Research Report

Motor and Cognitive Advantages Persist 12 Months After Exenatide Exposure in Parkinson's Disease

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Abstract.

Background: Data from an open label randomised controlled trial have suggested possible advantages on both motor and non-motor measures in patients with Parkinson's disease following 12 months exposure to exenatide.

Objective: Continued follow up of these same patients was performed to investigate whether these possible advantages persisted in the prolonged absence of this medication.

Methods: All participants from an open label, randomised controlled trial of exenatide as a treatment for Parkinson's disease, were invited for a further follow up assessment at the UCL Institute of Neurology. This visit included all 20 individuals who had previously completed twelve months exposure to exenatide 10ug bd and the 24 individuals who had acted as randomised controls. Motor severity of PD was compared after overnight withdrawal of conventional PD medication using blinded video assessment of the MDS-UPDRS, together with several non-motor tests. This assessment was thus 24 months after their original baseline visit, i.e. 12 months after cessation of exenatide.

Results: Compared to the control group of patients, patients previously exposed to exenatide had an advantage of 5.6 points (95% CI, 2.2–9.0; $p = 0.002$) using blinded video rating of the MDS-UPDRS part 3 motor subscale. There was also a difference of 5.3 points; (95% CI, 9.3–1.4; $p = 0.006$) between the 2 groups on the Mattis Dementia Rating scale.

Conclusions: While these data must still not be interpreted as evidence of neuroprotection, they nevertheless provide strong encouragement for the further study of this drug as a potential disease modifying agent in Parkinson's disease.

Keywords: Parkinson's disease, clinical trial, disease modifying treatment, UPDRS, exenatide, diabetes mellitus

INTRODUCTION

Multiple avenues of research have identified links between Parkinson's disease (PD) and Type 2 diabetes mellitus (T2DM) [1]. Several recent discoveries have highlighted common cellular pathways that potentially relate neurodegenerative processes with

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abnormal mitochondrial function and abnormal glucose metabolism [2]. In parallel with these advances, a treatment for insulin resistance (exenatide; a GLP-1 agonist) has been proposed as a disease modifying drug in PD, based on multiple *in vitro* and *in vivo* studies [3–9].

In view of these preclinical data and in view of the excellent safety profile in patients with T2DM, a small, open-label "proof of concept" randomized controlled trial was conducted at UCL Institute of Neurology, Queen Square, London to evaluate the effects of 12 months exposure to exenatide on the motor and cognitive deficits of patients with PD (Clinical trials.gov Identifier NCT01174810). Forty five patients with moderate severity PD were randomized to either self-administer exenatide in addition to their regular PD medications or to acts as controls, i.e. receive their conventional PD treatment only. Detailed assessments were performed to quantify the effects of 12 months exposure to exenatide followed by repeat assessment after a 2 month washout period. Results of these assessments at 12 and 14 months have been previously reported, potentially indicating advantages among patients exposed to exenatide compared to controls on both motor outcomes (Blinded video rating of the Movement Disorders Society Unified Parkinson's Disease Rating Scale MDS-UPDRS and timed tests) and non motor outcomes (Mattis Dementia Rating Scale (DRS-2)) [10]. In parallel, patients randomised to exenatide also experienced weight loss and an increase in dyskinesias that necessitated lowering of their Levodopa equivalent dose (LED).

The current manuscript adds to these data by describing the results of detailed motor and non motor assessments collected at 24 months post baseline assessment, i.e. 12 months after cessation of the trial drug to explore whether 1) any of the differences previously observed at 12 and 14 months had persisted and 2) and whether any confounding factors such as weight loss, or minor baseline differences in disease severity might contribute to these observed differences.

METHODS

Patients

The trial methods have been described in detail previously [10]. In brief, patients with moderate severity PD meeting trial inclusion and exclusion criteria were randomised into 2 groups; 1) to self administer exenatide by subcutaneous injection twice daily for 12 months in addition to their conventional PD medication or 2) to continue conventional PD medication only. Detailed motor assessments were performed in the practically defined "Off" medication state, and repeated in the "On" medication state together with a battery of non-motor scales at Baseline, 6, 12 and 14 months. All patients were then invited to have a repeat assessment at 24 months post baseline visit, i.e. 12 months after cessation of exenatide, using the same battery of validated motor and non motor scales. Ahead of their final trial visit, patients were sent the PDQ39, Smell identification test, Non Motor Symptoms (NMS) Questionnaire, SCOPA Aut, and SCOPA sleep questionnaire to self-complete and bring to the clinic. On the day of the visit, all patients withheld all conventional PD medications overnight, and had a video recording of the assessment of their MDS-UPDRS part 3 motor score, performed timed motor tests and then took their regular PD medication. The patients were then asked to complete MDS UPDRS part 1, 2, 4, and when they confirmed that their best "On" state was achieved, they had a further video of UPDRS part 3 motor score. During their "On" phase, the Dyskinesia rating scale, Montgomery Asberg Depression Rating scale (MADRS), and Mattis DRS-2 were completed. Clinical observations (weight, pulse and blood pressure) and any adverse events occurring during the previous year were systematically recorded. Oral Glucose tolerance test was performed at the 24 month follow up visit as an indirect measure of insulin resistance during the "off" phase.

