A randomised, double-blind, placebo controlled trial of Exenatide once-weekly in Parkinson's disease

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Research in context

Evidence before this study

We searched Pubmed for articles published in English before December 4, 2016, using the terms "Parkinson's disease", "glucagon-like peptide-1", "exenatide", "trial", "neuroprotection" and "disease modification" in any field. We found several pre-clinical studies of exenatide, a glucagon-like peptide-1 agonist, which demonstrated neuroprotective and neurorestorative effects in experimental animal-toxin models of Parkinson's disease. We identified a single "proof-of-concept" study evaluating exenatide as a possible disease modifying treatment in patients with Parkinson's disease. In this open-label trial, 21 patients randomised to receive 12 months of exenatide injections in addition to their regular medication demonstrated a mean improvement of 2.7 points on the MDS-UPDRS Part 3 OFF medication, compared to a decline of 2.2 points in 24 patients in the control group that received their regular medication only (mean difference 4.9 points, 95% CI, 0.3-9.4; p=0.037). In addition, patients treated with exenatide had a significant improvement of 2.2 points on a cognitive assessment scale (the Mattis-DRS-2) in comparison to a decline of 2.8 points in the control group (mean difference 5.0 points, 95% CI, 9.2-0.8; p=0.006). There were persistent statistically significant benefits in the exenatide group versus controls in motor disability as assessed by the MDS-UPDRS Part 3 OFF score (5.6 points, 95% CI, 2.2 – 9.0; p = 0.002) and cognitive function as assessed by the Mattis-DRS-2 (5.3 points, 95% CI, 9.3–1.4; p = 0.006) 12 months after the withdrawal of exenatide; however, due to the lack of a placebo control, these data could not be interpreted as proof of efficacy.

Added value of this study

Our study is the first randomised, placebo-controlled trial of exenatide as a potential disease modifying agent in Parkinson's disease. After 48 weeks, patients treated with 2mg exenatide once-weekly had a significant advantage on the primary outcome measure- the MDS-UPDRS Part 3 scale compared to the placebo group, which persisted as a statistically significant advantage following the end of the drug washout period 12 weeks later. Our study is also the first to demonstrate that

exenatide administered at a dose licensed for treatment in diabetes, can cross the blood brain barrier in humans and is detectable in the CSF in concentrations not dissimilar from those in pre-clinical PD models associated with advantageous outcomes. Exenatide was well tolerated, although injection site reactions and gastrointestinal symptoms were reported.

Implications of all the available evidence

We have replicated the results of our previous clinical study and demonstrated that patients treated with exenatide had positive effects on the practically defined off-medication motor scores of Parkinson's disease in comparison to the placebo group, and that these effects were sustained at least partially beyond the period of exposure. Whether exenatide impacts the underlying pathophysiology of Parkinson's disease or simply induces long lasting symptomatic effects remains uncertain, however these results represent a major new avenue for investigation in the treatment of Parkinson's disease.

Summary

Background

Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist has neuroprotective effects in pre-clinical models of Parkinson's disease (PD).

Methods

In this single-centre, randomised, double-blind, placebo-controlled trial, patients with moderate stage PD were randomly assigned (1:1) to receive subcutaneous injections of exenatide 2mg once-weekly or matched placebo for 48 weeks in addition to their regular medication. Randomisation was by web-based randomisation service with a two strata block design according to PD severity. Patients and investigators were blinded to treatment allocation. The primary outcome was the adjusted difference in the Movement-Disorders-Society-Unified-Parkinson's-Disease-Rating-Scale (MDS-UPDRS) motor subscale (Part 3) in the practically defined OFF medication state at 60 weeks (i.e. following a 12 week exenatide washout period). The study is registered at Clinicaltrials.gov (NCT01971242).

Findings

62 patients were enrolled between 18 June 2014, and March 13, 2015. The primary analysis included 29 patients in the placebo group and 31 patients in the exenatide group. At 60 weeks patients in the placebo group had declined by 2.1 (95%CI -0.6, 4.8) points from baseline while the exenatide group improved by 1.0 (95%CI -2.6, 0.7) – a mean difference of 3.5 points (95%CI -6.7 to -0.3, p=0.0318) favouring the exenatide group. Injection site reactions and gastrointestinal symptoms were common adverse events in both groups. There were 8 serious adverse events; 6 in the exenatide group and 2 in the placebo group though none were judged to be related to the study interventions.

Interpretation

Patients treated with exenatide had positive effects on the practically defined off-medication motor scores of PD in comparison to the placebo group, that were sustained beyond the period of exposure. Whether exenatide impacts the underlying disease pathophysiology or simply induces long lasting symptomatic effects is uncertain, however these results suggest that exenatide represents a major new avenue for investigation in the treatment of PD, and effects on everyday symptoms should be performed in future longer term trials.

Funding

Michael J. Fox Foundation for Parkinson's Research.

INTRODUCTION

Perhaps the most important unmet need in Parkinson's disease (PD) is the development of a neuroprotective or disease-modifying therapy that may slow or halt disease progression. To date none of the compounds that have indicated potential neuroprotective properties in in-vitro or animal models have conclusively demonstrated any effects on disease progression in clinical trials[1].

Glucagon-like peptide-1 (GLP-1) agonists are licensed for the treatment of Type 2 diabetes. These agents activate GLP-1 receptors to promote glucose-level-dependent insulin secretion, inhibit glucagon secretion and slow gastric emptying[2]. Exenatide is a synthetic version of exendin-4, a naturally occurring analog of human GLP-1 originally discovered in the saliva of the Gila monster (*Heloderma suspectum*), and resistant to the normal metabolic processes that degrade endogenous human GLP-1[3]. In addition to effects on glucose homeostasis, evidence from toxin-based rodent models of PD demonstrate that exenatide crosses the blood-brain-barrier and exerts neuroprotective and neurorestorative effects, mediated via GLP-1 receptors, at doses comparable to those used to treat Type 2 diabetes, resulting in improvements in motor performance, behaviour, learning and memory[4–8].

We previously conducted a small, proof of concept, open label trial of exenatide in moderate severity PD patients. Twelve months exposure to exenatide led to improvements in motor and cognitive assessments compared to the control group[9], which persisted 12 months following drug withdrawal[10]. Based on these encouraging observations, our primary aim was to conduct a randomised, placebo-controlled trial (Clinical trials.gov Identifier NCT01971242) to further assess the potential disease modifying effects of 48 weeks exposure to exenatide followed by a 12 week exenatide washout, on the motor severity of PD.

METHODS

Study Design

This study was a randomised, double blind, placebo controlled, single centre, 60 week trial of exenatide once weekly for the treatment of moderate severity PD. The trial utilised a parallel-group, "washout" design, comprising an initial 48-week exposure period to exenatide 2mg subcutaneous injection once-weekly, or matched placebo, followed by study drug withdrawal and a final assessment 12 weeks later. The study was co-ordinated by the UCL Comprehensive Clinical Trials Unit. Clinical oversight of the trial was provided by a trial steering committee, an independent data and safety monitoring board and was approved by the local ethics committee. Trial operations were supported by the Leonard Wolfson Experimental Neuroscience Centre and the National Institute of health research (NIHR) Biomedical Research Centre at the UCL Institute of Neurology and UCLH-National Hospital for Neurology and Neurosurgery, London, UK.

Patients

Eligible patients were men and women aged between 25 and 75 years old with idiopathic PD based on Queen Square Brain Bank criteria[11], were on dopaminergic treatment with wearing off phenomena, and were at Hoehn and Yahr stage 2.5 or less when on PD medication. Key exclusion criteria (See trial protocol for full list) included concurrent dementia (defined as score <120 points on the Mattis-Dementia Rating scale (DRS-2) and patients with Body mass index <18.5. Patients with diabetes (glycated haemoglobin [HbA1c] ≥ 48mmol/l at screening) were also excluded. All patients signed a written informed consent before entry into the study.

