail Patrick, Jemma Inches, Monty Silverdale, Bethan Blackledge, Jessica Whiston, Michele Hu, Jessica Welch, Gordon Duncan, Katie Power, Sarah Gallen, Jacqueline Kerr, K Ray Chaudhuri, Lucia Batzu, Silvia Rota, Edwin Jabbari, Huw Morris, Patricia Limousin, Nigel Greig, Yazhou Li, Vincenzo Libri, Sonia Gandhi, Dilan Athauda, Kashfa Chowdhury, Tom Foltynie

Summary

Background GLP-1 receptor agonists have neurotrophic properties in in-vitro and in-vivo models of Parkinson's disease and results of epidemiological studies and small randomised trials have suggested possible benefits for risk and progression of Parkinson's disease. We aimed to establish whether the GLP-1 receptor agonist, exenatide, could slow the rate of progression of Parkinson's disease.

Methods We did a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial at six research hospitals in the UK. Participants were aged 25–80 years with a diagnosis of Parkinson's disease, were at Hoehn and Yahr stage 2.5 or less when on dopaminergic treatment, and were on dopaminergic treatment for at least 4 weeks before enrolment. Participants were randomly assigned (1:1) using a web-based system with minimisation according to Hoehn and Yahr stage and study site to receive extended-release exenatide 2 mg by subcutaneous pen injection once per week over 96 weeks, or visually identical placebo. All participants and all research team members at study sites were masked to randomisation allocation. The primary outcome was the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III score, off dopaminergic medication at 96 weeks, analysed in the intention-to-treat population using a linear mixed modelling approach. This study is registered with ISRCTN (14552789), EudraCT (2018-003028-35), and ClinicalTrials.gov (NCT04232969).

Findings Between Jan 23, 2020, and April 23, 2022, 215 participants were screened for eligibility, of whom 194 were randomly assigned to exenatide (n=97) or placebo (n=97). 56 (29%) participants were female and 138 (71%) were male. 92 participants in the exenatide group and 96 in the placebo group had at least one follow-up visit and were included in analyses. At 96 weeks, MDS-UPDRS III OFF-medication scores had increased (worsened) by a mean of 5.7 points (SD 11.2) in the exenatide group, and by 4.5 points (SD 11.4) points in the placebo group (adjusted coefficient for the effect of exenatide 0.92 [95% CI -1.56 to 3.39]; p=0.47). Nine (9%) participants in the exenatide group had at least one serious adverse event compared with 11 (11%) in the placebo group.

Interpretation Our findings suggest that exenatide is safe and well tolerated. We found no evidence to support exenatide as a disease-modifying treatment for people with Parkinson's disease. Studies with agents that show better target engagement or in specific subgroups of patients are needed to establish whether there is any support for the use of GLP-1 receptor agonists for Parkinson's disease.

Funding National Institute for Health and Care Research and Cure Parkinson's.

Copyright © 2025 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Parkinson's disease is the second most common neurodegenerative disease and is predicted to lead to increasing demands on health-care resources over the next few decades.¹ Symptomatic treatments are currently available,² but have no effect on the underlying progression of the disease. Developing treatments that can slow the progression of the disease remains a priority.³

Exenatide (a synthetic exendin-4) is a licensed and effective treatment for type 2 diabetes. It is a GLP-1 receptor

agonist and stimulates insulin release in the presence of elevated blood glucose. Preclinical studies have shown that exenatide has beneficial effects on neuronal survival and growth and has been shown to be neuroprotective in in-vitro neuronal models^{4,5} (Athauda and colleagues⁶ published in preprint), as well as rescuing dopaminergic neurons in toxin and genetic animal models of Parkinson's disease.^{7–9} GLP-1 receptor agonists used in people with type 2 diabetes reduce the subsequent development of Parkinson's disease.^{10,11}

Published Online
February 4, 2025
[https://doi.org/10.1016/S0140-6736\(24\)02808-3](https://doi.org/10.1016/S0140-6736(24)02808-3)
See Online/Comment
[https://doi.org/10.1016/S0140-6736\(25\)00161-8](https://doi.org/10.1016/S0140-6736(25)00161-8)

Department of Clinical and Movement Neurosciences, University College London Queen Square Institute of Neurology, University College London, London, UK (N Vijaratnam MD, C Girges PhD, E Jabbari MD, Prof H Morris PhD, Prof P Limousin MD, Prof T Foltynie PhD); Comprehensive Clinical Trials Unit, University College London, London, UK (G Auld MSc, R McComish MSc, A King BA, S Hibbert MBA, K Chowdhury MSc); Surrey Clinical Trials Unit, University of Surrey, Guildford, UK (Prof S S Skene PhD); Royal Free London NHS Foundation Trust, London, UK (A Wong MSc, S Melander BSc); Cure Parkinson's, London, UK (H Matthews MA, R Gibson BSc); Institute of Nuclear Medicine, UCLH NHS Foundation Trust, London, UK (J Dickson PhD); University of Plymouth, Plymouth, UK (Prof C Carroll PhD, A Patrick, J Inches); Manchester Centre for Clinical Neurosciences, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK (M Silverdale MD, B Blackledge BSc, J Whiston MSc); Oxford University, Oxford, UK (Prof M Hu PhD, J Welch); Oxford University Hospitals NHS Foundation Trust, Oxford, UK (Prof M Hu, J Welch); University of Edinburgh, Edinburgh, UK (G Duncan MD, K Power MPH,

S Gallen BSc, J Kerr BSc; Western General Hospital, Edinburgh, UK (G Duncan, K Power, S Gallen, J Kerr); King's College London, London, UK (Prof K R Chaudhuri MD, L Batzu MD, S Rota MD); King's College Hospital NHS Foundation Trust, London, UK (Prof K R Chaudhuri, L Batzu, S Rota); National Institute on Aging, Baltimore, MD, USA (Prof N Greig PhD, Y Li PhD); National Institute for Health Research, University College London Hospital Clinical Research Facility, London, UK (Prof V Libri MD); The Francis Crick Institute, London, UK (Prof S Gandhi PhD, D Athauda PhD)

Correspondence to: Prof Tom Foltynie, Department of Clinical and Movement Neurosciences, University College London Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK t.foltynie@ucl.ac.uk

Research in context

Evidence before this study

We searched PubMed using the terms "Parkinson's disease", "Exenatide", "Glucagon-like peptide-1", "GLP-1", "Neuroprotection", and "Disease modification" for all articles published in English before Sept 1, 2024. Multiple laboratories have confirmed neuroprotective properties of GLP-1 receptor agonists, including exenatide, using a variety of in-vitro cell models or in-vivo rodent models of Parkinson's disease. There have been two large epidemiology studies showing that the risk of subsequently developing Parkinson's disease among people with type 2 diabetes is reduced following treatment with GLP-1 receptor agonists. Two small trials conducted over 1 year have shown an advantage in motor progression among people treated with exenatide, and a larger trial with 1-year follow-up showed an advantage in motor progression among people treated with a similar drug, lixisenatide. A trial of a modified (pegylated) form of exenatide (NLY-01) conducted over 36 weeks did not show any benefits, although a subgroup analysis raised the possibility of motor benefits in participants younger than 60 years.