Blinded video rating

To avoid the possibility of investigator bias, the videos of the MDS-UPDRS part 3 motor scale were rated by PD clinicians, trained and certified in MDS-UPDRS scoring, and blinded to patient treatment status. It is however impossible to rate "rigidity" on video therefore for the MDS-UPDRS part 3, the blinded scores are presented 1) excluding rigidity, and also 2) with the addition of the open label rigidity scores.

Analyses

All data are presented to enable comparisons in mean scores at baseline and at 24 months together with the interval change according to randomised treatment allocation. The primary outcome was the MDS-UPDRS Part 3 motor subscore in the practically defined "Off" medication state. Secondary outcomes

were; MDS-UPDRS part 3 motor subscore "On" medication, MDS-UPDRS part 1, 2, and 4, Dyskinesia rating Scale, timed motor tests, Levodopa Equivalent Dose (LED), PDQ39, MATTIS DRS-2, MADRAS, NMS Quest, SCOPA Sleep, and SCOPA AUT. All data are presented on an "intention to treat" basis including all patients who completed at least one follow up assessment.

Two sided t tests were performed to compare changes in scores from baseline to follow-up between treated and untreated groups, and p values presented. Further explorations whether there was any relationship between observed treatment effects and possible confounding factors such as weight loss, or biases such as disease duration, and age at onset of disease at baseline, were performed using Pearson's correlations. Data were analysed using IBM SPSS Statistics 20.

Patients who had undergone DBS

In total, three of the patients followed up at 24 months, had clinically deteriorated and had needed Deep Brain Stimulation for the treatment of the PD symptoms between the 12 and 24 month follow up assessments; 1 in the exenatide group, 16 months after baseline assessment and 2 in the Control group (One at 14 months and one at 16 months follow-up).

Patients undergoing DBS frequently have substantial lowering of their conventional PD medication. This can mean that assessments in the Off medication and OFF stimulation setting can be associated with much more profound severity of "OFF" symptoms and signs, presumably because of the long duration response to L-dopa replacement that is not seen in the "practically defined "Off" state after a short overnight withdrawal [18]. Therefore it was predicted that OFF-medication assessments in these 3 patients would be a potential source of bias (favouring the exenatide group) and not comparable with previous ratings or with the rest of the cohort. Similarly these patients' On drug and ON stimulation assessments would also be subject to a potential bias. For this reason, the decision was taken to use "last observation carried forward" (LOCF) for these patients for their motor scores (UPDRS, Dyskinesia rating Scale and Timed Tests) and L-dopa equivalent dose (LED) at the 24 month assessment and thus ensure as much available data as possible was used in the analysis. To ensure transparency, statistical analyses were nevertheless subsequently repeated for the primary outcome measure, including blinded ratings of off medication, off stimulation assessments at 24 months for these 3 patients.

RESULTS

Of the 45 patients who underwent the original randomisation, 1 patient dropped out prior to first follow up visit and was replaced as per protocol, and excluded from subsequent analyses. Two further patients withdrew from exenatide treatment: the first at 9 months due to dysgeusia combined with subjective PD deterioration, and the second at 10 months due to excessive weight loss. These patients continued follow up assessments and data collection as per protocol. All 44 patients that had completed at least 1 follow up visit (exenatide group: $n = 20$, Control group: $n = 24$) completed the further assessment at 24 months.

