# Clinical Trial Protocol

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| **Full title of trial** | An open label, single site, 12 month, Phase II, randomised controlled trial evaluating the safety and efficacy of Exendin-4 (Exenatide) in the treatment of patients with moderate severity Parkinson's disease. |
| **Short title** | Exendin-4 as a treatment for Parkinson's disease- pilot trial |
| **Version and date of protocol** | Final Version 2.0 02/07/2010 |
| **Sponsor:** | University College London (UCL) |
| **Sponsor protocol number** | 09/0391 |
| **Funder (if applicable):** | Cure Parkinson's Trust |
| **EudraCT no** | 2009-018137-37 |
| **Trial medication** | Exenatide |
| **Phase of trial** | Phase II |
| **Trial sites(s)** | National Hospital for Neurology & Neurosurgery |

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## Signatures

The Chief investigator and the sponsor have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing (as an urgent safety measure under section 10.3.6 requirements).

The investigator agrees to conduct the trial in compliance with the protocol, GCP and UK Regulations for CTIMPs, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent),Research Governance Framework, (2005), the Sponsor's SOPs and other regulatory requirements as appropriate.

**Chief investigator**

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| Dr Thomas Foltynie<br>National Hospital for<br>Neurology & Neurosurgery | Signature | Date |

**Sponsor Representative**

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| Dr. Nadeem Khan,<br>Divisional Manager<br>UCLH | Signature | Date |

# Contents

## List of abbreviations

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|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| ASR | Annual Safety Report |
| CA | Competent Authority |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CTA | Clinical Trial Authorisation |
| CTIMP | Clinical Trial of Investigational Medicinal Product |
| DMC | Data Monitoring Committee |
| EC | European Commission |
| EMEA | European Medicines Agency |
| EU | European Union |
| EUCTD | European Clinical Trials Directive |
| EudraCT | European Clinical Trials Database |
| EudraVIGILANCE | European database for Pharmacovigilance |
| GAfREC | Governance Arrangements for NHS Research Ethics |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| ISRCTN | International Standard Randomised |
| MA | Marketing Authorisation |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MRC | Medical Research Council |
| MS | Member State |
| Main REC | Main Research Ethics Committee |

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|---|---|
| NHNN | National Hospital for Neurology & Neurosurgery |
| NHS R&D | National Health Service Research & Development |
| PD | Parkinson's disease |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| QA | Quality Assurance |
| QC | Quality Control |
| QP | Qualified Person for release of trial drug |
| RCT | Randomised Control Trial |
| REC | Research Ethics Committee |
| SAR | Serious Adverse Reaction |
| SAE | Serious Adverse Event |
| SDV | Source Document Verification |
| SOP | Standard Operating Procedure |
| SmPC | Summary of Product Characteristics |
| SSA | Site Specific Assessment |
| SSAR | Suspected Serious Adverse Reaction |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UPDRS | Unified Parkinson's disease Rating Scale |

## Trial personnel

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|---|---|
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# 2 Summary

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| **Title:** | An open label, single site, 12 month, phase II, randomised controlled evaluation of the safety and efficacy of Exendin-4 (Exenatide) in the treatment of patients with moderate severity Parkinson's disease. |
| **Short title:** | Exendin-4 as a treatment for Parkinson's disease- pilot trial |
| **Trial medication:** | Exenatide |
| **Phase of trial:** | Phase II |
| **Objectives:** | Primary Objective- To collect pilot data from which to estimate the effectiveness of Exenatide in modifying the progression of the motor symptoms of patients with moderate severity of Parkinson's disease, using a validated scale -the UPDRS off medication motor score as the main primary outcome measure.<br><br>Secondary Objectives-To confirm the safety and tolerability of Exenatide among patients with moderate PD.<br><br>-To identify whether Exenatide treatment leads to any changes in (FP-CIT) DATscan appearances among patients with moderate PD.<br><br>-To evaluate the impact of Exenatide on activities of daily living, dyskinesias, timed motor tests, cognitive ability, mood, behaviour, non-motor symptoms and quality of life among patients with moderate PD using standard validated tools of assessment. |
| **Type of trial:** | Phase II, open label, randomised, parallel group, single site trial in Parkinson's disease. |
| **Trial design and methods:** | Exenatide is a licensed, safe and effective treatment for patients with Diabetes mellitus. Laboratory work has shown strong, reproducible evidence that this drug has beneficial "disease modifying" effects when given to animals with a range of experimental models of Parkinson's disease (PD). This project aims to make an initial evaluation of possible benefits of Exenatide among patients with moderate symptoms of PD. The drug will be given as a twice daily 10microgram injection under the skin in a similar way to one of the conventional "symptomatic" treatments for PD (Apomorphine).<br><br>Forty patients with moderate symptoms of PD will be recruited and randomised to receive Exenatide injections twice daily, or to act as controls in this open label trial. Detailed assessments will be made of all patients at baseline and periodically for a total of 14 months. The primary outcome measure will be the change between baseline |

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| | and follow up, in the severity of a validated PD assessment scale (the UPDRS part 3 motor score) after an overnight period free of conventional PD medication. Secondary measures will include adverse event reports, self completed questionnaires, and blood test results. Aside from these assessments, all patients will continue their regular PD medications throughout the trial with adjustments made only according to clinical need.<br>In a subgroup of patients (n=10), brain scans that assess the severity of PD, will be performed at both baseline and follow up to help understand possible mechanisms of action of Exenatide. |
| **Trial duration per participant:** | 15 months |
| **Estimated total trial duration:** | 18 months |
| **Planned trial sites:** | Single-site |
| **Total number of participants planned:** | 40 |
| **Main inclusion criteria:** | Diagnosis of Idiopathic Parkinson's disease of moderate severity- Male or female, Aged 45-70 years<br>Disease onset after age 40 years, Disease duration > 5 years<br>On L-dopa treatment with History of wearing off phenomena- duration of action of single dose of L-dopa < 6 hours<br>Able to give informed consent<br>Able to comply with trial protocol and willing to attend clinic necessary visits |
| **Statistical methodology and analysis:** | The primary effectiveness variable is change from baseline to month 14 in the UPDRS motor score off medication. The analysis will be performed using a two-sample *t*-test if the data collected is normally distributed. In the case where data is not normally distributed non-parametric tests will be used to analyze the data. |

# 3 Introduction

## 3.1 Background

Parkinson's disease (PD) is a progressive neurodegenerative condition that affects 120 000 people in the UK with a further 10 000 individuals being diagnosed with the condition each year. There is currently no agent in existence which can slow or reverse the disease process. All agents that are currently licensed for the treatment of the condition only temporarily mask its symptoms.

This trial is designed to collect preliminary data to evaluate whether a drug, Exenatide, licensed and approved for use in humans and showing consistent and reproducible neuromodifying effects in laboratory models of PD, has potential beneficial effects in patients with PD.

## 3.2 Investigational medicinal product(s)

Exenatide (manufactured as Byetta) 5µg and 10µg solution for injection in a pre-filled pen received European marketing authorisation in November 2006.

The marketing authorisation numbers are as follows for the 5µg pens:

EU/1/06/362/001 (1 pen)

EU/1/06/362/002 (3 pens)

The marketing authorisation numbers are as follows for the 10µg pens:

EU/1/06/362/003 (1 pen)

EU/1/06/362/004 (3 pens)

Bioavailability of Exenatide is comparable following subcutaneous injection into abdomen, thigh or arm and the 10µg dose compares favourably to the plasma levels in the rodent models namely 200pg/ml plasma[Calara *et al.* 2005;Li *et al.* 2009]. Exenatide cannot be administered orally.

Patients randomised to receive active drug will continue this for a period of 12 months, with 3 monthly assessments to inform on the possible time course of neuromodulatory action of the drug. Patients will have a further assessment 2 months after completion of the trial to allow any symptomatic effect to be distinguished from a disease modifying effect.

## 3.3 Preclinical data

Glucagon-like peptide-1 (GLP-1) is a naturally occurring hormone with conserved sequence homology in multiple vertebrate and invertebrate species indicating an important role in normal physiology. GLP-1 has been recently shown to have effects

on plasma insulin and glucose levels exerting its action on the GLP-1 receptor. This is a G-protein coupled receptor expressed in pancreatic islet cells, and is also present in the central and peripheral nervous systems as well as in heart, kidney, lung and gastrointestinal tract. Exendin-4 shares roughly 50% of its aminoacid sequence with mammalian GLP-1, and is a potent and selective agonist for the GLP-1 receptor[Goke *et al.* 1993]. It was discovered in the search for biologically active compounds in the venom of the "Gila monster" lizard (Heloderma suspectum)[Eng *et al.* 1992].

While native GLP-1 is rapidly degraded by dipeptidyl peptidase (DDP-4) in the bloodstream with a half-life of less than 2 minutes [Kieffer *et al.* 1995], Exendin-4 is resistant to DDP-4 mediated degradation. The synthetic version of Exendin-4 (Exenatide) has a circulating half life of 60-90 minutes, with increases in plasma concentrations lasting 4-6 hours after a single subcutaneous injection [Kolterman *et al.* 2005].

In the investigation of the role and function of Exendin-4 and GLP-1 receptors in nervous tissues, Exendin-4 has been shown to induce neurite outgrowth, promote neuronal differentiation and rescue degenerating neuronal cells in in-vitro cell lines [Perry *et al.* 2002b] as well as protecting against excitotoxic damage both in vitro and in vivo [Perry *et al.* 2002a]. Exendin-4 has been shown to increase transcription of Tyrosine Hydroxylase- (TH-the rate limiting enzyme in dopamine synthesis) in brainstem catecholaminergic neurons [Yamamoto *et al.* 2002], and enhances cognitive function in rodents [During *et al.* 2003]. These effects are blocked by GLP-1 receptor antagonists confirming that these actions are mediated through the GLP-1 receptor. Activation of GLP-1 receptors has been shown to lead to rapid increases in levels of cAMP and intracellular calcium [Drucker *et al.* 1987], with sustained signalling leading to activation of protein kinase A, and induction of gene transcription[Drucker and Nauck 2006].