Added value of this study

This trial evaluated the effect of extended-release exenatide in the largest number of patients to date and is the longest trial of any GLP-1 agonist in people with Parkinson's disease, assessing effects of exenatide over a period of 96 weeks.

Implications of all the available evidence

We found no advantage of using exenatide compared with placebo among the general population of people with moderate-severity Parkinson's disease using conventional measures of motor and non-motor symptom progression. We also did not find evidence to support any advantage in younger participants. Further analyses of biofluids from participants will assess the extent of target engagement of exenatide, and post-hoc testing of subgroups of participants according to baseline biochemical characteristics is needed to identify whether there is a recognisable population that reliably respond to this intervention.

An open-label clinical trial of exenatide in 45 participants with moderately severe Parkinson's disease showed that participants treated with exenatide had a mean Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (motor subscore) score that was 4.9 points lower (improved) than in randomly assigned, open-label control participants at 12 months, which persisted after a further 12-month washout period.^{12,13} A subsequent double-blind, randomised controlled trial showed participants treated with exenatide for 48 weeks had a mean 3.5-point advantage in the MDS-UPDRS part III OFF-medication score compared with participants in the placebo group, and that this difference persisted after drug washout.¹⁴ Biological specimens collected from trial participants confirmed changes according to treatment with exenatide in neuronal insulin pathways.¹⁵ A 1-year phase 2 trial of a similar GLP-1 receptor agonist, lixisenatide, reported an advantage in MDS-UPDRS part III scores compared with placebo,¹⁶ although findings from a study exploring a pegylated form of exenatide found no overall benefit compared with placebo (although a benefit was seen in people younger than 60 years).¹⁷

We aimed to confirm if previous positive results relating to participants with Parkinson's disease treated with exenatide could be reproduced in a multicentre trial design, including a larger number of participants evaluated over a longer treatment period (96 weeks).

Methods

Study design

This investigator-initiated, phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled, trial with a 96-week exposure period was conducted in

six research hospitals in the UK. The trial was sponsored by University College London (UCL) and coordinated by the UCL Comprehensive Clinical Trials Unit. An independent data monitoring committee and trial steering committee had oversight of the trial, which was conducted in accordance with Good Clinical Practice. The trial received research ethics committee (initial date of approval Oct 15, 2019, research ethics committee reference number 19/SC/0447) and regulatory approvals (Medicines and Healthcare products Regulatory Agency clinical trial authorisation 20363/0406/001-0001), and is registered with ISRCTN (14552789), EudraCT (2018-003028-35), and ClinicalTrials.gov (NCT04232969). The protocol is in the appendix (pp 5–11).

Participants

Participants aged 25–80 years with a diagnosis of Parkinson's disease meeting Queen Square Brain Bank criteria¹⁸ were recruited. Detailed eligibility criteria have previously been published.¹⁹ Participants were at Hoehn and Yahr stage 2.5 or less when on dopaminergic treatment, on dopaminergic treatment for at least 4 weeks before enrolment, and able to self-administer the investigational medicinal product. Key exclusion criteria included a suspicion of another cause for parkinsonism, being unable to attend the clinic visits in the practically defined OFF-medication state, a BMI of less than 18.5 kg/m², clinically significant cognitive impairment defined by a score of less than 21 on the Montreal Cognitive Assessment (MoCA), and concurrent severe depression defined by a score of 16 or more on the Patient Health Questionnaire (PHQ-9). The OFF-medication state refers to the patient assessment conducted in the absence of their regular medication with the aim of exposing the

severity of the underlying Parkinson's disease. Patients attended the hospital in the morning having not taken any of their prescribed Parkinson's disease medication for 8 h (overnight) in the case of levodopa, or 36 h or longer in the case of longer-acting agents such as ropinirole or pramipexole prolonged release. This is a practically defined OFF-medication state, although long duration responses of dopaminergic medications are likely to have persisted in some participants.²⁰ Patients with previous exposure to exenatide, impaired renal function with creatinine clearance less than 50 mL/min, a history of pancreatitis, type 1 or type 2 diabetes, severe gastrointestinal disease, hyperlipidaemia, medullary thyroid cancer (or family history), and multiple endocrine neoplasia 2 syndrome, a known brain abnormality likely to compromise compliance with the trial protocol, previous intracerebral neurosurgical intervention for Parkinson's disease, participation in another clinical trial within the preceding 30 days, or known hypersensitivity to exenatide were also excluded. Female participants who were pregnant or breastfeeding, or those who were of child-bearing potential and unwilling to use an acceptable method to avoid pregnancy were excluded. All trial participants provided written informed consent. Participant sex data were self-reported as either male or female. Ethnicity was self-reported according to the following categories: White, mixed, Black or Black British, Asian or Asian British, other, or prefer not to say.

Randomisation and masking

Eligible participants were randomly assigned (1:1) to self-administer either exenatide or placebo. Randomisation was performed using a web-based system with minimisation according to Hoehn and Yahr stage and study site. Placebo was visually identical to the exenatide. An unblinded statistician generated unique five-digit identifiers for every active or placebo drug kit, which were then allocated to participants by the web-based system according to their randomisation outcome. The statistician had no involvement in the randomisation allocation. All participants and all research team members at study sites were masked regarding randomisation allocation. Separate team members were used to collect efficacy data from those collecting adverse event data.

The degree to which masking remained successful throughout the duration of the trial was not objectively assessed.

Procedures

Participants self-administered either extended-release exenatide 2 mg by subcutaneous pen injection once per week, or visually identical placebo by subcutaneous pen injection once per week for 96 weeks. The first dose was administered at the baseline assessment following injection teaching and subsequent injections were self-administered at home. Adherence to exenatide was reviewed by the trial team at each visit. Adjustments to concomitant medications for Parkinson's disease were

permitted as required according to standard of care, at the judgement of their treating physician. All concomitant medication use was recorded at every trial visit.

Participants attended detailed evaluations at baseline and at 24, 48, 72, and 96 weeks and shorter assessments at weeks 12, 36, 60, and 84. Assessments at detailed evaluations included the MDS-UPDRS parts I to IV, Hoehn and Yahr status, MoCA, the Non-Motor Symptom Scale (NMSS), PHQ-9, the Parkinson's Disease Quality of Life Questionnaire (PDQ-39), EQ-5D-5L, the Unified Dyskinesia Rating Scale (UDysRS), and the timed sit-stand-walk test. The MDS-UPDRS part III and timed walk tests were done in the OFF-medication state, defined as the scores obtained after withholding all short-acting conventional Parkinson's disease medications (levodopa-containing preparations) for at least 8 h and all long-acting conventional Parkinson's disease medications (dopamine agonists and monoamine oxidase inhibitors) for at least 36 h. These assessments were repeated in the ON-medication state, which was performed 1 h after the patient had taken all their usual medication. Participants' levodopa equivalent daily dose (LEDD) was calculated using published methodology²¹ at each detailed visit. Participants completed a 3-day Hauser diary before baseline and at weeks 48 and 96. Potential adverse events and safety blood tests were assessed during short and detailed assessments. Adverse events were recorded until 10 weeks after participants' last trial injections and were graded for severity according to International Conference on Harmonisation Good Clinical Practice guidelines.