Baseline differences

Despite randomisation, there were minor (nonsignificant) differences at baseline between treated and untreated groups. The exenatide group had an older age at study enrolment 61.4 (6.0) years versus control group 59.4 (8.4) years. Exenatide patients also had a shorter disease 9.6 (3.4) years v control group 11.0 (5.9) years,

Blinded video rating of MDS-UPDRS part 3 "off medication"

Patients allocated to the exenatide group had a mean improvement at 24 months compared with baseline of 1.1 points (SD, 5.9) on the MDS-UPDRS part 3 motor score, while controls had a mean decline of 4.5 points (SD, 5.3) (a difference of 5.6 points (95% CI, 2.2–9.0; $p = 0.002$); Table 1 and Fig. 1B). Addition of open label rating of rigidity scores to the blinded data equated to a decline of 0.5 points (SD, 7.3) in the exenatide group, compared with a decline of 8.5 points (SD, 6.3) in the control group (difference, 8.0 points; 95% CI, 3.8–12.2; $p < 0.001$); (Table 1 and Fig. 1A). Repeat analysis of the MDS-UPDRS part 3 motor score Off medication/ off stimulation including data from the 3 patients who had undergone DBS showed a persistent advantage for the exenatide group (difference of 5.2 points; 95% CI, 1.0–9.1; $p < 0.01$).

MDS UPDRS on medication subscores

Open label rating of MDS-UPDRS part 3 "on medication" showed an improvement in "on medication" scores in the exenatide group (mean improvement 0.9 points, SD (6.8)) at the 24-month visit compared to

Table 1

Change in the scores on MDS-UPDRS, LED, DRS and timed walking test at 24 month. A. Blinded rating excluding open label rigidity scores in Off medication condition. B. Open label rating including rigidity scores in On medication condition

	Baseline mean (SD)	24 months mean (SD)	Difference baseline to 24 months mean (SD); 95% CI	*P* value
Blinded-MDS UPDRS Part III. [A]	"off medication"			
Exenatide	31.0 (11.2)	29.8 (9.8)	−1.1 (5.9); −3.9, 1.6	*P* = 0.002
Conventional PD medication	34.0 (16.1)	38.5 (15.1)	4.6 (5.3); 2.2, 6.7	
MDS UPDRS Part III. [B]	"on medication"			
Exenatide	23.5 (6.3)	22.5 (7.2)	−0.9 (6.9); −4.2, 2.3	*P* < 0.001
Conventional PD medication	25.3 (10.7)	33.2 (11.4)	7.8 (6.7); 5.0, 10.7	
MDS-UPDRS Part I				
Exenatide	10.4 (4.1)	12.4 (5.0)	2.0 (4.2); 0.0, 4.0	*P* = 0.049
Conventional PD medication	11.6 (4.7)	16.7 (8.2)	5.1 (5.5); 2.8, 7.4	
MDS-UPDRS Part II				
Exenatide	10.2 (5.2)	12.9 (7.1)	2.7 (5.4); 0.2, 5.3	*P* = 0.009
Conventional PD medication	12.9 (6.2)	19.9 (7.2)	7.0 (5.0); 4.9, 9.1	
MDS-UPDRS Part IV				
Exenatide	6.3 (2.4)	5.9 (3.4)	−0.3 (2.6); −1.6, 09	*P* = 0.107
Conventional PD medication	6.3 (3.4)	7.3 (3.5)	1.0 (2.8); −0.1, 2.2	
LED				
Exenatide	973 (454)	1104.6 (506.5)	131.9 (192.3); 41.9, 221.9	*P* = 0.308
Conventional PD medication	977 (493)	1189.1 (679.5)	211.9 (298.7); 85.8, 338.1	
Dyskinesia rating scale	(on medication)			
Exenatide	2.3 (2.8)	3.5 (4.2)	0.8 (6.0); −2.0, 3.6	*P* = 0.328
Conventional PD medication	2.6 (2.9)	2.0 (2.5)	−0.6 (3.0); −1.8, 0.7	
Timed walk	"off medication"			
Exenatide	17.3 (5.2)	17.1 (7.1)	−0.2 (6.6); −3.2, 2.9	*P* = 0.85
Conventional PD medication	23.8 (22.4)	23.1 (19.0)	−0.9 (15.8); −7.5, 5.8	
Timed walk	"on medication"			
Exenatide	13.9 (3.1)	14.4 (3.4)	0.5 (5.0); −1.8, 2.8	*P* = 0.213
Conventional PD medication	13.7 (4.4)	16.7 (10.0)	3.4 (9.3); −0.5, 7.4	

baseline. In contrast, individuals in the conventional PD medication group deteriorated over the 24-month trial period by 7.8 points SD (6.7). Both groups had a decline in the MDS UPDRS part 1 and 2 sub-scores although this was more modest in patients previously treated with exenatide compared with controls. There was no clear difference between groups for MDS-UPDRS part IV, LED or Dyskinesia Rating Scale (Table 1). The group randomised to Exenatide had a smaller increase in LED than the group randomised to be controls over the 24 month follow up period.

