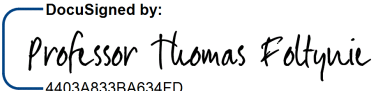


Exenatide-PD3

A randomised, double blind, parallel group, placebo controlled, Phase 3 trial of Exenatide once weekly over 2 years as a potential disease modifying treatment for Parkinson's disease.

Version	5.0
Date	11 Nov 2022
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/2016/278
Trial registration	
EudraCT #	2018-003028-35
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REC #	19/SC/0447


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1 Administrative information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 5. It describes the Exenatide-PD3 trial, sponsored by UCL and co-ordinated by 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 CCTU.

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) 2013 Statement for protocols of clinical trials¹. The SPIRIT Statement Explanation and Elaboration document² can be referred to, or a member of 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 Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) UK Policy Framework for Health and Social Care. International sites will comply with the principles of GCP as laid down by International Conference on Harmonisation (ICH) topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable), the EU Tissue and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC, and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that 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-PD3 trial to CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the CCTU Director.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	Clinicaltrials.gov: NCT04232969
Date of Registration in Primary Registry	ISRCTN: 08 Oct 2019 Clinicaltrials.gov: 16 Jan 2020
Secondary Identifying Numbers	ISRCTN: ISRCTN14552789 EudraCT#: 2018-003028-35 UCL R&D ID#: 18/0320 CTU Trial Adoption Group #: CTU/2016/278 IRAS#: 263481
Source of Monetary or Material Support	This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. Project number: 16/167/19. The views expressed in this document are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care. Exenatide and placebo provided free of charge by Astra Zeneca.
Sponsor	University College London with sponsor responsibilities delegated to CCTU.
Contact for Public Queries	CCTU.exenatidePD3@ucl.ac.uk
Contact for Scientific Queries	Prof T Foltynie T.Foltynie@ucl.ac.uk 0203 448 8726 Box 146 National Hospital for Neurology & Neurosurgery Queen Square London, WC1N 3BG
Public Title	Phase 3 Trial of exenatide for Parkinson's disease
Scientific Title	A randomised, double blind, parallel group, placebo controlled phase 3 trial of exenatide once weekly over 2 years as a potential disease modifying treatment for Parkinson's disease.
Countries of Recruitment	UK
Health Condition(s) or Problem(s) Studied	Parkinson's disease
Intervention(s)	Exenatide 2.0 mg (powder and solvent for prolonged release, suspension for injection, prefilled pen) once weekly for 96 weeks. Placebo Exenatide (powder and solvent for prolonged release, suspension for injection, prefilled pen) once weekly for 96 weeks.
Key Inclusion and Exclusion Criteria	Inclusion Criteria <ol style="list-style-type: none"> 1. Diagnosis of Parkinson's disease. 2. Hoehn and Yahr stage ≤ 2.5 in the ON medication state. 3. Between 25 and 80 years of age. 4. On dopaminergic treatment for at least 4 weeks before enrolment. 5. Ability to self-administer, or to arrange carer administration of trial medication.

	<p>6. Documented informed consent to participate.</p> <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Diagnosis or suspicion of other cause for Parkinsonism. 2. Patients unable to attend the clinic visits in the practically defined OFF medication state. 3. Body mass index <18.5. 4. Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol. 5. Significant cognitive impairment defined by a score <21 on the Montreal Cognitive Assessment. 6. Concurrent severe depression defined by a score ≥ 16 on the Patient Health Questionnaire (PHQ-9). 7. Prior intra-cerebral surgical intervention for Parkinson's disease. 8. Previous participation in one of the following Parkinson's disease trials (Biogen SPARK trial, Prothena Pasadena trial, Sanofi Genzyme MOVES-PD trial, UDCA-PD UP Study or any other trial still considered to involve a potentially PD modifying agent). 9. Participation in another clinical trial of a device, drug or surgical treatment within the last 30 days 10. Previous exposure to exenatide. 11. Impaired renal function with creatinine clearance <50ml/min. 12. History of pancreatitis. 13. Type 1 or Type 2 diabetes mellitus. 14. Severe gastrointestinal disease (e.g. gastroparesis) 15. Hyperlipidaemia. 16. History or family history of medullary thyroid cancer (MTC). 17. Multiple endocrine neoplasia 2 (MEN2) syndrome. 18. Hypersensitivity to any of exenatide's excipients. 19. Females that are pregnant or breast feeding. 20. WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire trial period and up to 3 months after the last dose of trial medication. 21. Participants who lack the capacity to give informed consent 22. Any medical or psychiatric condition or previous conventional/experimental treatment which in the investigator's opinion compromises the potential participant's ability to participate.
Study Type	This is an interventional, multi-centre, phase 3 trial including randomisation, double-blinding, placebo control, parallel group evaluation of exenatide as a treatment for Parkinson's disease.
Date of First Enrolment	January 2020
Target Sample Size	200