Dopamine transporter–single-photon-emission CT (DaT–SPECT) imaging and cerebrospinal fluid (CSF) collection were performed at baseline and week 96 in consenting participants at the primary trial site (UCL). DaT imaging was performed 3 h after the injection of [¹²³I]ioflupane (DATSCAN, GE Healthcare, Chalfont St Giles, UK) using a SPECT scan of 40 min duration.

Seed amplification assay for α -synuclein was performed at the National Institutes of Health Rocky Mountain Laboratories (RML; Hamilton, MT, USA) using the baseline CSF samples as per an established protocol,²² with each sample analysed as four separate replicate reactions within a plate of samples. Application of both the RML and commercial α -synuclein assay (Amprion, San Diego, CA, USA) to CSF samples from participants in the Parkinson's Progressive Markers Initiative cohort, a large, long-standing cohort of patients with Parkinson's disease, sponsored by the Michael J Fox Foundation, has yielded concordant results.^{23,24}

Outcomes

The primary outcome was the MDS-UPDRS part III OFF-medication score at 96 weeks. Secondary outcomes were changes in MDS-UPDRS parts I–IV in the ON-medication state, the timed sit-stand-walk test in the OFF-medication and ON-medication states, the

For the web-based system see <https://www.sealedenvelope.com/>

See Online for appendix NMSS, PDQ-39, PHQ-9, EQ-5D-5L, MoCA, UDysRS, LEDD, and 3-day Hauser diary, as well as adverse events. The change in DaT-SPECT striatal binding ratio between baseline and week 96 was also studied as an exploratory endpoint. Assessment of plasma and CSF concentrations of exenatide was done in a blinded manner in duplicate across all samples as an exploratory endpoint by fluorescent ELISA immunoassay (FEK-070-94; Phoenix Pharmaceuticals, Burlingame, CA, USA) at the National Institute on Aging (Baltimore, MD, USA). Serum samples from the previous exenatide trial¹⁴ were tested simultaneously to allow comparison between trials.

Statistical analysis

The statistical analysis plan was finalised and approved on May 30, 2024, before database lock on June 19, 2024,

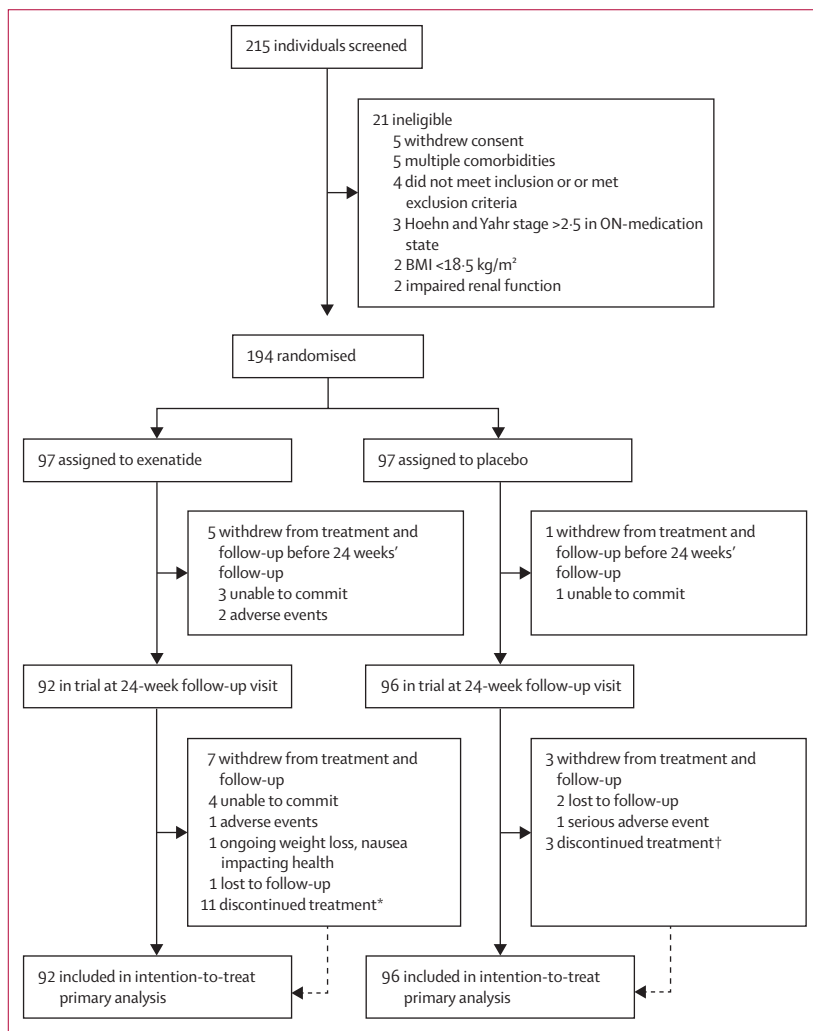


Figure 1: Trial profile

*Reasons for treatment discontinuation were adverse events (n=8), weight loss and worsening of Parkinson's disease (n=1), potential product complaint, unsatisfactory response, and unwilling to continue (n=1), and increased anxiety regarding comorbid health issues (n=1). †Reasons for treatment discontinuation were adverse events (n=1) and serious adverse events (n=2).

and is in the appendix (pp 112–142). The planned sample size of 200 participants divided equally between the two groups would provide 90% power to detect a difference of 5.0 MDS-UPDRS part III points in the OFF-medication state between the groups, adjusting for baseline MDS-UPDRS part III OFF-medication scores and assuming 20% attrition (withdrawal or loss to follow-up). The required evaluable sample size was 160. This effect size was a reasonable expectation based on the previous exenatide trial.¹⁴ The calculations were based on a common SD of 13.5, a correlation of 0.70 between the baseline and follow-up MDS-UPDRS measurements, and an overall type 1 error rate of 5%.

The primary analysis was conducted following the intention-to-treat principle, in accordance with the randomly assigned intervention. All randomly assigned participants with an outcome measure at baseline and at one follow-up timepoint were included in the primary analysis. Safety was analysed in all participants who were randomly assigned.

A linear mixed-effects model was used to estimate the difference between the groups for the primary and secondary outcomes and included fixed effects for treatment, baseline MDS-UPDRS part III OFF-medication scores, time (24, 48, 72, and 96 weeks) as a categorical variable, treatment and time interaction, and the minimisation factor Hoehn and Yahr status. A random site effect and patient effect was included to take account of clustering. Results are presented as an adjusted treatment effect and the associated 95% CI. Statistical tests were done using a two-sided significance level of 5%. A modified intention-to-treat analysis of the primary outcome was carried out, including all participants who completed 12 weeks on treatment and for whom outcome data were available.

