Exenatide-PD

A randomised, double blind, placebo controlled, single centre, 60 week trial of Exenatide once weekly for the treatment of moderate severity Parkinson’s disease
Authorisation: Senior Operations Staff

Name: Kate Maclagan  
Role: Clinical Project Manager  
Signature: [Signature]

Date: 01-Oct-15

Authorisation: Statistician

Name: Dr Simon Skene  
Role: Trial Statistician  
Signature: [Signature]

Date: 05-Oct-2015
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1 Administrative information

This document was constructed using the UCL Comprehensive Clinical Trials Unit (CCTU) Protocol template Version 2.0. It describes the Exenatide-PD trial, sponsored by UCL and co-ordinated by UCL CCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial’s scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at UCL CCTU.

UCL CCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials. The SPIRIT Statement Explanation and Elaboration can be referred to, or a member of UCL CCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, the EU Tissue and Cells Directives 2004/23/EC, 2006 17/EC and 2006/86/EC, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). An agreement that includes detailed roles and responsibilities will be in place between the participating site and UCL CCTU.

Participating sites must inform UCL CCTU as soon as they are aware of a possible serious breach of compliance, so that UCL CCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a ‘serious breach’ is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

UCL is the trial sponsor and has delegated responsibility for the overall management of the Exenatide-PD trial to UCL CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the Director, UCL CCTU, or via the trial team.
### 1.3 Structured trial summary

<table>
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<th><strong>Primary Registry and Trial Identifying Number</strong></th>
<th>Clinicaltrials.gov: NCT01971242</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Registration in Primary Registry</strong></td>
<td>September 2013</td>
</tr>
<tr>
<td><strong>Secondary Identifying Numbers</strong></td>
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<tr>
<td>• FoxTrialFinder: 3583</td>
<td></td>
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<tr>
<td>• UCL R&amp;D ref: 13/0384</td>
<td></td>
</tr>
<tr>
<td>• UCL data protection registration number:</td>
<td></td>
</tr>
<tr>
<td>Z6364106/2013/07/33</td>
<td></td>
</tr>
<tr>
<td>• BMS ref: MB001-094</td>
<td></td>
</tr>
<tr>
<td><strong>Source of Monetary or Material Support</strong></td>
<td>Michael J Fox Foundation</td>
</tr>
<tr>
<td><strong>Primary Sponsor</strong></td>
<td>University College London</td>
</tr>
<tr>
<td><strong>Secondary Sponsor</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sponsor responsibilities for Trial Management</strong></td>
<td>are delegated to UCL CCTU.</td>
</tr>
<tr>
<td></td>
<td>Exenatide drug supply under contractual arrangement with Bristol-Myers Squibb</td>
</tr>
<tr>
<td><strong>Contact for Public Queries</strong></td>
<td><a href="mailto:ExenatidePD@ucl.ac.uk">ExenatidePD@ucl.ac.uk</a></td>
</tr>
<tr>
<td><strong>Contact for Scientific Queries</strong></td>
<td>Dr T Foltynie</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:T.Foltynie@ucl.ac.uk">T.Foltynie@ucl.ac.uk</a></td>
</tr>
<tr>
<td></td>
<td>0203 448 8726</td>
</tr>
<tr>
<td></td>
<td>Box 146</td>
</tr>
<tr>
<td></td>
<td>National Hospital for Neurology &amp; Neurosurgery</td>
</tr>
<tr>
<td></td>
<td>Queen Square</td>
</tr>
<tr>
<td></td>
<td>London, WC1N 3BG</td>
</tr>
<tr>
<td><strong>Public Title</strong></td>
<td>Trial of Exenatide for Parkinson’s disease</td>
</tr>
<tr>
<td><strong>Scientific Title</strong></td>
<td>A randomised, double blind, placebo controlled, single centre, 60 week trial of Exenatide once weekly for the treatment of moderate severity Parkinson’s disease. (Exenatide –PD)</td>
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<tr>
<td><strong>Countries of Recruitment</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Health Condition(s) or Problem(s) Studied</strong></td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td><strong>Intervention(s)</strong></td>
<td>Exenatide (extended-release for injectable suspension) 2mg once weekly for 48 weeks.</td>
</tr>
<tr>
<td></td>
<td>Placebo Exenatide (extended-release for injectable suspension) once weekly for 48 weeks.</td>
</tr>
<tr>
<td><strong>Key Inclusion and Exclusion Criteria</strong></td>
<td><strong>Inclusion Criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• Diagnosis of Parkinson’s disease.</td>
</tr>
<tr>
<td></td>
<td>• Males or Females.</td>
</tr>
<tr>
<td></td>
<td>• Hoehn and Yahr stage ≤ 2.5 in the On medication state.</td>
</tr>
<tr>
<td></td>
<td>• Between 25 and 75 years of age.</td>
</tr>
<tr>
<td></td>
<td>• On dopaminergic treatment with wearing off phenomena.</td>
</tr>
<tr>
<td></td>
<td>• Ability to self-administer, or to arrange carer administration of trial drug.</td>
</tr>
<tr>
<td></td>
<td>• Documented informed consent to participate.</td>
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</tbody>
</table>
Exclusion criteria

- Diagnosis or suspicion of other cause for Parkinsonism. Subject without DaTscan appearances consistent with diagnosis of PD will not be eligible.
- Body mass index <18.5.
- Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol/DaTSCAN acquisition.
- Concurrent dementia defined by a score lower than 120 on the Mattis Dementia Rating Scale.
- Concurrent severe depression defined by a score >16 on the MADRS.
- Prior intra-cerebral surgical intervention for Parkinson’s disease.
- Already actively participating in a trial of a device, drug or surgical treatment for Parkinson’s disease.
- Previous exposure to Exenatide.
- Severely impaired renal function with creatinine clearance <30ml/min.
- History of pancreatitis.
- Type 1 or Type 2 Diabetes mellitus.
- Severe gastrointestinal disease (e.g. gastroparesis)
- Hyperlipidaemia.
- History or suspicion of thyroid cancer
- Known or suspected intolerance of DaTSCAN or Potassium Iodide administration.
- Females that are pregnant or breast feeding. WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and up to 4 weeks after the last dose of study drug.
- Participants who lack the capacity to give informed consent
- Any medical or psychiatric condition which in the investigator’s opinion compromises the potential participant’s ability to participate.

Study Type

This is an interventional phase 2 trial including randomisation, double-blinding, placebo control, parallel group evaluation of Exenatide as a treatment for moderate severity Parkinson’s disease.

Date of First Enrolment
18th June 2014

Target Sample Size
60

Primary Outcome(s)
Outcome name-Motor score in practically defined “OFF” medication state.

Metric - Movement Disorder Society Unified Parkinson’s Disease Rating Scale part 3 Motor subsection score

Timepoint- 60 weeks (i.e. 12 weeks following end of treatment).
### Secondary Outcomes

Differences at 48 & 60 weeks for each of the secondary outcomes listed below will be compared between groups according to treatment allocation, (using ANCOVA to adjust for differences at baseline):

- Movement Disorder Society Unified Parkinson’s Disease Rating Scale part 3 Motor subsection Off medication score at 48 weeks.
- Movement Disorder Society Unified Parkinson’s Disease Rating Scale part 1,2,3 and 4 On medication scores
- Mattis Dementia Rating scale (DRS-2)
- Safety and tolerability of Exenatide as indicated by changes in Vital signs, weight, clinical laboratory measures and Adverse Effects

### Exploratory outcomes

Differences at 48 & 60 weeks for each of the exploratory outcomes listed below will be compared between groups according to treatment allocation, (using ANCOVA to adjust for differences at baseline):

- Unified Dyskinesia Rating scale
- 3 day Hauser diary of PD state (Time-On, Off, Non troublesome Dyskinesia, Troublesome dyskinesia, Asleep)
- Montgomery and Asberg Depression Rating Scale (MADRS)
- Parkinson’s Disease 39 item Quality of life questionnaire (PDQ39)
- Non-Motor Symptoms scale (NMSS)
- Levodopa equivalent doses (LED)
- Quantitative change in Dopamine Transporter availability as measured by DaTSCAN uptake between baseline and 60 week evaluations
- Exenatide level in blood, urine every 12 weeks, CSF (at 12 and 48 weeks)
- Cerebrospinal fluid levels of Brain derived Neurotrophic factor (at 12 and 48 weeks)
- Timed tests
1.4 Roles and responsibilities

1.4.1 Protocol contributors

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Thomas Foltynie</td>
<td>UCL Institute of Neurology</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>Julie Bakobaki</td>
<td>UCL CCTU</td>
<td>Clinical Operations Manager</td>
</tr>
<tr>
<td>Guy Schroeter</td>
<td>UCL CCTU</td>
<td>Clinical Project Manager</td>
</tr>
<tr>
<td>Steve Hibbert</td>
<td>UCL CCTU</td>
<td>IT Manager</td>
</tr>
<tr>
<td>Dr Gareth Ambler</td>
<td>UCL Statistical Science</td>
<td>Statistician</td>
</tr>
<tr>
<td>John Dickson/ Peter Ell</td>
<td>UCLH Dept Nuclear Medicine</td>
<td>DATSCAN acquisition</td>
</tr>
<tr>
<td>Rita Gupta</td>
<td>UCLH</td>
<td>Trial Pharmacist</td>
</tr>
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1.4.2 Role of trial sponsor and funders

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Role</th>
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<tbody>
<tr>
<td>Susan Tebbs</td>
<td>UCL CCTU</td>
<td>Overall supervision of UCL CCTU sponsorship. Ultimate authority for writing the report and decision to submit for publication will lie with the Chief Investigator.</td>
</tr>
<tr>
<td>Maurizio Facheris</td>
<td>MJFF</td>
<td>Funding</td>
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1.4.3 Trial Team

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<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Role and responsibilities</th>
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<tbody>
<tr>
<td>Dr Thomas Foltynie</td>
<td>UCL ION</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>Dr Dilan Athauda</td>
<td>UCL ION</td>
<td>Clinical Researcher</td>
</tr>
<tr>
<td>Kate Maclagan</td>
<td>UCL CCTU</td>
<td>Clinical Project Manager</td>
</tr>
<tr>
<td>Dr Simon Skene</td>
<td>UCL CCTU</td>
<td>Trial Statistician</td>
</tr>
<tr>
<td>Joanne Siwoniku</td>
<td>UCL CCTU</td>
<td>Trial Manager</td>
</tr>
<tr>
<td>Dawn Letchford</td>
<td>UCL CCTU</td>
<td>Data Manager</td>
</tr>
<tr>
<td>Garrie Powers</td>
<td>UCL CCTU</td>
<td>IT Programmer</td>
</tr>
<tr>
<td>Rita Gupta/ Nathalie Passeron/</td>
<td>UCLH</td>
<td>Trial Pharmacists</td>
</tr>
<tr>
<td>Alan Wong</td>
<td>Royal Free Hospital</td>
<td>Trial packaging and supplies</td>
</tr>
<tr>
<td>Gary Bennett</td>
<td>Royal Free Hospital</td>
<td>QP</td>
</tr>
<tr>
<td>John Dickson</td>
<td>UCLH Dept Nuclear Medicine</td>
<td>DATSCAN Acquisition</td>
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## 1.4.4 Trial Management Group

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Role and responsibilities</th>
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</thead>
<tbody>
<tr>
<td>Dr Thomas Foltynie</td>
<td>UCL ION</td>
<td>CI</td>
</tr>
<tr>
<td>Dr Dilan Athauda</td>
<td>UCL ION</td>
<td>Clinical Researcher</td>
</tr>
<tr>
<td>Dr Simon Skene</td>
<td>UCL CCTU</td>
<td>Trial Statistician</td>
</tr>
<tr>
<td>Kate Maclagan</td>
<td>UCL CCTU</td>
<td>Clinical Project Manager</td>
</tr>
<tr>
<td>Joanne Siwoniku</td>
<td>UCL CCTU</td>
<td>Trial Manager</td>
</tr>
<tr>
<td>Dawn Letchford</td>
<td>UCL CCTU</td>
<td>Data Manager</td>
</tr>
</tbody>
</table>

## 1.4.5 Trial Steering Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Role and responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof T Warner</td>
<td>Reta Lila Weston Institute</td>
<td>Independent Chair</td>
</tr>
<tr>
<td>Dr T Foltynie</td>
<td>UCL ION</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>Prof P Limousin</td>
<td>UCL ION</td>
<td>Co-investigator</td>
</tr>
<tr>
<td>Prof Andrew Lees</td>
<td>Reta Lila Weston Institute</td>
<td>Co-Investigator</td>
</tr>
<tr>
<td>Dr Iciar Aviles-Olmos</td>
<td>UCL ION</td>
<td>Independent PD clinician</td>
</tr>
<tr>
<td>Tom Isaacs</td>
<td>Cure Parkinson’s Trust</td>
<td>Independent Lay representative</td>
</tr>
</tbody>
</table>