Primary Outcome(s)	<p>Outcome name - Motor score in practically defined "OFF" medication state.</p> <p>Metric - Movement Disorder Society Unified Parkinson's Disease Rating Scale part 3 Motor subsection score.</p> <p>Timepoint - 96 weeks</p>
Key Secondary Outcomes	<p><u>Difference between 96 week scores for each of the secondary outcomes listed below will be compared between groups according to treatment allocation:</u></p> <ul style="list-style-type: none"> • Movement Disorder Society Unified Parkinson's Disease Rating Scale part 1,2,3 and 4 ON medication scores • Timed Walk assessment ON and OFF medication • Montreal Cognitive Assessment • Safety and tolerability of exenatide as indicated by changes in vital signs, weight, clinical laboratory measures and adverse events • Unified Dyskinesia Rating Scale • Patient Health Questionnaire (PHQ-9) • Parkinson's Disease 39 item Quality of life questionnaire • Non-Motor Symptoms scale • Levodopa equivalent dose • 3 day Hauser diary of PD state (Time-On, Off, Non troublesome Dyskinesia, Troublesome dyskinesia, Asleep) <p><u>Difference between total values over 96 week for each of the secondary outcomes listed below will be compared between groups according to treatment allocation:</u></p> <ul style="list-style-type: none"> • Health and social care resource use on the modified Client Service Receipt Inventory (CSRI) • Health and social care costs • Paid and unpaid carer costs • Quality adjusted life years (QALYs) calculated using the EQ-5D-5L UK tariff and adjusting for baseline. <p><u>Difference between 48 and between 48 to 96 week scores for each of the secondary outcomes listed below will be compared between groups according to treatment allocation</u></p> <ul style="list-style-type: none"> • Movement Disorder Society Unified Parkinson's Disease Rating Scale part 3 Motor subsection OFF medication score • Movement Disorder Society Unified Parkinson's Disease Rating Scale part 1,2,3 and 4 ON medication scores

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Prof Thomas Foltynie	UCL Institute of Neurology	Chief Investigator
Dr Kate Maclagan	UCL CCTU	Previous Clinical Project Manager (Co-Applicant)
Dr Helen Knowles	UCL CCTU	Trial Manager
Prof Simon Skene	University of Surrey	Senior Statistician (Co-Applicant)
Dr Camille Carroll	University of Plymouth	Co-Investigator (Co-Applicant)
Dr Michele Hu	University of Oxford	Co-Investigator (Co-Applicant)
Prof Ray Chaudhuri	Kings College London	Co-Investigator
Dr Monty Silverdale	University of Manchester	Co-Investigator
Dr John Dickson	UCLH NHS trust	Nuclear Medicine Acquisition
Assistant Professor Rachael Hunter	UCL HEART	Health Economist
Grace Auld	UCL CCTU	Previous Trial Manager

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Prof Nick Freemantle	UCL CCTU	Overall supervision of UCL CCTU sponsorship. Ultimate authority for writing the report and decision to submit for publication will lie with the Chief Investigator.
Delegated Programme Manager	NIHR MRC and NIHR Partnership-EME	NIHR Programme Manager

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Prof Thomas Foltynie	UCL Institute of Neurology	Chief Investigator
Dr Christine Girges	UCL Institute of Neurology	Research Assistant
Dr Nirosen Vijjaratnam	UCL Institute of Neurology	Clinical Research Fellow
Grace Auld	UCL CCTU	Clinical Project Manager
Rachel McComish	UCL CCTU	Trial Manager
Prof Simon Skene	University of Surrey	Senior Statistician (Co-Applicant)