Timed tasks

No significant differences were found in the timed walk test ON or OFF medication (Table 1). While there were sustained improvements in the number of hand taps that could be performed with either hand in both On and Off medication state in patients that had received exenatide, only the number of hand taps for the Left hand in the on medication state achieved conventional threshold for significance (p = 0.026).

Mattis DRS-2

At 24 months patients in the exenatide group showed a mean improvement in the Mattis DRS-2 of 1.8 points compared with deterioration by mean of 3.5 points in the control patients (difference, 5.3 points; 95% CI, 9.3–1.4; p = 0.006) (Fig. 2).

Montgomery asberg depression rating scale

At 24 months there was a mean improvement on the MADRS of 1.9 points in the exenatide group SD (5.2), and a mean deterioration in the control group of 1.5 points, SD (7.0) although this difference of 3.4 points failed to reach statistical significance (Table 2).

PDQ39

While the scores favoured the exenatide patients in both motor and non-motor measures listed above, there was no improvement in the overall PDQ39 summary index in the exenatide patients, nor in the comparison between the 2 groups at 24 months (Table 2).
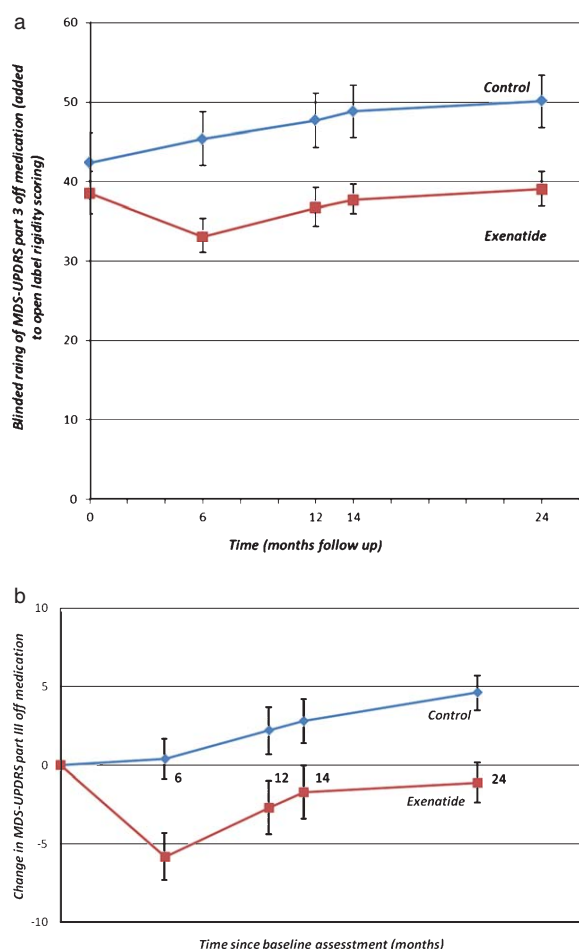
Fig. 1. A. Mean values of the MDS-UPDRS part 3 score by study visit. (Data represent mean ± SEM). B. Change in MDS-UPDRS part III Off medication by study visit (mean ± SEM).

Inspection of the PDQ39 subdomains reveals substantial variability between treatment groups even at baseline.

Non motor symptoms questionnaires

Patients randomised to exenatide showed mean improvements in NMS Quest, in night-time and overall sleep quality while control patients deteriorated on all these measures, although none of these measures reached statistical significance (Table 2).

Adverse events

Patients allocated to the exenatide group had experienced weight loss when measured at 12 and 14 months (a recognised side effect of exenatide). At the 24 month assessment, exenatide patients had a mean weight loss
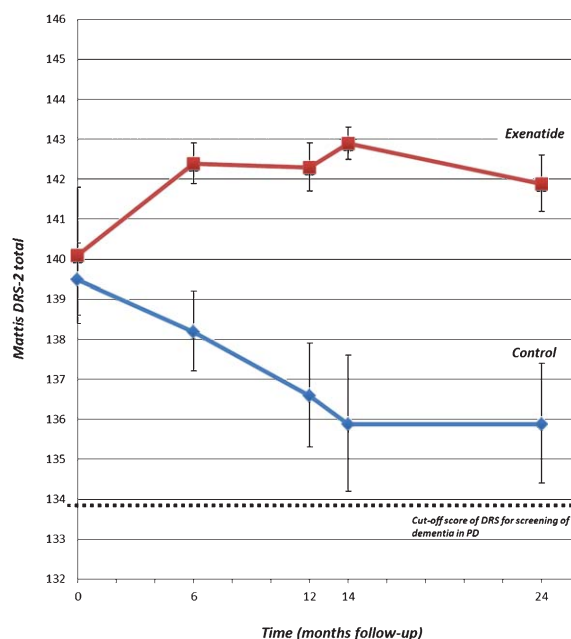
Fig. 2. Change from baseline in the Mattis DRS-2 score by study visit. Data represent mean ± SEM.