Randomisation

Randomisation was by a web-based randomisation service (Sealedenvelope.com) with a block design of two strata according to PD severity (H&Y 1.0-2.0 and H&Y 2.5). Patients were randomised (1:1) to self-administer exenatide once weekly 2mg subcutaneous injections or matched placebo injections, in addition to their regular medications. Unique 3 digit identifiers for every active/placebo drug kit were generated by the trial statistician and uploaded to Sealedevenlope.com in order to allow allocation of masked study drug kits (sufficient for 12 weeks) at randomisation and follow up visits

by assessing clinicians. Patients and investigators were blinded to treatment allocation throughout the study. Exenatide and matched placebo injection kits were provided by Astra Zeneca and were identical in appearance. Empty drug vials and questionnaires were collected at each visit to assess compliance.

Study procedures

At screening, each patient had a physical and neurological examination, assessments of mood and cognition, blood sampling for clinical laboratory tests and a pregnancy test for women of childbearing potential. Electrocardiogram and [^{123}I]FP-CIT SPECT (Datscan) imaging were also performed. Following confirmation of patient eligibility, subsequent visits were performed at baseline (0) and at weeks 12, 24, 36, 48 and 60. Patients were supplied with study drug kits sufficient for 12 weeks and instructed how to assemble and self-administer the once-weekly, subcutaneous injections. At each visit, patients attended in the OFF medication state – defined as a period of withdrawal of levodopa for at least 8 hours (overnight) or 36 hours in the case of longer acting agents such as ropinirole, pramipexole, rasagiline or rotigotine. Patients were evaluated with the Movement Disorders Society Unified Parkinson's Disease rating Scale (MDS-UPDRS) and timed motor tests (10m timed walk, timed keyboard taps in 30 seconds utilising a novel web based program – Braintaptest.com) by a dedicated trial team. They also had repeat motor assessments approximately 1 hour after taking their regular PD medications (to allow uniformity across patients) alongside assessments of cognition, dyskinesia, quality of life, mood and non-motor symptoms.

After 48 weeks, study drugs were withdrawn. A final clinical assessment and repeat Datscan imaging was performed at 60 weeks. Blood and urine were collected at each visit and cerebrospinal fluid was collected at week 12 and 48 for exenatide pharmacokinetic measurements. Changes in concurrent medication were permitted throughout the trial period (to minimise patient drop out) and the levodopa equivalent dose (LED) was calculated at each visit[12]. To prevent the possibility of adverse events compromising rater blinding, all adverse events, biochemical results, vital signs (blood

pressure and heart rate) and weight were recorded separately, by clinicians also blinded to treatment allocation.

Outcomes

The primary outcome was to compare the difference in MDS-UPDRS Part 3 score in the practically defined OFF medication state at 60 weeks, according to treatment allocation. Predefined secondary outcomes were the differences between exenatide and placebo in each subsection of the MDS-UPDRS in the ON states and the Mattis DRS-2 at both the 48 and 60 week time-points. Additional secondary measures included adverse event frequency, changes in vital signs, weight and clinical laboratory values. Exploratory outcomes included the differences between groups in; dopamine transporter availability as measured by Datscan[13]; timed motor tests in both OFF and ON states; the Unified Dyskinesia Rating Scale (UDysRS); Montgomery and Asberg Depression Rating Scale (MADRS); Non-Motor Symptoms severity scale (NMSS); the Parkinson's disease questionnaire-39 (PDQ39); 3 day Hauser diary of PD state; EuroQol five dimensions questionnaire (EQ-5D)-3L and levodopa equivalent dose (LED).

Statistical Analysis

All study analyses were performed according to a predefined Statistical Analysis plan using STATA/MP (StataCorp, Version 14.1 MP, College Station, TX, USA) and SPSS (IBM, Version 21.0. Armonk, NY: IBM Corp). The primary outcome analysis was to evaluate the impact of treatment allocation (exenatide or placebo) on the difference between MDS-UPDRS part 3 scores in the practically defined "OFF" state at 60 weeks follow up (i.e. after any possible symptomatic effects of exenatide should have washed out). The analysis used a regression (ANCOVA, analysis of co-variance) approach to adjust for stratification factors (Hoehn and Yahr stage) and baseline raw MDS-UPDRS part 3 values. Using previously collected pilot data[9] and using a two-sided 5% significance level, we estimated a sample size of 60 patients would be required to detect a difference of 5.8 MDS-UPDRS points between the 2 groups. The calculations were based on a common standard deviation of 13, 90% power and an overall type 1 error rate of 5%. In addition, a correlation of 0.85

was assumed between the baseline and follow up MDS-UPDRS measurements. All efficacy analyses were based on a modified intention-to-treat principle and included all patients who completed any post randomisation follow up assessments.

Differences in continuous motor and non-motor outcome measures in the ON medication state were estimated using the same regression approach adjusted for stratification factors (Hoehn and Yahr stage) and baseline scores and were additionally adjusted for any change from baseline in LED to account for the possible confounding effect of PD medication changes during the trial. Comparison of gastrointestinal (GI) adverse events between treatment groups were performed using chi-squared tests. Further exploration to ascertain whether there was any relationship between observed treatments effects and possible confounding factors such as weight loss and change in LED were performed using Pearson's correlation. A post-hoc exploratory analysis on the primary outcome (MDS UPDRS part 3 Off medication scores) additionally adjusted for change from baseline in LED was also subsequently conducted to address the possibility that differential increases in LED may have confounded motor assessments even in the OFF medication state.

Statistical parametric mapping (SPM 12, Wellcome Department of Imaging Neuroscience) was used to perform a quantitative analysis of the Datscan data. Baseline and delayed images for each subject were smoothed and coregistered before spatial normalisation into Montreal Neurological Institute space via a Datscan template. Using a fully flexible model, and following image scaling, differences in loss of Datscan uptake between baseline and 60 week scans according to randomisation allocation were assessed with a univariate ANCOVA, adjusting for baseline differences in Datscan signal, Hoehn and Yahr stage and change in LED at 60 weeks. Further analysis was also performed to assess the differences in the changes between the two allocations. The resulting statistical parametric maps were masked to limit differences to bilateral caudate and putamen regions at a height threshold of $P<0.01$ uncorrected for multiple comparisons, and an extent threshold of 10 voxels.

Role of funding source

The funder of the study (MJFF) had no role in the data collection, data analysis, or in the writing of the report. The funder did make helpful comments in the original study design, as well as in the data interpretation at a post trial feedback meeting. A planned interim analysis was performed after 60 subjects completed 24 weeks follow up. The change in the MDS-UPDRS Part 3 score between baseline and 24 weeks was compared between placebo and exenatide treated groups. The analysis was performed by the trial statistician at UCL CCTU, who ensured the trial team remained blinded to treatment allocations. The results of the interim analysis were communicated to the IDMC only and recommendations to continue the trial based on recruitment, and adverse event profiles only, were communicated to both the TSC and the Michael J Fox Foundation who remained blinded to individual treatment allocation**.** All authors had full access to all of the data in the study, and TF had responsibility for the final decision to submit the report for publication.

RESULTS

Between 18 June 2014, and March 13 2015, 68 patients were screened for eligibility, having completed telephone pre-screening against inclusion/exclusion criteria. Of these, 62 underwent randomisation to either exenatide or placebo (Figure 1). Baseline characteristics of all patients included in the final analysis are presented in Table 1. Patients randomly allocated to exenatide were slightly older, had higher baseline MDS-UPDRS part 3 scores and had lower LED. Based on questionnaires and collection of empty drug vials at each visit, treatment compliance with study drugs was judged to be excellent for all patients (58 patients reported not missing a single dose).

At 60 weeks (end of the 12 week washout period), patients in the placebo group had declined by 2.1 (95%CI -0.6, 4.8) points in the MDS-UPDRS Part 3 OFF medication state while the exenatide group improved by 1.0 (95%CI -2.6, 0.7) - conferring a significant advantage of 3.5 points favouring the exenatide group (95%CI -6.7, -0.3, p=0.0318) (Table 2 and Figure 2). At 48 weeks (end of the study drug exposure period), the placebo group had declined by 1.7 (95%CI -0.6, 4.0) points while the exenatide group improved by 2.3 (95%CI -4.1, -0.7) points, resulting in a significant advantage of 4.3 points (95%CI -7.1, -1.6, p=0.0026) compared to the placebo group. There were no statistically

248 significant differences in MDS-UPDRS part 1,2 and 4, nor in the MDS-UPDRS part 3 in the ON
249 medication state (Table 2). There was only 1 participant who had missing data for the 60 week visit,
250 therefore no sensitivity analyses for the primary outcome were performed.