Kashfia Chowdhury	UCL CCTU	Trial Statistician
Alexa King	UCL CCTU	Data Manager

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Prof Thomas Foltynie	UCL Institute of Neurology	Chief Investigator
Dr Camille Carroll	University of Plymouth	Co-Investigator (Co-Applicant)
Dr Michele Hu	University of Oxford	Co-Investigator (Co-Applicant)
Prof Ray Chaudhuri	Kings College London	Co-Investigator
Dr Monty Silverdale	University of Manchester	Co-Investigator
Dr Gordon Duncan	University of Edinburgh	Co-Investigator
TBC	UCL Institute of Neurology	Research Nurse
Rachel Gibson	N/A	Lay representative
Grace Auld	UCL CCTU	Clinical Project Manager
Kashfia Chowdhury	UCL CCTU	Trial Statistician
TBC	UCL CCTU	Trial Manager
Prof Simon Skene	University of Surrey	Senior Statistician (Co-Applicant)

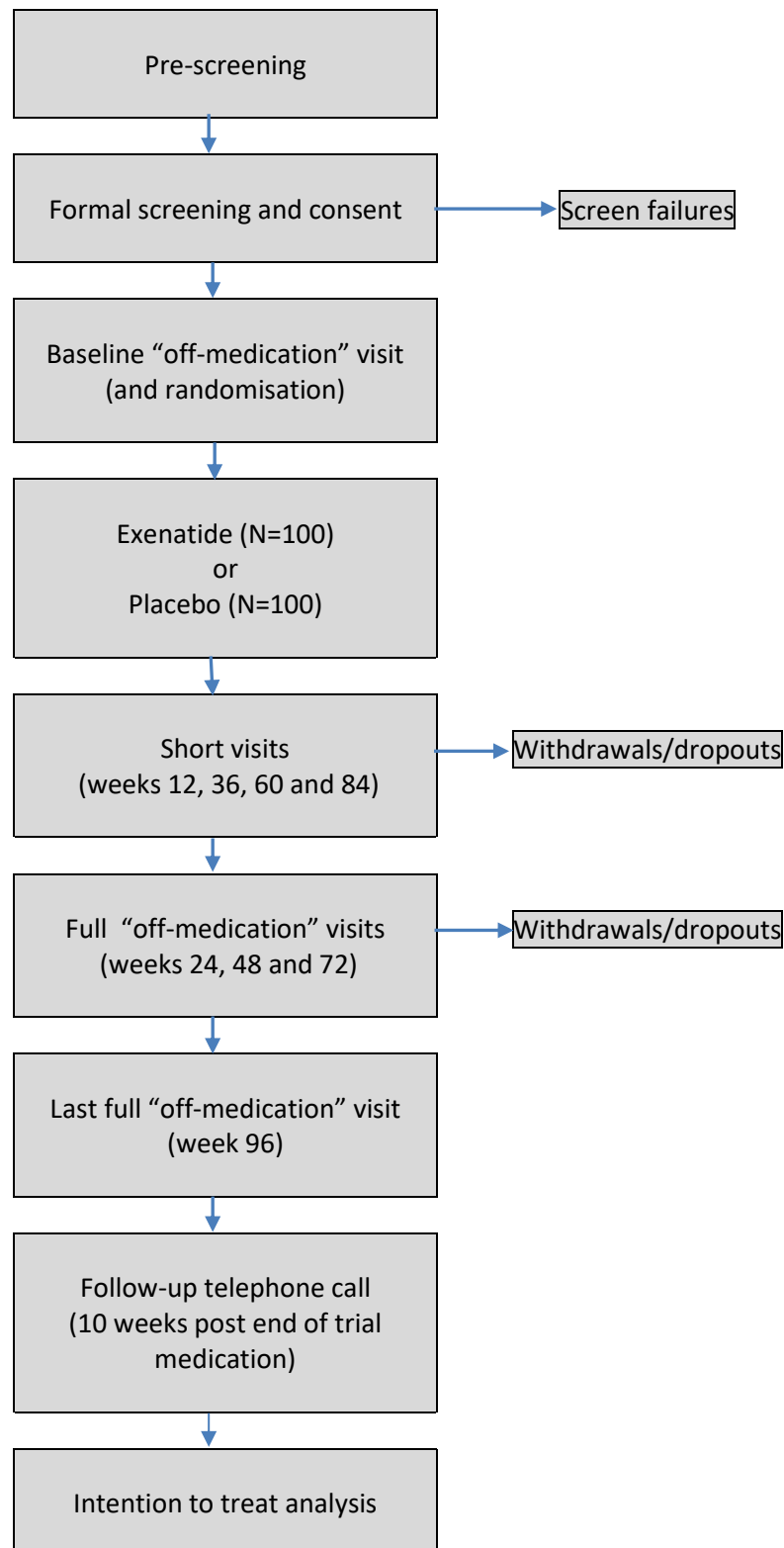
1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Prof Carl Clarke	University of Birmingham	Independent Chair
Prof T Foltynie	UCL Institute of Neurology	Non-independent, Chief Investigator
Dr Caroline Williams-Gray	University of Cambridge	Independent Clinician
Dr Victoria Cornelius	Imperial College	Independent Statistician
TBC	TBC	Independent Health Economist
Helen Matthews	Cure Parkinson's Trust	Independent Lay Representative
Dr Clive Bartram	N/A	Patient & Public Involvement Representative
Mr Zia Mursaleen	N/A	Patient & Public Involvement Representative