Three groups have independently investigated and confirmed beneficial effects of Exendin-4 administration in multiple rodent models of Parkinson's disease. At the School of Pharmacy in London, twice daily intraperitoneal injections of 0.1 or 0.5µg/Kg, administered to rats 7 days after either unilateral Lipopoysaccharide (LPS) or unilateral 6-hydroxydopamine(6-OH DA) toxins markedly decreased abnormal amphetamine induced circling, increased striatal dopamine levels to near normal, and increased both striatal and nigral TH activity compared with vehicle injections[Harkavyi *et al.* 2008].

A Swedish group (NeuroNova) performed a series of experiments demonstrating that GLP-1 receptors are expressed in neural stem cells from the subventricular zone (SVZ) of adult mice, and Exendin-4 is able to stimulate adult neurogenesis from both neural stem cell neurospheres in vitro and SVZ cells in vivo. Administration of Exendin-4 at a dose of 0.1µg/Kg bd to rats after 6-OH DA toxin again led to near complete normalisation of amphetamine induced rotations that persisted for several weeks after the administration of the drug was terminated. Histological examination

of the substantia nigra revealed a doubling of TH and Vesicular monoamine transporter 2 positive neurons (VMAT-2- responsible for the proper storage and handling of dopamine) among the animals treated with Exendin-4 compared to those treated with vehicle [Bertilsson *et al.* 2008].

The beneficial effects of Exendin-4 in a different model of rodent PD has also been independently confirmed in Baltimore USA, using mice given Exendin-4 for 7 days before the neurotoxin MPTP. MPTP induces a PD like syndrome in humans, monkeys and mice. It is metabolised by the brain into MPP+, which is selectively transported into dopaminergic neurons causing oxidative stress, mitochondrial dysfunction and cell death. Mice pre-treated with Exendin-4 had complete protection against the toxicity of MPTP. While untreated mice had 71% loss of dopaminergic neurons in the SN, TH neurons in Exendin-4 treated mice were no different from control mice not given MPTP. Furthermore the Exendin-4 treated mice had normal DA levels and motor activity after MPTP in stark contrast to untreated mice given MPTP [Li *et al.* 2009].

In summary, a range of measures have indicated a neuroprotective effect of Exendin-4 in animal models of Parkinson's disease, and also suggest that this agent is able to rescue dopaminergic neurons once damage is established and can stimulate neurogenesis of cells with a dopaminergic phenotype. Furthermore, it appears that Exendin 4 may have beneficial effects on non-motor symptoms as well as on motor disability. While the precise underlying cellular mechanisms are as yet unclear, additional possibilities are that Exendin-4 may restore neuronal function through both reduction of inflammation[Kim *et al.* 2009] and apoptosis. The trophic and protective actions of Exendin-4 in neurons are in parallel to the well established role of GLP-1 receptor stimulation in balancing cell survival versus death in pancreatic cells. This pilot study is designed to evaluate whether there is any indication that the neuroprotective and neurogenic effects seen in animal models of PD translate to clinical disease modification in patients with mild to moderate Parkinson's disease.

## 3.4 Clinical data

Exenatide has been the subject of phase III drug trials investigating the efficacy of subcutaneous administration (5 or 10μg twice daily) in the treatment of patients with Type 2 Diabetes [Buse *et al.* 2004;DeFronzo *et al.* 2005;Kendall *et al.* 2005;Drucker *et al.* 2008] and was approved by the FDA for the treatment of type 2 Diabetes in April 2005 and received European marketing authorisation for the treatment of Diabetes in November 2006.

Safety of Exendin-4 following subcutaneous administration at the doses used for Diabetes is excellent. The risk of hypoglycaemia among non-diabetic patients is negligible. The positive actions of Exendin-4 seen in the animal models of PD were achieved at doses equivalent to or lower than those used in the treatment of Type 2 diabetes which is already a licensed indication for Exendin use. Combined with an

extensive impressive safety record, backed up by the FDA and EMEA regulator websites, a further advantage of Exendin-4 / Exenatide is the ability to readily cross the blood brain barrier after peripheral administration, due to its high lipophilicity [Kastin and Akerstrom 2003;Banks *et al.* 2004].

## 3.5 Rationale and risks/benefits

No drug has been shown to slow or reverse the neurodegenerative process of PD. All currently licensed therapies act as symptom relieving agents but have a limited lifespan of effectiveness because of continued brain cell loss. The preclinical work in laboratory models of PD suggest that Exenatide may work as a neuromodulatory agent that may slow or reverse the neurodegenerative process of PD.

Exenatide carries very strong scientific credentials that suggest that it will be highly effective in the treatment of patients with mild to moderate PD, beyond that achieved by existing therapies. Despite the strong safety record of Exenatide, this trial will record and report and systematically monitor patients for all adverse events and the development of minor complications of Exenatide use observed in the phase 3 trials of Exenatide for diabetes treatment.

Risks v benefits- The mechanism of action through which Exenatide has beneficial effects in the animal models of PD is unproven. For this reason, we have incorporated a small imaging arm into the trial design which will evaluate whether there is any evidence of a change in pre-synaptic dopaminergic integrity (DAT SPECT scans).

The safety of Exenatide administration to humans has been extensively assessed among patients with diabetes prior to being granted a license. The most common side effect from Exenatide use is nausea. This can be reduced by initiation with low dose (5 microgram bd) treatment for the first month. Thirty patients treated with Exenatide have developed pancreatitis; of these 27 had additional risk factors for the development of pancreatitis, patients with these risk factors will be excluded from this trial (see section 6.2). Patients with PD have not previously been given this drug therefore this trial will continuously collect adverse event data, in addition to periodic collection of fasting blood samples to alert the trial investigators to the possibility of low blood sugar or alterations in serum amylase. Patients will have the contact details of clinically qualified trial investigators in case of any unanticipated adverse events occurring.

Participation in this trial will require the patients to make additional trips to the hospital. While additional trips to hospital will be burdensome, patients will benefit from the access to experienced PD clinical advice at each visit.

In addition to undergoing a clinical examination and assessment, patients will be helped to complete all the questionnaires. Travel expenses incurred by patients and carers as a result of trial participation will be reimbursed.

Repeat fasting blood samples will be required from patients; these will be taken by experienced personnel first thing in the morning. All patients will be informed regarding the need for fasting blood samples before they provide informed consent.

On five occasions, patients will need to have an overnight period free of medication to allow an evaluation of the underlying severity of their PD. This is the primary outcome of the trial and is therefore essential to gauge the effectiveness of the trial drug. Only patients able to tolerate medication free periods will be recruited. Evidence that Exenatide modifies disease progression in PD will have potential benefits for all trial participants.

### 3.6 Sponsor's risk assessment outcome

Based on the risk assessment performed by the sponsor this trial has the following risk assessment category: Low/Moderate.

# 4 Objectives

*Primary:* To collect pilot data from which to estimate the effectiveness of Exenatide in modifying the progression of the motor symptoms of patients with moderate severity of Parkinson's disease, using the UPDRS off medication motor score as the main primary outcome measure.

*Secondary:* To confirm the safety and tolerability of Exenatide among patients with PD.

-To distinguish symptomatic effects of Exenatide form disease modifying effects.

-To identify whether Exenatide treatment leads to any changes in DAT SPECT scan appearances among patients with moderate PD.

-To evaluate the impact of Exenatide on activities of daily living, dyskinesias, timed motor tests, cognitive ability, mood, behaviour, non-motor symptoms and quality of life among patients with moderate PD using standard validated tools of assessment.

# 5 Trial design

## 5.1 Overall design

This is a non-commercial trial of a licensed drug to provide preliminary efficacy and safety data for the use of Exenatide in PD. The current trial was designed in

collaboration between the Cure Parkinson's Trust and the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.

The trial has been designed as an open label, randomised controlled trial to make an initial assessment of possible efficacy of Exenatide given as a treatment to 20 patients with PD for 12 months, and comparing outcomes with a further 20 PD patients. Recruited patients will randomised into 2 groups to receive either active drug or to act as a control in a parallel group, open label design. Patients randomised to active drug will be taught how to self administer injections and receive 1 months treatment with 5 microgram injections twice daily. The dose will be increased after 1 month to 10 micrograms twice daily. This dose titration has been associated with lower rates of nausea. Detailed assessments will be performed at baseline and at 1,3,6,9 and 12 months at which point Exenatide treatment will be withdrawn. A final assessment will be performed at 14 months to ensure complete washout of any symptomatic effects and enable disease modifying effects to be distinguished from purely symptomatic effects. These assessments will be video recorded. All patients will continue to have optimal conventional PD treatment administered throughout the trial period with the exception of "off-medication" evaluations to be performed at baseline, 3, 6, 12 and 14 months.