251 Table 3 presents the data for the remaining secondary outcome measures. There were no
252 statistically significant differences in the Mattis-DRS2, MADRS, UDysRS, NMSS, PDQ39 summary
253 index and EQ5D-3L, nor were there differences in the timed motor tests or Hauser diaries between
254 exenatide and placebo treated groups.

255 Although there was no significant difference in total LED at 60 weeks between the exenatide and
256 placebo treated groups, patients treated with exenatide had a mean 19.4mg higher increase in LED
257 at the end of the trial compared with placebo. To address this as a possible unanticipated
258 confounding effect on the primary outcome, a post hoc exploratory analysis additionally adjusting
259 for differences in LED from baseline was performed. This showed that the exenatide treated group
260 maintained a significant advantage of 3.6 MDS-UPDRS part 3 points in the off medication state (95%
261 CI -6.8 to -0.4, p=0.0294) at 60 weeks and 4.4 points (95 CI -7.2 to -1.6, p=0.0023) at 48 weeks
262 compared to the placebo group. There was no significant correlation between the change in LED and
263 change in the primary outcome (rho =0.17, p= 0.3588).

264 Figure 3 presents the Datscan data analysis. SPM analysis contrasted to show regions with
265 decreased Datscan binding between the first and the second scan showed significant declines in
266 both groups. The contrasts to show differences in rate of decline between groups, (adjusted for
267 baseline scan differences, Hoehn and Yahr stage and change in LED at 60 weeks) height thresholded
268 at $p<0.01$ uncorrected with an extent threshold of 10 voxels, indicated a reduced rate of decline of
269 Datscan binding in the exenatide group compared to the placebo group in the right putamen (x, y, z:
270 22, 8, 22; T= 2.98, 24voxels), p=0.0018 (uncorrected); left putamen (x, y, z: -26, -18, 10; T=2.76, 12
271 voxels), p=0.0034 (uncorrected); and right caudate (x, y, z: 26, 20, 6; T=3.83, 10voxels), p=0.0001
272 (uncorrected).

The median peak serum exenatide concentration in patients randomised to exenatide was 543.3pg/ml, and was undetectable in the placebo group. Exenatide patients had median CSF levels 11.4pg/ml at 12 weeks and 11.7pg/ml at 48 weeks, while all placebo patients had CSF levels below the limit of the assay specificity.

There were an equal number of adverse effects in both groups (Table 4). Weight change occurred in both groups but was more common in the exenatide treated group. At 48 weeks patients in the exenatide group lost a mean of 2.6kg (95% CI -4.0 to -1.2) in comparison to patients in the control group who lost 0.6kg (95% CI -1.9 to 0.8). There was no significant correlation between the degree of weight loss and change in the primary outcome (rho =0.30, p= 0.0986). Other GI symptoms associated with exenatide occurred in both groups, however there was no statistically significant association between the presence/absence of weight loss/ nausea/ loss of appetite/ abdominal pain and treatment allocation $X^2(1)= 0.388$, p= 0.5330. There were 8 serious adverse events; 6 occurred in the exenatide group and 2 in the placebo group though none were judged to be related to the study interventions. There were no other clinically relevant changes in biochemical indices or vital signs.

Three patients discontinued the study drug prior to 48 weeks but continued follow up assessments as per protocol. 1 patient in the exenatide group had asymptomatic hyperamylasemia at 12 weeks (pre-defined as a rise greater than 50% above baseline level and the laboratory reference range) and the study drug was withdrawn; 2 patients in the placebo group discontinued injections after 9 and 36 weeks due to worsening anxiety and dyskinesia respectively. An emergency unblinding procedure was required for 1 patient in the placebo group who developed pancreatic cancer shortly following the end of the trial monitoring period.

DISCUSSION

In this study, moderate severity PD patients treated with exenatide for 48 weeks had a statistically significant advantage of 4.3 points on the MDS-UPDRS Part 3 in the practically defined OFF medication state compared with placebo, that persisted as a statistically significant 3.5 point advantage 12 weeks after stopping exenatide. There were no significant differences in the scores of

MDS-UPDRS Part 1, 2 and 4, and in assessments of cognition (Mattis-DRS2), mood (MADRS), dyskinesia (UDysRS), non-motor symptoms (NMSS) and quality of life (PDQ39 summary index and EQ5D-3L). Adverse events were not significantly different between the 2 groups and were not significantly related to change in motor scores. The study exploited the ready availability of patients at the moderate stages of PD, and utilised the fluctuating nature of symptom severity according to dopaminergic treatment to judge disease progression by performing all assessments in the early morning in the "practically defined OFF-medication state". Patients with moderate stage PD with wearing off phenomenon were recruited in preference to de novo or "early" stage PD in part to; minimise inclusion of patients with atypical forms of parkinsonism; to facilitate speed of recruitment and minimise the number of necessary recruiting centres hence reducing costs; to minimise the risk of differential dropout among treatment naive patients receiving placebo; and to limit floor effects on rating assessment scales.

The simple washout trial design we chose also enabled rapid and cost efficient data collection in comparison to more complex and expensive pivotal trial designs such as "Delayed start", "Randomised withdrawal" or "Long term simple" approaches. The study was a single centre study which eliminated inter-site variability in data collection, and potentially facilitated the detection of significant effects despite the small sample size, and had an extremely low dropout rate (only 1.7% of data was missing for the primary outcome). Patients were also permitted to seek medication adjustments via their treating clinicians throughout the trial, similar to routine clinical practice in PD, which may have also contributed to patient retention.

Exenatide was well tolerated in this patient group, who reported its previously recognised adverse effects including gastrointestinal symptoms and injection site reactions in similar frequencies to previously reported diabetes trials[14], none of which affected compliance. Early observational studies have suggested that exenatide may be associated with pancreatic cancer however more recent studies have found no significant association[15]. Asymptomatic hyperamylasaemia was reported in one patient treated with exenatide necessitating drug withdrawal. Exenatide can induce amylase secretion in vitro and increased amylase levels have been reported in patients with Type 2 diabetes

treated with similar agents[16], and this seems a possible explanation (although the contribution of other co-morbid conditions cannot be excluded). Patients lost a mean of 2.6kg which reversed on drug cessation. Excessive weight loss (>10% of body mass index during a 12 week interval) necessitated temporary withdrawal of the study drug in only 1 patient (assigned to placebo).

Our study had some limitations. Firstly, in order to ensure preservation of blinding of the rating of PD severity, we specified that recording of adverse events and measurement of vital signs and weight was performed by independent clinicians, however there remains the possibility that patients might have been partially unblinded to their treatment allocation as a result of adverse effects (though injection site reactions were similar across both groups). In addition the small size of our study meant that despite randomisation, with a block design according to Hoehn & Yahr status, the exenatide group had MDS-UPDRS Part 3 scores 5.7 points higher at baseline, while being on 51.6mg lower LED than the placebo group, confirming the necessity that these baseline differences were adjusted for in the primary analysis. Our statistical analyses suggest that none of the differences in our outcome measures are however explicable by differences in adverse events, baseline disease severity or adjustment to conventional PD medications.

To allow us to recruit patients already treated with dopaminergic replacement, we were compelled to use the practically defined off-medication MDS UPDRS part 3 scores as our primary outcome measure. While this provides a better insight into disease severity than on-medication scores, it is possible that additional variability in scores may relate to differences in timing since last PD medication, despite the consistent instructions given to patients, and all assessments being done at consistent times in the morning. This is of particular importance since the differences we observed in off-medication scores were not supported by statistically significant differences in our clinical secondary outcome measures. This is likely to be due in part to the major effects of dopaminergic replacement on any scores assessed in the on-medication state, (which reflects the usual situation of patients). Whether the lack of change in the off-medication timed tests or diaries relate to differences in the sensitivity or precision within these measures, and the small sample size recruited in the trial, or the stage of disease of the population selected for study needs to be further explored.