## 1.4.6 Independent Data Monitoring Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Role and responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof David Burn</td>
<td>University of Newcastle</td>
<td>DMC Chair (PD Academic clinician)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feedback outcome of DMC meetings to TSC.</td>
</tr>
<tr>
<td>Prof Roger Barker</td>
<td>University of Cambridge</td>
<td>DMC Member (PD Academic clinician)</td>
</tr>
<tr>
<td>Prof Yoav Ben-Shlomo</td>
<td>Bristol University</td>
<td>DMC Member (PD Epidemiologist, with statistical knowledge)</td>
</tr>
<tr>
<td>Prof Huw Morris</td>
<td>Royal Free Hospital</td>
<td>DMC Member (PD Academic clinician)</td>
</tr>
</tbody>
</table>
2 Trial Diagram

Patient Information sheet & Pre-screening

Consent, Screening & Imaging

Baseline Evaluation & Randomisation

Active treatment

Commence Treatment (Injection teaching)

Placebo treatment

12 week follow up including CSF analysis

24 week follow up

36 week follow up

48 week follow up including CSF analysis & active treatment stopped

60 week follow up
Imaging follow up
3 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AR</td>
<td>Adverse Reaction</td>
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<tr>
<td>BDNF</td>
<td>Brain derived Neurotrophic factor</td>
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<tr>
<td>BMS</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>CI</td>
<td>Chief Investigator</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<tr>
<td>CTA</td>
<td>Clinical Trial Authorisation</td>
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<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for adverse events</td>
</tr>
<tr>
<td>CTSA</td>
<td>Clinical Trial Site Agreement</td>
</tr>
<tr>
<td>CCTU</td>
<td>Comprehensive Clinical Trials Unit</td>
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<tr>
<td>DPP-4</td>
<td>Dipeptidyl peptidase</td>
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<tr>
<td>DRS-2</td>
<td>Mattis Dementia Rating Scale 2</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>FDA</td>
<td>(US) Food and Drug Administration</td>
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<td>FWA</td>
<td>Federal Wide Assurance</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<td>ITT</td>
<td>Intention to Treat</td>
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<tr>
<td>LED</td>
<td>Levodopa Equivalent Dose</td>
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<td>LWENC</td>
<td>Leonard Wolfson Experimental Neurology Centre</td>
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<tr>
<td>MADRS</td>
<td>Montgomery Asberg Depression Rating Scale</td>
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<td>MDS</td>
<td>Movement Disorders Society</td>
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<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<td>Michael J Fox Foundation</td>
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<td>MoU</td>
<td>Memorandum of Understanding</td>
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<td>National Hospital for Neurology and Neurosurgery</td>
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<tr>
<td>NMS</td>
<td>Non-Motor Symptoms</td>
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<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PDQ39</td>
<td>Parkinson’s disease quality of life questionnaire</td>
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<td>PI</td>
<td>Principal Investigator</td>
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<tr>
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<td>Participant Information Sheet</td>
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<td>Royal Free Hospital</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<td>SAR</td>
<td>Serious Adverse Reaction</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>SSA</td>
<td>Site Specific Assessment</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<tr>
<td>TMF</td>
<td>Trial Master File</td>
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<tr>
<td>TMG</td>
<td>Trial Management Group</td>
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<tr>
<td>TMT</td>
<td>Trial Management Team</td>
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<tr>
<td>ToR</td>
<td>Terms of Reference</td>
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<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
</tr>
<tr>
<td>UCL</td>
<td>University College London</td>
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<td>WR</td>
<td>(1) (1)</td>
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4  Glossary

**Hoehn & Yahr stage**

A simple method of staging PD that can be applied to patients in either the ON or OFF drug state. For the purposes of the trial inclusion criteria, staging will be applied according to their ON drug state. Stage 1 – Unilateral signs, Stage 2- Bilateral signs, Stage 2.5- Bilateral signs with recovery on the pull test, Stage 3- Moderate bilateral disease with some postural instability, Stage 4- severe disability, still able to walk or stand unassisted, Stage 5- wheelchair bound or bedridden unless aided.

**Hyperlipidaemia**

Hyperlipidaemia is a group of inherited or acquired conditions in which an abnormally elevated level of serum triglyceride or serum cholesterol is seen (typically in the range of 2-3 times the upper limit of normal). This is distinguishable from elevated levels of cholesterol resulting from high dietary fat intake. Hyperlipidaemia is a risk factor for pancreatitis and is therefore a contraindication for Exenatide usage.

**Gastroparesis**

Gastroparesis (or delayed gastric emptying) is a partial paralysis of the stomach and results in food remaining in the stomach for a longer time than normal. It may be seen in Parkinson’s disease and is associated with chronic nausea, vomiting, abdominal pain and a feeling of fullness after eating small amounts of food.

**Practically defined “Off” medication state.**

This refers to the patient assessment conducted in the absence of their regular medication with the aim of exposing the severity of the underlying PD. Patients will attend the hospital in the morning having not taken any of their prescribed PD medication for 8 hours (overnight) in the case of. Levodopa, or ≥ 36 hours in the case of longer acting agents such as Ropinirole, Pramipexole or Rasagiline. Participants will be admitted to the National hospital overnight if the severity of their PD is such that being “Off” medication would make it difficult for them to travel to the hospital.

**Women of Child-Bearing Potential (WOCBP):**

- WOCBP must be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized.
- WOCBP must have a negative serum or urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) within 0 to 72 hours before the first dose of study drug.
- Women must not be breast-feeding.

WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilisation (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal (see definition below). The following women are WOCBP:

- Women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or
injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).

- Women who are practicing abstinence.
- Women who have a partner who is sterile (e.g., due to vasectomy).
- Post-menopause is defined as:
  - Women who have had amenorrhea for ≥12 consecutive months (without another cause) and who have a documented serum follicle-stimulating hormone (FSH) level > 35 mIU/mL.
  - Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL.

5 Introduction

5.1 Background and Rationale

Exenatide (Exendin-4) is a licensed and effective treatment for patients with Diabetes mellitus. It is an agonist for the Glucagon-like peptide 1 (GLP-1) receptor and stimulates insulin release (in the presence of elevated blood glucose), in addition to increasing pancreatic beta islet cell mass and reducing apoptosis. Whereas endogenous human GLP-1 is rapidly metabolized by an enzyme called dipeptidyl peptidase-IV (DPP) and has a half-life of only a couple of minutes, Exenatide is not degraded by DPP-IV and has a half-life of 60-120 minutes. Exenatide has been the subject of multiple phase 3 trials in patients with Type 2 diabetes and was granted a license for the treatment of Type 2 diabetes in 2006.

In parallel with the confirmation of the beneficial effects of Exenatide on glucose control, laboratory work has shown that Exenatide has beneficial effects on neurons in vitro. Much of this work was performed at NIH by a team led by Dr. Nigel Greig. In rat phaeochromocytoma cells, (known to express the GLP-1 receptor), Exenatide induced neurite outgrowth, promoted neuronal differentiation and rescued degenerating neuronal cells. The effects of endogenous GLP-1 and Exenatide were likened to the trophic effects of Nerve Growth Factor, although it is clear that its effects are mediated through the GLP-1 receptor rather than the TrkB receptor. The same team then explored the effects of Exenatide as a neuroprotective agent against excitotoxic damage and were able to demonstrate not only protection but reversal of damage provoked by glutamate or ibotenic acid, by the administration of Exenatide both in vitro and in vivo animal models.

Activation of GLP-1 receptors was shown to lead to rapid increases in levels of cyclic AMP and intracellular calcium, with sustained signalling leading to activation of protein kinase A, and/or activation of PI3 kinase and ERK MAP kinase.

The neurotrophic properties of Exenatide have sparked interest into its potential use as a neurodegenerative disease modifying agent not only in Parkinson’s disease (PD) but also by clinicians and scientists working on Alzheimer’s disease. GLP-1 deficient mice have been shown to have learning deficits that can be restored by GLP-1 receptor gene transfer, whereas rats over-expressing GLP-1 receptors have improved learning and memory ability. Furthermore, administration of Exenatide has been shown to lower amyloid beta and amyloid precursor protein levels in vitro and in vivo. This work has rapidly led to clinical trials of the use of Exenatide in people with mild cognitive impairment of Alzheimer’s disease (www.clinicaltrials.gov).
The specific relevance of Exenatide to Parkinson’s disease has also been extensively evaluated. Exenatide has been shown to increase transcription of Tyrosine Hydroxylase- (TH-the rate limiting enzyme in dopamine synthesis) in brainstem catecholaminergic neurons. These effects are blocked by GLP-1 receptor antagonists confirming that these actions are mediated through the GLP-1 receptor. Furthermore, although the details of the cellular mechanisms are not yet clear, it also appears that stimulation of GLP-1 receptors may have beneficial effects on the neurodegenerative processes of PD through several (non-mutually exclusive) pathways downstream from second messenger levels of cAMP, Protein kinase A, PI3 kinase or ERK MAP kinase.

1. **Exenatide reduces levels of pro-inflammatory molecules such as TNF-alpha**

   The possible role of neuro-inflammation in the pathogenesis of Parkinson’s disease is gaining increasing evidence reviewed in, broadly based on a) epidemiological data hinting at lower rates of PD among patients using non-steroidal anti-inflammatory drugs, b) a consistent association between the HLA locus and PD risk from the meta-analyses of Genome wide association studies, c) the presence of activated microglia seen in PD patients using PK11195 PET ligand and d) the presence of pro-inflammatory mediators seen in the post mortem tissue of PD patients. In an animal model of PD, Exenatide was shown to reduce microglial activation and reduce the expression of pro-inflammatory molecules - matrix metalloproteinase-3, TNF-alpha and interleukin 1B. Similar findings have been observed in a transgenic model of Alzheimer’s disease accompanied by further data indicating that Exenatide protects against deleterious effects of oligomeric species on synapse integrity though the GLP-1 receptor, insulin signalling, TNF-alpha induced JNK activation and tau hyperphosphorylation. The close analogy between PD and Alzheimer’s with respect to toxicity of oligomeric species of alpha-synuclein and Beta amyloid highlights that molecules that may be efficacious in Alzheimer’s might also be of use in PD.

2. **Exenatide increases signal transduction of STAT3 which leads to a shift in macrophage phenotype to M2, which produce anti-inflammatory molecules such as IL-10 and TGF-beta**

   In parallel with the reduction of pro-inflammatory molecules listed above, authors from a separate institution have evaluated the effects of Exenatide on macrophages. GLP-1 receptors are expressed on macrophages and in the presence of Exenatide, human monocyte derived macrophages develop an M2 phenotype, through activation of STAT3 leading to upregulation of anti-inflammatory molecules such as Interleukin-10 and TGF-Beta. Any effects of Exenatide mediated through an increase in anti-inflammatory molecules or a decrease in pro-inflammatory molecules are likely to be indistinguishable.

3. **Exenatide can induce mitochondrial mRNA expression, increase mitochondrial enzyme activity in association with an increase in the number of mitochondria**

   Increasing evidence indicates that mitochondrial function is central to the pathogenesis of PD either related to, or independently from neuro-inflammation. Many of the Mendelian genes associated with PD (parkin, PINK-1, DJ-1) are implicated in mitochondrial function. The impact of Exenatide on mitochondrial number and function has been evaluated by colleagues researching its mechanisms of action in Type 2 diabetes. In vitro work performed using human amyloid polypeptide as a toxin for Insulinoma cells showed that Exenatide increased cell survival through a reduction in apoptosis. This was then shown to be mediated through activation of the AKT pathway known to be a critical step in
normal mitochondrial function. Furthermore, it was shown that Exenatide induced mitochondrial gene expression and led to recovery of mitochondrial enzyme activity and mitochondrial number.

4. **Exenatide/GLP-1 receptor stimulation increases neurogenesis in the subventricular zone**\(^{21,22}\).

Exenatide (and related GLP-1 agonists Liraglutide and Lixisenatide) has been shown to increase the number of neural stem/progenitor cells in the subventricular zone in animal models. GLP-1 receptor mRNA has been identified in the subventricular zone, and the co-administration of Exenatide with BrDU (a marker for actively dividing cells) revealed a doubling of dividing cells in the subventricular zone in response to peripheral Exenatide administration to adult animals. Additional staining with doublecortin confirmed that these cells were neuroblasts. Whether clinically beneficial effects might relate to neurogenesis, or whether neurogenesis in an adult animal is merely facilitated as a result of reduction in inflammation or recovery of mitochondrial activity has not been addressed.