A treatment adherence analysis was done using baseline characteristics (age, sex, ethnicity, BMI, Hoehn and Yahr status, LEDD, and MDS-UPDRS part III OFF-medication score) to model patients in the placebo group who would have potentially adhered to treatment ($\geq 80\%$ of the 96 weeks of injections administered) if allocated to the exenatide group, based on their baseline characteristics. We also did a predefined subgroup analysis of the primary outcome by participants' age at recruitment (<60 years), sex, age at diagnosis (<55 years), and Hoehn and Yahr stage. We did a preplanned sensitivity analysis to evaluate any potential impact on the primary outcome of differential changes in weight or BMI and LEDD.

After tomographic reconstruction, DaT-SPECT data analysis was performed by Datquant software (GE Healthcare) using a fully automated quantification method.²⁵ Striatal binding ratios of the DaT radiopharmaceutical were determined in the striata and striatal substructures (anterior and posterior putamen and caudate) compared with the occipital lobe, which represented non-specific uptake. A mean score for the

whole striatum and each subregion was determined by averaging right and left scores for further analysis. Wilcoxon paired sign rank tests were used to compare change in DaT-SPECT striatal binding ratio between baseline and 96 weeks in each group.

The number and severity of adverse events, as well as changes in vital signs, weight, BMI, and clinical laboratory measures, are summarised by treatment group throughout the trial period.

Statistical analyses were performed in Stata 18 (release 18).

Role of the funding source

The funders of the study provided feedback on the study design, but had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 23, 2020, and April 23, 2022, 215 participants were screened for eligibility, of whom 194 were recruited to the trial (figure 1). This was a shortfall of six participants compared with the planned recruitment total and occurred as a result of delays introduced by the COVID-19 pandemic and associated lockdowns, and the expiry date for exenatide that necessitated premature closure to recruitment. 97 participants were assigned to exenatide and 97 to placebo. 16 (8%) of 194 patients withdrew from the trial before 96 weeks and had missing MDS-UPDRS scores at the primary analysis timepoint (figure 1). 188 (97%) patients who had at least one follow-up visit were included in the mixed model for the primary outcome analysis. The power calculation required 160 evaluable patients to contribute to the primary outcome (allowing for 20% attrition).

Participants had a mean age of 60·7 years (SD 9·1), 56 (29%) were female, and 138 (71%) were male (table 1). The two groups were balanced in regard to participants' demographics and baseline measures of outcomes. The mean age at random assignment and at diagnosis of the 16 patients who withdrew from the trial was similar to the mean of all those randomly assigned.

At 96 weeks, OFF-medication scores in MDS-UPDRS part III had worsened (increased) by a mean of 5·7 points (SD 11·2) in the exenatide group and 4·5 points (11·4) in the placebo group (adjusted coefficient for effect of exenatide 0·92 [95% CI -1·56 to 3·39]; $p=0\cdot47$; figure 2 and table 2). The modified intention-to-treat analysis also showed no significant difference in primary outcome between the treatment groups (appendix p 1). Adherence data were available for 178 patients who completed the 96-week follow-up visit. 165 (93%) patients, 74 (87%) of 85 who continued follow-up in the exenatide group and 91 (98%) of 93 in the placebo group, administered 80% or more of the 96 weeks of injections. A treatment adherence analysis model did not have sufficient discriminatory ability to identify participants with

	Exenatide group (n=97)	Placebo group (n=97)	Total (n=194)
Age, years	61·02 (9·05)	60·35 (9·26)	60·68 (9·14)
Age at diagnosis, years	56·37 (9·60)	56·30 (9·53)	56·33 (9·54)
Weight, kg	79·57 (14·73)	78·39 (13·55)	78·98 (14·13)
Sex			
Female	28 (29%)	28 (29%)	56 (29%)
Male	69 (71%)	69 (71%)	138 (71%)
Ethnicity			
White	92 (95%)	88 (91%)	180 (93%)
Mixed	1 (1%)	1 (1%)	2 (1%)
Black or Black British	1 (1%)	0	1 (1%)
Asian or Asian British	3 (3%)	5 (5%)	8 (4%)
Other or prefer not to say	0	3 (3%)	3 (2%)
Hoehn and Yahr stage at randomisation			
≤2·0	83 (86%)	82 (85%)	165 (85%)
2·5	14 (14%)	15 (15%)	29 (15%)
BMI, kg/m ²	25·80 (23·50–28·60)	25·20 (23·10–28·00)	25·60 (23·40–28·10)
Levodopa equivalent daily dose	475 (340–615)	475 (300–700)	475 (300–90)

Data are mean (SD), n (%), or median (IQR). All 194 randomly assigned participants were on Parkinson's disease medication at baseline.

Table 1: Baseline characteristics

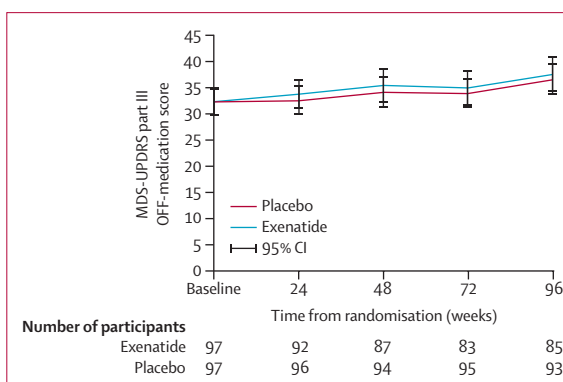


Figure 2: Mean MDS-UPDRS part III OFF-medication score by group over 96 weeks

MDS-UPDRS=Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale.

80% or more adherence in the placebo group based on predefined baseline characteristics. The mean MDS-UPDRS part III OFF-medication score among patients in the exenatide group who adhered to treatment was similar to that of patients in the placebo group at all timepoints (appendix p 2).

In the analysis of secondary outcomes, there were no significant differences between the groups in any of the sub-items of the MDS-UPDRS in the ON-medication state at 96 weeks (table 2). There were no significant differences between the exenatide and placebo groups in scores on the MoCA, PHQ-9, UDysRS, NMSS, PDQ-39 summary index, or EQ-5D-5L (table 3), nor in results on timed motor tests or Hauser diaries (appendix pp 3–4).