Withdrawal of medications

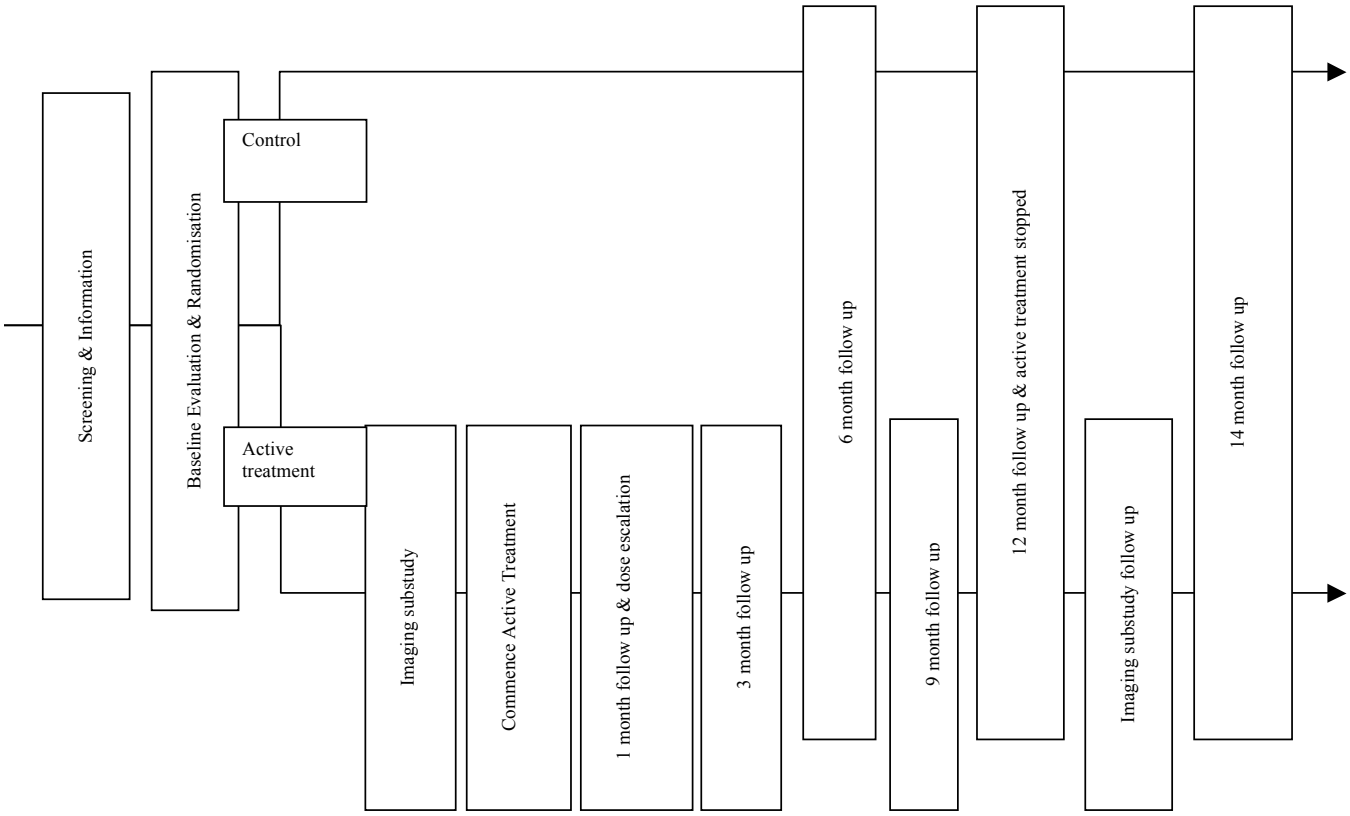
Patients attending for assessment at baseline (and at their 3 month, 6 month, 12 month and 14 month assessments) will withhold all PD medications (including Exenatide) for at least 12 hours (overnight). To ensure uniformity of off medication assessments at baseline and follow up, and take account of patients taking long acting dopamine agonists, individuals taking Ropinirole MR, or Cabergoline will be instructed to stop this medication 24 hours before assessment. They will be asked not to have eaten and to have drunk water only for 6 hours to enable fasting blood samples to be taken. If required, the research team will provide the patient with all necessary assistance. Patients that are physically unable to tolerate being off medication will not undergo randomization.

The control group of patients are very important in view of the continued neurodegenerative process of PD that leads to a mean 3 point decline in UPDRS motor scores per year. The trial will be continued for 12 months to minimize the impact of placebo responses that are less likely to be sustained for this duration of time.

This trial will also assess the safety and tolerability of Exenatide when administered to patients with PD. Encouraging results will be used as a basis for application for funding for a larger double blind placebo controlled RCT and will be used to inform upon sample size calculations for such a trial. This drug already has a license for the treatment of patients with Type II Diabetes and there is extensive safety data from phase 3 trials of its use in this patient group. This trial has therefore been configured as an off-label evaluation at the suggestion of the UK government regulatory agency

–the Medicines Health Regulatory Agency (MHRA). Exenatide carries very strong scientific credentials that suggest that it will be highly effective in the treatment of patients with mild to moderate PD, beyond that achieved by existing therapies.

- Schematic diagram(s) of overall trial design.




# 6 Selection of Subjects

## 6.1 Inclusion criteria

Diagnosis of Idiopathic Parkinson's disease of moderate severity- equivalent to Hoehn/ Yahr stage 2 to 2.5 (Bilateral symptoms but still physically independent).

Male or female. Female patients to be post menopausal (defined as 12 months of spontaneous amenorrhoea or 6 months spontaneous amenorrhoea with FSH levels greater than 40mIU/ml), surgically sterilised (post hysterectomy and/or oophorectomy). Male patients with female partners that have child bearing potential must use adequate contraception (condoms +/-spermicidal gel/foam) throughout the duration of the trial period.

Age 45-70 years

Disease onset after age 40 years

Disease duration > 5 years

On L-dopa treatment. Patient must be on oral L-dopa treatment - with or without dopamine agonist including Apomorphine, MAO-B inhibitor, COMT inhibitor, Amantadine, Beta blocker, anticholinergic treatment

History of wearing off phenomena- duration of action of single dose of L-dopa < 6 hours

Stable PD medication for preceding 3 months- i.e. no change in medication type or dose.

UPDRS motor off medication score >15

L-dopa responsiveness. Defined as >33% improvement in UPDRS motor off medication score following L-dopa challenge

Able to give informed consent

Able to comply with trial protocol and willing to attend necessary clinic visits off medication.

## 6.2 Exclusion criteria

Diagnosis or suspicion of other cause for parkinsonism including Vascular parkinsonism, post traumatic parkinsonism, drug or toxin induced parkinsonism, or other neurodegenerative condition including Multiple System Atrophy, Progressive Supranuclear Palsy, Huntington's disease, Wilson's disease, Pantothenate kinase Neurodegeneration (PKAN), Alzheimer's disease, Creutzfeld Jacob disease.

Known abnormality on CT or MRI brain imaging considered to be causing symptoms or signs of neurological dysfunction, or considered likely to compromise compliance with trial protocol.

Concurrent dementia defined by a score lower than 120 on the Mattis Dementia Rating Scale.

Concurrent severe depression defined by a score greater than 16 on the MADRS

Exposure to neuroleptic drugs within 6 months prior to baseline assessment

Prior intracerebral surgical intervention for Parkinson's disease including Deep Brain stimulation, lesional surgery, growth factor administration, gene therapy or cell transplant

Already actively participating in a trial of a device, drug or surgical treatment for Parkinson's disease, or trial participation within previous 30 days.

Type 1 Diabetes mellitus

Type 2 Diabetes mellitus on insulin treatment

End stage renal disease or severely impaired renal function with creatinine clearance <30ml/min

History of severe cardiac disease (Angina, Myocardial infarction or cardiac surgery in preceding 2 years)

History of pancreatitis

History of alcoholism

Severe gastrointestinal disease including gastroparesis

Ongoing treatment with sulphonylurea

Females that are pregnant or breast feeding or of child bearing potential.

### 6.3 Concomitant medication

Trial participants will be permitted to use any licensed PD medication throughout the course of the trial that is recommended by their referring Neurologist. Patients will be given advice in any necessary minor adjustments to their pre-existing PD drug therapy at each of their follow up visits and note made of L-dopa equivalent doses at each visit. No routine adjustment of PD medications will be made by the Investigator(s) unless at the request of the patients. Patients will be asked not to have any form of intra-cerebral surgery for their Parkinson's disease until the end of the trial period. Patients will be asked not to enrol in any other experimental treatment for PD until the end of this trial period.

INR measurements must be closely monitored in any patients on Warfarin.

## 7 Recruitment

Patient contact at a site will only be made once the study receives documented main REC approval, regulatory approval, Local Trust R&D approval, signed site agreement and the site has been initiated by the Sponsor.

Patients will be recruited from the National Hospital for Neurology & Neurosurgery, London. Patients attending their routine follow up appointments will be informed about the trial by their Neurologist and given a Patient Information Sheet. Each

potential patient will be pre-screened according to those inclusion/exclusion criteria which can be assessed ahead of obtaining informed consent. At the individual's request, their contact details will be passed to the trial Investigator.

# 8 Study procedures and schedule of assessments

## 8.1 Informed consent procedure

The Chief Investigator, or a person delegated by the Investigator will obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. All potential patients/subjects will be properly informed as to the purpose of the trial and the potential risks and benefits known, or that can be reasonably predicted or expected. All personnel obtaining consent from patients will have up to date GCP training. The Investigator or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

The CI will record when the Patient Information Sheet (PIS) was given to the patient. All patients will have had greater than 24 hours between the Patient Information sheet being given and Informed Consent being sought. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site and a third copy will be filed in the patients hospital notes. Only the consent form approved by the relevant trial ethics committee will be used.

Each patient wishing to participate in the trial and who provides informed consent will be evaluated with the inclusion/exclusion criteria for eligibility. A thorough review of medical records for each patient will be necessary to review treatment history and ensure the patient meets all the inclusion/exclusion criteria. This review will also any examine any prior non-compliance to treatment issues. This review will take place after the patient signs the informed consent. Results of blood tests will be reviewed prior to baseline evaluation to ensure eligibility.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, given a copy of the revised form and will give their consent to continue in the study.

## 8.2 Screening and eligibility assessment

Patients who wish to be considered for inclusion in the trial having read the Patient Information sheet will be invited for an in-person evaluation to confirm eligibility. A narrative of what trial participation entails, will be used to educate potential participants on trial requirements. Each patient will be aware that they will have a

50% chance of being allocated randomly to active Exenatide treatment or as a control. They will confirm their willingness and ability to attend the clinic in a fasted state and after an overnight off medication period and an estimate of this ability based on their symptoms severity will also be gauged by the Investigator.

The patient will be instructed re withdrawal of any long acting PD medications for the purposes of their off medication assessment. As part of their informed consent, the contact details of the research team will be given to each patient.