5. **GLP-1 receptor agonists enhance synaptic plasticity.**

There is mounting evidence that synaptic dysfunction plays a critical role in PD pathogenesis. Alpha synuclein plays a pivotal role in presynaptic neurotransmitter vesicle pools\(^ {23}\); LRRK2 impacts on synaptic vesicle motility and recycling\(^ {24}\) while DJ-1, parkin and PINK-1 knockout mice all exhibit presynaptic deficits\(^ {25,26}\). It has recently been shown that the administration of GLP-1 agonists into the cerebral ventricles enhances synaptic function (long term potentiation) that is blocked by antagonists of the GLP-1 receptor\(^ {27}\). These data confirm the effects of GLP-1 receptor agonists on neurotransmission in the brain and synaptic plasticity. The link between synaptic plasticity, enhancement of physiological brain signalling and neurodegeneration is a further area of research in PD pathogenesis.

Irrespective of the precise mechanism of action, there is mounting evidence to support peripheral subcutaneous administration of Exenatide as a possible intervention to slow the neurodegenerative process(es) of Parkinson’s disease. Four groups have independently investigated and confirmed beneficial effects of Exenatide administration in multiple rodent models of PD.

1. In London, intraperitoneal injections of 0.1 or 0.5μg/Kg bd, administered to rats 7 days after either unilateral Lipopolysaccharide (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\(^ {28}\).

2. In Sweden, administration of Exenatide 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 Exenatide compared to those treated with vehicle\(^ {21}\).

3. In the USA, mice pre-treated with Exenatide had complete protection against the toxicity of MPTP. While untreated mice had 71% loss of dopaminergic neurons in the SN, TH neurons in Exenatide treated mice were no different from control mice not given MPTP. Furthermore the Exenatide treated mice had normal DA levels and motor activity after MPTP in stark contrast to untreated mice given MPTP\(^ {29}\).
4. In Korea, Exenatide attenuated toxicity in the MPTP mouse model, sparing neurons in the Substantia nigra pars compacta and their striatal dopaminergic projections, in association with reduced activation of microglia, matrix metalloproteinase-3 and TNF-alpha.

In summary, a range of measures have indicated a neuroprotective effect of Exenatide 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, the data from the Alzheimer’s laboratory work raises the possibility that Exenatide may have beneficial effects on non-motor symptoms as well as on motor disability.

In response to the encouraging data emerging from the laboratory, an investigator initiated pilot trial of Exenatide as a treatment for patients with PD was undertaken, sponsored by University College London and funded by the Cure Parkinson’s Trust. This trial was configured as an open label evaluation given the absence of commercial involvement and funding restriction that did not allow manufacture/availability of a matched placebo preparation. A parallel group, randomised controlled design, was chosen to allow evaluation of the tolerability of Exenatide (as Byetta) in a population of 45 patients with moderately severe PD. This group of patients was targeted to formally examine safety and tolerability in the presence and absence of additional dopaminergic treatment as well as provide preliminary indication regarding potential positive/ or negative biological effects of Exenatide over an exposure period of 12 months. To minimise the bias associated with an open label design, the patients had video assessments at 3 monthly intervals which were evaluated by experienced PD clinicians blinded to treatment status. A broad battery of assessments was chosen including cognitive assessments considered to be less susceptible to placebo effects. The patients were evaluated at the end of the 12 month exposure period and then again after a washout period of a further 2 months to allow further diminution of any potential placebo response.

The primary outcome was the change in the score in the MDS UPDRS part 3 scale in the absence of conventional PD medication, as judged using blinded video assessments. This showed an advantage of 4.9 points in the Exenatide treated patients at 12 months which persisted after a 2 month washout period. This was accompanied by clinically relevant advantages seen across the majority of the secondary outcome measures. There were clinically important differences in the change in a global measure of cognition – the Mattis Dementia rating scale. Patients receiving Exenatide had a mean improvement of 2.8 points over the course of the trial whereas control individuals deteriorated by 3.5 points over the course of the trial. Serial DaTscan showed no progression between baseline and 12 months in the Exenatide treated patients, in fact 2 patients had improvement in the DaTscan uptake.

Three patients from the group randomised to Exenatide withdrew/dropped out from the study, 1 withdrew due to worsening PD (recurrent L-dopa dose failures) prior to the first follow up visit. Exenatide (as Byetta) is known to cause slowing of gastric emptying and is the most likely explanation for this observation in this patient. Two further patients withdrew from treatment at 9 and 10 months (due to dysgeusia combined with subjective PD deterioration and the second one due to excessive weight loss, despite reduction to the 5μg bd dose). No clinically relevant changes in ECG, haematological or biochemical indices were observed. Weight loss and nausea were more common in the patient group treated with Exenatide. Patients on Exenatide lost a mean of 3.2Kg (SD 3.9, range 3.5Kg increase to 12.3Kg decrease) over 12 months, necessitating two patients to reduce
to the 5μg bd dose. There was a greater increase in the mean Dyskinesia rating scale score in the Exenatide patients compared with the control patients at both 12 and 14 months. This necessitated lowering of LED in 5 Exenatide patients, while 8 Exenatide patients had unchanged and 7 patients increased dopaminergic medication over the period of study. Data from this open label trial has been published 30.

Safety of Exenatide in humans has been demonstrated by several phase 3 trials culminating in a license for the treatment of patients with Type 2 diabetes. 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 those used in the treatment of Type 2 diabetes which is already a licensed indication for Exenatide use. It is monitored intensively by the UK safety regulators- the MHRA. Commonly occurring adverse events are; nausea, gastrointestinal effects, and weight loss.

Exenatide has also been linked with an increased risk of pancreatitis, and renal failure and should be avoided in subjects with additional risk factors for these conditions. The risk of developing pancreatitis has been the subject of ongoing surveillance and of several publications. A meta-analysis of published reports of Exenatide use in 58 290 patients with diabetes found 82 cases of acute pancreatitis (0.1%) with an odds ratio of 0.84 compared to diabetes patients in control arms of these trials 31. In a health insurance database, 24 237 users of Exenatide were identified, and compared to 457 797 patients initiated on other antidiabetic drugs (initiators of Exenatide had more severe diabetes than initiators of other antidiabetic therapy). The authors found an Odds ratio of pancreatitis of 0.95 in patients treated with Exenatide32. A further study by Elashoff examined the FDA Medwatch database to retrospectively quantify reports of acute pancreatitis in patients exposed to GLP-1 agonists; finding a 6 fold increase risk in diabetic patients using GLP-1 agents (this included 971 pancreatitis events among Exenatide users, however the denominator of individuals at risk was not stated)33. To try and gauge the absolute size of this risk, a further study looked in a registry of 1.1 million patients with Type 2 diabetes, and found 1269 hospitalised cases of acute pancreatitis (0.1%), and again there was an adjusted odds ratio of 2.24 for acute pancreatitis in users of GLP-1 agonists 34. Although the percentages are very small, the concern remains whether acute pancreatitis is the tip of the iceberg, and greater numbers of patients may have subclinical chronic pancreatitis which may in turn be a risk factor for pancreatic cancer. Type 2 diabetes and obesity are known risk factors for chronic pancreatitis and pancreatic cancer, and it has been speculated that such individuals have an increased incidence of premalignant lesions in the pancreas. These lesions might be targets for GLP-1 induced proliferation.

Debate about the possible association between GLP-1 agonist use and the small increased risk of pancreatitis (in patients with T2DM) continues 35-36, nevertheless in the absence of definitive data, vigilance for possible adverse events resulting from the use of GLP-1 agonists must be paramount, and patients must be made aware of this potential risk. The FDA states that “while these adverse events are very serious, the number of reported cases of acute pancreatitis, haemorrhagic and necrotising pancreatitis, and altered kidney function represent a small percentage of the total number of patients that have used the medication”49.

In female rats given Exenatide for 2 years, an increased incidence of benign thyroid C-cell adenomas was observed at the highest dose, 250 μg/kg/day, a dose that produced an Exenatide plasma
exposure 130-fold the human clinical exposure. The human relevance of these findings is currently unknown however in the FDA database, there was also a statistically significant association between Exenatide and thyroid cancer (30 cases compared to 1433 cases in individuals on other diabetes drugs- denominators not given)\cite{33}. In view of these data, Exenatide should not be used in patients at risk of thyroid cancer.

In our open label study, Exenatide (as Byetta) was well tolerated and no serious adverse reactions occurred. There are no data available to indicate any difference in the safety or tolerability of Exenatide (as Bydureon) in PD patients compared with Exenatide (as Byetta). Approximately 10 weeks after discontinuation of Bydureon therapy, mean plasma Exenatide concentrations fall below minimal detectable concentrations.

The current trial objective is to evaluate whether the beneficial effects seen in the previous open label design can be replicated using double blind placebo controlled methodology.

5.1.1 Explanation for choice of comparators
Exenatide is licensed for the treatment of Type 2 Diabetes mellitus as a short acting formulation (Byetta-administered 5 or 10ug subcutaneously twice daily) or a long acting formulation (Bydureon-2mg administered subcutaneously once weekly) in which Exenatide is released from microspheres. Bydureon has advantages in comparison to Byetta with respect to frequency of administration, no requirement for incremental dose introduction and improved side effect profile with respect to gastrointestinal effects.

In neuronal cultures, 50% GLP-1 receptor occupancy is achieved with 14Nm Exendin-4\cite{49}, while complete protection against toxicity in vitro is achieved with 100nm Exendin-4\cite{29}. In vivo effects are seen at 20Nm Exendin-4 with little variation between 10 and 100Nm during intracerebroventricular infusion\cite{29}. (These experiments were performed to confirm that beneficial effects of Exendin-4 are indeed mediated centrally rather than peripherally).

There is evidence that Exenatide can cross the BBB in rodents\cite{37}. While the ratio of distribution of Exenatide between serum and brain is uncertain, data using radiolabelled Exendin9-39 suggests a ratio of ~ 20% (See Fig 3 in Banks 2004\cite{38}). Therefore, assuming similar ratios apply to Exenatide, the theoretical target concentrations in serum would need to be ~5-Fold that shown to be efficacious in brain i.e. 50-500Nm. Our open label proof of concept study used Exenatide (as 10ug bd Byetta), a dosing regimen leading to plasma levels ~200pg/ml\cite{39}; 200pg/ml Is Equivalent To 48Nm\cite{29}.

Plasma levels of Exenatide (as Bydureon) have been investigated in patients with Diabetes. The 0.8mg dose led to plasma concentrations of 81.2pg/ml (19Nm), while the 2mg dose led to levels of 344.5pg/ml (82Nm)\cite{40}. The 2mg dose therefore closely equates to the efficacious dose seen in rodent models.
5.2 Aim
To generate clinical and pharmacokinetic data to examine the safety, tolerability and potential effectiveness of 48 weeks exposure to Exenatide compared to placebo.

5.2.1 Objectives
The primary objective is to compare the effectiveness of Exenatide once weekly versus placebo on the MDS UPDRS part 3 motor subscale in the “practically defined OFF medication state” in patients with moderate severity PD. The hypothesis is that Exenatide will be associated with reduced MDS UPDRS part 3 scores at the 60 week time-point.

Secondary objectives are to
- Compare differences at 48 and 60 weeks between the Exenatide and placebo trial arms in:
  - Movement Disorder Society Unified Parkinson’s Disease Rating Scale part 1,2,3 and 4 On medication scores
  - Movement Disorder Society Unified Parkinson’s Disease Rating Scale part 3 Motor subsection Off medication score at 48 weeks.
  - Mattis Dementia Rating scale (DRS-2).
  - Safety and tolerability of Exenatide as indicated by changes in Vital signs, weight, clinical laboratory measures and Adverse Effects

Exploratory outcomes:
- Compare differences at 48 and 60 weeks between the Exenatide and placebo trial arms in:
  - Unified Dyskinesia Rating scale
  - 3 day Hauser diary of PD state (Time-On, Off, Non troublesome Dyskinesia, Troublesome dyskinesia, Asleep)
  - Montgomery and Asberg Depression Rating Scale (MADRS)
  - Parkinson’s Disease 39 item Quality of life questionnaire (PDQ39)
  - Non-Motor Symptoms scale (NMSS)
  - Levodopa equivalent doses (LED)
  - Quantitative change in Dopamine Transporter availability as measured by DaTSCAN uptake between baseline and 60 week evaluations
  - Exenatide level in blood, urine every 12 weeks, CSF (at 12 and 48 weeks)
  - CSF levels of BDNF (at 12 and 48 weeks)
  - Timed tests

5.3 Trial Design
A simple parallel group design as a proof of concept phase 2 trial. This will include a 48 week exposure period and a subsequent 12 week washout period. Detailed evaluations of all patients will take place at Screening, Baseline, 12, 24, 36, 48 and 60 weeks.