	Baseline	24 weeks	48 weeks	Change from 0 to 48 weeks	At 48 weeks		72 weeks	96 weeks	Change from 0 to 96 weeks	At 96 weeks		
					Adjusted coefficient* (95% CI)	p value				Adjusted coefficient* (95% CI)	p value	
Primary outcome: MDS-UPDRS part III OFF-medication												
Exenatide	32.2 (12.5)	33.8 (13.8)	35.4 (15.3)	3.5 (11.1)	0.94 (-1.53 to 3.40)	0.46	35.0 (15.2)	37.6 (15.2)	5.7 (11.2)	0.92 (-1.56 to 3.39)	0.47	
Placebo	32.3 (13.3)	32.5 (13.3)	34.1 (13.9)	2.0 (9.6)	33.9 (12.7)	36.6 (14.1)	4.5 (11.4)	
Secondary outcomes												
MDS-UPDRS part I ON-medication												
Exenatide	7.9 (4.9)	8.2 (5.4)	8.8 (5.7)	1.0 (3.7)	1.57 (0.51 to 2.63)	0.0038	8.3 (5.0)	8.9 (5.6)	1.1 (3.8)	0.31 (-0.76 to 1.38)	0.57	
Placebo	7.5 (4.8)	7.3 (4.6)	7.0 (4.3)	-0.4 (4.2)	7.4 (4.4)	8.3 (5.1)	0.9 (4.4)	
MDS-UPDRS part II ON-medication												
Exenatide	7.4 (4.9)	8.9 (6.2)	9.0 (5.9)	1.7 (3.7)	1.25 (0.04 to 2.47)	0.044	9.3 (6.7)	10.0 (6.9)	2.7 (5.1)	0.69 (-0.54 to 1.92)	0.27	
Placebo	7.5 (4.9)	8.1 (5.1)	7.9 (5.2)	0.4 (3.8)	8.0 (5.1)	9.4 (5.6)	2.0 (4.7)	
MDS-UPDRS part III ON-medication												
Exenatide	20.0 (10.2)	23.1 (13.0)	23.6 (13.2)	3.8 (10.3)	1.52 (-0.87 to 3.91)	0.21	24.5 (13.6)	25.5 (13.4)	5.7 (11.3)	0.74 (-1.66 to 3.14)	0.55	
Placebo	20.8 (10.4)	22.1 (11.0)	22.5 (11.9)	1.8 (8.2)	23.1 (11.3)	25.2 (11.0)	4.6 (8.9)	
MDS-UPDRS part IV ON-medication												
Exenatide	3.9 (3.3)	3.6 (3.2)	3.6 (3.1)	-0.1 (2.7)	-0.05 (-0.80 to 0.69)	0.89	3.4 (2.9)	3.8 (3.4)	0.1 (3.1)	-0.22 (-0.97 to 0.53)	0.57	
Placebo	3.8 (3.2)	3.8 (3.2)	3.8 (3.1)	-0.1 (3.0)	3.8 (3.4)	4.1 (3.6)	0.3 (3.3)	

Data are mean (SD) except where otherwise stated. MDS-UPDRS=Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale. *A negative coefficient indicates an advantage in the exenatide group and a positive coefficient indicates an advantage in the placebo group.

Table 2: MDS-UPDRS subscores

The change in LEDD levels over the course of the trial was the same in the two groups (table 3).

Preplanned subgroup analyses did not show any difference between the two groups in participants younger than 60 years at recruitment, nor according to sex, age at diagnosis, Hoehn and Yahr stage 1.0–2.0, or site of recruitment. Of the 66 participants who contributed CSF at baseline, 63 (95%) met fully defined criteria for α -synuclein seed amplification assay positivity (31 [100%] of 31 in the exenatide group and 32 [91%] of 35 in the placebo group). There was no difference between these subgroups who met criteria for the α -synuclein seed amplification assay positivity analysis of the primary outcome according to randomisation allocation, nor among people according to their BMI at baseline (appendix p 3).

77 participants underwent DaT-SPECT imaging at baseline, of whom 73 (36 in the exenatide group and 37 in the placebo group) had repeat DaT-SPECT imaging at 96 weeks. There was no difference in the change in striatal binding ratios between the groups for whole striatum, anterior or posterior putamen, or caudate nucleus.

Exenatide was generally safe and well tolerated. There were ten serious adverse events in the exenatide group and 12 in the placebo group (table 4). Transient increases in serum amylase were seen in nine (9%) participants in the exenatide group and one (1%) in the placebo group, but no participants had clinically confirmed pancreatitis. An allergic reaction to an injection occurred

in one (1%) participant on placebo. A further allergic reaction occurred in one (1%) participant in the exenatide group, but the timing of this serious adverse event made it considered to be unlikely to be related to trial injections. Gastrointestinal symptoms occurred more frequently in the exenatide group than in the placebo group. Participants in the exenatide group lost a mean of 1.8 kg (SD 4.9) over 96 weeks compared with 1.3 kg (4.1) in the placebo group (appendix p 3).

The mean plasma exenatide concentration among participants fully compliant with treatment was 1142 pg/mL (SD 409). The mean CSF exenatide concentration among participants fully compliant with treatment was 11.3 pg/mL (SD 3.7; approximately 1% of the plasma concentration). The mean serum exenatide concentration detected following repeat testing of samples from participants from the previous trial¹⁴ was 1137 pg/mL (SD 558).

Discussion

In this double-blind, randomised, placebo-controlled trial, including participants with moderate-severity Parkinson's disease, we found no advantage in the use of 2 mg extended-release exenatide by pen injection once per week compared with placebo on any measures of Parkinson's disease severity. This finding is in contrast to the positive results seen in a previous phase 2 trial of exenatide 2 mg once per week and a phase 2 trial of lixisenatide in participants with Parkinson's disease.¹⁴ We chose to use a long-term simple trial design to help

	Baseline	24 weeks	48 weeks	Change from 0 to 48 weeks	At 48 weeks		72 weeks	96 weeks	Change from 0 to 96 weeks	At 96 weeks	
					Adjusted coefficient (95% CI)	p value				Adjusted coefficient (95% CI)	p value
MoCA*											
Exenatide	27.8 (1.9)	..	27.6 (2.0)	-0.2 (1.7)	-0.34 (-0.84 to 0.16)	0.18	..	27.7 (2.4)	-0.1 (2.0)	-0.22 (-0.73 to 0.28)	0.39
Placebo	27.8 (1.8)	..	28.0 (1.8)	0.1 (1.8)	27.9 (2.1)	0.1 (1.9)
UDysRS†											
Exenatide	4.6 (7.1)	4.1 (7.3)	4.9 (8.8)	5.6 (8.4)	7.0 (11.0)	2.0 (8.9)	0.11 (-1.78 to 2.00)	0.91
Placebo	5.3 (8.4)	4.9 (8.1)	5.3 (8.8)	6.2 (9.6)	7.2 (11.0)	1.9 (7.6)
NMSS‡											
Exenatide	30.5 (24.9)	32.5 (25.8)	33.2 (30.0)	31.8 (25.7)	34.9 (26.0)	4.1 (20.4)	1.73 (-3.35 to 6.80)	0.51
Placebo	28.2 (24.0)	29.1 (26.3)	25.3 (22.0)	26.3 (21.9)	31.8 (25.2)	3.1 (19.6)
PDQ-39†											
Exenatide	11.9 (9.3)	12.7 (11.1)	12.2 (10.1)	12.4 (10.2)	13.3 (10.9)	1.5 (8.5)	0.72 (-1.35 to 2.79)	0.49
Placebo	10.6 (8.0)	10.1 (7.1)	9.9 (6.8)	9.1 (6.2)	11.8 (8.5)	1.3 (8.9)
EQ-5D-5L index*											
Exenatide	0.80 (0.18)	0.80 (0.16)	0.79 (0.18)	0.78 (0.17)	0.78 (0.17)	-0.03 (0.18)	-0.01 (-0.04 to 0.03)	0.78
Placebo	0.83 (0.12)	0.83 (0.17)	0.84 (0.13)	0.83 (0.14)	0.80 (0.18)	-0.04 (0.15)
EQ-5D-5L visual analogue scale*											
Exenatide	76.9 (14.4)	75.3 (13.0)	75.2 (13.5)	72.6 (16.1)	72.8 (16.8)	-4.9 (16.1)	-1.47 (-5.25 to 2.31)	0.45
Placebo	76.6 (16.3)	77.0 (14.4)	77.6 (14.3)	76.8 (13.7)	74.2 (16.7)	-2.7 (17.4)
PHQ-9†											
Exenatide	3.3 (3.1)	3.7 (3.5)	3.6 (3.7)	3.5 (3.4)	3.4 (3.4)	0.2 (3.1)	0.01 (-0.81 to 0.82)	0.99
Placebo	3.5 (2.9)	2.8 (3.0)	2.7 (3.1)	2.8 (3.2)	3.4 (3.4)	0.1 (3.5)
Levodopa equivalent dose, mg†											
Exenatide	97; 475 (340-615)	93; 530 (375-700)	86; 548 (400-700)	0 (0-100)	85; 600 (420-725)	85; 650 (490-805)	100 (0-275)
Placebo	97; 475 (300-700)	95; 480 (300-600)	94; 572 (375-767)	50 (0-125)	96; 595 (380-781)	93; 580 (400-850)	100 (0-240)