compared to baseline of 1.6 Kg SD(3.1), while controls had a mean weight loss of 1.7 kg SD(5.8), with a difference of 0.1 points (95% CI, 3.0–2.8; $p = 0.93$).

Oral glucose tolerance test

There was no difference in glucose tolerance between the exenatide and control groups; In the exenatide group the mean (SD) fasting glucose was 5.0 (0.5) mmol/L. The mean glucose level 2 hours later was 5.6 (1.4) mmol/L. While one patient met the threshold for glucose intolerance (>7.7 mmol/L), no patients met criteria for Diabetes mellitus. In the control group the mean (SD) fasting glucose was 5.2 (1.5) mmol/L, and 2 hours later was 5.6 (1.3) mmol/L.

Correlations of clinical outcomes with baseline variables

The change in MDS UPDRS part 3 between baseline and 24 months was not significantly correlated with age at PD onset, nor age at the start of the trial. Furthermore there was no significant correlation between change in MDS UPDRS part 3 and change in weight at 12, 14 or 24 month timepoints. There were no correlations between changes in Mattis DRS-2 and age at onset of the trial, nor age at symptoms onset.

Table 2
Change in the score on Mattis-DRS2, MADRAS, PDQ39-SI, NMS Quest, SCOPA Sleep and SCOPA AUT

	Baseline mean (SD)	24 months mean (SD)	Difference baseline to 24 months mean (SD); 95% CI	P value
Mattis DRS-2				
Exenatide	140.1 (7.7)	141.9 (3.1)	1.8 (65); −1.2, 4.8	P = 0.006
Conventional PD medication	139.5 (4.5)	135.9 (7.3)	−3.5 (6.4); −0.8, −6.3	
MADRAS				
Exenatide	10.9 (5.1)	9.0 (4.6)	−1.9 (5.2); 0.5, −4.3	P = 0.79
Conventional PD medication	11.0 (5.4)	12.5 (8.6)	1.5 (7.0); −1.4, 4.4	
PDQ39 summary index				
Exenatide	19.2 (13.5)	19.1 (13.5)	−0.1 (12.3); −5.9, 5.6	P = 0.682
Conventional PD medication	24.5 (12.8)	25.7 (16.5)	1.2 (9.3); −2.7, 5.1	
NMS Quest				
Exenatide	10.4 (3.6)	9.6 (4.7)	−0.8 (3.8); −2.6, 1.0	P = 0.403
Conventional PD medication	10.5 (5.5)	10.7 (6.0)	0.2 (4.3); −1.6, 2.1	
SCOPA Sleep night time				
Exenatide	6.3 (3.6)	5.4 (3.0)	−0.9 (2.8); −2.2, 04	P = 0.278
Conventional PD medication	5.6 (3.5)	5.7 (4.3)	0.1 (3.3); −1.3, 1.5	
SCOPA Sleep day time				
Exenatide	4.1 (3.5)	4.9 (4.0)	0.7 (1.9); −0.2, 1.6	P = 0.658
Conventional PD medication	4.3 (2.7)	4.7 (2.7)	0.4 (2.3); −0.5, 1.4	
SCOPA AUT				
Exenatide	11.7 (5.8)	12.7 (4.3)	1.0 (5.1); −1.4, 3.4	P = 0.750
Conventional PD medication	12.7 (6.7)	13.2 (8.3)	0.4 (5.9); −2.0, 3.0	

DISCUSSION

In this open label, proof of concept trial, we have observed multiple differences in clinical outcome measures between patient groups according to treatment allocation, that have persisted for 24 months (ie 12 months after cessation of exenatide injections). The absolute magnitude of the difference observed is of potential clinical relevance. Inclusion of the rigidity scoring made by the unblinded investigator equated to an 8.0 points difference in MDS-UPDRS part 3 score at 24 months. Adding the blinded video rating of MDS-UPDS part 3 to the differences seen in parts 1, 2, and 4 of the scale equated to a 14.5 point advantage in favour of exenatide at 24 months. This was accompanied by effects seen across a range of other measures; Mattis DRS-2, MADRS, Timed tests, LED and Dyskinesia rating scale. However, due to the open label design of the trial it remains impossible to establish without doubt, if the nature of this effect is real, entirely placebo driven or a combination of the two.