Patients will be randomly allocated into 2 groups to receive either;
- Exenatide extended release 2mg subcutaneous injection (Bydureon) once weekly for 48 weeks n=30, or
- Exenatide extended release placebo subcutaneous injection once weekly for 48 weeks n=30
Separate randomisation lists will be generated for patients of greater (Hoehn & Yahr stage 2.5) or lesser (Hoehn & Yahr stage 2.0 or less) disease severity (in the on medication state) to balance this as a possible prognostic factor.

The overriding priority for this trial is to provide evidence to support or refute any signal of efficacy of Exenatide as a disease modifying agent, and thus provide the justification for rapid further investment in this drug if appropriate. In parallel with this, is the aim to maximise the potential for learning about the pharmacokinetic and pharmacodynamic actions of the drug in humans with PD. With this in mind, consideration has been given to a range of possible trial designs to enable preliminary yet robust confirmation of any biological effect(s) of Exenatide relevant to PD, given the well-known difficulties in distinguishing symptomatic effects from possible “disease modifying” effects.

Parallel group designs with a washout period have been used previously in the evaluation of potential neuroprotective agents\textsuperscript{41-42}. This design is subject to possible long duration symptomatic effects and even a lengthy washout period cannot necessarily distinguish a true neuroprotective effect from a symptomatic effect (in view of preservation of healthy behaviours with long term impacts such as exercise \textsuperscript{43}). However more complex trial designs such as the delayed start design \textsuperscript{44-46} are likely useful only in agents known to have a symptomatic effect and they too can be criticised as being unable to reliably distinguish neuroprotective effects from “cumulative” symptomatic effects \textsuperscript{47}. An alternative approach is to adopt a “Long term simple” design, using a composite outcome measure with long term follow up to look for response to potential disease modifying therapies being used in NET-PD LS-1 Creatine in Parkinson’s Disease (www.clinicaltrials.gov). This does not address the urgency of the need to confirm or exclude potential agents for study, and again the long term and substantial investment needed requires robust pilot data of efficacy in advance of this approach. We have considered that an exposure period of 48 weeks is the minimum necessary to allow clinically detectable differences to emerge between the Exenatide and placebo groups.
6 Methods

6.1 Site Selection
The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to UCL CCTU.

6.1.1 Study Setting
All patient assessments will be performed at the National Hospital for Neurology & Neurosurgery, Queen Square, London (part of UCLH NHS Trust). The exception will be that all DaTSCAN imaging will be performed at the Department of Nuclear Medicine, UCLH NHS Trust.

6.1.2 Site/Investigator Eligibility Criteria
It is not anticipated that we will recruit from more than one site. However, if recruitment falls far below expected rates and jeopardises trial completion within the pre-agreed period of trial funding we will consider adding additional sites. If this becomes necessary, once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol and relevant Summary of Product Characteristics (SPC).

To participate in the Exenatide-PD trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the Exenatide-PD Trial Management Group (TMG) and that are defined below.

Trial sites meeting eligibility criteria and that are accepted by the TMG as being suitable to recruit to the trial, will be issued with the Exenatide-PD Trial Master File (TMF) documentation to use when applying for Site-Specific Approval (SSA).

6.1.2.1 Principal Investigator’s (PI) Qualifications and Agreements
The investigator(s) must be willing to sign a UCL CCTU Clinical Trial Site Agreement (CTSA) or an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site that have been delegated significant trial related duties.

6.1.2.2 Resourcing at site
The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (ie the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to UCL CCTU.
6.2 Site approval and activation
The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare products Regulatory Agency (MHRA) is supplied with the names and addresses of all participating site Principal Investigators. Trial staff at UCL CCTU will perform this task.

On receipt of the signed Clinical Trial Agreement or Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority(ies) (as appropriate), and which was given favourable opinion by the Research Ethics Committee (REC) and/or Institutional Review Board (IRB). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at UCL CCTU.

6.3 Participants
6.3.1 Eligibility Criteria

6.3.1.1 Participant selection
There will be NO EXCEPTIONS (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria
Diagnosis of Parkinson’s disease. PD is a clinical diagnosis and is based on the opinion of the PI on site after review of the clinical history, examination findings and response to PD medication. The Queen Square brain bank criteria MAY be used to help assist in the diagnosis although this need not be a formal inclusion criteria, and the relevance of a positive family history of PD, or a confirmed genetic basis for an individual’s symptoms will be evaluated in the context of other clinical features in determining diagnosis and eligibility.

Males or Females.

Hoehn and Yahr stage ≤ 2.5 in the On medication state. This implies that all patients will be mobile without assistance during their best “On” medication periods.

All patients will be ≥25 and ≤75 years of age.
On dopaminergic treatment with wearing off phenomena. All patients must have had previous or ongoing exposure to L-dopa. If L-dopa has been stopped due to side effects, patients must report an improvement in symptom control with other forms of dopaminergic treatment. Wearing off will be determined according to the history supplied by the patient that their symptom control fluctuates according to the timing of their dopaminergic therapy.

Ability to self-administer, or to arrange carer administration of trial drug.

Documented informed consent to participate.

6.3.1.3 Participant Exclusion Criteria

Diagnosis or suspicion of other cause for Parkinsonism. Patients with clinical features indicating a diagnosis of Progressive Supranuclear Palsy, Multiple Systems Atrophy, and Drug induced Parkinsonism, Dystonic tremor or Essential tremor will not be recruited. Subjects without DaTscan appearances consistent with diagnosis of PD will not be eligible.

Body mass index <18.5. (Exenatide is known to cause weight loss therefore individuals that may not tolerate further weight loss will not be recruited).

Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol/DaTSCAN acquisition.

Concurrent dementia defined by a score lower than 120 on the Mattis Dementia Rating Scale. Although Exenatide may have positive effects on cognition, for the purposes of this trial, patients with dementia will be excluded.

Concurrent severe depression defined by a score >16 on the MADRS.

Prior intra-cerebral surgical intervention for Parkinson’s disease. Patients who have previously undergone Deep Brain Stimulation, intra-cerebral administration of growth factors, gene therapy or cell therapies will not be eligible.

Already actively participating in a trial of a device, drug or surgical treatment for Parkinson’s disease.

Previous exposure to Exenatide.

Type 1 or Type 2 Diabetes mellitus.

Severely impaired renal function with creatinine clearance <30ml/min.

Hyperlipidaemia. A lipid profile will be tested at the screening visit. Cholesterol or Triglyceride levels greater than 2 x the upper limit of normal will raise suspicion of a familial or acquired hyperlipidaemia and will prompt referral to a relevant specialist for investigation and treatment.

History of pancreatitis. Baseline serum amylase value must fall within laboratory normal range +/- 20%.

Severe gastrointestinal disease (e.g. gastroparesis).

History or suspicion of thyroid cancer. Undiagnosed neck lump, hoarse voice or difficulty swallowing (not attributable to PD diagnosis).
Known or suspected intolerance of DaTSCAN or Potassium Iodide administration.

Females that are pregnant or breast feeding. There are no safety data regarding Exenatide use in pregnancy. Female participants who are able to become pregnant (defined as women of child bearing potential; see section 4, Glossary) will undergo a pregnancy test prior to randomisation and will be asked at each visit to confirm regular use of an effective method of contraception (see section 4, Glossary). WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and up to 4 weeks after the last dose of study drug.

Potential participants who lack the capacity to give informed consent

Any medical, psychiatric or other condition which in the investigator’s opinion compromises the potential participant’s ability to participate fully

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions
All assessments will be performed by individuals trained in the use of the relevant PD related scales. A certificate to confirm training in the use of the MDS-UPDRS will be obtained for all raters. These individuals will also be trained on the use of Exenatide using an online teaching video and accompanying product literature and the latest version of the SPC. This knowledge will form the basis of them teaching enrolled patients how to self-administer Exenatide, together with the online teaching video.

In the event that Exenatide injections will be administered by care-givers (e.g. spouse), their willingness to perform this will be documented and they will be trained using the online teaching video. It will also be ascertained that the care-giver either lives with the PD participant or confirms their willingness to meet with the PD participant on a weekly basis to administer the injections for the 48 week period of the trial.

It is anticipated that the patient or carer will administer their first dose of Exenatide/Placebo following the injection teaching, while still in clinic, in order that the trial team can be satisfied that the medication can be administered appropriately.

6.3.1.5 Co-enrolment Guidance
Patients previously exposed to Exenatide will not be permitted to enrol in this trial. Patients who have previously been involved in clinical trials related to PD will be permitted to enrol provided that all previous trial related activities have been completed. Patients who are actively participating in a trial of a device, drug or surgical treatment for Parkinson’s disease will be excluded.

Given that recruitment will take place at a single centre, co-enrolment (enrolment more than once in the current trial) is not envisaged.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations
Written informed consent to enter and be randomised into the trial must be obtained from participants, after explanation of the aims, methods, benefits and potential hazards of the trial and BEFORE any trial-specific procedures are performed or any blood is taken for the trial. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as usual standard of care.
Patients will be screened using the history of their Parkinson’s disease, supported by any available clinical correspondence according to usual standard of care. Informed consent will be obtained prior to collection of formal scales necessary to apply Inclusion & Exclusion criteria (Mattis Dementia rating scale and Montgomery Asberg Depression rating scale) and ahead of blood tests (Full Blood Count, Urea & Electrolytes, Liver Function tests, Thyroid Function tests, blood glucose, HbA1C, serum amylase, Lipid profile, serum sample stored) and a pregnancy test for women of child bearing potential.

Participants fulfilling eligibility criteria at this stage will then proceed to have DaTscan imaging. The DaTSCAN imaging results will be used to confirm final eligibility for participation prior to randomisation.

6.4 Interventions

All Investigational Medical Products will be supplied by Bristol-Myers Squibb / AstraZeneca in accordance with Good Manufacturing Practice and will be QP released in the European Union ahead of trial use.

Patients will be taught how to perform the subcutaneous injections by the clinical trial team using online video, demonstration packs and written literature. They will be told about common side effects previously reported e.g. nausea, vomiting, diarrhoea and weight loss by the clinical trial team, and will be advised on the processes for safety reporting as described in section 6.11.3 of the protocol.

6.4.1 Active Treatment

6.4.1.1 Products

Exenatide (extended-release for injectable suspension)- “Bydureon”

Each dose of Exenatide extended release is supplied as a vial containing the Exenatide powder and an inactive ingredient called polylactide-co-glycolide and sucrose. This is supplied together with diluent (sterile water containing carboxymethylcellulose sodium, polysorbate 20, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate and sodium chloride) to allow reconstitution of the powder in solution for subcutaneous administration by the patient on a weekly basis.

6.4.1.2 Treatment Schedule

2mg once weekly for 48 weeks. First dose will be administered in clinic following injection teaching and subsequent injections given every 7 days. Injections will be given into the abdomen, arm, thigh or buttocks.

6.4.1.3 Dispensing

All trial products will be dispensed by UCLH Pharmacy on a 12 weekly basis to coincide with trial follow up visits.

6.4.1.4 Dose Modifications, Interruptions and Discontinuations

Patients experiencing abdominal pain consistent with a clinical diagnosis of pancreatitis will receive investigation and treatment according to NHS standard of care and the trial medication will be
stopped pending confirmation or exclusion of the diagnosis. Confirmation of a diagnosis of acute pancreatitis will result in the trial medication being permanently stopped.

Patients found to have an elevation in serum Amylase (>50% above baseline) will have their trial medication stopped.

Patients developing clinical suspicion of thyroid malignancy will receive treatment according to NHS standard of care and the trial medication will be stopped.

Subjects MUST discontinue investigational product in the event of accelerated disease progression. While PD is an ongoing neurodegenerative process, accelerated decline (defined as greater than 50% (and absolute value of 20 points) decline in MDS UPDRS part 3 motor sub-score from baseline in both the ON medication and the practically defined OFF medication states) will result in discontinuation of investigational product.

Patients experiencing excessive/undesirable weight loss (>10% of body weight during a 12 week interval) will have study medication temporarily stopped. Study medication may be restarted once the patient has gained weight such that their weight is within 10% of their weight recorded at their previous visit.

6.4.2 Placebo

6.4.2.1 Products
Placebo Exenatide (extended-release for injectable suspension).

Each dose of Placebo- Exenatide extended release is supplied as a vial containing a powder together with diluent to allow reconstitution of solution for subcutaneous administration by the patient on a weekly basis.

6.4.2.2 Treatment Schedule
Once weekly for 48 weeks. First dose will be administered in clinic following injection teaching and subsequent injections given every 7 days.

6.4.2.3 Dispensing
All trial products will be dispensed by UCLH Pharmacy to each patient on a 12 weekly basis to coincide with trial follow up visits. Handling and management will be subject to standard procedures of the pharmacy.