Data are mean (SD), n; median (IQR), or median (IQR), except where otherwise stated. MoCA=Montreal Cognitive Assessment. NMSS=Non-Motor Symptom Scale. PDQ-39=Parkinson's Disease Quality of Life Questionnaire. PHQ-9=Patient Health Questionnaire. UDysRS=Unified Dyskinesia Rating Scale. *A positive coefficient indicates an advantage in the exenatide group and a negative coefficient indicates an advantage in the placebo group. †A negative coefficient indicates an advantage in the exenatide group and a positive coefficient indicates an advantage in the placebo group.

Table 3: Secondary outcomes

disentangle any possible symptomatic effects from disease-modifying effects, but found no evidence for any clinical benefit on any outcome measure. Our chosen design was associated with high levels of patient retention and the data collected allow high levels of confidence in the results.

The population of participants with Parkinson's disease recruited in this trial were of similar age and disease severity to those recruited in the previous positive exenatide trial.¹⁴ The high positivity rates for the α -synuclein seed amplification assay (among participants who had CSF collected) provide some reassurance regarding the precision of diagnoses. However, the majority of participants did not have CSF collected;

therefore, the potential impact of Parkinson's disease misdiagnosis rate remains uncertain. The absence of any signal of clinical effect across patient-reported and clinician-reported outcome measures was mirrored by the absence of effect on DaT-SPECT imaging. We did not find any evidence to suggest a participant subgroup defined by age or BMI was more likely to respond to exenatide than other groups. Despite our efforts to be inclusive during recruitment, the majority of participants in the current trial were White; therefore, we have limited ability to explore whether exenatide might have different effects across ethnic subgroups.

In the previous positive phase 2 trial, 2 mg extended-release exenatide was self-administered over 48 weeks

	Exenatide (n=97)	Placebo (n=97)	Total (n=194)
Number of patients with at least one serious adverse event or serious adverse reaction	9 (9%)	11 (11%)	20 (10%)
Number of serious adverse events	10	13*	23*
Orthopaedic procedures	5	4	9
Abdominal cyst	0	1	1
Elevated alanine aminotransferase	1	0	1
Allergic reaction	1	1	2
Atrial flutter	1	0	1
Epistaxis	0	1	1
Elevated amylase level	0	1	1
Haematuria	0	1	1
Headache	0	1	1
Hospitalised for suspected angina	0	1	1
Open colposuspension and paravaginal repair	1	0	1
Other psychiatric disorders (anxiety, depression, suicidal ideation, confusion)	0	1	1
Squamous cell carcinoma	1	0	1
Viraemia	0	1	1
Number of patients reporting at least one adverse event	96 (99%)	92 (95%)	188 (97%)
Number of adverse events	689	492	1181
Skin disorders or injection site reactions	100	100	200
Nervous system disorders	61	54	115
Nausea	51	20	71
Infections and infestations including upper respiratory tract infection and urinary tract infection	49	45	94
Weight loss	36	23	59
Anorexia	33	7	40
Musculoskeletal disorders	30	16	46
Gastrointestinal disorders	27	9	36
Constipation	23	9	32
Diarrhoea	19	11	30
Fall	13	9	22
Fatigue	13	6	19
Surgical and medical procedures	12	8	20
Lethargy	12	2	14
Hypotension or syncope	11	0	11
Abdominal pain	10	3	13
Serum amylase increased	9	1	10
Vomiting	8	3	11
Bloating	7	9	16
Insomnia	7	9	16
Injury poisoning and procedural complications	7	3	10
Anxiety	6	3	9
Cardiac disorders	6	0	6
Other categories	139	142	281

*Including one serious adverse reaction.

Table 4: Adverse events

using the tray preparation,¹⁴ whereas in the current trial, the pen device over 96 weeks was used. To ensure comparability between trials, we conducted plasma exenatide ELISA assays for the current trial samples

alongside repeating the exenatide assays from serum samples remaining from the previous trial contemporaneously. There was no difference in the peripheral levels of exenatide as an explanation for the difference in the clinical results. We did not see any evidence of any difference between the exenatide group and the placebo group at 48 weeks in the current trial.

The mean weight loss in participants in the exenatide group was 1.8 kg compared with 1.3 kg in the placebo group (between-group difference in weight loss of 0.5 kg), whereas in the previous phase 2 trial,¹⁴ participants in the exenatide group had a mean weight loss of 2.6 kg compared with 0.6 kg in the placebo group (between-group difference in weight loss of 2.0 kg). In both trials, independent raters were used for all efficacy outcomes separately from individuals collecting adverse event data and providing clinical management advice, in an attempt to minimise rater bias. It is possible that the greater degree of weight loss seen in the phase 2 trial led to greater rates of unblinding of participants, which might have led to greater placebo effects among the active treatment group in that trial compared with this trial. Although we did not observe obvious placebo effects (manifesting as an improvement in scores on any measure) in either group, we cannot exclude that placebo effects contributed to a reduction in the rate of deterioration for individual participants.

Conversely, reduction in the extent of weight loss with exenatide might be indicative of insufficient target engagement in this trial. Although we cannot exclude a relationship between exenatide target engagement, magnitude of weight change, and clinical response for specific individuals, we did not identify any significant relationship between degree of weight loss and change in MDS-UPDRS part III scores, neither among all trial participants, nor when restricted to the exenatide group. Other peripheral side-effects of exenatide were similar between the two trials except that transient hyperamylasaemia was more frequently observed among participants in the exenatide group in the current trial than in the previous trial (n=9).