## 8.3 Randomisation procedures

Eligible individuals who have given informed consent will be randomised to receive active drug or to act as a PD control. Block randomisation will be used with random block sizes. Separate randomisation lists will be generated for patients of greater (Hoehn & Yahr stage 2.5) or lesser (Hoehn & Yahr stage 2.0) disease severity to balance this as a possible prognostic factor, i.e. disease severity will act as a stratification variable. Randomisation lists will be created prior to trial commencement, and stored by the trial pharmacist. The randomisation list will be sufficiently long (n=50) to enable continued randomisation should any patients drop out within the first 3 months. All randomisation procedures will take place during working hours.

## 8.4 Emergency unblinding

Not applicable

## 8.5 Screening assessments

Each patient will have a review of their demographics and data regarding their PD history, medication history, family history, previous imaging, previous genetic tests, and previous drug compliance issues. Their current PD medication regime will be noted.

An ECG, baseline blood tests (including blood count, renal function, HbA1c, serum amylase, serum stored according to the laboratory's standard SOP for future study) and clinical observations (pulse, blood pressure and weight) will be performed.

## 8.6 Baseline assessments

The patient will be sent the PDQ39, NMS Quest, SCOPA Sleep, SCOPA AUT, & Smell Identification test self-assessment forms to complete and bring with them to their baseline evaluation.

Baseline Evaluations comprise the following:

Blood tests to measure Blood count, renal function, liver function, serum amylase,HbA1c, Fasting serum glucose, & lipid profile. Serum will be stored. The patient will then be allowed to eat and drink as they wish.

Urine and stool samples will be requested and collected and stored for use in a separate study. This is not an essential part of trial participation and patients will be able to decline giving these samples.

The UPDRS which is the standard validated tool for the assessment of patients with Parkinson's disease. This scale includes subsections collecting data regarding the impact of Parkinson's disease on a patient's mood and mental state, (UPDRS part 1), their activities of daily living (UPDRS part 2) an examination of the motor features of PD (UPDRS part 3), and complications arising from the use of Parkinson's medications (UPDRS part 4). Part 3 of the UPDRS will be performed twice and video recordings will be taken on each occasion- first at a time when the patient has been free of all PD medications for at least 12 hours (including Exenatide) and free of all long acting dopamine agonists (Ropinirole MR, Cabergoline) for at least 24 hours. The first UPDRS part 3 assessment will take place as soon as the patient arrives to minimize their duration of any discomfort from not having taken medication. The UPDRS 3 motor score will then be repeated 1 hour after the patient has taken their regular medication and confirms that they have achieved their best medication response. Their current PD medication regime will be noted. If the patient does not feel that they achieved their best on medication response at any point during the baseline evaluation as a result of having omitted medication prior to clinic visit, they will be invited back for the UPDRS 3 on medication video assessment 1 week later, and both UPDRS 3 on medication scores stored for later comparison.

Timed Motor Tests include a hand tapping task to evaluate the number of hand taps that an individual can perform within 30 seconds and a timed, sit, stand, walk task.

The Dyskinesia Rating scale is an objective assessment of the severity of involuntary movements in 7 body regions with each region receiving a score of 0-4.

The Mattis Dementia Rating scale is a widely used scale to evaluate cognitive functioning in older adults. It assesses Attention, Initiation/Perseveration, Constructional ability, Conceptualisation and Memory and has been previously used in the assessment of cognitive impairment among patients with Parkinson's disease.

The Montgomery and Asberg Depression Rating Scale is a 10 item physician rated depression severity scale constructed to be sensitive to change with treatment.

The PDQ39 is a 39 item quality of life assessment especially designed for patients with IPD, by the Health Services Research Unit, Oxford 1998. Patients are given the questionnaire for self-completion. The completed questionnaire is designed to be de-constructed into a score for 8 separate dimensions; mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. Reliability and validity of the scale has been confirmed.

The NMS Questionnaire is a rating scale designed to capture the presence of the Non-motor features of Parkinson's disease.

The EQ-5D is a generic instrument for measuring health related quality of life, designed to be self-completed by the respondent. It essentially consists of the EQ-5D descriptive system, where the respondent is asked to describe his/her own health state on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension provides three levels from which the respondent can choose: no problems, some problems, severe problems. In addition to the descriptive system the EQ-5D contains a visual analogue scale (VAS), where the respondent is asked to mark his/her current health on a vertical visual analogue scale with endpoints ranging from 'worst imaginable health state' to 'best imaginable health state'. The information derived from both sections of the EQ-5D can be used to derive a single index (between 0 and 1) that can also be used for the calculation of quality adjusted life years (QALYs) and cost-utility analyses.

The SCOPA SLEEP is a 12 item questionnaire enquiring about day time and night time sleepiness.

The SCOPA AUT is a 26 item questionnaire enquiring about the existence of symptoms involving the autonomic nervous system often seen in PD patients and requiring Yes/No responses.

The Smell Identification test is a validated set of scratch and sniff tests used to quantify deficiencies in sense of smell.

## 8.7 Treatment procedures

Patients will be taught how to self administer subcutaneous injections of the trial drug using the pre-filled pen devices. Patients randomised to active treatment will be given supplies of 5µg bd subcutaneous injections for 1 month. Further supplies of pre-filled pens will be given to the patient at each follow up visit.

They will then return for their 1 month assessment and supplied with 2 months supply of Exenatide 10µg bd subcutaneous injections to be continued and replenished at subsequent follow up visits. Initial introduction of Exenatide using the 5µg dose prior to using the 10µg dose has been associated with lower rates of nausea and vomiting than immediate introduction of 10µg dose[Fineman *et al.* 2004].

Exenatide will be provided through the hospital pharmacy of the NHNN. It has a shelf life of 2 years if stored at 2-8 degrees. Each pre-filled pen can provide 60 doses of drug i.e. sufficient for 1 calendar month.

## 8.8 Subsequent assessments

Follow up assessments

One month assessment

At one month after baseline evaluation, each patient will be telephoned to complete an adverse events report and document their anti PD medication regime. Patients randomised to receive Exenatide will be asked to attend the trial clinic taking their regular PD medication (and Exenatide). They will be asked not to have eaten and to have drunk water only for 6 hours to enable fasting blood samples to be taken. Clinical observations including Pulse, Blood pressure and weight will be measured and blood tests sent to measure renal function, liver function, serum amylase & Fasting serum glucose. Serum will be stored. Each patient will be given a 2 month supply of Exenatide 10µg bd and supply of needles for the subcutaneous pen injection system.

Three month assessment

At three months after baseline evaluation, each patient will be telephoned to complete an adverse events report and document their anti PD medication regime. Appointments will be made for each patient on Exenatide to attend the trial clinic. The patients will withhold all PD medications (including Exenatide) for at least 12 hours (overnight). Individuals taking Ropinirole MR, or Cabergoline will be instructed to stop this medication 24 hours before assessment. They will be asked not to have eaten and to have drunk water only for 6 hours to enable fasting blood samples to be taken.

Attending patients will have - blood tests to measure renal function, liver function, serum amylase & Fasting serum glucose. Serum will be stored. They will then be allowed to eat as they wish. They will have a video recording of UPDRS part 3 score, perform timed motor tests and then will take their regular medication. The patient will be asked to complete UPDRS part 1, 2, 4 and when they have confirmed that their best on state achieved, they will have a further video of UPDRS part 3 score. During their on phase, the Dyskinesia Rating scale, MADRS, Mattis DRS will be completed. An ECG, and clinical observations- weight, pulse, blood pressure will be performed. Their current PD medication regime will be noted. Any patients who feel that they fail to achieve their best on-medication response during the clinic visit as a result of having with-held medication previously will be invited to return to the clinic for an on-medication assessment one week later. Each patient will be given a 3 month supply of Exenatide 10µg bd and supply of needles for the subcutaneous pen injection system.

Six month assessment

Patients will be telephoned 2 weeks in advance to remind them of this visit and will be sent the PDQ39, and NMS QUEST to self-complete at home and bring to the clinic.

Appointments will be made for all patients (both taking Exenatide and controls) to attend the trial clinic. All patients will withhold all PD medications (including Exenatide) for at least 12 hours (overnight). Individuals taking Ropinirole MR, or

Cabergoline will be instructed to stop this medication 24 hours before assessment. They will be asked not to have eaten and to have drunk water only for 6 hours enable fasting blood samples to be taken.

Each patient will have - blood tests to measure renal function, liver function, serum amylase, HbA1c, Fasting serum glucose, & lipid profile. Serum will be stored. , They will then be allowed to eat as they wish. Urine and stool samples will be stored if provided.

All patients (both on Exenatide and controls) will have a video recording of UPDRS part 3 score, perform timed motor tests and then will take their regular medication. The patient will be asked to complete UPDRS part 1, 2, 4 and when they have confirmed that their best on state achieved, they will have a further video of UPDRS part 3 score. During their on phase, the Dyskinesia Rating scale, MADRS, Mattis DRS will be completed. An ECG, and clinical observations- weight, pulse, blood pressure will be performed. Their current PD medication regime will be noted. They will complete an Adverse events form. Any patients who feel that they fail to achieve their best on-medication response during the clinic visit as a result of having with-held medication previously will be invited to return to the clinic for an on-medication assessment one week later. Patients on Exenatide will be given a further 3 months supply of Exenatide 10μg bd and supply of needles for the subcutaneous pen injection system.

Nine month assessment

At nine months after baseline evaluation, each patient will be telephoned to complete an adverse events report and document their anti PD medication regime. Patients randomised to receive Exenatide will be asked to attend the trial clinic taking their regular PD medication (and Exenatide). They will be asked not to have eaten and to have drunk water only for 6 hours enable fasting blood samples to be taken. Clinical observations including Pulse, Blood pressure and weight will be measured and blood tests sent to measure renal function, liver function, serum amylase & Fasting serum glucose. Serum will be stored.

Twelve month assessment

Patients will be telephoned 2 weeks in advance to remind them of this visit and will be sent the PDQ39, EQ5D and NMS QUEST to self-complete at home and bring to the clinic.