6.4.2.4 Dose Modifications, Interruptions and Discontinuations
Patients experiencing abdominal pain consistent with a clinical diagnosis of pancreatitis will receive investigation and treatment according to NHS standard of care and the trial medication will be stopped pending confirmation or exclusion of the diagnosis. Confirmation of a diagnosis of acute pancreatitis will result in the trial medication being permanently stopped.

Patients developing clinical suspicion of thyroid malignancy will receive treatment according to NHS standard of care and the trial medication will be stopped.
Patients found to have an elevation in serum Amylase (>50% greater than baseline) or with a clinically relevant deterioration in renal or thyroid function will have their trial medication stopped.

Subjects MUST discontinue investigational product in the event of accelerated disease progression. While PD is an ongoing neurodegenerative process, accelerated decline (defined as greater than 50% (and absolute value of 20 points) decline in MDS UPDRS part 3 motor sub-score from baseline in both the ON medication and the practically defined OFF medication states) will result in discontinuation of investigational product.

Patients experiencing excessive/undesirable weight loss (>10% of body weight during a 12 week interval) will have study medication temporarily stopped. Study medication may be restarted once the patient has gained weight such that their weight is within 10% of their weight recorded at the previous visit.

6.4.3 Accountability
The trial pharmacist within the hospital pharmacy department will be accountable for trial drug supplies. No additional reconstitution or other preparation will be required prior to dispensing. All used IMP that is dispensed will be disposed of at home by the patient or carer, into an incineration bin that will be provided. Unused IMP will be brought to the next trial visit by the patient and will be checked by the clinical trial team then disposed of in the incineration bin.

6.4.4 Compliance and Adherence
The importance of compliance with the trial protocol will be explained to the patient at baseline and at each follow up visit. Compliance will be optimised by informing all patients of the most commonly experienced side effects and ways of minimising these. Patients will be given adequate instruction regarding administration of injections and will be provided with a diary to record administration of the IMP throughout the trial. Good relationships will be established with all trial participants to maximise honest reporting of compliance. Inability to administer IMP injections on three consecutive occasions will be defined as a protocol deviation, which must be explained and documented.

Compliance will be assessed by directly questioning patients, at each visit, with carers also asked to provide estimates of compliance, along with review of the drug administration diary. Reasons for non-compliance will be sought and addressed as far as possible at each follow up visit.

Biological samples will be collected from each patient at each visit. These will include serum and urine samples to allow measurement of Exenatide levels. Patients will be aware that their compliance will be measurable on the basis of these results. All analyses will be performed at the end of the trial. Guidance for sample collection and transport can be found in the Laboratory Manual.

6.4.5 Concomitant Care

6.4.5.1 Permitted Concomitant Medications
Any formulations of the following drugs used for the routine treatment of PD will be permitted.
• Sinemet- Levodopa/ Carbidopa
• Madopar- Levodopa/ Benserazide
• Stalevo- Levodopa/ Carbidopa/ Entacapone
• Entacapone,
• Tolcapone,
• Ropinirole,
• Pramipexole,
• Rotigotine,
• Apomorphine,
• 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.

Adjustment to PD medications will be permitted based on the clinical judgement of the treating neurologist and/or the clinical trial team to optimise PD symptom control throughout the duration of the trial. Doses of PD medication will be recorded at each trial visit and converted to a Levodopa equivalent dose (LED)- see Appendix. Analysis of ON medication MDS UPDRS part 3 scores (secondary outcome) according to randomised treatment intervention will use ANCOVA to adjust for LED- see section 6.10.4.2.

6.4.5.2 Concomitant Medications to be used with care
Patients receiving warfarin may be at risk of increased INR and associated bleeding; therefore INR should be monitored closely during initiation of Exenatide therapy in patients on Warfarin or cumarol derivatives.

There have been rare reported events of altered renal function with Exenatide; therefore patients receiving the following concomitant medications should be closely monitored:

• angiotensin converting enzyme inhibitors,
• angiotensin-II antagonists,
• non-steroidal anti-inflammatory medicinal products
• diuretics

6.4.6 Overdose of Trial Medication
Accidental or deliberate overdose of trial medication will be treated as necessary according to clinical indices and haematological and biochemical parameters. Reintroduction of scheduled trial medication dosing following accidental over-dosage will be according to the best judgement of the investigator to maintain appropriate serum dosage throughout the trial period. All possible measures to reduce the risk of further over-dosage will be implemented. Any patient taking a
deliberate overdose of trial medication will exit from the trial and will be referred for appropriate psychiatric evaluation.

6.4.7 Protocol Treatment Discontinuation
In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable treatment toxicity or adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant’s condition that in the clinician’s opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant’s rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis. Please refer to sections 6.4.1.4 and 6.4.2.4 for more information.

6.5 Outcomes
6.5.1 Primary Outcomes
Comparison of MDS UPDRS motor sub-score in the practically defined OFF medication state at 60 weeks between patients according to treatment allocation, using ANCOVA to adjust for baseline scores. The scores for these assessments will be collected and recorded by trained clinical trial personnel as per delegation log. Patient weight, amylase and adverse event data will be collected separately by a different individual to ensure that the primary outcome rater remains as blinded as is practically possible to adverse events. Responsible individuals will be listed in the delegation log. Part 3 of the MDS UPDRS will also be recorded on video to allow for rating by an independent person if concerns emerge regarding the quality of the scores documented by the primary outcome rater.

The Movement Disorder Society Unified Parkinson’s Disease Rating Scale part 3 Motor subsection Off medication score (MDS UPDRS motor sub-score) is a widely accepted measure of the motor disability of PD. The scale can be performed in the ON medication state and in the practically defined OFF medication state. This is defined as the score obtained in a patient who has withheld all short acting conventional PD medications for at least 8 hours and all long acting conventional PD medications for at least 36 hours - see Glossary for further details.

6.5.2 Secondary Outcomes
Comparison of each of the secondary outcomes listed below, at 48 and 60 weeks between patients according to treatment allocation, using ANCOVA to adjust for baseline differences.
The MDS UPDRS motor subscore in the practically defined OFF medication state at 48 weeks. Whereas the analysis of the 60 week scores according to randomisation group will represent the primary outcome for this trial, differences emerging at the end of the 48 week treatment period and also the difference between scores at 48 and 60 weeks will be important secondary outcomes.

Movement Disorder Society Unified Parkinson’s Disease Rating Scale part 1, 2, 3 and 4 On medication scores. Part 3 of the MDS UPDRS as well as the other elements (Part 1, 2 & 4) of the scale will also be evaluated in the presence of conventional PD medication (ON state) to evaluate any change in some of the non-motor symptoms of PD, activities of daily living and the complications of chronic PD treatment. Part 3 of the MDS UPDRS will be recorded on video to allow for data quality control.

Mattis Dementia Rating scale (DRS-2). This scale is a validated global measure of cognitive ability. This will be assessed in the ON medication condition.

Safety and tolerability of Exenatide as indicated by changes in vital signs, weight, clinical laboratory measures and Adverse Effects. Each patient will have pulse, blood pressure and weight documented at baseline and at each follow up visit. Their height will be recorded at baseline to enable calculation of body mass index. Exenatide is known to cause weight loss. Each patient will be questioned about adverse effects at each visit and responses documented on their adverse event log. Patients will be specifically questioned about the known adverse effects of Exenatide including nausea, gastrointestinal upset, loss of taste (dysgeusia) and weight loss. The known complications of PD and its treatment will be quantitatively captured on the PD related scales and therefore will not be additionally routinely logged as adverse events.

6.5.3 Exploratory Outcomes
Comparison of each of the outcomes listed below, at 48 and 60 weeks between patients according to treatment allocation, using ANCOVA to adjust for baseline differences.

Timed Tests
Patients will be asked to perform a Sit-stand-walk timed test and timed keyboard taps with left and right hand separately, in both the OFF medication and ON medication condition.

The timed Sit-stand-walk test will incorporate time taken from seated position to stand and walk 10 metres, turn and return to original seated position.

Timed keyboard taps will use online website Braintaptest.com to quantify number of alternate taps from key “S” to key “;”, using a conventional QWERTY keyboard in a 30 second period with each hand in turn. The software is validated and records number of key strokes, dwell time, accuracy & rhythmicity in an automated fashion, is freely available online, allows for coded repeatable assessments which are pseudo-anonymised, and date/time stamped.

Unified Dyskinesia Rating scale. This is considered to be the most useful and objective way of quantifying dyskinesia severity. This will be assessed in the ON medication condition.

Montgomery and Asberg Depression Rating Scale (MADRS). This scale allows for physician quantification of Depression severity. This will be assessed in the ON medication condition.
Non-Motor Symptoms (NMS) severity scale. This validated scale is a tool to collect data on the frequency and severity of 30 non-motor symptoms sometimes experienced by PD patients. This will be assessed in the ON medication condition.

3 day Hauser diary of PD state (Time- On, Off, Troublesome Dyskinesia, Non-troublesome dyskinesia, Asleep). Diary data allows quantification of the amount of time during a 3 day period that patients spend in the varying states of movement ability.

The PDQ39 (Parkinson’s disease questionnaire-39). This is the standard disease specific measure of quality of life in PD comprising 39 questions. It has been extensively validated in previous studies.

Levodopa equivalent doses (LED). To facilitate comparisons between patients taking different regimes of conventional PD medications, a set of conversion factors have been used to convert each of the commonly used PD medications to a “Levodopa equivalent dose (LED)” . The LED of each of their medications can then be summed for inter-patient / inter-group comparisons (see Appendix).

EQSD-3L. This is a simple 5 question form and visual analogue scale that allows calculation of quality adjusted life years (QALY) to enable health economic analyses to be performed.

Quantitative change in Dopamine Transporter availability as measured by DaTSCAN uptake between baseline and 60 week evaluations. “DaTSCAN” is a SPECT ligand which can precisely quantify the presence of dopamine transporters, present on surviving pre-synaptic dopaminergic terminals. These scans are acquired at the department of Nuclear Medicine, UCLH NHS trust. Patients are given Potassium Iodide by the Department of Nuclear Medicine with instructions to take 2 doses of this in the 24 hours before the scan to minimise ligand uptake by the thyroid gland.

Exenatide level in serum, urine every 12 weeks. Biological samples collected from patients at baseline and at each follow up visit, will be labelled and stored at dedicated specimen storage facilities at UCL. These specimens will allow pharmacokinetic measurements of Exenatide.

Exenatide levels in CSF (at 12 and 48 weeks). Lumbar punctures will be performed on 2 occasions to coincide with follow up visits. As per standard of care practice, coagulation factors/clotting will be collected at baseline (prior to the 3 month lumbar puncture) and at 36 weeks (prior to the 48 week lumbar puncture). These will be performed by clinical staff specifically trained in this skill. Patients will be instructed to lie flat for at least 1 hour after the procedure to minimise post lumbar puncture headache. CSF will be stored to allow future Exenatide PK determination and will also be examined for levels of Brain Derived Neurotrophic Factor (BDNF) and will undergo Mass spectroscopy.
### 6.6 Participant Timeline