Interestingly, in this patient population, there was little evidence of any placebo effect in the control group. In contrast, among exenatide treated patients, improvements in MDS-UPDRS part 3 scores were already detectable at the 12 week time-point suggesting that this agent might have symptomatic effects on PD. Furthermore, the advantage seen in the exenatide group at 48 weeks was greater than the advantage seen by the 60 week time-point also potentially indicative of a symptomatic effect. Nevertheless, the persisting advantage seen at 60 weeks makes it impossible to exclude the possibility that exenatide exposure has a longer lasting impact on PD severity, above and beyond conventional drug effects on dopaminergic receptors.

The demonstration that exenatide might have novel symptomatic effects in PD is an important discovery in the treatment of this disease. Pre-clinical studies suggest exenatide can normalise dopaminergic function in lesioned rodents[5,17], but whether symptomatic effects relate to improvement in functioning in surviving dopaminergic neurons or via an impact on the pharmacokinetics of L-dopa or other dopaminergic therapies requires further study. Beyond the identification of an agent which might have novel symptomatic effects in PD, our original aim and study design was to assess whether the long lasting advantages we have previously seen in an open label trial might be reproducible in a placebo controlled design. Having demonstrated a statistically significant difference in our pre-defined primary outcome, further investigation into exenatide as a potential disease modifying treatment for PD must also be warranted.

Distinguishing between long lasting symptomatic effects, and effects which impact on the underlying disease pathophysiology have been the subject of previous discussions with no simple solution[18,19]. Most notably, rasagiline, approved for symptomatic treatment in PD, demonstrated inconclusive results in a delayed start study designed to assess its effects on disease progression[20]. In our washout design, it is tempting to view persistent benefits detectable after the washout period as evidence of disease modification. Although exenatide was undetectable in the serum at 60 weeks, we have to consider that the 12 week washout period may have been insufficient to eliminate unexpected long-lasting symptomatic effects, contributing to the benefits seen in motor function and other modalities. Indeed, PD severity can be altered by symptomatic therapies that induce

preservation of healthy behaviours such as exercise which can have long term impacts without affecting the underlying neuropathological process[21].

The possibility that exenatide may in fact have neuroprotective effects is supported by robust pre-clinical studies which indicate that exenatide affects pathological mechanisms relevant to PD[22]. This includes inhibitory effects on inflammation[5,8], promotion of mitochondrial biogenesis[23,24], neurotrophic effects[25,26], stimulation of neurogenesis[7], and restoration of neuronal insulin signalling[27]. Whether some or all of these mechanisms contributed to the clinical effects seen in this study cannot yet be definitively answered, but it is possible that one or several of these mechanisms act in synergy to promote cell survival, preserving and preventing compensatory and maladaptive responses respectively.

Our Datscan analysis used statistical parametric mapping, which is a modern approach for the statistical analysis of imaging changes that can also allow for adjustment of baseline differences[28] and has been used previously in PD clinical trials[29]. Although overall uptake of Datscan declined in both groups, a quantitative analysis performed using SPM suggests a possible reduced rate of decline in the binding in the exenatide group. However, given that this signal was only detectable at uncorrected height thresholds of p=0.0034 or less, this data would benefit from larger confirmatory studies, and/or recruiting patients at an earlier disease stage when the rate of change of Datscan uptake is greater[30], making group differences more readily detectable.

We have shown that 12 months of treatment with exenatide has a statistically significant impact on the MDS UPDRS Part 3 in the practically defined OFF state, however it did not appear to have a statistically significant impact on PD severity or quality of life above and beyond that delivered by dopaminergic replacement. Longer term exposure using a “long-term simple”, multi-site trial design will be necessary to determine the long term consequences of exenatide treatment on daytime function in PD and specifically whether it can delay the development of dopa-refractory symptoms in PD. Furthermore, since the development of exenatide, additional GLP-1 receptor agonists have been developed based either on the structure of exendin-4 or human GLP-1. Although comparative

clinical efficacy data to support the use of one agent against another are few, there are some studies which suggest significant differences in glycaemic control and frequency of adverse events between agents in diabetes trials[31,32], and preliminary data indicate that some may exert greater neuroprotective effects than others[33,34]. While the current study has also confirmed for the first time that exenatide administered at a dose licensed for treatment in Type 2 diabetes, can cross the blood brain barrier in humans and can access the CSF in concentrations equivalent to those in pre-clinical PD models associated with advantageous outcomes[6,25], further studies investigating the safety, efficacy and CNS penetration of other members of this drug class, in parallel with mechanism of action studies will help to clarify the eventual role that GLP-1 receptor agonists might play in PD. Furthermore the potential relevance of these agents to other neurodegenerative disorders (such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis) and other neurological diseases (cerebrovascular disorders, traumatic brain injury)[32], is the subject of ongoing preclinical studies/ clinical trials.

In conclusion, we have replicated the findings from our previous open label study and demonstrated that exenatide treatment is associated with positive and persistent effects on the practically defined off-medication motor scores. Whether this drug acts as a novel symptomatic agent or whether it also influences compensatory responses/behaviours, or indeed has neuroprotective effects on the underlying pathology still remains uncertain, but nevertheless there is now a strong indication that this group of drugs may play a useful role in the future treatment of PD patients.

Contributors

TF (Principal Investigator) was responsible for study design, study oversight, statistical analysis, data interpretation and critical review and writing of the manuscript. TF, SS, KC, DA were involved in the statistical analysis and data interpretation. DA, NB and LZ recruited and followed up the patients. JD, DA were involved in Datscan acquisition and data analysis. KM, MBJ, DL, DA, SH, IAO, TW, PL, AL, ST were responsible for study oversight and critical review of the manuscript. NHG, YL were involved in

acquisition of exenatide pharmacokinetic data and critical review of the manuscript. DA wrote the first draft, and all authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

Declaration of interests

DA, KM, SS, MBJ, DL, KC, SH, NB, LZ, JD, ST, IAO declare no competing interests. AL reports grants from Frances and Renee Hock Fund, consulting fees from Britannia Pharmaceuticals (Genus), BIAL Portela, honoraria from Profile Pharma, Teva, Lundbeck, BIAL, Roche, Britannia, UCB, Nordiclnfu Care, NeuroDerm, Decision Resources; NHG is a named inventor on a NIH patent describing the use of GLP-1 receptor agonists for neurodegenerative disorders. All rights to this patent belong solely to the US Government, and not to NHG. TW received honoraria from Britannia Pharmaceuticals. PL has received honoraria from Medtronic and St. Jude Medical. TF has received honoraria from Profile Pharma, BIAL, Abbvie, Genus, Medtronic, and St Jude Medical.

Acknowledgements

We thank the patients and their families who participated in the Exenatide-PD trial. This study was funded by the Michael J. Fox Foundation for Parkinson's Research and co-ordinated by the UCL Comprehensive Clinical Trials Unit. Representatives of Astra Zeneca were provided with a copy of the protocol and final trial manuscript before submission, but had no role in the conduct of the trial, data analysis or the preparation of the manuscript. Serum and CSF evaluation of exenatide levels was undertaken in a blinded manner in duplicate across all samples by fluorescent ELISA immunoassay (Cat # FEK-070-94, Phoenix Pharmaceuticals, USA) at NIA, Baltimore, MD, USA. This analysis was supported in part by the Intramural Research Program of the NIH, National institute on Aging. A full copy of the trial protocol is available at; https://www.ucl.ac.uk/exenatide-pd

455

456 **Figure legends**

457 Figure 1. Following randomisation, 2 patients withdrew from the study prior to the first follow up (12
458 weeks); 1 patient from the group randomised to exenatide was unable to tolerate OFF medication
459 assessments and 1 patient from the placebo group withdrew consent. Given that these individuals
460 therefore could not contribute any data to the primary outcome, both were replaced (as per
461 protocol) and all of the eventual 60 patients who completed at least the initial 12 week follow up
462 were included in the primary analysis. One patient randomised to exenatide was found to have
463 asymptomatic hyperamylasemia at 12 weeks and the study drug was withdrawn. Two patients in the
464 placebo group discontinued the study drug at 9 and 36 weeks due to worsening anxiety and
465 worsening dyskinesia respectively.