Appointments will be made for all patients (both taking Exenatide and controls) to attend the trial clinic. All patients will withhold all PD medications (including Exenatide) for at least 12 hours (overnight). Individuals taking Ropinirole MR, or Cabergoline will be instructed to stop this medication 24 hours before assessment. They will be asked not to have eaten and to have drunk water only for 6 hours enable fasting blood samples to be taken.

Each patient on Exenatide will have - blood tests to measure renal function, liver function, serum amylase, HbA1c, Fasting serum glucose, & lipid profile. Serum will be stored. They will then be allowed to eat as they wish. Urine and stool samples will be stored if provided.

All patients (both on Exenatide and controls) will have a video recording of UPDRS part 3 score, perform timed motor tests and then will take their regular medication. The patient will be asked to complete UPDRS part 1, 2, 4 and when they have confirmed that their best on state achieved, they will have a further video of UPDRS part 3 score. During their on phase, the Dyskinesia Rating scale, MADRS, Mattis DRS will be completed. An ECG, and clinical observations- weight, pulse, blood pressure will be performed. Their current PD medication regime will be noted. They will complete an Adverse events form. Any patients who feel that they fail to achieve their best on-medication response during the clinic visit as a result of having with-held medication previously will be invited to return to the clinic for an on-medication assessment one week later. All patients will then cease injections of Exenatide but will continue on other PD medications.

Fourteen month assessment

Patients will be sent the PDQ39, and NMS QUEST to self-complete at home and bring to the clinic.

Appointments will be made for all patients to attend the trial clinic. All patients will withhold all PD medications for at least 12 hours (overnight). Individuals taking Ropinirole MR, or Cabergoline will be instructed to stop this medication 24 hours before assessment. They will be asked not to have eaten and to have drunk water only for 6 hours enable fasting blood samples to be taken.

Each patient will have - blood tests to measure renal function, liver function, serum amylase, & Fasting serum glucose. Serum will be stored. They will then be allowed to eat as they wish. Urine and stool samples will be stored if provided.

All patients will have a video recording of UPDRS part 3 score, perform timed motor tests and then will take their regular medication. The patient will be asked to complete UPDRS part 1, 2, 4 and when they have confirmed that their best on state achieved, they will have a further video of UPDRS part 3 score. During their on phase, the Dyskinesia Rating scale, MADRS, Mattis DRS will be completed. An ECG, and clinical observations- weight, pulse, blood pressure will be performed. Their current PD medication regime will be noted. They will complete an Adverse events form. Any patients who feel that they fail to achieve their best on-medication response during the clinic visit as a result of having with-held medication previously will be invited to return to the clinic for an on-medication assessment one week later.

## 8.9 Flowchart of study assessments

| Timing of assessment | Activities during assessment | Forms to be completed |
|---|---|---|
| Initial discussion during Outpatient clinic visit | Participant education re trial.<br>Patient Information sheet given. | |
| In person screen | Patient questions answered<br>Patient confirms ability to attend clinic after overnight off medication period.<br>Patient signs Informed consent<br>Review of<br>-Demographic data re PD<br>-medication history<br>-Family history<br>-Previous imaging<br>-Previous genetic tests<br>-previous drug compliance issues<br>Clinical examination<br>Patient instructed re withdrawal of long acting medications<br>ECG, Bloods (FBC, U&E, LFT, Glucose, Amylase, HbA1C), Obs<br>Research team contact details given<br><br>PDQ39, EQ5D, NMS QUEST<br>SCOPA Sleep, SCOPA AUT<br>Smell Identification test (to be given to patient and brought to baseline evaluation) | Inclusion/Exclusion criteria<br>Consent Form<br>PD details<br>Levodopa Equivalent Dose (LED) |
| Final recruitment & randomisation | *Results of blood tests reviewed prior to baseline evaluation to ensure patient eligibility.*<br><br>Randomisation 20:20 | Randomisation form |

| | | |
|---|---|---|
| | Exenatide:Control | |
| *Imaging study* | *10 patients will be selected for a DAT SPECT imaging sub-study at baseline.* | *SPECT scans among n=10 subgroup* |
| Baseline evaluation | <u>Recruited consenting patients to attend in fasted state off regular PD meds n=40</u><br>Fasting blood samples taken (FBC, U&E, LFT, Lipid profile, Glucose, Amylase, HbA1C).<br>Patient can then eat and drink as they wish.<br>Urine and stool sample<br>Video of UPDRS part 3 off medication score<br>Timed motor tests<br>Patient takes regular medication<br>Levodopa equivalent dose (LED) noted<br>Patient completes UPDRS part 1,2, 4<br>Patient confirms best on state achieved<br>Video of UPDRS part 3 on medication score<br>Dyskinesia Rating scale<br><br><u>Patients for active treatment n=20</u><br>Teaching injections<br>Supply of Exenatide 5µg bd<br>Supply of needles/sharps disposal | PDQ39<br>EQ-5D<br>NMS QUEST<br>MADRS<br>Mattis<br>SCOPA Sleep<br>SCOPA AUT<br>Smell Identification test<br>UPDRS x2<br>DRS<br>LED |
| 1 month evaluation | <u>Patients telephoned re adverse events n=40</u><br><br><u>Patients randomised to treatment attend in fasted state on medication n=20</u><br>Fasting blood samples taken<br>Patient can then eat and drink as they wish.<br>Clinical Obs- P, BP | AE |

| | | |
|---|---|---|
| | Supply of Exenatide 10µg bd<br>Supply of needles | |
| 3 month evaluation | <u>Patients telephoned re adverse events n=40</u><br><br><u>Patients randomised to treatment attend in fasted state off regular PD meds n=20</u><br>Fasting blood samples taken<br>Patient can then eat and drink as they wish.<br>Video of UPDRS part 3 score<br>Timed tests<br>Patient takes regular medication<br>Patient completes UPDRS part 1,2,4<br>Patient confirms best on state achieved<br>Video of UPDRS part 3 score<br>Dyskinesia Rating scale<br>MADRS, Mattis DRS<br>ECG, Clinical Obs- P, BP<br>Supply of Exenatide 10µg bd<br>Supply of needles | AE<br><br>UPDRS x2<br>DRS<br>MADRS<br>MATTIS<br>LED |
| 6 month evaluation | <u>All Patients attend in fasted state off regular PD meds n=40</u><br>Fasting blood samples taken<br>Patient can then eat and drink as they wish.<br>Video of UPDRS part 3 score<br>Timed tests<br>Patient takes regular medication<br>Patient completes UPDRS part 1,2, 4<br>Patient confirms best on state achieved<br>Video of UPDRS part 3 score | AE<br><br>UPDRS x2<br>DRS<br>MADRS<br>MATTIS<br>PDQ39<br>NMS Quest<br>SCOPA Sleep<br>SCOPA AUT<br>LED<br>Smell Identification test |

| | | |
|---|---|---|
| | Dyskinesia Rating scale<br>MADRS, Mattis DRS<br>ECG, Clinical Obs- P BP<br><br>PDQ39, NMS Quest, SCOPA sleep, SCOPA AUT<br>Smell Identification test returned to Investigator (sent out pre-appointment)<br><br><u>Patients randomised to active treatment n=20</u><br>Supply of Exenatide 10µg bd<br>Supply of needles<br>Urine and stool sample | |
| 9 months | <u>Patients telephoned re adverse events n=40</u><br><u>Patients randomised to treatment attend in fasted state on medication n=20</u><br>Fasting blood samples taken<br>Patient can then eat and drink as they wish.<br>Clinical Observations- P, BP<br>Supply of Exenatide 10µg bd<br>Supply of needles | AE |
| 12 months | <u>All Patients attend in fasted state off regular PD meds n=40</u><br>Fasting blood samples taken<br>Patient can then eat and drink as they wish.<br>Video of UPDRS part 3 score<br>Timed tests<br>Patient takes regular medication<br>Patient completes UPDRS part 1,2, 4<br>Patient confirms best on state achieved<br>Video of UPDRS part 3 score | AE<br><br>UPDRS x2<br>DRS<br>MADRS<br>MATTIS<br>PDQ39<br>EQ-5D<br>NMS QUEST<br>SCOPA Sleep<br>SCOPA AUT<br>Smell Identification test<br>LED |

| | | |
|---|---|---|
| | Dyskinesia Rating scale<br>MADRS, Mattis DRS<br>ECG, Clinical Obs- P, BP<br><br>PDQ39, EQ5D, NMS QUEST<br>SCOPA Sleep, SCOPA AUT<br>Smell Identification test returned to Investigator (sent out pre-appointment)<br>Urine and stool sample | |
| *Follow up SPECT scan study* | *Patients with baseline DAT SPECT scans to have repeat DAT SPECT Scan at study end* | *DAT SPECT scan* |
| 14 months | <u>All Patients attend in fasted state off regular PD meds n=40</u><br>Fasting blood samples taken<br>Patient can then eat and drink as they wish.<br>Video of UPDRS part 3 score<br>Timed tests<br>Patient takes regular medication<br>Patient completes UPDRS part 1,2, 4<br>Patient confirms best on state achieved<br>Video of UPDRS part 3 score<br>Dyskinesia Rating scale<br>MADRS, Mattis DRS<br>ECG, Clinical Obs- P, BP<br><br>PDQ39, EQ5D, NMS QUEST<br>SCOPA Sleep, SCOPA AUT<br>returned to Investigator (sent out pre-appointment)<br>Urine & Stool sample | AE<br><br>UPDRS x2<br>DRS<br>MADRS<br>MATTIS<br>PDQ39<br>EQ-5D<br>NMS QUEST<br>SCOPA Sleep<br>SCOPA AUT<br>LED |

## 8.10 Methods

### *8.10.1 Laboratory procedures*

All patient blood samples will be analysed by the standard accredited hospital routine laboratories of the National Hospital for Neurology and Neurosurgery and UCLH.