<table>
<thead>
<tr>
<th>Timing of assessment</th>
<th>Activities during assessment</th>
<th>Forms to be completed</th>
</tr>
</thead>
</table>
| Referral and initial contact for consideration of trial participation | Patient Information sheet given to patient  
Pre-screening via telephone/email                                                                                                                                                                                        | Stickers with date of PIS given  
Screening Log                                                                                                                                              |
| In person screen (Visit 1)                    | Patient questions answered.  
Patient confirms willingness and ability to adhere to trial protocol as explained in PIS including;  
- attendance at research clinic after overnight off medication period.  
- equivalent chance of randomisation to active drug/placebo  
- collection of DaTSCAN data  
- collection of CSF on 2 occasions  
Patient signs Informed consent  
Contact details noted including next of kin/ GP.  
Review of  
- Demographic data re PD  
- Past medical history  
- Medication history  
- Family history  
- Previous imaging  
- Previous genetic tests  
- Clinical examination  
Patient instructed re withdrawal of PD medications  
ECG  
Blood tests (Full Blood Count, Urea & Electrolytes, Liver Function Tests, Glucose, serum Amylase, HbA1C, Thyroid function tests, lipid profile, saved serum) and pregnancy test.  
Pulse, Blood pressure, weight, height  
Research team contact details given  
Self-completed scales (3 Day Hauser Diary, PDQ39, EQ5D to be given to patient with appropriate instruction and brought to baseline evaluation)  
Mattis Dementia Rating scale  
MADRS | Consent Form  
Screening and Enrolment Log  
Screening CRF (Visit 1)  
MADRS  
Mattis DRS |
<table>
<thead>
<tr>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check inclusion/ exclusion criteria &amp; blood results. Appointment arranged for DaTSCAN.</td>
<td></td>
</tr>
<tr>
<td>DaTSCAN</td>
<td>Patients will be given instructions re DaTSCAN (including Potassium Iodide intake), and timetable for attendance at Nuclear Medicine dept, UCLH NHS Trust, for DaTSCAN scan.</td>
</tr>
</tbody>
</table>
| Randomisation & Baseline evaluation (Visit 2) | Results of DaTSCAN and blood tests reviewed prior to baseline evaluation to ensure patient eligibility.  
Patient contacted and arrangements made to attend research clinic in practically defined Off state. Self-completed diary/ questionnaires to be brought along.  
Known adverse events enquiry  
Video of MDS-UPDRS part 3 off medication score  
Timed motor tests  
Randomisation  
Patient takes regular medication  
Levodopa equivalent dose (LED) noted  
Patient completes UPDRS part 1, 2, 4  
Patient confirms best on state achieved  
MDS-UPDRS part 3 on medication score  
Timed Motor tests  
Unified Dyskinesia Rating scale NMSS  
Teaching injections  
12 week supply of Exenatide/Placebo³  
First dose of Exenatide/Placebo administered while in clinic | Baseline CRF (Visit 2)  
Adverse events form  
Concomitant medication log  
MDS UPDRS  
Unified Dyskinesia Rating Scale  
Timed Motor tests  
PDQ39  
3 Day diary  
EQ-5D  
NMSS |
| 1 week to 4 weeks | As required telephone calls to provide support/ optimise compliance. |
| 12 week evaluation (Visit 3) | Patient contacted and arrangements made to attend research clinic in practically defined Off state. Self-completed diary/ questionnaires to be sent/emailed to patient and brought | Visits 3-7 CRF  
Adverse Events form  
Concomitant Events form  
MDS UPDRS  
Unified Dyskinesia Rating Scale |
<table>
<thead>
<tr>
<th>24 week evaluation (Visit 4)</th>
<th>Patient contacted and arrangements made to attend research clinic in practically defined Off state. Self-completed diary/questionnaires to be sent/ emailed to patient and brought along.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Known adverse events enquiry Video of MDS-UPDRS part 3 off medication score Timed motor tests</td>
</tr>
<tr>
<td></td>
<td>Patient takes regular medication Levodopa equivalent dose (LED) noted Patient completes UPDRS part 1, 2, 4 Patient confirms best on state achieved MDS-UPDRS part 3 on medication score Timed Motor tests Unified Dyskinesia Rating scale Mattis Dementias Rating scale</td>
</tr>
</tbody>
</table>

| Timed Motor tests PDQ39 3 Day diary EQ-5D NMSS MADRS Mattis DRS |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 12 week supply of Exenatide/Placebo³ |

| Visits 3-7 CRF Adverse Events form Concomitant medication log MDS UPDRS Unified Dyskinesia Rating Scale Timed Motor tests PDQ39 3 Day diary EQ-5D NMSS MADRS Mattis DRS |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 36 week evaluation (Visit 5) | Patient contacted and arrangements made to attend research clinic in practically defined Off state. Self-completed diary/questionnaires to be sent/emailed to patient and brought along.  
Known adverse events enquiry  
Video of MDS-UPDRS part 3 off medication score  
Timed motor tests  
Patient takes regular medication  
Levodopa equivalent dose (LED) noted  
Patient completes UPDRS part 1, 2, 4  
Patient confirms best on state achieved  
MDS-UPDRS part 3 on medication score  
Timed Motor tests  
Unified Dyskinesia Rating scale  
MADRS  
NMSS  
Vital signs, weight  
Blood sampling- Urea & Electrolytes, Thyroid function, Liver Function Tests, serum amylase, saved serum for PK measurements.  
Urine sampling for PK measurements.  
12 week supply of Exenatide/Placeboa | Visits 3-7 CRF  
Adverse Events form  
Concomitant medication log  
MDS UPDRS  
Unified Dyskinesia Rating Scale  
Timed Motor tests  
PDQ39  
3 Day diary  
EQ-5D  
NMSS  
MADRS  
Mattis DRS |
| 48 week evaluation (Visit 6) | Patient contacted and arrangements made to attend research clinic in practically defined Off state. Self-completed diary/questionnaires to be sent/emailed to patient and brought along.  
Visits 3-7 CRF  
Adverse Events form  
Concomitant medication log  
MDS UPDRS  
Unified Dyskinesia Rating Scale  
Timed Motor tests  
PDQ39 |
<table>
<thead>
<tr>
<th>60 week evaluation (Visit 7)</th>
<th><strong>Known adverse events enquiry</strong>&lt;br&gt;Video of MDS-UPDRS part 3 off medication score&lt;br&gt;Timed motor tests</th>
<th><strong>3 Day diary</strong>&lt;br&gt;EQ-5D&lt;br&gt;NMSS&lt;br&gt;MADRS&lt;br&gt;Mattis DRS</th>
</tr>
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<tr>
<td>Patient takes regular medication&lt;br&gt;Lvodopa equivalent dose (LED) noted&lt;br&gt;Patient completes UPDRS part 1, 2, 4&lt;br&gt;Patient confirms best on state achieved&lt;br&gt;MDS-UPDRS part 3 on medication score&lt;br&gt;Timed Motor tests&lt;br&gt;Unified Dyskinesia Rating scale&lt;br&gt;Mattis Dementia Rating scale&lt;br&gt;MADRS&lt;br&gt;NMSS&lt;br&gt;Vital signs, weight</td>
<td>Blood sampling- Urea &amp; Electrolytes, Thyroid function, Liver Function Tests, serum amylase, saved serum for PK measurements.&lt;br&gt;Urine sampling for PK measurements.&lt;br&gt;Lumbar puncture &amp; CSF collection</td>
<td><strong>Visits 3-7 CRF</strong>&lt;br&gt;Adverse Events form&lt;br&gt;Concomitant medication log&lt;br&gt;MDS UPDRS&lt;br&gt;Unified Dyskinesia Rating Scale&lt;br&gt;Timed Motor tests&lt;br&gt;PDQ39&lt;br&gt;3 Day diary&lt;br&gt;EQ-5D&lt;br&gt;NMSS&lt;br&gt;MADRS&lt;br&gt;Mattis DRS</td>
</tr>
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</table>

**3 Day diary**<br>EQ-5D<br>NMSS<br>MADRS<br>Mattis DRS
<table>
<thead>
<tr>
<th>MADRS</th>
<th>NMSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs, weight</td>
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</table>

Blood sampling- Urea & Electrolytes, Thyroid function, Liver Function Tests, serum amylase, saved serum for PK measurements. Urine sampling for PK measurements.

**DaTSCAN**

Patients will be given instructions re DaTSCAN (including Potassium Iodide intake), and timetable for attendance at Nuclear Medicine dept, UCLH NHS Trust, for DaT-SPECT/CT scan

Patients will be given an appointment to attend for this scan as close as possible to the Visit 7 appointment.

*a* an additional kit to be dispensed at one or more of these visits to ensure patients have sufficient supply of IMP in the event of vial breakages.
# Table of Assessments

<table>
<thead>
<tr>
<th></th>
<th>Screening Visit 1</th>
<th>DATSCAN</th>
<th>Baseline evaluation and Randomisation Visit 2</th>
<th>12 week evaluation Visit 3</th>
<th>24 week evaluation Visit 4</th>
<th>36 week evaluation Visit 5</th>
<th>48 week evaluation Visit 6</th>
<th>60 week evaluation Visit 7</th>
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<td>Informed consent</td>
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<td>Review of PD medication history, past medical history, family history, previous imaging, previous genetic tests, clinical examination and pregnancy test</td>
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<td>ECG</td>
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<td>Blood tests (FBC, glucose, HBA1C, lipid profile)</td>
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<tr>
<td>Blood tests (U &amp; E, Thyroid function tests, Liver Function Tests, Serum amylase)</td>
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<td>Height, Weight, Pulse &amp; blood pressure (height only to be measured at Visit 1)</td>
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<td>Give/send patient 3 day Hauser Diary, PDQ39, EQ5D to be completed prior to upcoming trial visit</td>
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<td>MDS-UPDRS part 1,2,4 ON medication</td>
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<td>Unified Dyskinesia Rating Scale</td>
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<td>Collect completed 3 day Hauser Diary, PDQ39, EQ5D</td>
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<td>12 week supply of Exenatide/Placebo</td>
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<td>Lumbar Puncture</td>
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</tbody>
</table>

**a** = Height, Weight, Pulse and Blood Pressure; Mattis Dementia Rating Scale and MADRS to be repeated at Visit 2 if the time period between Visit 1 and 2 is more than 3 months

**b** = DaTSCAN to be performed at the Visit 7 time-point or as close to visit 7 as possible

**c** = an additional kit to be dispensed at one or more of these visits to ensure patients have sufficient supply of IMP in the event of vial breakages.
6.6.1 Early Stopping of Follow-up
If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the trial. UCL CCTU should be informed of the withdrawal in writing using the appropriate Exenatide-PD trial documentation. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early. See sections 6.9.1.1 & 6.10.4. All participants dropping out from the trial will continue to receive treatment for their PD in accordance with NHS Standard of care.

Participants who stop trial follow-up early prior to the 12 week follow up visit will be replaced by new recruits.

6.6.2 Participant Transfers
In the event that more than one centre is activated and a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating trial centre. Written consent should be taken at the new centre and then a copy of the participant’s CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

6.6.3 Loss to Follow-up
Every effort will be made to continue to follow up recruited patients. Only patients that cannot be contacted via their own contact details, via next of kin or General Practitioner will be deemed “lost to follow up”.

6.6.4 Trial Closure
The end of trial will be defined as the date of the last patient’s last visit. MHRA and REC will be notified within 90 days of trial completion.

6.7 Sample Size
The sample size calculations have been based on the detectable effect size (primary outcome is the MDS-UPDRS motor subsection) for a two arm (active drug versus placebo) study design. The calculations have been based on a common standard deviation of 13, 90% power and an overall type 1 error rate of 5%. In addition, a correlation of 0.85 is assumed between the baseline and follow up MDS-UPDRS measurements.

A sample size of 60 patients divided equally between the 2 groups will have 90% power to detect a difference of 5.8 MDS UPDRS points between the 2 groups using an ANCOVA analysis to adjust for baseline MDS UPDRS score, (or 80% power to detect a difference of 5.0 MDS UPDRS points between the 2 groups), assuming no loss of data. This effect size is a reasonable expectation based on the previously collected pilot data.
6.8 Recruitment and Retention

6.8.1 Recruitment
A cohort of patients with interest in participation in this trial already exists as a result of participation as “Controls” in the previous pilot trial. Publication of the results of the pilot trial has already led to further multiple enquiries regarding participation in this project. Neurologists in London with an interest in PD will be informed when the trial is open to recruitment and provided with details of eligibility criteria, to allow referral of potential recruits to the clinical trial team.

The REC approved “lay summary of the trial” will be provided to the Cure Parkinson’s Trust, Parkinson’s UK and MJFF Fox Trial finder website managers, and the UCL Institute of Neurology and UCLH NHS trust and NIHR CLRN portfolio websites. Contact details for the trial team will be included to allow potentially eligible interested patients to make direct enquiries to the trial team.

It is anticipated that recruitment of 60 patients will be completed within 9 months of trial commencement.

6.8.2 Retention
The importance of complete follow up and trial completion will be explained to all potential participants at the screening visit. Patients likely to have difficulty adhering to the trial protocol will not be recruited. The clinical team will make every effort to establish good relationships with trial participants from the first contact to maximise retention.

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. Appropriate medical advice and treatment will be made available to any individuals experiencing adverse events from trial participation. Patients with excessive 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.
6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

A random sequence for study arm allocation will be computer generated by a randomisation service provider (Sealed Envelope.com). Sealed Envelope will provide a unique trial identification code for each recruited participant. Stratified randomisation will be performed with strata defined by PD severity. Blocking will be used within strata to enable achievement of equal numbers in each group.

Strata 1= Absent, Unilateral or bilateral signs of Parkinsonism in the “ON” condition with normal balance as assessed by the Pull test i.e. Hoehn & Yahr stage 1.0-2.0.

Strata 2= Unilateral or bilateral signs of parkinsonism in the “ON” condition with retropulsion or difficulty recovering balance in the pull test, i.e. Hoehn & Yahr stage 2.5.

At the baseline visit, the clinical investigator will enter the patient’s initials, gender, date of birth, date of consent, criteria fulfilment and PD severity strata into the SealedEnvelope.com secure website which will then allocate the appropriate trial identification code to the patient. The randomisation list will be long enough to enable continued recruitment should patients drop out within the first 12 weeks of the trial. In accordance with the statistical analysis plan, any patients dropping out within the first 12 weeks of the trial will still be included in the Intent to treat analysis. Recruitment will continue until a total of 60 patients have completed a minimum of 12 weeks exposure to their assigned treatment. All patients will be randomly assigned to treatment via the Sealed Envelope.com website. A list of trial identification codes and active/placebo treatment allocation will be given to the QP and a copy held at UCL CCTU. Neither the clinical team nor the NHNN Pharmacy team will have access to this list.