1.4.6 Independent Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Prof David Burn	University of Newcastle	Chair (PD Academic clinician)
Prof Roger Barker	University of Cambridge	Member (PD Academic clinician)
Prof Oliver Bandmann	University of Sheffield	Member (PD Academic clinician)
Dr Lorna Aucott	University of Aberdeen	Member (Statistician)

2 Trial Diagram



3 Abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
AMP	Adenosine Monophosphate
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
BDI	Beck Depression Inventory
CCTU	Comprehensive Clinical Trials Unit
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CSF	Cerebrospinal Fluid
CSRI	Client Service Receipt Inventory
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug Induced Liver Injury
DPP	Dipeptidyl Peptidase
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EQ-5D-5L	EuroQol EQ-5D 5-Level Health Related Quality of Life Questionnaire
EU	European Union
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GLP-1	Glucagon-Like Peptide-1
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HRA	Health Research Authority
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
ITT	Intention to Treat
LED	Levodopa Equivalent Dose
MDS-UPDRS	Movement Disorders Society - Unified Parkinson's Disease Rating Scale

MHRA	Medicines and Healthcare products Regulatory Agency
MoCA	Montreal Cognitive Assessment
MPTP	Methyl, Phenyl Tetrahydropyridine
mRNA	Messenger Ribonucleic Acid
NHS	National Health Service
NHNN	National Hospital for Neurology and Neurosurgery
NIH	National Institute of Health
NIHR	National Institute for Health Research
NIMP	Non Investigational Medicinal Product
NMS	Non-Motor Symptoms Questionnaire
6-OH DA	6-Hydroxydopamine
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Quality of Life Questionnaire
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PI3	Phosphatidylinositide
QALY	Quality Adjusted Life Years
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
QP	Qualified Person
R&D	Research and Development
REC	Research Ethics Committee
RFHPMU	Royal Free Hospital Pharmacy Manufacturing Unit
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SN	Substantia Nigra
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGF	Transforming Growth Factor
TH	Tyrosine Hydroxylase
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team

ToR	Terms of Reference
TrkB	Tropomyosin receptor kinase B
TSC	Trial Steering Committee
UCL	University College London
UDysRS	Unified Dyskinesia Rating Scale
ULN	Upper Limit of Normal
UK	United Kingdom
WOCBP	Women of Child-Bearing Potential

4 Glossary

Hoehn & Yahr stage: A simple method of staging PD that can be applied to patients in either the ON or OFF medication state. For the purposes of the trial inclusion criteria, staging will be applied according to their ON medication 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 XL, Pramipexole Prolonged Release or Rasagiline.