### *8.10.2 Radiology or other procedures*

Ten of the 20 patients randomised to Exenatide treatment will be invited to have a DAT SPECT scan at baseline and after 12 months. The potential mechanism of action of Exenatide leading to improvements seen in animal models of PD is unclear. One hypothesis is that the drug leads to dopaminergic neurogenesis which would be accompanied by increases in the activity measured by DAT scan. Ten patients receiving Exenatide will therefore have DAT scans at baseline and at study end. All imaging will take place at University College Hospital NHS Trust. Quantitative analysis of scans will be performed by an experienced trained individual.

## 8.11 Definition of end of trial

The end of the trial will be the date of the last visit by the last participant.

## 8.12 Discontinuation/withdrawal of participants and 'stopping rules'

Appropriate symptomatic treatment for common side effects of Exenatide including nausea, vomiting and diarrhoea will be made available to patients wishing to continue trial participation. Patients experiencing persistent side effects despite these measures while receiving the high dose (10micrograms bd) will be invited to resume the low dose (5 micrograms bd) treatment.

Patients wishing to discontinue participation with the trial will be free to do so. The reasons for withdrawal will be sought from all individuals and recorded. Any individual issue that can be satisfactorily addressed to minimise dropout will be implemented. Adverse events will be recorded systematically throughout the trial and from all patients wishing to withdraw. Appropriate medical advice and treatment will be made available to any individuals experiencing adverse events from trial participation. Patients that withdraw will be invited to have an exit checkup as per the 14 month follow up visit. Patients randomised to active treatment that are clearly non-compliant with treatment will be withdrawn. Patients withdrawing after less than 3 months will be replaced by the recruitment of additional randomised patients, and will be continue to be followed up with continued consent. Patients that have received active drug for 3 months or longer will continue to be followed up for the duration of the trial with continued consent.

The trial will be stopped prematurely if there are doubts regarding the safety or scientific validity of its continuation, in accordance with the principles of Good Clinical Practice and the Medicines for Human Use (Clinical Trials) Regulations 2004 Part 4.

# 9 Name and description of all drugs used in the trial

IMP- Exenatide

NIMP- Background treatments used as standard care for the treatment of PD- Sinemet, Madopar, Stalevo, Entacapone, Tolcapone, Ropinirole, Pramipexole, Rotigotine, Rasagiline, Selegiline, Domperidone.

## 9.1 Name and description of each IMP

IMP- Exenatide. Manufactured under license as “Byetta”. No other brand of Exenatide is currently available therefore the trial will use Byetta for all patients randomised to active drug.

## 9.2 Source of IMPs including placebo

The following IMPs will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the pharmacy.

Exenatide

## 9.3 Accountability procedures for the investigation product(s), including the placebo(s) and comparator(s), if any.

The trial pharmacist within the hospital pharmacy department will be accountable for trial drug supplies. No additional reconstitution or other preparation will be required. IMP accountability will be managed by the hospital pharmacy and the CI.

## 9.4 Route of administration, dosage, dosage regimen, and treatment period(s) of the IMPs.

Patients randomised to receive active drug will be taught how to perform the subcutaneous injections. They will be taught about the commonly occurring side effects previously reported e.g. nausea, vomiting and diarrhoea. They will be given a supply of Exenatide 5 micrograms twice daily as a pre-filled pen injection system. After one month, all patients will be reviewed and adverse events recorded. Patients that tolerate the 5 microgram dose will be given a supply of Exenatide 10 micrograms twice daily as a pre-filled pen injection system.

Patients with adverse reactions to the low dose injection e.g. nausea will be given a supply of Domperidone 10mg tablets to be taken orally up to three times daily as a treatment to relieve nausea. In previous studies, the frequency and severity of nausea diminished with continued Exenatide therapy. Patients that are unable to tolerate the low dose injections despite this measure will be given the option to withdraw from the trial. The higher dose of Exenatide will only be introduced once patients tolerate the lower dose. Patients not able to tolerate the higher dose despite the use of agents such as Domperidone, will be restarted on the lower dose.

Patients randomised to receive the active drug will continue to administer the drug for a total of 12 months at the maximally tolerated dose.

## 9.5 Assessment of compliance

Compliance will be optimised by informing all patients randomised to receive the study drug, of the most commonly experienced side effects and ways of minimising these. Patients will be given adequate instruction regarding administration of injections and developing a twice daily routine for their administration. Good relationships will be established with all trial participants to maximise honest reporting of compliance.

Compliance will be assessed by directly questioning patients, at each visit, with carers also asked to provide estimates of compliance. Patient estimates will be checked against reports of how long each pen (with 60 pre-filled doses) lasts before it needs replacing. A compliance score will be derived from the estimated number of injections actually administered each month and this figure recorded in the patient's clinical file at each visit.

Patients identified to clearly have very low levels of compliance in the first month will be withdrawn from study and replaced by new trial participants.

## 9.6 Post-trial IMP arrangements

No arrangements are in place to provide Exenatide to trial subjects post trial participation. This will be made clear in the Patient Information sheet.

## 9.7 Name and description of each NIMP

Sinemet- Levodopa/ Carbidopa

Madopar- Levodopa/ Benserazide

Stalevo- Levodopa/ Carbidopa/ Entacapone

Entacapone,

Tolcapone,

Ropinirole,

Pramipexole,

Rotigotine,

Rasagiline,

Selegiline,

Domperidone.

Any UK licensed oral L-dopa treatments, dopamine agonists, monoamine oxidase inhibitors or catechol-O-methyl transferase inhibitors used by patients in the treatment of their PD will be considered non-IMPs (NIMPs). Domperidone (oral 10mg) for the treatment of IMP related gastric symptoms will be considered a NIMP. NIMP suspected Adverse Drug Reactions or side effects will be reported through the standard yellow card system.

# 10 Recording and reporting of adverse events and reactions

## 10.1 Definitions

***Adverse event*** means any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product;

***Adverse reaction*** means any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject;

***Serious adverse event***, ***serious adverse reaction*** or ***unexpected serious adverse reaction*** means any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect;

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

***Unexpected adverse reaction*** means an adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out:

(a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product,
(b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

***Suspected unexpected serious adverse reaction*** is also known as a **SUSAR**.

## 10.2 Recording adverse events

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be done according to the sponsor's SOP.

All adverse events will be recorded in the hospital notes in the first instance. A record will also be kept in the CRF of all adverse events, whether believed to be related or unrelated to the treatment.

If the investigator suspects that the disease has progressed faster due to the administration of the IMP, then he will report this as an unexpected adverse event to the sponsor.

Clinically significant abnormalities in the results of objective tests (laboratory variables and ECG) will be also be recorded as adverse events.

The record of adverse events will include the following.

- Clinical symptoms: a simple, brief description.
- Severity. The following categories will be used:

  *Mild:* the adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort.

  *Moderate:* the adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort.

  *Severe:* the adverse event results in alteration, discomfort or disability which is clearly damaging to health.

- Relationship to treatment: The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used:

  *Definitely:* There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

*Probably:* There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

*Possibly:* There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).

*Unlikely:* There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).

*Not related:* There is no evidence of any causal relationship.

*Not Assessable*

- Expectedness: The following categories will be used:

  *Expected*: An adverse event that is classed in nature as serious and which is consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP)

  *Unexpected:* An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP)

- Seriousness as defined for an SAE in section 10.1.

## 10.3 Procedures for recording and reporting Serious Adverse Events

For all serious adverse events, the Chief Investigator will complete the sponsor's serious adverse event form and the form will be faxed to the sponsor on 020 7380 9937, within one working day of his / her becoming aware of the event. The chief or principal investigator will respond to any SAE queries raised by the sponsor as soon as possible. Reporting to the sponsor will be done as per the sponsor's SOP.

All SUSARs will be notified to the sponsor immediately (or at least within one working day) according to the sponsor's written SOP.

### *10.3.1 Notification of deaths*

All deaths will be immediately (within one working day of the CI becoming aware of the death) reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event.

### *10.3.2 Reporting SUSARs*

The sponsor will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

#### *10.3.2.1 Procedures for reporting SUSARs in double blind trials*

Not applicable

### *10.3.3 Annual safety reports*

The sponsor will provide the main REC and the MHRA with an annual safety report (ASR). The ASR will be prepared, using the sponsor's ASR form, by the Chief investigator or a delegated PI, reviewed by the sponsor and when necessary be referred to an independent committee (independent to the trial) such as the safety committee. This will be done in accordance with the sponsor's SOP.

### *10.3.4 Annual progress reports*

An annual progress report (APR) will be submitted to the main REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

The chief investigator will prepare the APR. The sponsor will review the document before it is sent to the main REC.

### *10.3.5 Pregnancy*

Females of child bearing potential are excluded from trial participation, as listed within the exclusion criteria. There are no adequate data from the use of Exenatide in pregnant women therefore the potential risk to humans is unknown. All male participants with female partners of child bearing potential, will be asked to use adequate contraception. In the event of any male patients conceiving a child during the trial period, the outcome of the pregnancy will be documented. All pregnancies occurring will be recorded and reported to the sponsor on the sponsor's SOP.

- Any child born to a male trial subject who is the partner of the pregnant woman will be followed up to term to check for congenital abnormalities.

### *10.3.6 Reporting Urgent Safety Measures*

Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928

states " the Sponsor and the Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. If measures are taken, the Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures."
In order to prevent any delays in the reporting timelines the sponsor has delegated this responsibility to each PI site. Therefore the PI must report any urgent safety measures to the MHRA directly and in parallel to the sponsor.

### *10.3.7 Notification of Serious Breaches to GCP and/or the protocol*

**"**Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928, contains a requirement for the notification of "serious breaches" of GCP or the trial protocol:
**"29A.** (1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of -
(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.
(2) For the purposes of this regulation, a "serious breach" is a breach which is **likely** to effect to a significant degree –
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial".

The sponsor must be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor's SOP on the *Notification of Violations, Urgent safety measures and serious breaches* must be followed.