The Trial Statistician will also generate a sequence of unique 3 digit identifiers for every active/placebo drug kit. The drug kit identification codes will be provided to Sealed Envelope and the QP at Royal Free Hospital who will ensure that trial drug and placebo packs are labelled appropriately, and that the trial team and participants remain blind to treatment allocation. At baseline and then at each follow up visit, the clinical investigator will enter the patient’s unique trial identification code into the SealedEnvelope.com website which will then provide the 3 digit identification code of the active/placebo drug kit to be dispensed. RFH will ensure that appropriate amounts of the labelled uniquely identified active/placebo drug kits will be delivered to NHNN pharmacy to allow adequate supplies (of the relevant numbered kits) for Pharmacy dispensing.

6.9.1.2 Allocation concealment mechanism

Each trial drug kit will contain a 4 week supply of trial drug and will be identified by a kit number only. Three trial drug kits, with 3 different codes (sufficient for 12 weeks) will be dispensed at each follow up visit. Due to the high level of vial breakages experienced, at one of the visits an additional kit will be dispensed to ensure patients have sufficient supply of IMP. This additional kit will be replaced at subsequent study visits as required. The kit numbers allocated to the patient at each visit will be revealed to the investigator through Sealed Envelope.com (a password protected, secure web-based system) on entry of the participant’s trial identification code and date of birth. The investigator will write the allocated kit numbers on a prescription for the participant to take to
pharmacy for dispensing. A printed hard copy or electronic copy of the kit numbers allocated to the patient for each visit will accompany the trial prescription to allow Pharmacy confirmation and avoid transcription errors. A full accountability trail will be maintained from receipt of trial drug in pharmacy, up to the point of dispensing and destruction of undispensed trial drug. The pharmacist will remain blind to trial arm and trial drug/placebo kit allocation. No study kits dispensed to patients will be returned to pharmacy. BMS will provide the study with a sufficient supply to account for lost or damaged vials.

6.9.1.3 Allocation Implementation
The responsibility for enrolling participants and prescribing trial drug to them lies with the CI. Eligibility decisions will be made in line with the approved protocol. Other physicians employed at the same clinical site may enrol and prescribe trial drug to patients only if they have received appropriate training on the trial and appear on the Exenatide-PD Trial Delegation log, signed off by the CI.

6.9.2 Blinding
Sealed Envelope will provide the patient trial identification codes at randomisation. The trial drug kit identification code list will be prepared by the Trial Statistician and provided separately to Sealed Envelope and to the QP who will ensure that labelling of trial drug packs occurs appropriately and so as to ensure complete blinding of the IMP to all investigators, participants and the pharmacy staff on the study. A secure website enables unblinding of a patient in the event of need, and the trial drug kit labelling strategy ensures that the unblinding of one patient will not unblind the entire trial arm.

6.9.3 Emergency Unblinding
All recruited participants will be given a card with contact details for the trial team including emergency contact 24 hours a day, 7 days per week. In the event of unblinding becoming necessary, emergency unblinding can occur at any time through the 24 hour web-based service offered by Sealed Envelope.com. It will occur for any participant experiencing a serious adverse event for which the clinical management of the SAE will be facilitated by the unblinding of the patient’s treatment allocation. The CI will make this decision. It is anticipated that for the majority of instances, appropriate clinical management can proceed with the assumption that the patient has been treated with Exenatide without needing to unblind the patient.

Unblinding should usually only be performed in the case of a SUSAR Unblinding will be carried out using the secure website access provided by Sealed Envelope and according to trial specific working practices. Details of the unblinding should be documented.

6.10 Data Collection, Management and Analysis
6.10.1 Data Collection Methods
All patient data will be collected by members of the clinical trial team as described in the Delegation log. Clinical trial team members will receive protocol training and will be taught on the use of the PD assessment scales including certification from the MDS on the use of the MDS UPDRS. Data will be recorded on a paper CRF. 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 code number, will be used for identification.
Case report forms will be designed and produced by the investigator and trial team. The final version will be approved by senior operations staff at UCL CCTU. 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 initialed 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 identification code number
- Demographic data re PD
- Past medical history (including documentation of all previous/ongoing medical problems)
- Medication history
- Family history- including age at onset of all affected relatives
- Clinical examination
- Adverse events

The following study-specific information will be documented directly onto the CRF.

- Levodopa Equivalent Dose
- Vital signs- pulse, BP, weight
- Biological specimens collected.

The following data are from standardised tools that have been extensively validated in previous clinical trials. The printed questionnaires completed at each visit will be the source documents which will be filed in the CRF.

- Blood test results printout- anonymised, coded and dated
- ECG printout- anonymised, coded and dated

- MDS- UPDRS. The MDS-UPDRS training program & exercise are obtainable from; www.movementdisorders.org/updrs/


- MATTIS Dementia Rating Scale-2 obtainable from; www4.parinc.com/Products/Products.aspx?ProductID=DRS-2

- PDQ39 obtainable from; University of Oxford, Health Services Research Unit.

- 3 Day Hauser diary obtainable from; Hauser et al. Clinical Neuropsychology 2000, 23(2) p75-81.
6.10.2 Non-Adherence and Non-Retention
The number of subcutaneous injections successfully self-administered will be estimated at each visit based on directly questioning the patient/their carer, as well as noting the amount of trial product dispensed at previous visit, the interval between visits and the number of unused injections remaining. Reasons for non-adherence to protocol will be noted in the medical notes and CRF. Outcome data will continue to be collected on all contactable patients continuing to provide informed consent.

6.10.3 Data Management
Case Report Forms will be completed at site and collected in person by CCTU staff on routine visits. Data entry, coding and security will be the responsibility of a dedicated Data manager based at UCL CCTU. A custom designed database will be created (using InferMed’s MACRO V4) to store all trial data. The database will only be available to specified users who will require a username and password for access. MACRO V4 supports a role based security model, granting different users different database privileges. MACRO V4 implements data validations to assist data quality, including range checks on individual items and consistency checks between multiple items. This will be compliant with all necessary regulatory requirements including audit trail to allow for date/time stamped corrections accompanied by justification/explanation for any data amendments.

All data storage will adhere to Data Protection Act 1998.

6.10.4 Statistical Methods

6.10.4.1 Statistical Analysis Plan
All study analyses will be according to the Statistical Analysis Plan, which will be prepared before the first substantive unblinded analysis and agreed in advance by the Trial Steering Committee (TSC). A single main analysis will be performed at the end of the trial when follow-up is complete. The statistical analysis will be based on all participants as randomised, irrespective of subsequent compliance with allocated treatment (intention to treat analysis).

A CONSORT diagram will be used to describe the course of patients through the trial. Baseline characteristics will be summarised by randomised group. Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. The impact of missing data and non-compliance will be investigated.
6.10.4.2 Statistical Methods – Outcomes

Primary outcome analysis will evaluate the impact of treatment allocation (Exenatide or placebo) on the difference between MDS UPDRS part 3 scores in the practically defined “Off” state at 60 weeks follow up. All analyses will be performed by the Trial Statistician at UCL CCTU. The analysis will use a regression (ANCOVA, analysis of co-variance) approach that adjusts for stratification factors and the baseline raw value of each outcome measurement. A significance level of 5% will be used to judge significance for the primary outcome measure.

Analyses of the remaining secondary/ exploratory outcomes will be presented for the difference between groups according to treatment allocation at 48 & 60 weeks follow up using ANCOVA to adjust for baseline values of each outcome, and confounding factors such as LED.

Patients that discontinue trial medication will continue to be followed up in accordance with the trial protocol and their data included in accordance with the intention to treat analyses.

Sensitivity Analysis: a per protocol analysis will also be performed for the primary outcome measure including only those participants who completed the trial in accordance with the approved protocol.

6.10.4.2.1 Economic evaluations

The 5 questions contained within EQ5D will allow calculation of QALY, although formal health economic analyses are not currently planned.

6.10.4.3 Additional Analyses - Subgroup

Results on the primary efficacy outcome will be presented by stratum, i.e., according to Hoehn & Yahr stage (stage 2.0 or less versus 2.5), and an interaction between Hoehn & Yahr and treatment will be added to the primary analysis model to investigate whether the effect of treatment differs according to the Hoehn & Yahr stage.

6.10.4.4 Additional Analyses – Adjusted

Analysis of covariance (ANCOVA) will be used for the primary analysis to adjust for baseline values of each outcome. In the event of substantial missing data, this will be mitigated against by incorporating information from earlier time points using a mixed model approach. In case missingness would be informative, additional approaches than mixed model will be applied for assessing the sensitivity of the conclusions against the strategy for dealing with missing values.

6.10.4.5 Analysis Population and Missing Data

The impact of missing data will be mitigated against by incorporating information from earlier timepoints using a mixed model approach. Please refer to previous subsection for more information on missingness.

6.11 Data Monitoring

6.11.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be convened including at least 3 individuals independent from the trial team and sponsor who have experience in the conduct of clinical trials for PD. The IDMC will review the trial results and make a recommendation to the trial steering committee (TSC) regarding continuation/ stopping of the trial based on safety data. The UCL CCTU Trial Statistician will generate the summaries of trial results for the IDMC to review. No statistical
stopping rules will be used. Further details of the roles and responsibilities of the IDMC, including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the Exenatide-PD, IDMC Terms of Reference (ToR).

6.11.2 Interim Analyses
A planned interim analysis will be performed when the first 30 subjects have completed 24 weeks in follow up. This will include a comparison of the mean difference between baseline and 24 weeks follow up of the MDS UPDRS part 3 in the practically defined OFF medication state according to treatment allocation. The analysis will be performed by the Trial Statistician at UCL CCTU, who will ensure that the Trial Team remain blinded as to treatment allocation. Any difference detectable at 24 weeks will be used to gauge whether any signal of efficacy is emerging at this timepoint. The results of this interim analysis will be communicated to the Independent Data Monitoring Committee and recommendations based on the analysis will be communicated to both the TSC and the Michael J Fox Foundation who will remain blinded to treatment allocation.

6.11.3 Data Monitoring for Harm

6.11.3.1 Safety reporting
Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

6.11.3.1.1 Adverse Events
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

• Related: There is a reasonable causal relationship between study drug administration and the AE.

• Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship. Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.).
6.11.3.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or causes prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardise the subject or may require intervention (eg, medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation.) Potential drug induced liver injury (DILI) is also considered an important medical event (see Section 6.11.3.3.2 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalisations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event);
- elective surgery, planned prior to signing consent;
- admissions as per protocol for a planned medical/surgical procedure;
- routine health assessment requiring admission for baseline/trending of health status;
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases;
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.11.3.1.3 Nonserious Adverse Events

A nonserious adverse event is an AE not classified as serious.

The nonserious adverse event collection and reporting should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.
6.11.3.2 Laboratory test abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE;
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted;
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anaemia versus low haemoglobin value).

6.11.3.3 Other Notifiable Adverse Events

Suspicion of chronic pancreatitis based on a rise in serum amylase greater than 50% above both baseline level AND the laboratory reference range will be notified in an expedited manner in the same way as an SAE.

Overdose and potential drug induced liver injury (DILI) events and excessive/undesirable weight loss (>10% of body weight during a 12 week interval) must be handled as SAEs.

Pregnancy is not a Serious Adverse Event and should be reported through the Pregnancy form. The pregnancy outcome may or may not be considered a SAE.

6.11.3.3.1 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important and it must always be reported as SAE.

6.11.3.3.2 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. Potential drug induced liver injury is defined as:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
  AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
  AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.11.3.3.3 Procedures to follow in the event of female participants becoming pregnant

There are no safety data to inform on the use of Exenatide during pregnancy. Male patients and female participants of child-bearing potential will be advised to use an effective form of contraception whilst they are in the study. If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner.
Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated. Trial follow-up assessments will continue as per protocol. The patient’s General Practitioner will be informed of the potential unknown risk that may have followed Exenatide exposure during pregnancy. Emergency unblinding will only occur in the event that there is a clinical indication.

The investigator must immediately notify the UCL CCTU of this event. The CCTU will forward the Pregnancy Surveillance Form to BMS/AstraZeneca according to pregnancy procedures described in the study Safety Management Plan.

6.11.3.4 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, and any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6.11.3.5 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient’s medical notes. SAEs and SARs should be notified to UCL CCTU within 24 hours day of the investigator becoming aware of the event.