466

467 Figure 2 (a). MDS-UPDRS part III (OFF medication) score by study visit. Data represents mean ± SEM.

468 Figure 2(b). Change in MDS-UPDRS part III OFF medication by study visit (data represents mean ±
469 SEM)

470

471 Figure 3. ANCOVA comparing decline in Datscan binding between placebo and exenatide treated
472 groups. Panel A – Placebo group showing reduced Datscan binding in the left caudate, right caudate,
473 left putamen. Panel B – Exenatide group showing reduced Datscan binding in the left caudate and
474 right caudate. Panel C – Significant clusters derived from the first level of analysis used to perform an
475 ANCOVA between placebo and exenatide groups indicating a reduced rate of decline in the right
476 caudate, left putamen and right putamen. Panel D – Boxplots showing mean change in Datscan
477 binding ratio for the relevant volume of interest. Montreal Neurological Institute of standardized
478 space are shown in each slice.

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Table 1. Patient characteristics at baseline (excludes 2 patients recruited but who did not complete any follow up visits).

Characteristic	**Exenatide N = 31**	**Placebo N = 29**
Age - years (SD)	61.6 (8.2)	57.8 (8.0)
Gender Female – no. (%) Male – no. (%)	 9 (29.0) 22 (71.0)	 7 (29.1) 22 (75.9)
Age at diagnosis – years (SD)	55.9 (7.9)	52.2 (7.7)
Duration of diagnosis at baseline - years (SD)	6.4 (3.3)	6.4 (3.3)
Hoehn & Yahr Stage Stage 1.0 – 2.0 – no. (%) Stage 2.5 – no. (%)	 29 (93.5) 2 (6.5)	 29 (100.0) 0 (0.0)
MDS-UPDRS Part3 at baseline OFF medication – points (SD)	32.8 (9.7)	27.1 (10.3)
Levodopa equivalent dose – mg (SD)*	773.9 (260.9)	825.7 (215.0)

Table 2. MDS-UPDRS scores between baseline and Week 60.

	Baseline	12 weeks	24 weeks	36 weeks	48 weeks	Change, Baseline to 48 weeks	Adjusted difference, baseline to 48 weeks	60 weeks	Change, Baseline to 60 weeks	Adjusted difference, baseline to 60 weeks
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI) P value	Mean (SD)	Mean (95% CI)	Mean (95% CI) P value
In OFF medication state										
MDS-UPDRS Part 3										
Exenatide	32.8 (9.7)	30.3 (10.9)	30.6 (10.8)	31.2 (11.3)	30.2 (11.1)	-2.3 (-4.1, -0.7)	-4.3 (-7.1, -1.6) 0.0026	31.9 (12.0)	-1.0 (-2.6, 0.7)	-3.5 (-6.7, -0.3) 0.0318
Placebo	27.1 (10.3)	27.6 (11.8)	28.5 (11.0)	28.6 (9.5)	28.8 (10.8)	1.7 (-0.6, 4.0)		29.2 (12.0)	2.1 (-0.6, 4.8)	
In ON medication state										
MDS-UPDRS Part 1										
Exenatide	9.8 (4.8)	8.6 (4.2)	8.3 (3.6)	8.0 (4.2)	8.8 (4.4)	-1.0 (-2.4, 0.4)	-1.3 (-3.4, 0.8) 0.21	9.3 (4.0)	-0.5 (-2.0, 1.1)	-1.2 (-3.2, 0.8) 0.22
Placebo	9.2 (3.8)	8.7 (5.0)	8.9 (4.4)	9.3 (4.6)	9.7 (5.6)	0.5 (-1.2, 2.2)		10.1 (5.3)	0.7 (-0.8, 2.3)	
MDS-UPDRS Part 2										
Exenatide	12.5 (6.7)	10.9 (7.0)	11.2 (7.4)	11.7 (7.8)	11.7 (6.3)	-0.7 (-2.1, 0.7)	-0.6 (-2.7, 1.5) 0.58	11.6 (6.6)	-0.8 (-2.2, 0.6)	-0.6 (-2.7, 1.5) 0.55
Placebo	10.7 (5.3)	10.2 (5.6)	11.1 (6.0)	10.1 (6.1)	10.8 (5.6)	0.1 (-1.6, 1.9)		11.0 (6.7)	0.2 (-1.4, 1.8)	
MDS-UPDRS Part 3										
Exenatide	19.4 (8.4)	19.3 (9.1)	20.4 (9.7)	19.6 (8.8)	20.5 (9.5)	1.1 (-0.8, 3.0)	-0.002 (-2.4, 2.4) 0.99	19.9 (10.3)	0.5 (-1.9, 3.0)	0.7 (-2.1, 3.6) 0.61
Placebo	14.4 (8.2)	15.4 (8.3)	16.0 (7.1)	16.7 (7.7)	15.7 (7.1)	1.3 (-0.4, 3.0)		14.5 (7.1)	-0.02 (-1.8, 1.8)	
MDS-UPDRS Part 4										
Exenatide	4.7 (3.1)	4.1 (3.4)	4.2 (2.0)	4.6 (2.5)	4.9 (2.5)	0.3 (-0.9, 1.4)	-0.5 (-1.8, 0.9) 0.48	5.2 (2.3)	0.5 (-0.5, 1.6)	-0.6 (-2.1, 0.9) 0.42
Placebo	5.3 (3.0)	5.8 (2.7)	5.2 (3.2)	5.3 (3.4)	5.6 (3.0)	0.3 (-0.9, 1.5)		6.1 (3.7)	0.7 (-0.7, 2.1)	

Table 3. Scores for Mattis-DRS2, UDysRS, MADRS, NMSS, PDQ-39 Summary index, Keyboard taps in 30seconds, 10m Timed walk, patient diaries, LED and vital signs between baseline and Week 60 according to randomisation allocation. All scores in ON-medication state. *Higher scores reflect improved status on these scales.

Domain		Baseline	12 weeks	24 weeks	36 weeks	48 weeks	Change Baseline to 48 weeks	Adjusted difference, baseline to 48 weeks	60 weeks	Change Baseline to 60 weeks	Adjusted difference, baseline to 60 weeks
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI) P value	Mean (SD)	Mean (95% CI)	Mean (95% CI) P value
Cognition	**In ON-medication state**										
	MATTIS Dementia Rating scale *										
	Exenatide	138.0 (5.0)	139.0 (6.1)	139.5 (4.2)	140.3 (3.7)	139.7 (4.1)	1.7 (0.4, 2.9)	0.4 (-1.0, 1.9) 0.57	139.9 (3.6)	1.9 (0.6, 3.1)	0.8 (-0.9, 2.5) 0.32
	Placebo	139.8 (3.7)	140.3 (3.1)	139.7 (5.8)	140.3 (4.1)	140.2 (3.9)	0.4 (-0.6, 1.5)		140.2 (4.6)	0.4 (-1.1, 1.8)	
Dyskinesia	**Unified Dyskinesia Rating Scale**										
	Exenatide	5.4 (7.9)	5.4 (8.0)	4.4 (6.5)	5.6 (7.9)	5.1 (7.1)	-0.3 (-2.3, 1.8)	-0.8 (-3.6, 1.9) 0.53	6.2 (7.2)	0.8 (-1.7, 3.3)	-1.6 (-5.1, 1.8) 0.35
	Placebo	7.3 (9.4)	6.8 (9.7)	6.9 (9.8)	6.8 (9.9)	7.4 (10.7)	0.1 (-1.7, 1.8)		9.0 (12.4)	1.7 (-0.8, 4.2)	
Mood	**MADRS**										
	Exenatide	4.1 (3.7)	3.4 (3.5)	2.2 (1.8)	2.7 (3.1)	2.5 (2.7)	-1.6 (-3.4, 0.07)	-1.4 (-3.2, 0.5) 0.15	2.1 (2.6)	-1.6 (-2.7, -0.4)	-0.9 (-2.2, 0.3) 0.15
	Placebo	3.7 (3.0)	2.9 (3.8)	3.5 (4.4)	3.9 (4.4)	3.8 (4.2)	0.2 (-1.8, 2.2)		2.8 (2.6)	-0.9 (-2.3, 0.5)	
Non motor symptoms	**NMSS**										
	Exenatide	24.6 (19.8)	17.7 (15.4)	16.4 (12.4)	16.5 (10.3)	19.7 (12.4)	-4.9 (-11.6, 1.8)	-4.0 (-11.8, 3.8) 0.30	22.3 (14.2)	-2.3 (-9.6, 5.1)	-3.3 (-11.7, 5.1) 0.43