The decision to extend the follow up for a further 12 months was taken to allow inevitable placebo effects at trial onset, to at least begin to diminish. While we are unaware of previous reports of placebo effects lasting 24 months, the continued existence of a placebo driven effect cannot be ruled out. Nevertheless, these data were collected in a highly cost efficient manner and this type of trial design has thus been the subject

for discussion as a possible means of gaining preliminary supportive evidence of clinical safety and efficacy ahead of the major financial investment necessary for formal double blind evaluations of clinical efficacy [11].

The additional data collected have also been used to explore whether there are any other explanations for the observed persisting differences. In any randomised trial, chance differences between groups can be present at baseline despite randomisation. This is more likely in trials with small numbers of patients, and such differences can be an important source of confounding. In this trial, minor differences in age at onset and disease duration were observed. On one hand older age of onset has been associated with more rapid progression [12] but on the other hand it has been proposed that the rate of progression in early PD is faster than in later disease [13–15]. Either way, we did not identify any positive correlation between age at onset, disease duration and change in either the MDS UPDRS or the Mattis DRS-2 to suggest that differences observed may have been explicable by these potential confounders.

Of note is the observed discrepancy between the improvement in some of the motor and non-motor scales and the lack of improvement in PDQ39 Summary Index. Exploring this further revealed quite marked differences between some of the PDQ39 subdomains comparing exenatide patients with controls at baseline. This is likely an example of how, despite the

randomisation process, differences at baseline, particularly in the subdomains of scales can occur, and it is likely that these baseline differences may impact on observed differences emerging over the subsequent 2 years. It is envisaged that future trials with larger numbers of participants will be less vulnerable to differences in baseline scale scores.

The adverse events at 24 months are well in keeping with what would be expected in moderate severity PD patients and the known side effects of exenatide. Weight loss was reversible upon stopping exenatide injections, and there was no difference in the change in body mass index at 24 months between patients in exenatide and control groups. No correlation was found between the change in part 3 MDS UPDRS at 12, 14 and 24 months and weight loss, making it less likely that exenatide patients had improved motor scores as a result of their BMI being reduced during the first 12 month trial period. Our exenatide group of patients frequently described gastrointestinal symptoms, in keeping with the known adverse event profile of exenatide.

We did not find evidence in our data to suggest that glucose tolerance is different in PD patients who received Exenatide for 12 months in addition to best medical therapy. Based on these results, we find little to suggest that any biological effects of exenatide in PD are solely related to improvement in peripheral glucose metabolic control. Central mechanisms of glucose sensing and insulin signalling warrant further explorations.

Reassuringly, the increase in Dyskinesia Rating Scale scores necessitating the reduction in LED seen at 12 and 14 months in the exenatide group were no longer significantly different from controls at 24 months. Four patients in the exenatide group who had worsening of peak dose dyskinesia at 12 and 14 months that necessitated lowering the LED, subsequently had their LED re-increased by the 24 month visit. Although not reaching significance, exenatide patients still had slightly more dyskinesias than controls despite lower increases in LED overall, therefore it remains possible that exenatide may exacerbate dyskinesia particularly during the period of exposure.

To date, the design of trials of putative disease modifying agents has focused on the demonstration of sustained effects on motor function [16]. However it has been proposed that identifying effects which delay the development of major milestones such as dementia, would be a more useful approach [17]. In our trial, cognitive decline was measured with Mattis DRS-2 scale during the on medication state at every time point. There was divergence in cognitive performance

between the groups, with a 5-point advantage in the Mattis DRS-2 at 12 months that persisted as a 6.3-point advantage at 14 months and 5.3-points at 24 months. No correlations were found between age at PD onset and Mattis DRS-2 at baseline nor between change in Mattis DRS-2 at 12, 14 or 24 months.

In conclusion, aside from the changes in MDS-UPDRS scores, there was also persistent divergence in cognitive performance between the groups, with significant differences which were sustained along the trial period, far beyond the 12 month period of drug exposure. These data provide continued support for formal double blind trials of GLP-1 agonists as disease modifying drugs in PD.

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CONFLICT OF INTEREST DISCLOSURES

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