6.11.3.5.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as ‘serious’ then an SAE form must be completed and UCL CCTU (or delegated body) notified within 24 hours. UCL CCTU will report the SAE to BMS/AstraZeneca (see Section - 6.11.3.6.2).

6.11.3.5.2 Severity or grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the study specific toxicity grading system and the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) version 4. SUSARs will be coded via MedDRA for the purpose of expedited reporting to MHRA/REC.

6.11.3.5.3 Causality

The investigator must assess the causality of all adverse events (AEs) and serious adverse events (SAEs) or reactions (SARs) in relation to the trial therapy.

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to the relevant Interventions sections of the protocol.

6.11.3.5.4 Expectedness

If there is at least a possible involvement of the trial medications (including any comparators), the investigator and sponsor must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the current IB or SPCs, or one that is more frequently reported or more severe than previously reported. See the current SPC for a list of expected toxicities associated with Exenatide. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) and MHRA and REC reporting guidelines apply (see Notifications sections of the protocol).
6.11.3.6 Serious Adverse Event Collection and Reporting

6.11.3.6.1 Notifications by the Investigator to UCL CCTU

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs that occur either during the screening period or within 30 days of discontinuation of dosing will also be collected by UCL CCTU. The investigator should report any SAE that occurs until the end of the trial and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to UCL CCTU within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form.

The SAE form must be scanned and sent via encrypted email to the trial team at UCL CCTU on exenatidepd@ucl.ac.uk

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report (clearly marked as follow up) should be sent within 24 hours to the UCL CCTU using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

Additional information and/or copies of test results etc may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant’s name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

After the end of the trial, any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/) by healthcare professionals or patients.

6.11.3.6.2 UCL CCTU responsibilities

Medically qualified staff at UCL CCTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality
assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The delegated staff at UCL CCTU will review the assessment of expectedness and, based on possible wider knowledge of the reference material for the treatment or comparator, and after discussion with the CI, may over-rule the investigator assessment of expectedness for the purposes of onward reporting.

UCL CCTU will notify the Bristol-Myers Squibb Safety Team within 24 hours of becoming aware of the event. SAEs, whether related or not related to the study drug, and pregnancies will be reported in the SAE report form and Pregnancy Surveillance Form, respectively. Follow up forms will be sent using the same procedure and timelines used for transmitting the initial report to:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax number: +1 609 818 3804
Email: worldwide.safety@bms.com

AstraZeneca will be notified through their ESR System:
http://az_medi.envisionpharma.com/vt_az_medi

UCL CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and the RECs as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within seven days of UCL CCTU becoming aware of the event; other SUSARs must be reported within 15 days.

UCL CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

The sponsor or their delegate will submit Development Safety Update Reports (DSURs) to competent authorities.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment
The Quality Assurance (QA) and Quality Control (QC) considerations for the Exenatide-PD trial are based on the standard UCL CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.
6.11.4.2 Central Monitoring at UCL CCTU
UCL CCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the Exenatide-PD trial Data Management Plan.

6.11.4.3 On-site Monitoring
The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the Exenatide-PD Quality Management Plan (QMP). The QMP will also detail the procedures for review and sign-off of monitoring reports.

6.11.4.3.1 Direct access to participant records
Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.11.4.4 Trial Oversight
Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the compliance section of the protocol. Independent trial oversight complies with the UCL CCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the Exenatide-PD Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Management Team
The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management.

6.11.4.4.2 Trial Management Group
A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.3 Independent Trial Steering Committee
The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, UCL CCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.
6.11.4.4 Independent Data Monitoring Committee
The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TMG on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TMG through its Chair.

6.11.4.5 Trial Sponsor
The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to UCL CCTU via an agreed roles and responsibilities document.

7 Ethics and Dissemination

7.1 Research Ethics Approval
Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

The safety data from large phase III trials of Exenatide given to diabetes patients provides reassurance that risks to the patients will be minimal. All patients will be made aware of the known adverse effects including the ongoing suspicion that Exenatide may increase the risk of pancreatitis, which may in turn increase the risk of pancreatic cancer.

Measuring improvement in underlying PD severity among PD patients requires an assessment to be performed after an overnight period off medication. Patients 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 various aspects of PD management even among patients 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.
7.2 Competent Authority Approvals
This protocol will be submitted to the national competent or equivalent authority (MHRA/Food and Drug Administration (FDA) etc), as appropriate in each country where the trial will be conducted.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the Competent Authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices.

7.3 Other Approvals
The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site. A copy of the local R&D approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the UCL CCTU Protocol Review Committee.

7.4 Protocol Amendments
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.

7.5 Consent or Assent
Consent for trial participation will only be performed by named individuals in accordance with the delegation log. All named individuals will be trained in the principles of informed consent and will have had full training in the trial protocol to allow full discussion with each potential participant. During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Consent will be re-sought if new information becomes available that affects the participant’s consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

A copy of the approved consent form is available from the UCL CCTU trial team.

7.5.1 Consent or Assent in Ancillary Studies
All patients will be asked to provide informed consent for the use of their clinical data and biological specimens in ancillary studies that may help inform on the mechanism of action of Exenatide. This will include;

- Measurement of Exenatide levels in serum, urine and Cerebrospinal fluid (CSF).
- Measurement of BDNF levels in CSF.
- Mass spectroscopy of CSF.
- Antibodies against Exenatide in serum.

All biological specimens will be coded and will only remain identifiable through a linking coded list stored securely in a separate location. Withdrawal from the trial will not be accompanied by withdrawal of previously collected specimens. No individual information derived from this specimen related research will be communicated to the participants.

7.6 Confidentiality
Each participant’s data will be collected and kept secure. SealedEnvelope.com will provide a unique trial identification code for each participant and their name will be thus replaced by a depersonalised code using an unrelated sequence of characters. SealedEnvelope.com is a secure method of generating trial identification codes to participants in clinical trials and is recognised as such by the MHRA. For safety, the linking code will also be stored in a separate location within UCL CCTU in password protected folders and storage media with limited access by the minimum number of individuals necessary for quality control, audit and analysis. Linking codes will not be communicated during data transfer.

7.7 Declaration of Interests
The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Archiving
The investigators agree to archive and/or arrange for secure storage of Exenatide-PD trial materials and records for a minimum of 5-10 years after the close of the trial unless otherwise advised by the UCL CCTU.

7.9 Access to Data
Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the independent TSC. Considerations for approving access are documented in the TSC Terms of Reference.

7.10 Ancillary and Post-trial Care
No arrangements are in place to provide Exenatide to trial subjects post trial participation. This will be made clear in the Patient Information Sheet.

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.

7.11 Publication Policy

7.11.1 Trial Results
The results of this trial will be submitted for publication in a peer reviewed journal, in addition to reports at appropriate specialist conferences. The results of the trial will be disseminated regardless of the direction of effect.

7.11.2 Authorship
Authorship will be granted to individuals making a substantial contribution to the design, setup or conduct of the trial and/or analysis and interpretation of trial data.

7.11.3 Reproducible Research
The latest version of the trial protocol will be made available as Supplementary material upon publication of the final trial report.

8 Ancillary Studies

All patients will be asked to provide informed consent for the use of their clinical data and biological specimens in ancillary studies that may help inform on the mechanism of action of Exenatide. This will include:

- Measurement of Exenatide levels in serum, urine and Cerebrospinal fluid (CSF).
- Measurement of BDNF levels in CSF.
- Mass spectroscopy of CSF.
- Antibodies against Exenatide in serum.
9 Protocol Amendments

<table>
<thead>
<tr>
<th>Protocol version number</th>
<th>Protocol date</th>
<th>List of Substantial Amendments (for full description, please refer to the “Summary of changes to the protocol” document)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>03.09.2013</td>
<td>New protocol</td>
</tr>
</tbody>
</table>
| 2.0                     | 15.01.2014      | - Inclusion of “once weekly” to the full title: A randomised, double blind, placebo controlled, single centre, 60 week trial of Exenatide once weekly for the treatment of moderate severity Parkinson’s disease  
- Additional language on women of childbearing potential has been added to section 4, Glossary  
- Addition of AstraZeneca as the drug supplier company (BMS/AstraZeneca)  
- Secondary Outcomes have been reduced to four and the remaining are now designated “Exploratory Outcomes”. This will deal with concerns related to multiple testing  
- The exclusion criteria (Diagnosis or suspicion of other causes of Parkinsonism) had a new wording amended: “Subjects without DaTscan appearances consistent with diagnosis of PD will not be recruited”  
- Exclusion Criteria: a new criteria has been added to the trial: Severe gastrointestinal disease (e.g. gastroparesis)  
- Exclusion Criteria: Type 1 and Type 2 Diabetes Mellitus has been deleted  
- A new Appendix linked to the exploratory outcome “Levodopa equivalent dose” has been amended with conversion factors used to convert commonly PD medications to a “Levodopa equivalent dose (LED)”  
- Pregnancy and liver function tests have been added to the study  
- Primary outcomes had a sentence included to clarify that only trained clinical trial personnel as per delegation log will conduct assessments  
- FDA statement added to balance with the publication citations regarding adverse events  
- New wording in the “Allocation concealment mechanism” section: BMS/AstraZeneca will provide the study with a sufficient supply to account for lost and damaged vials  
- The section “Statistical Methods – Outcomes” has been re-phrased and the analysis of secondary outcomes is now clearly explained  
- Section 6.9.1.1 had the study Intention-to-treat-analysis clarified  
- Section 6.11.3 has been re-phrased in order to clarify safety  
- Additional information regarding missing data  
- Additional comments on dealing with adjustments or
modifications to the PD drugs both while patients are receiving blinded study drug and in the case of a patient who withdraws from the study. Also, how will the motor responses be assessed in those circumstances.

<table>
<thead>
<tr>
<th>Date</th>
<th>Amendment Details</th>
</tr>
</thead>
</table>
| 19.12.2014 | - Inclusion of Type 1 or Type 2 Diabetes mellitus as exclusion criteria  
- Clarification that coagulation factors/clotting will be collected as standard of care prior CSF  
- Amylase data will be collected separately by a different individual to ensure that the primary outcome rater remains blinded  
- Interaction between Hoehn & Yahr and treatment will be added to the primary analysis model to investigate whether the effect of treatment differs according to the Hoehn & Yahr stage  
- Interim analyses will be performed when the first 30 subjects have completed 24 weeks in follow up and not when 60 patients as previously stated  
- Pregnancy to be reported as Pregnancy and not SAE  
- SAE forms to be reported via encrypted email  
- Minor orthographic alterations throughout the entire protocol |
| 25.03.2015 | - All PD medication (except Levodopa) is being withheld for ≥ 36 hours  
- Clarification of primary outcome analysis  
- Patients are not being shown an instructional video re lumbar puncture |
| 16.07.2015 | - Additional kit to be dispensed at one or more of the 12 weekly visits |
| 01.10.2015 | - Timed tests added as an exploratory outcome  
- Statement that excessive weight loss will result in dose temporarily stopped not discontinued  
- Statement to define protocol deviation regarding number of missed IMP injections  
- Clarification regarding blinding the primary rater  
- Clarification of the use of MDS-UPDRS part 3 video recordings  
- Additional blood test at Visit 7  
- Excessive weight loss added as Notifiable Adverse Event  
- Change in Trial Steering Committee composition  
- Other minor administrative changes throughout |
10 References


(22) Hunter K, Holscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. BMC Neurosci 2012; 13:33.


(37) Kastin AJ, Akerstrom V. Entry of exendin-4 into brain is rapid but may be limited at high doses. Int J Obes Relat Metab Disord 2003; 27(3):313-318.


(44) Olanow CW, Hauser RA, Jankovic J, Langston W, Lang A, Poewe W et al. A randomized, double-blind, placebo-controlled, delayed start study to assess rasagiline as a disease modifying therapy in Parkinson’s disease (the ADAGIO study): rationale, design, and baseline characteristics.


## Appendix
Conversion factors used to convert each of the commonly used PD medications to a Levodopa equivalent dose (LED)\(^8\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Conversion factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release L-dopa</td>
<td>X 1</td>
</tr>
<tr>
<td>Controlled release L-dopa</td>
<td>X 0.75</td>
</tr>
<tr>
<td>Entacapone (or Stalevo(^\ast))</td>
<td>LD X 0.33</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>LD X 0.5</td>
</tr>
<tr>
<td>Duodopa(^\ast)</td>
<td>X 1.11</td>
</tr>
<tr>
<td>Pramipexole (as salt)</td>
<td>X 100</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>X 20</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>X 30</td>
</tr>
<tr>
<td>Selegiline-Oral</td>
<td>X 10</td>
</tr>
<tr>
<td>Selegiline-Sublingual</td>
<td>X 80</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>X 100</td>
</tr>
<tr>
<td>Amantadine</td>
<td>X 1</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>X 10</td>
</tr>
</tbody>
</table>