	Placebo	28.3 (24.7)	22.0 (22.4)	22.1 (20.2)	23.1 (21.6)	25.8 (22.8)	-2.5 (-9.5, 4.6)		27.6 (23.3)	-1.5 (-9.0, 6.0)	
Quality of Life	**PDQ-39 Summary index**										
	Exenatide	19.9 (13.7)	17.1 (10.7)	16.8 (10.6)	17.2 (11.4)	18.7 (12.7)	-1.2 (-4.7, 2.3)	-1.7 (-5.6, 2.1) 0.38	18.4 (11.1)	-1.5 (-5.4, 2.4)	-3.3 (-8.0, 1.5) 0.17
	Placebo	21.1 (13.0)	17.8 (10.9)	18.6 (14.2)	20.5 (15.6)	20.1 (12.8)	-1.1 (-4.2, 2.1)		22.2 (14.8)	0.3 (-3.4, 4.0)	
	EQ5D Index*										
	Exenatide	0.71 (0.20)	0.72 (0.17)	0.76 (0.14)	0.81 (0.14)	0.74 (0.23)	0.03 (-0.07, 0.12)	0.06 (-0.03, 0.15) 0.21	0.72 (0.18)	0.005 (-0.08, 0.09)	-0.003 (-0.09, 0.09) 0.95
	Placebo	0.79 (0.16)	0.72 (0.19)	0.77 (0.14)	0.75 (0.16)	0.74 (0.14)	-0.05 (-0.10, 0.002)		0.75 (0.14)	-0.06 (-0.12, 0.01)	
	EQ5D VAS (%) EQ5D VAS*										
	Exenatide	73.6 (14.5)	72.3 (13.7)	71.5 (15.6)	71.4 (16.6)	70.1 (15.6)	-3.2 (-8.9, 2.5)	6.9 (-1.0, 14.8) 0.08	68.1 (14.4)	-5.6 (-12.2, 1.1)	5.3 (-3.0, 13.5) 0.21
	Placebo	74.5 (16.0)	68.6 (13.2)	68.5 (18.7)	69.0 (19.7)	64.7 (20.5)	-9.3 (-15.4, -3.1)		65.1 (20.2)	-10.6 (-16.4, -4.8)	
Timed motor tests	**In OFF-medication state**										
	Right hand taps in 30sec*										
	Exenatide	46.5 (9.9)	48.3 (10.7)	48.5 (13.8)	46.9 (12.4)	47.9 (11.2)	1.1 (-2.5, 4.8)	-1.1 (-5.8, 3.6) 0.69	46.6 (12.1)	0.4 (-3.0, 3.8)	1.1 (-4.3, 6.4) 0.64
	Placebo	53.9 (13.1)	54.0 (13.0)	52.2 (12.2)	52.9 (11.4)	50.5 (11.0)	-3.1 (-7.8, 1.7)		52.7 (9.8)	-1.0 (-4.5, 2.5)	
	Left hand taps in 30 sec*										
	Exenatide	47.8 (9.3)	48.8 (9.4)	49.0 (10.5)	48.3 (8.7)	47.7 (9.8)	0.3 (-2.7, 3.3)	-0.9 (-4.8, 2.9) 0.69	47.2 (9.7)	-0.6 (-3.8, 2.6)	0.2 (-4.0, 4.4) 0.62

	Placebo	50.6 (11.5)	52.6 (11.8)	50.2 (11.0)	49.9 (10.5)	49.7 (10.2)	-0.9 (-4.6, 2.8)		49.5 (9.7)	-0.3 (-3.0, 2.3)	
	10m Timed walk (sec)										
	Exenatide	17.2 (4.5)	16.2 (7.8)	17.3 (9.6)	16.7 (8.1)	17.4 (11.1)	0.2 (-3.1, 3.4)	0.8 (-4.6, 6.1) 0.69	19.5 (16.5)	2.5 (-2.5, 7.5)	-0.7 (-4.2, 2.8) 0.78
	Placebo	17.1 (6.3)	16.2 (5.4)	16.4 (7.1)	14.8 (4.8)	16.6 (8.8)	-0.5 (-2.9, 1.9)		19.1 (16.0)	1.8 (-2.5, 6.1)	
	In ON-medication state										
	Right hand taps in 30sec*										
	Exenatide	52.8 (11.7)	53.0 (12.0)	51.5 (11.9)	51.5 (12.9)	51.3 (12.9)	-1.5 (-7.0, 3.9)	-3.2 (-8.4, 2.1) 0.28	52.6 (11.4)	-0.7 (-5.7, 4.3)	-3.4 (-9.6, 2.8) 0.23
	Placebo	59.1 (14.5)	59.3 (11.6)	59.3 (12.4)	59.7 (10.0)	57.6 (10.3)	-1.3 (-5.9, 3.4)		58.7 (11.5)	0.4 (-2.9, 3.7)	
	Left hand taps in 30 sec*										
	Exenatide	52.9 (10.0)	49.8 (12.7)	50.6 (10.1)	50.5 (10.8)	49.0 (10.2)	-4.1 (-7.4, -0.9)	-1.2 (-5.2, 2.8) 0.18	50.9 (12.0)	-2.1 (-5.3, 1.2)	-2.9 (-7.1, 1.4) 0.54
	Placebo	56.6 (13.0)	56.3 (12.1)	55.8 (10.3)	56.3 (10.0)	54.6 (11.9)	-2.2 (-5.6, 1.2)		54.1 (10.8)	-1.1 (-3.4, 1.2)	
	10m Timed walk (sec)										
	Exenatide	15.2 (2.7)	14.9 (3.4)	14.7 (3.3)	14.4 (3.3)	15.1 (5.5)	-0.03 (-1.5, 1.4)	-1.5 (-4.6, 1.6) 0.61	15.0 (5.8)	-0.1 (-1.6, 1.4)	0.3 (-0.9, 1.6) 0.35
	Placebo	14.7 (3.1)	14.3 (3.2)	14.4 (3.7)	14.2 (3.3)	13.6 (3.0)	-1.1 (-1.8, -0.4)		15.3 (7.5)	0.6 (-2.4, 3.7)	
Patient Diaries	**Hauser Diary - Asleep (%)**										
	Exenatide	30	29	30	31	30			28		
	Placebo	26	26	27	27	27			25		

	Hauser Diary - OFF (%)										
	Exenatide	17	14	15	12	16			18		
	Placebo	20	20	17	19	20			22		
	Hauser Diary-On without dyskinesia (%)										
	Exenatide	49	53	48	52	49			50		
	Placebo	49	50	50	48	47			47		
	Hauser Diary- On with non-troublesome dyskinesia (%)										
	Exenatide	3	3	5	4	5			5		
	Placebo	3	2	5	3	4			4		
	Hauser Diary- On with troublesome dyskinesia (%)										
	Exenatide	1	4	2	1	1			5		
	Placebo	1	2	1	3	2			3		
Vital signs	**Blood Pressure - Mean Arterial Pressure (mmHg)**										
	Exenatide	95.4 (15.8)	95.8 (12.1)	96.2 (11.5)	93.8 (12.2)	96.8 (11.0)	1.4 (-2.7, 5.6)		95.8 (13.6)	0.4 (-4.2, 4.9)	
	Placebo	94.2 (7.9)	93.1 (11.2)	93.8 (9.1)	93.8 (9.5)	95.0 (9.6)	0.8 (-2.2, 3.7)		95.2 (7.6)	1.3 (-2.1, 4.7)	
	Weight (kg)										
	Exenatide	81.8 (16.6)	80.0 (16.3)	79.3 (16.5)	78.1 (15.9)	79.2 (16.1)	-2.6 (-4.0, -1.2)		80.9 (16.6)	-0.9 (-2.6, 0.7)	