## 10.4 The type and duration of the follow-up of subjects after adverse events.

All subjects will be followed up with detailed assessments including reporting of adverse events for 2 months after the last dose of Exenatide has been administered. Any SUSAR related to the IMP will be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

Following an adverse drug reaction, patients will be given all care and attention necessary by trial personnel and/ or by individuals with additional relevant clinical expertise for as long as necessary.

# 11 Data management and quality assurance

## 11.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the subject's name. The subject's initials, date of birth and trial identification number, will be used for identification. Video tapes and/or electronic video files will be coded by the individual patient's trial ID number and stored in a secure University Research facility.

## 11.2 Data collection tools and source document identification

Case report forms will be designed and produced by the investigator, according to the sponsor's CRF template. The final version will be approved by the sponsor. All data will be entered legibly in black ink with a ball-point pen. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the person making the alteration. Overwriting or use of correction fluid will not be permitted.'

The following standard data will be entered into the medical records (source) and then onto the Case Report Form (CRF)

Informed consent
Trial participant number
Randomisation outcome
Demographic data re PD
Medication history
Family history- including age at onset of all affected relatives
Previous imaging
Previous genetic tests
Previous drug compliance issues
Clinical examination
Adverse events

The following study-specific information will be documented directly onto the CRF.
Levodopa Equivalent Dose
Clinical Observations- pulse, BP
Compliance
Blood test tick box

The following data are from standardised tools and the printed questionnaires completed at each visit will be the source documents which will be filed in the CRF.

Blood test results printout
ECG printout
UPDRS

DRS
MADRS
MATTIS
PDQ39
EQ5D
NMS QUEST
SCOPA Sleep
SCOPA AUT
Smell Identification test

Subjects will be sent forms for self completion (PDQ39, EQ5D, NMS QUEST, SCOPA Sleep, SCOPA AUT, Smell Identification test) 1 week prior to their clinic assessment with the intention that they are brought to the clinic with the patient. Questionnaires left at home by the patient will be posted back to the CI or replaced and completed at the time of the visit. All other data will be collected during the face to face clinic assessments.
It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

### 11.3 Data handling and analysis

A Microsoft Access database will be specifically designed for data entry and storage. Numerical limits (e.g. valid values 0-4) will be put in place to prevent erroneous data being entered. This database will be stored on a single UCL computer with secure server backup to prevent data loss in case of hardware failure. This computer will have restricted access, will be username and password protected, and will be kept in a secure University research facility.

The CI will delegate responsibility for data entry and quality to a named individual who will be part of the trial team. The CI will be responsible for data analysis which will be done independently of data entry.

All data storage will adhere to Data Protection Act 1998.

## 12 Record keeping and archiving

The Chief Investigator is responsible for the secure archiving of trial documents and the trial database.

The site files, video recordings, CRFs and consent forms, and the trial database will be retained for 20 years after completion of the study. Data will be stored to enable additional retrospective subgroup analyses to be performed or to look at long term follow up outcomes, should future data indicate that this may be of interest or importance.

These data will be stored in a secure University Research facility.

# 13 Statistical Considerations

Dr Foltynie has been formally trained in Epidemiology and Biostatistics at the University of Cambridge (MPhil 2000), and has taken the statistical decisions in the design of the protocol. Additional statistical advice has been sought through the UCL JRBU- Dr Gareth Ambler.

## 13.1 Endpoints

### *13.1.1 Primary endpoints*

Change from baseline to 12 months & 14 months between patients on active Exenatide treatment and PD controls in respect of their UPDRS-off-medication motor subscore.

### *13.1.2 Secondary endpoints*

Adverse event profile among patients treated with Exenatide compared with matched PD controls.

Change from baseline to 12 months/ 14 months between patients on active treatment and PD controls in respect of;

-the UPDRS on medication motor subscore

-the UPDRS ADL subscore

-dyskinesia rating scale

-timed motor tests

-the Mattis Dementia rating scale

-the Montgomery & Asberg Depression rating scale

-the PDQ39

- the EQ-5D

-the NMS Quest

-the SCOPA Sleep scale

-the SCOPA AUT scale

-the Smell Identification test

-DAT (SPECT) scan appearances.

## 13.2 Sample size and recruitment

### *13.2.1 Sample size calculation*

In previous studies involving patients on stable treatment regimes of either Pramipexole or L-dopa, there was a UPDRS decline of approximately 3 UPDRS points per year(SD of 6.8 points) [Holloway et al. 2004]. PD Trials that have used change in off-medication motor UPDRS scores as an outcome measure have shown similar rate of decline (1.7 points after 6 months) among patients on "best medical treatment" [Weaver et al. 2009].

We can thus expect our group of PD controls to decline at a rate of 3 UPDRS points over the course of the study. The basic science work leading up to this proposal suggests that this drug not only halts the disease process but has neuro-restorative properties.

Using the formula, $n= 42 \times (\text{SD of Difference/Difference})^2$ , the patient sample size (n=40) in this trial would have 90% power to detect a difference of 7 UPDRS points between the treated and untreated patients at a significance level of 5% assuming normality in distribution of response and a SD of 6.8 points. This translates to a mean improvement of 4 UPDRS points in the treated patients. This will be a very clinically important effect size. Less optimistically, this sample size would still have 80% power to detect a difference of 6.1 points, i.e. a mean improvement of 3.1 points in the treated patients. Whether the current estimate of the possible magnitude of effect of Exenatide is realistic will only be established once pilot data has been collected.

This trial has been designed to be large enough to provide initial pilot clinical data of PD patients exposed to Exenatide upon which to base a more precise power calculation for a future randomised placebo controlled trial. With 40 patients we can estimate the treatment effect to within +/- 4.2 units ($1.96 \times \sqrt{(2 \times \text{sigma}^2/n)}$). No subgroup analyses will be performed.

Twenty patients will receive the active trial drug Exenatide and 20 will act as PD controls. Patients that drop out within the first three months will be replaced by further patients who will undergo the same randomisation process. A sensitivity analysis will be performed to investigate systematic differences between patients completing the trial and patients dropping out. Multiple imputation techniques will be used to derive scores for patients with missing data. Following completion of this trial, a refined estimate of the potential efficacy of this drug can then be used in the design and sample size calculation in a future larger trial. This pilot data will also provide evidence of safety of the drug in this patient group.

### *13.2.2 Planned recruitment rate*

Initial discussions with patients at scientific and patient support meetings shows very high interest in this study. There are no other trials of potentially disease modifying agents currently in progress. There are in excess of 500 patients with PD followed up at the National Hospital for Neurology and Neurosurgery. With the small sample size, we anticipate that recruitment will be completed within a 3 month period.

## 13.3 Statistical analysis plan

### *13.3.1 Summary of baseline data and flow of patients*

Recruited individuals will be randomised to have the trial drug added to their treatment or to continue to receive existing treatment alone. The summary of baseline data for each group will be presented as their means, and standard deviations, prior to analysis of outcomes from treatment.

### *13.3.2 Primary endpoint analysis*

The difference between UPDRS part 3 off medication score at baseline and at 14 months will be calculated for each patient. The mean difference and SD for patients randomised to treatment and for patients acting as controls will be presented. It is anticipated that there will be a high correlation between the baseline and follow up measures. The analysis will be performed on an intention to treat basis including all patients who complete at least one follow up assessment.

Every effort will be made to ensure that missing data is kept to a minimum. Patients dropping out prior to 3 months who refuse follow up assessments will have their reason for dropping out reported. Additional patients will be recruited and randomised to replace patients who drop out prior to their first follow up assessment.

The distribution of scores will be checked for normality. If data are normally distributed a two-sample t test will be used to assess the difference between the means. If the data are not normally distributed, non-parametric tests will be used. No subgroup analyses are planned.

Regression models will be used to allow evaluation of treatment effects with adjustment for confounding factors - age, sex, disease duration, and disease severity at baseline.

### *13.3.3 Secondary endpoint analysis*

The difference between each of the secondary outcome measures at baseline and at 12 months will be calculated for each patient. The mean difference and SD for

patients randomised to treatment and for patients acting as controls will be presented. The analysis will be performed on an intention to treat basis including all patients who complete at least one follow up assessment.

Every effort will be made to ensure that missing data is kept to a minimum for all secondary endpoints. Missing data due to dropout or selective refusal of particular assessments beyond 3 months of the study will use the last observation carried forward for analysis.

The distribution of scores will be checked for normality. If data are normally distributed a paired t test will be used to assess the difference between the means. If the data are not normally distributed, a non-parametric test e.g the sign test will be used. No subgroup analyses are planned.

### *13.3.4 Sensitivity and other planned analyses*

Sensitivity analyses will be performed to identify differences between patients who drop out or have missing data and patients with complete data for each variable.

## 13.4 Randomisation

Eligible individuals who have given informed consent will be randomised 1:1 to receive Exenatide or act as a PD control. Separate randomisation lists will be generated for patients with more severe and less severe disease to ensure groups are balanced and ensure that patients randomised to treatment are of similar PD phenotype to patients acting as controls. All randomisation procedures will take place during working hours with the trial pharmacist holding the randomisation list. The randomisation list will be long enough to enable continued recruitment should patients dropout within the first 3 months of the trial. Since all patients will be recruited from a single centre and the study is small, commercial randomisation procedures and their expense can be avoided.

## 13.5 Interim analysis

A planned interim analysis will be performed when all patients have completed 6 months. This will be performed by Dr Foltynie and will analyse the primary endpoint and adverse event profiles only. The outcome of these analyses will be discussed by the trial management group. Worsening of PD (>9 UPDRS point deterioration) among patients randomised to treatment or concern that continuation of the trial compromises the safety of the patients will lead to early termination of the trial.

Trial results will be outlined in detail in a full report at the end of the trial or at the time of discontinuation.

### 13.6 Other statistical considerations

Any deviation(s) from the original statistical plan will be described and justified in the final report.

## 14 Name of Committees involved in trial

A Trial Management Group (TMG) will be created to supervise the conduct of the trial. This will comprise the chief investigator, two collaborating senior principal investigators, and the research fellow coordinating data collection and data entry. This group will meet to discuss the trial progress every 3 months.