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 3 months after the last dose of trial medication in such a manner that the risk of pregnancy is minimised.
- 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 total abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), occasional abstinence and withdrawal are not acceptable methods of contraception.
- 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

Acceptable methods of contraception:

- Hormonal contraceptives (e.g. oral, patch, injection medications).
- Double barrier (e.g. male condom plus spermicide, or female diaphragm plus spermicide).
- Intrauterine device.
- Male partner has had a vasectomy.
- Total abstinence from intercourse with male partners. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), occasional abstinence and withdrawal are not acceptable methods of contraception.

5 Introduction

5.1 Background and Rationale

Parkinson's disease (PD) is the second most common neurodegenerative disease. It affects over 10 million people worldwide and its prevalence is increasing. It can affect all ages, but incidence increases with age. Symptomatic treatments are available and mainly focus on dopamine replacement strategies. These can provide transient improvement in the core motor features of PD, namely tremor, limb rigidity and slowness of movement (bradykinesia). These conventional treatments do not have any impact on the progressive nature of the disease and, with time, patients will develop dopa refractory gait and balance problems (leading to falls and risk of fractures), speech and swallowing problems (leading to difficulty in communication and aspiration pneumonia), cognitive impairment, visual hallucinations and dementia and mounting NHS and social care needs. These later disabilities are difficult to treat effectively and ultimately result in premature death. Parkinson's disease therefore represents a major burden for the public and the NHS and it is predicted to become an increasing burden on NHS resources over the next decades.

Exenatide (Exendin-4) is a licensed and effective treatment for patients with type 2 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 metabolised 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 Greig³. In rat pheochromocytoma cells, known to express the GLP-1 receptor, exenatide induced neurite outgrowth, promoted neuronal differentiation and rescued degenerating neuronal cells³. 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 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 models⁴. Activation of GLP-1 receptors was shown to lead to rapid increases in levels of cyclic AMP and intracellular calcium⁵, with sustained signalling leading to activation of protein kinase A⁶, and/ or activation of PI3 kinase and ERK MAP kinase³.

The neurotrophic properties of exenatide has sparked interest into its potential use as a neurodegenerative disease modifying agent not only in Parkinson's disease (PD)⁷ but also by clinicians and scientists working on Alzheimer's disease⁸. 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 ability⁹. Furthermore administration of exenatide has been shown to lower amyloid beta and amyloid precursor protein levels *in vitro* and *in vivo*¹⁰. This work has rapidly led to clinical trials of the use of exenatide in people with mild cognitive impairment of Alzheimer's disease (<https://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 neurons¹¹. 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 evidence¹², broadly based on a) epidemiological data hinting at lower rates of PD among patients using non-steroidal anti-inflammatory drugs¹³, b) a consistent association between the HLA locus and PD risk from the meta-analyses of Genome wide association studies¹⁴, c) the presence of activated microglia seen in PD patients using PK11195 PET ligand¹⁵ and d) the presence of pro-inflammatory mediators seen in the post mortem tissue of PD patients¹⁶. In an animal model of PD¹⁷, 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 through the GLP-1 receptor, insulin signalling, TNF-alpha induced JNK activation and tau hyperphosphorylation¹⁸. 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, Shiraishi et al. have evaluated the effects of exenatide on macrophages¹⁹. 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 Fan et al. researching its mechanisms of action in type 2 diabetes²⁰. 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.

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^{21,22}. 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 pools²³; LRRK2 impacts on synaptic vesicle motility and recycling²⁴ 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 receptor²⁷. 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.

6. GLP-1 receptor agonists reduce neuroinflammation through an action on microglia.

A modified version of exenatide most recently showed efficacy in 2 alpha synuclein transgenic rodent models. In an investigation regarding mechanism of action in these models, strong evidence indicated that neuroprotection occurred via GLP receptor stimulation on microglia which resulted in reduced conversion of astrocytes into toxic astrocytes²⁸.

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 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 injections²⁹.

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 (SN) 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 vehicle²¹.

3. In the USA, mice pre-treated with exenatide had complete protection against the toxicity of Methyl, Phenyl Tetrahydropyridine (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 MPTP³⁰.

4. In Korea, exenatide attenuated toxicity in the MPTP mouse model, sparing neurons in the SN pars compacta and their striatal dopaminergic projections in association with reduced activation of microglia, matrix metalloproteinase-3 and TNF-alpha¹⁷.