Although this trial did not detect therapeutic benefits of exenatide among people with Parkinson's disease, the laboratory data supporting neuroprotective actions of this GLP-1 receptor agonist class of drugs remain very strong. We have previously established that exenatide can penetrate the human CNS, but only at very low concentrations compared with serum (approximately 2% of the serum level).¹⁴ In the current trial, only 1% of the plasma concentration of exenatide was detected in CSF; however, the difference between these percentages should be interpreted with caution for several reasons. Although the peripheral exenatide concentrations might differ due to differences in the sensitivity of the ELISA technique comparing plasma exenatide concentrations in the current trial with serum exenatide concentrations taken in the earlier trial, the mean absolute concentrations of

exenatide detected in the CSF are similar in both trials (11.3 pg/mL vs 11.7 pg/mL). There is also some inconsistency introduced, as shown by our repeated testing of previously collected serum samples, which, on this occasion, showed a mean concentration of 1137 pg/mL (thus ensuring exact contemporaneous comparison of exenatide using identical laboratory reagents), but this differed from the original serum exenatide results reported from the same samples as 543 pg/mL. We did not have CSF still available from the earlier trial to allow contemporaneous comparisons of CSF concentrations. Therefore, we cannot rule out that the explanation for the negative results in this trial relates to insufficient CNS concentrations of exenatide. Accordingly, we believe further research regarding improving peripheral tolerability of higher doses of GLP-1 receptor agonists or enhancing the CNS penetration of GLP-1 receptor agonists to provide better target engagement is required. Previous attempts at achieving better target engagement using a pegylated formulation of exenatide (NLY01) have not yet led to clinical success.¹⁷ We cannot confirm whether benefits of NLY01 in analyses restricted to younger participants with NLY01 are indicative of a subgroup who might be more amenable to GLP-1 receptor agonist therapy.

There are further ongoing trials of semaglutide and liraglutide in populations with Parkinson's disease (NCT03659682) and Alzheimer's disease (NCT0477396 and NCT01843075), and the results of these trials will inform further on the necessity for CNS penetration, as these agents have been shown to have reduced CNS penetration in rodent models.^{26,27} Tolerability in relation to weight loss will likely also remain an issue for participants with low baseline BMI, especially in the semaglutide trial, which has greater potency for weight loss. There are also clear differences between GLP-1 receptor agonists on the basis of their signalling fingerprints in different subcellular compartments, which might differentially affect their potential efficacy in people with neurodegenerative diseases.²⁸

There are strong epidemiological data supporting a protective effect of GLP-1 receptor agonists against the development of Parkinson's disease among people with type 2 diabetes.^{10,11} Given the potential beneficial effects on improved glucose control against the complications of diabetes, such as cerebrovascular disease and peripheral neuropathy, we did not want to risk misinterpreting any impact of these mechanisms on balance, gait, limb tone, or cognition as being due to improvements in Parkinson's disease pathophysiology. We therefore deliberately excluded participants with type 2 diabetes from this trial. We cannot exclude the possibility that specific beneficial effects of exenatide might exist among people with comorbid type 2 diabetes and Parkinson's disease because of an impact of exenatide on accelerated neurodegeneration occurring as a result of peripheral or central insulin resistance (ie, whether there is a subgroup

of participants with Parkinson's disease with peripheral or central insulin resistance who might be more responsive to exenatide treatment). Both peripheral insulin resistance and hepatic insulin resistance (seen in association with non-alcoholic fatty liver disease) are associated with the production of peripheral neuro-inflammatory mediators that can access the CNS and exacerbate neuroinflammation and neurodegeneration.^{29,30} Therefore, it is possible that CNS penetration is not an essential prerequisite for efficacy of a GLP-1 receptor agonist on neurodegeneration in a subgroup of individuals where peripheral insulin resistance is a contributing factor. It is also possible that earlier intervention with a GLP-1 receptor agonist, for example in a prodromal cohort, might be of benefit in preventing onset of Parkinson's disease. However, there are as yet insufficient epidemiological data from non-diabetic patients using exenatide or other GLP-1 receptor agonists to support this.

The results of this trial are discordant with previous laboratory and epidemiology data and previous trial results. We aim to do further post-hoc analyses to try and explain the reasons for this inconsistency. We do not believe that the results of this trial completely discount the GLP-1 pathway as an important target for manipulation in neurodegenerative diseases, especially in view of further recent evidence from a study published in preprint⁶ supporting the neuroprotective potential of these drugs in the laboratory. Understanding target engagement within the trial will be crucial, and quantification of peripheral and central insulin resistance pathways, inflammation, and α -synuclein aggregates will provide information on whether exenatide at this dose modified central insulin resistance and downstream pathways. Future post-hoc analyses will also explore whether any subgroups defined according to biochemical assays, such as modestly elevated glycated haemoglobin A_{1c} levels, might have differential clinical, target engagement, or biochemical responses to exenatide.

Contributors

Data were collected by NV, CG, TF, CC, AP, JI, MS, BB, JWe, MH, JWh, GD, KP, SGal, JK, KRC, LB, and SR. Statistical analysis was performed by KC. DaT-SPECT analysis was performed by JD. CSF analysis was performed by EJ and HMo. Plasma and CSF exenatide levels were analysed by NG and YL. Trial coordination and operations were conducted by GA, RM, AK, SSS, SH, AW, SM, HMa, RG, PL, VL, SGan, and DA. TF and KC have both directly accessed and verified the data. TF had final responsibility to submit the data for publication. All authors had access to the data and had final responsibility for the decision to submit for publication.

Declaration of interests

TF has received grants from the National Institute of Health Research, Edmond J Safra Foundation, Michael J Fox Foundation, John Black Charitable Foundation, Cure Parkinson's, Innovate UK, Janet Owens Research Fellowship, Rosetrees Trust, Van Andel Research Institute, and Defeat MSA; has served on advisory boards for Peptron, Voyager Therapeutics, Handl Therapeutics, Gain Therapeutics, Living Cell Technologies, AbbVie, Bluebird bio, Bayer, and Bial; and has received honoraria for talks sponsored by Bayer, Bial, Profile Pharma, Boston Scientific, and Novo Nordisk. CC has received advisory, consulting,

or lecture fees from AbbVie, Bial, Britannia, Scient, Global Kinetics, Kyowa Kirin, Medscape, Mission Therapeutics, MODAG, and Roche, and research funding from Parkinson's UK, Edmond J Safra Foundation, National Institute of Health and Care Research, and Cure Parkinson's. MS has received grants from Parkinson's UK, Michael J Fox Foundation, and Medical Research Council; and has received honoraria for lecturing and consulting from Bial and Medtronic. DA has received grant funding from Cure Parkinson's, the National Institute for Health Research, and Medical Research Council Clinical Academic Research Partnership. EJ has received grant funding from Progressive Supranuclear Palsy Association, Cure Progressive Supranuclear Palsy, and Medical Research Council. GD has received honoraria for talks sponsored by GE Healthcare and AbbVie and support from Bial. JD has received consulting fees from Clario. HMO has received funding from Michael J Fox Foundation, Cure Parkinson's, Progressive Supranuclear Palsy Association, Corticobasal Degeneration Solutions, Drake Foundation, Parkinson's UK, and the Medical Research Council; has received consulting fees from Roche, Amylyx, and Aprinoia; and has received honoraria for speaking at meetings supported by Kyowa Kirin, The British Medical Journal, and Movement Disorders Society. All other authors declare no competing interests.

Data sharing

De-identified individual participant data from this trial that underlie the results reported in this Article will be shared with Critical Path for Parkinson's (<https://c-path.org/program/critical-path-for-parkinsons/>), beginning 9 months after publication of this Article.