	Placebo	80.8 (12.9)	80.1 (14.3)	80.2 (14.0)	79.5 (13.6)	80.2 (13.3)	-0.6 (-1.9, 0.8)		80.5 (14.3)	-0.09 (-1.5, 1.3)	
Levodopa Equivalent doses (LED)	**Levodopa Equivalent dose (mg)**										
	Exenatide	773.9 (260.9)	804.5 (288.3)	851.7 (336.5)	849.3 (368.6)	895.6 (337.7)	121.8 (47.7, 195.8)		906.1 (328.8)	132.2 (61.5, 203.0)	
	Mean Change per visit		↑30.6	↑47.2	↓2.4	↑46.3			↑10.5		
	Placebo	825.7 (215.0)	828.8 (225.4)	897.5 (225.0)	883.3 (218.9)	913.0 (243.4)	87.3 (-2.4, 177.1)		942.7 (235.2)	112.6 (40.7, 184.4)	
	Mean Change per visit		↑3.1	↑68.7	↓14.2	↑29.7			↑29.7		
Medication	**PD medication by drug class (n=)**										
	Exenatide										
	L-DOPA	31	31	31	31	31			31		
	DA agonist	24	25	24	24	24			24		
	MAO-B	17	17	17	17	17			17		
	Placebo										
	L-DOPA	29	29	29	29	29			29		
	DA agonist	23	23	25	25	25			25		
	MAO-B	13	13	14	14	15			15		

Table 4. Serious adverse events and adverse events reported (per event) according to randomisation allocation.

		Exenatide	Placebo	Total
Serious Adverse Event				
Fall*		2	0	2
Atrial flutter**		1	0	1
Acute urinary retention		1	0	1
Collapse		1	0	1
Significant weight loss***		0	1	1
Faecal impaction		0	1	1
Postural hypotension		1	0	1
Total		**6**	**2**	**8**
Adverse Event				
Injection site reaction		27	26	53
Weight loss from baseline****		24	18	42
	0-2kg	11	10	
	2-4kg	2	3	
	>4kg	11	5	
Nausea		16	10	26
Other pain		13	11	24
Constipation		12	11	23
Increased OFF time		8	12	20
Diarrhoea		8	6	14
Weight gain from baseline****		7	11	18
Lower urinary tract symptoms		6	7	13
Sleep disorder		3	6	9
Abdominal pain		5	3	8
Increased dystonia		3	5	8
Back pain		2	5	7
Upper respiratory tract infection		5	3	8
Dyskinesia		2	3	5
Loss of appetite		3	1	4
Anxiety		2	1	3
Freezing		1	2	3
Urinary tract infection		0	3	3
Hyperamylasemia		1	1	2
Rash		1	1	2
Vomiting		2	0	2
Fever		1	0	1

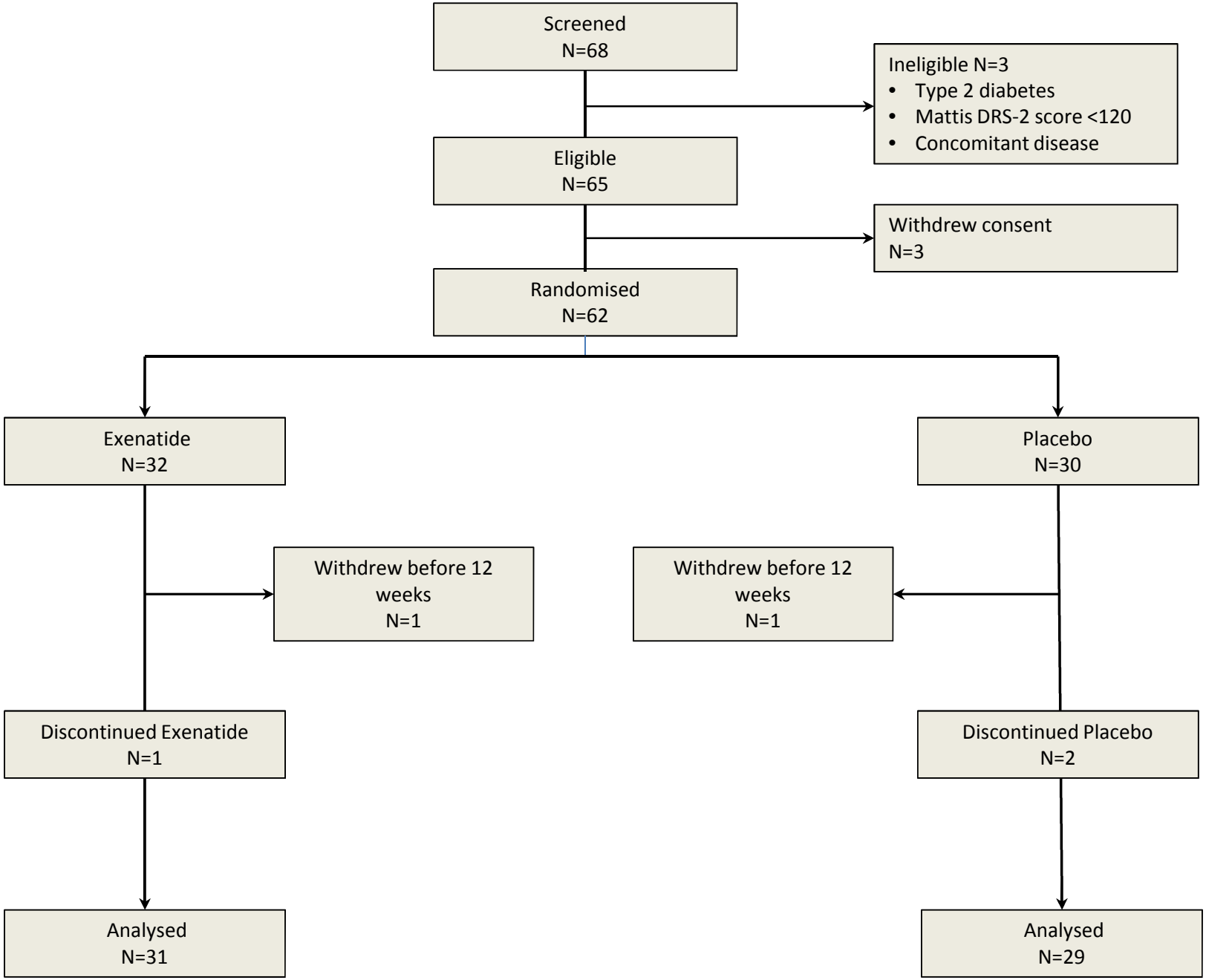
Worsening tremor	0	1	1
Miscellaneous	64	46	110
Total	**216**	**193**	**409**

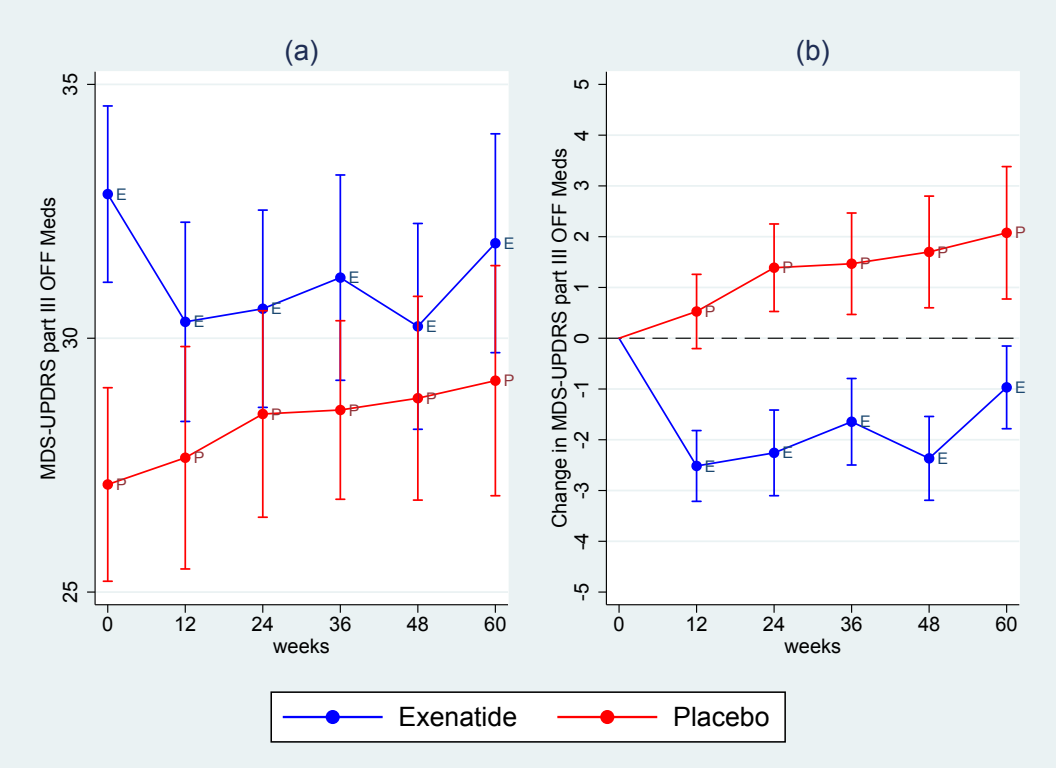
*One fall occurred in an individual prior to randomisation