## 15 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion.

## 16 Ethics

No data exists to decide whether the beneficial effects seen in the laboratory translate to clinical improvements in patients with PD. True equipoise exists for the purposes of randomising patients. The safety data from large phase III trials of Exenatide given to Diabetes patients provides reassurance that risks to the patients will be minimal. Measuring improvement in underlying PD severity among PD patients requires an assessment to be performed after an overnight period off medication. They will be assessed first thing in the morning to minimize the duration of inconvenience of being off medication. This is a standard approach in the assessment of clinical severity used in varying aspects of PD management among patients even with advanced PD. The clinical assessor will have extensive experience in the assessment of PD severity and will have additional formal training to ensure consistency and validity. Both the patient and the clinical assessor will be aware of whether the patient has been on active drug or is a control. To minimize bias, all assessments will be video recorded to enable re-assessment of accuracy and objectivity. Videos will be stored securely, either physically under lock and key in the case of tapes, or on a secure IT system for digital films. These will be retained indefinitely. Other drugs will be modified according to clinical need as is standard practice in PD follow up.

This drug can only be administered by subcutaneous injection therefore patients randomised to receive the drug will be taught how to perform the injections. Patients recruited to this trial will have moderate PD. A symptomatic treatment of subcutaneous injections (Apomorphine) already exists and is well tolerated by

patients with advanced PD. Despite the strong safety record of Exenatide, this trial will also record and report and systematically monitor patients for all adverse events at 3 monthly intervals as well as the development of minor complications of Exenatide use observed in the phase 3 trials of Exenatide for diabetes treatment. Patients will have fasting blood samples taken at each of their assessments to check for any subclinical change in glucose or amylase levels. All patients will have the contact details of clinically trained trial personnel in case of problems occurring between assessments.

The mechanism of action through which Exenatide has beneficial effects in the animal models of PD is unproven. For this reason, we have incorporated a small imaging arm into the trial design which will evaluate whether there is any evidence of a change in pre-synaptic dopaminergic integrity (DAT SPECT scans). The DAT scans are frequently used to help in the diagnosis of patients that do not have typical features of PD and as an additional surrogate measure of disease progression in clinical trials. These scans will all be performed in the same centre and assessed by an individual with experience of their quantitative assessment.

This trial will be conducted in accordance with the Seoul revision of the Declaration of Helsinki (2008), the principles of Good Clinical Practice according to the EU directive 2005/28/EC (GCP Directive) and The Medicines for Human Use (Clinical Trials) Regulations Statutory Instruments 2004/1031 and 2006/1938 in the UK.

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by appropriate regulatory body (MHRA) and main REC prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

# 17 Monitoring plan for the trial

The trial will be monitored according to the monitoring plan agreed by the sponsor, based on the self-monitoring template risk assessment. It is the responsibility of the CI to ensure that the sponsor’s self-monitoring template is completed throughout the trial (recommended every two months) and submitted to the JBRU at the regularity determined by the sponsor’s risk assessment of the trial phase. It is the responsibility of the CI to determine the monitoring risk assessment and explain the rationale.

# 18 Finance

This trial will be funded in its entirety by the Cure Parkinson’s Trust.

1 St Clement's Court, London EC4N 7HB

0207 929 7656
Registered charity number 1111816

www.cureparkinsons.org.uk

## 19 Insurance

University College London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

## 20 Publication policy

The results of this pilot trial will be submitted for publication in a peer reviewed journal, in addition to reports at appropriate specialist conferences.

## 21 Statement of compliance

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

## 22 References

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## Instructions

**The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.**

## 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

## 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

## 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence,or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

## 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Thomas

2. Surname (Last Name): Foltynie

3. Effective Date (07-August-2008): 05-February-2013

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: Exenatide as a disease-modifying treatment for Parkinson's disease- proof of concept trial

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☐ | ☐ | ☑ | Cure Parkinson's Trust | | × |

ADD

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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**Relevant financial activities outside the submitted work**

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 2. Consultancy | ☐ | ☑ | ☐ | Oxford Biomedica | Data Safety Monitoring Committee | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☐ | ☐ | ☑ | Brain Research Trust | | × |
| 5. Grants/grants pending | ☐ | ☐ | ☑ | European Union FP7 | | × |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☐ | ☑ | ☐ | Abbott Pharmaceuticals | | × |
| 6. Payment for lectures including service on speakers bureaus | ☐ | ☑ | ☐ | St Jude Medical | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

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Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

## 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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## 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Patricia
2. Surname (Last Name): Limousin
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Dr Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☐ | ☐ | ☑ | Cure Parkinson Trust | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## The Work Under Consideration for Publication

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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## Relevant financial activities outside the submitted work

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☐ | ☑ | ☐ | St Jude | Honorarium for lecture | × |
| 6. Payment for lectures including service on speakers bureaus | ☐ | ☑ | ☐ | Medtronic | Honorarium for lecture | × |
| | | | | | | ADD |

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| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 7. Payment for manuscript preparation | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): John
2. Surname (Last Name): Dickson
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thomas Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

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## The Work Under Consideration for Publication

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts on this study.
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## Relevant financial activities outside the submitted work

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 7. Payment for manuscript preparation | ☑ | ☐ | ☐ | | | × |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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**Relevant financial activities outside the submitted work**

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ☑ | ☐ | ☐ | | | × |
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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Thomas
2. Surname (Last Name): Isaacs
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

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**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

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## The Work Under Consideration for Publication

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts on this study.
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|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
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|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
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| | | | | | | ADD |
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| | | | | | | ADD |
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| | | | | | | ADD |
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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Richard
2. Surname (Last Name): Wyse
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## The Work Under Consideration for Publication

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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## Relevant financial activities outside the submitted work

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☑ | ☐ | ☐ | | | × |
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| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Iciar
2. Surname (Last Name): Aviles-Olmos
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

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**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
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| | | | | | | ADD |
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| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

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|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
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|---|---|---|---|---|---|---|
| | | | | | | ADD |
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| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Zinovia
2. Surname (Last Name): Kefalopoulou
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

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|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

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|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

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| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
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| | | | | | | ADD |
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| | | | | | | ADD |
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| | | | | | | ADD |
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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Therese
2. Surname (Last Name): Soderlund
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

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|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
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|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
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## Section 3. Relevant financial activities outside the submitted work.

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Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

## Relevant financial activities outside the submitted work

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 7. Payment for manuscript preparation | ☑ | ☐ | ☐ | | | × |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

**Relevant financial activities outside the submitted work**

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

## Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Hide All Table Rows Checked 'No'  SAVE

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## 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

## 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

## 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence,or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Atbin
2. Surname (Last Name): Djamshidian
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## The Work Under Consideration for Publication

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

## Section 3. Relevant financial activities outside the submitted work.

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## Relevant financial activities outside the submitted work

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 7. Payment for manuscript preparation | ☑ | ☐ | ☐ | | | × |

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**Relevant financial activities outside the submitted work**

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

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Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Andrew
2. Surname (Last Name): Lees
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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## The Work Under Consideration for Publication

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |

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## Relevant financial activities outside the submitted work

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |
| 2. Consultancy | ☐ | ☑ | ☑ | Andrew Lees is a consultant for Genus | | ✕ |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |
| 5. Grants/grants pending | ☐ | ☐ | ☑ | grants from the PSP Association, | | ✕ |
| 5. Grants/grants pending | ☐ | ☐ | ☐ | Weston Trust – The Reta Lila Howard Foundation. | | ✕ |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☑ | ☐ | ☐ | | | ✕ |

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**Relevant financial activities outside the submitted work**

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Payment for manuscript preparation | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☐ | ☑ | ☐ | Novartis | | × |
| 10. Payment for development of educational presentations | ☐ | ☑ | ☐ | Teva | | × |
| 10. Payment for development of educational presentations | ☐ | ☑ | ☐ | Ipsen | | × |
| 10. Payment for development of educational presentations | ☐ | ☑ | ☐ | Meda | | × |
| 10. Payment for development of educational presentations | ☐ | ☑ | ☐ | Boehringer Ingelheim | | × |
| 10. Payment for development of educational presentations | ☐ | ☑ | ☐ | GSK | | × |
| 10. Payment for development of educational presentations | ☐ | ☑ | ☐ | Allergan | | × |
| 10. Payment for development of educational presentations | ☐ | ☑ | ☐ | Orion | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

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Hide All Table Rows Checked 'No' SAVE

## Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Peter
2. Surname (Last Name): Whitton
3. Effective Date (07-August-2008): 06-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial.

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

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**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

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## The Work Under Consideration for Publication

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |

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|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |
| 5. Grants/grants pending | ☐ | ☐ | ☑ | Cure Parkinson's Trust | | ✕ |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☑ | ☐ | ☐ | | | ✕ |
| | | | | | | ADD |
| 7. Payment for manuscript preparation | ☑ | ☐ | ☐ | | | ✕ |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

**Relevant financial activities outside the submitted work**

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

## Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'  SAVE

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Evaluation and Feedback

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Instructions

**The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.**

## 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

## 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

## 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence,or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

## 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

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## Section 1. Identifying Information

1. Given Name (First Name): Peter
2. Surname (Last Name): Ell
3. Effective Date (07-August-2008): 07-February-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Dr T Foltynie

5. Manuscript Title: Exenatide as a disease modifying treatment for Parkinson's disease- proof of concept trial

6. Manuscript Identifying Number (if you know it): 68295

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ☑ | ☐ | ☐ | | | × |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## The Work Under Consideration for Publication

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 7. Other | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

## Relevant financial activities outside the submitted work

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 2. Consultancy | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Employment | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Expert testimony | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Grants/grants pending | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 7. Payment for manuscript preparation | ☑ | ☐ | ☐ | | | × |

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**Relevant financial activities outside the submitted work**

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|---|---|---|---|---|---|---|
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 11. Stock/stock options | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

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