Acknowledgments

Funding for the study was provided by the National Institute for Health and Care Research (NIHR; Efficacy and Mechanism Evaluation scheme number 16/167/19) with imaging (DaT-SPECT) funding by Cure Parkinson's. AstraZeneca provided the investigational medical product (exenatide) but were not involved in the design of the trial, analysis of data, or writing of the manuscript. This study was sponsored and coordinated by University College London (UCL) Comprehensive Clinical Trials Unit. Trial operations were supported by the NIHR University College London Hospitals (UCLH) Clinical Research Facility/Leonard Wolfson Experimental Neurology Centre and the NIHR UCLH/UCL Biomedical Research Centre at the UCL Institute of Neurology and the UCLH National Hospital for Neurology and Neurosurgery (London, UK). NV was supported by the Janet Owens Bequest. The analysis of exenatide concentrations was partly supported by the Intramural Research Program of the US National Institutes of Health's National Institute on Aging. This research was conducted with support from AstraZeneca UK. We are grateful to staff in pharmacies across trial sites who ensured accurate trial dispensing and laboratories who ensured safe handling and storage of trial research specimens. Exenatide and matched placebo packaging, labelling, storage, and distribution were performed at Royal Free London NHS Foundation Trust and WGK Clinical Group. We are grateful to members of our trial steering committee: Carl Clarke, Caroline Williams-Gray, Clive Bartram, Helen Matthews, Victoria Cornelius, and Zia Mursaleen. We are grateful to members of our independent data monitoring committee: David Burn, Lorna Aucott, Roger Barker, Oliver Bandmann, and Andrew Embleton-Thirsk. Most of all, we thank the people with Parkinson's disease and their families who participated in the trial, and who contributed to its design and conduct.

References

- Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet* 2021; **397**: 2284–303.
- Folynie T, Bruno V, Fox S, Kühn AA, Lindop F, Lees AJ. Medical, surgical, and physical treatments for Parkinson's disease. *Lancet* 2024; **403**: 305–24.
- Vijjaratnam N, Simuni T, Bandmann O, Morris HR, Folynie T. Progress towards therapies for disease modification in Parkinson's disease. *Lancet Neurol* 2021; **20**: 559–72.
- Perry T, Haughey NJ, Mattson MP, Egan JM, Greig NH. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. *J Pharmacol Exp Ther* 2002; **302**: 881–88.
- Kopp KO, Glotfely EJ, Li Y, Greig NH. Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: implications for neurodegenerative disease treatment. *Pharmacol Res* 2022; **186**: 106550.
- Athauda D, Evans JR, Mahoney-Sanchez L, et al. GLP1 receptor agonism ameliorates Parkinson's disease through modulation of neuronal insulin signalling and glial suppression. *BioRxiv* 2024; published online Feb 28. <https://doi.org/10.1101/2024.02.28.582460> (preprint).
- Chen S, Yu S-J, Li Y, et al. Post-treatment with PT302, a long-acting exendin-4 sustained release formulation, reduces dopaminergic neurodegeneration in a 6-hydroxydopamine rat model of Parkinson's disease. *Sci Rep* 2018; **8**: 10722.
- Athauda D, Folynie T. Insulin resistance and Parkinson's disease: a new target for disease modification? *Prog Neurobiol* 2016; **145-146**: 98–120.
- Yun SP, Kam TI, Panicker N, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nat Med* 2018; **24**: 931–38.
- 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.
- Tang H, Lu Y, Okun MS, et al. Glucagon-like peptide-1 receptor agonists and risk of Parkinson's disease in patients with type 2 diabetes: a population-based cohort study. *Mov Disord* 2024; **39**: 1960–70.
- Aviles-Olmos I, Dickson J, Kefalopoulou Z, et al. Exenatide and the treatment of patients with Parkinson's disease. *J Clin Invest* 2013; **123**: 2730–36.
- Aviles-Olmos I, Dickson J, Kefalopoulou Z, et al. Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease. *J Parkinsons Dis* 2014; **4**: 337–44.
- 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.
- Athauda D, Gulyani S, Karnati HK, et al. Utility of neuronal-derived exosomes to examine molecular mechanisms that affect motor function in patients with Parkinson disease: a secondary analysis of the Exenatide-PD trial. *JAMA Neurol* 2019; **76**: 420–29.
- Meissner WG, Remy P, Giordana C, et al. Trial of lixisenatide in early Parkinson's disease. *N Engl J Med* 2024; **390**: 1176–85.
- 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.
- 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**: 181–84.
- Vijjaratnam N, Girges C, Auld G, et al. Exenatide once weekly over 2 years as a potential disease-modifying treatment for Parkinson's disease: protocol for a multicentre, randomised, double blind, parallel group, placebo controlled, phase 3 trial: the 'Exenatide-PD3' study. *BMJ Open* 2021; **11**: e047993.
- Nagao K, Ding C, Ganga G, et al. Inferring the long duration response to levodopa in Parkinson's disease. *Parkinsonism Relat Disord* 2019; **60**: 133–37.
- 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.
- Groveman BR, Orrù CD, Hughson AG, et al. Rapid and ultra-sensitive quantitation of disease-associated α -synuclein seeds in brain and cerebrospinal fluid by α Syn RT-QuIC. *Acta Neuropathol Commun* 2018; **6**: 7.
- Russo MJ, Orrù CD, Concha-Marambio L, et al. High diagnostic performance of independent alpha-synuclein seed amplification assays for detection of early Parkinson's disease. *Acta Neuropathol Commun* 2021; **9**: 179.
- Rossi M, Candelise N, Baiardi S, et al. Ultrasensitive RT-QuIC assay with high sensitivity and specificity for Lewy body-associated synucleinopathies. *Acta Neuropathol* 2020; **140**: 49–62.
- Brogley JE. DaTQUANT: the future of diagnosing Parkinson disease. *J Nucl Med Technol* 2019; **47**: 21–26.

-
- 26 Salameh TS, Rhea EM, Talbot K, Banks WA. Brain uptake pharmacokinetics of incretin receptor agonists showing promise as Alzheimer's and Parkinson's disease therapeutics. *Biochem Pharmacol* 2020; **180**: 114187.
- 27 Rhea EM, Babin A, Thomas P, et al. Brain uptake pharmacokinetics of albiglutide, dulaglutide, tirzepatide, and DA5-CH in the search for new treatments of Alzheimer's and Parkinson's diseases. *Tissue Barriers* 2024; **12**: 2292461.
- 28 Wright SC, Motso A, Koutsilieri S, et al. GLP-1R signaling neighborhoods associate with the susceptibility to adverse drug reactions of incretin mimetics. *Nat Commun* 2023; **14**: 6243.
- 29 Spielman LJ, Little JP, Klegeris A. Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration. *J Neuroimmunol* 2014; **273**: 8–21.
- 30 Asimakidou E, Saipuljumri EN, Lo CH, Zeng J. Role of metabolic dysfunction and inflammation along the liver-brain axis in animal models with obesity-induced neurodegeneration. *Neural Regen Res* 2025; **20**: 1069–76.