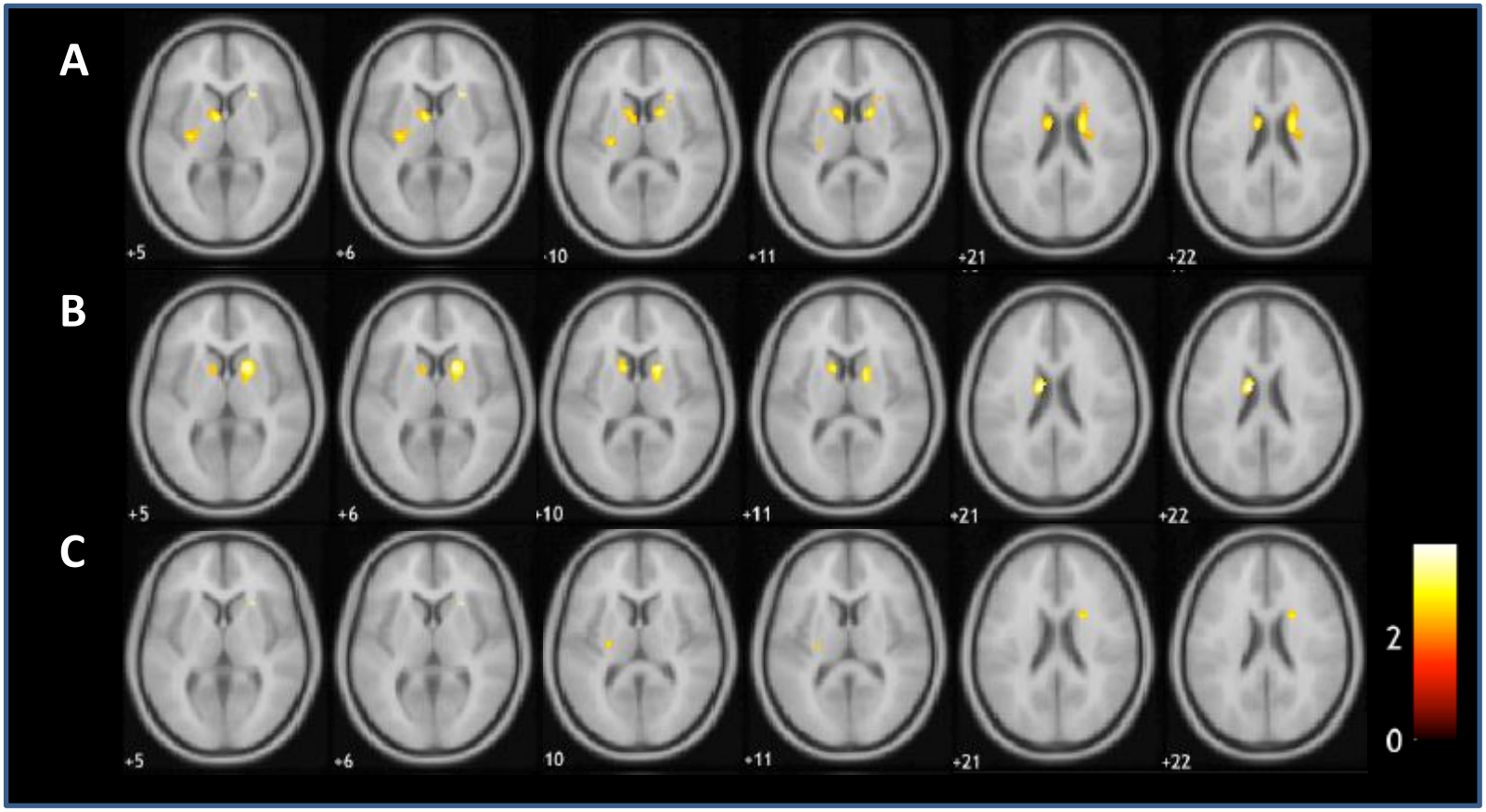
**Occurred prior to first dose of exenatide

*** Defined as loss of weight of >10% BMI in 12 week period

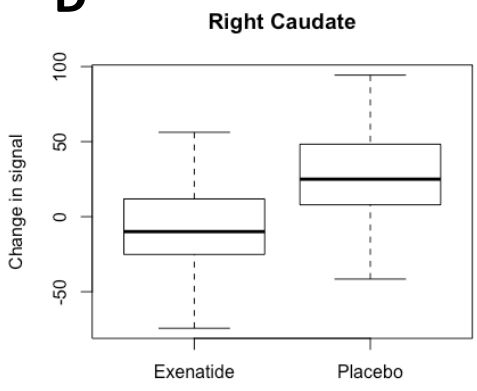
****After 48 weeks exenatide / placebo exposure- (figures for weight change are presented per patient rather than per event).

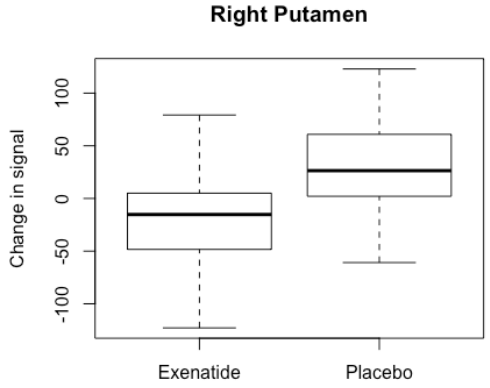

Screened
N=68
Ineligible N=3
• Type 2 diabetes
• Mattis DRS-2 score <120
• Concomitant disease
Eligible
N=65
Withdrew consent
N=3
Randomised
N=62
Exenatide
N=32
Placebo
N=30
Withdrew before 12 weeks
N=1
Withdrew before 12 weeks
N=1
Discontinued Exenatide
N=1
Discontinued Placebo
N=2
Analysed
N=31
Analysed
N=29

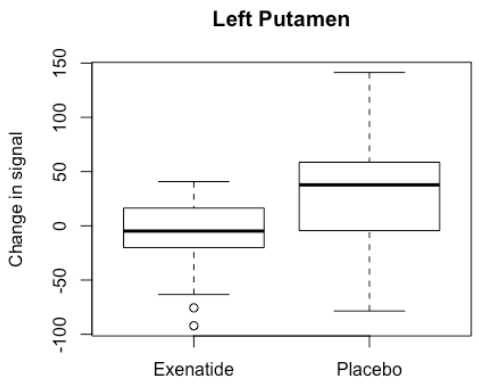

(a)
MDS-UPDRS part III OFF Meds
35
30
25
0
12
24
36
48
60
weeks
E
P
(b)
Change in MDS-UPDRS part III OFF Meds
5
4
3
2
1
0
-1
-2
-3
-4
-5
0
12
24
36
48
60
weeks
E
P
Exenatide
Placebo


A
B
C
+5
+6
+10
+11
+21
+22
2
0

D


Right Caudate
Change in signal
100
50
0
-50
Exenatide
Placebo


Right Putamen
Change in signal
100
50
0
-50
-100
Exenatide
Placebo


Left Putamen
Change in signal
150
100
50
0
-50
-100
Exenatide
Placebo