5. In the USA, a pegylated form of exenatide called NLY01 protected against the loss of dopaminergic neurons in the 2 animal models of PD, arguably the most representative of the human form of PD i.e. alpha synuclein preformed fibril mouse model, and the A53T alpha synuclein transgenic mouse model²⁸.

In summary, a range of measures has 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 disability¹⁷.

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 Trust³¹. 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 48 weeks. To minimise the bias associated with an open label design, the patients had video assessments at 12 weekly 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 48 week exposure period and then again after a washout period of a further 12 weeks to allow further diminution of any potential placebo response.

The primary outcome was the change in the score in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 (motor sub-score) 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 12 week 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 48 weeks in the exenatide treated patients, in fact two patients had improvement in the DaTscan uptake.

Three patients from the group randomised to exenatide withdrew/ dropped out from the study, one 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 36 and 40 weeks (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 48 weeks, 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 48 and 60 weeks. This necessitated lowering of LED in five exenatide patients, while eight exenatide patients had unchanged and seven patients increased dopaminergic medication over the period of study. Data from this open label trial has been published³¹.

A formal double blind randomised controlled trial evaluating the effects of exenatide in 60 patients with PD has subsequently been performed³². Patients were randomised into two groups to self-inject a long acting form of exenatide, (Bydureon 2mg) once weekly, or matched placebo for 48 weeks. They had detailed assessments every 12 weeks for the duration of the treatment, then a further assessment at the 60 week time point to explore any lasting effects following washout of the trial medication. Patients randomised to receive exenatide had a mean 3.5 point advantage in their MDS-UPDRS part 3 OFF medication scores (the primary outcome measure) compared to patients randomised to receive placebo at the 60 week timepoint of the trial. This was statistically significant (p=0.03) even following adjustment for possible confounders including baseline MDS-UPDRS part 3 scores, and Levodopa equivalent dose (LED). Patients randomised to receive exenatide lost a mean of 2.6kg in weight. There was no correlation between degree of weight loss and the primary outcome. Other adverse events were similar between groups. Biological specimens collected from trial participants confirmed changes according to treatment with exenatide in IRS1 phosphorylation status, and levels of phosphorylated Akt and its downstream effector mTOR³³.

The 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. The safety of exenatide is monitored intensively by the UK safety regulators (Medicines and Healthcare products Regulatory Agency, MHRA). Commonly occurring adverse reactions 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 trials³⁴. 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 exenatide³⁵. 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 six-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)³⁶. To try to 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 1,269 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 agonists³⁷. 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 type 2 diabetes mellitus) continues^{38,39}, 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 US regulatory agency (Food and Drug Administration, 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”⁴⁰.

In female rats given exenatide for two 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)³⁶. In view of these data, exenatide should not be used in patients at risk of thyroid cancer.

Rationale and risks/benefits: why is the research needed now?

In the two previous trials of exenatide in patients with PD^{31,32}, both Byetta and Bydureon were well tolerated and no serious adverse reactions occurred. Approximately 12 weeks after discontinuation of Bydureon therapy, mean plasma and CSF exenatide concentrations fall below minimal detectable concentrations.

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 an improved side effect profile with respect to

gastrointestinal effects. The current trial objective is to confirm whether the previous positive results can be reproduced in a multicentre trial design, including a larger number of participants evaluated over twice as long a period as previously. An important secondary objective is to explore whether any positive effects seen after 48 weeks exenatide exposure remain static or increase in amplitude by the 96 week time point.

5.1.1 Explanation for choice of comparators

Exenatide placebo powder and solvent for prolonged release, suspension for injection, prefilled pen will be used as the comparator. Placebo is appropriate in this trial because there is no known licensed effective disease modifying treatment for PD.

5.2 Objectives

The primary objective is to compare the effectiveness of exenatide once weekly versus placebo on the MDS-UPDRS part 3 motor sub-score in the “practically defined OFF medication state” in patients with PD. (Change in the MDS-UPDRS part 3 score reflects accumulation of motor deficit and therefore is a measure of PD motor progression.) The hypothesis is that exenatide will be associated with reduced MDS-UPDRS part 3 scores at the 96 week time-point.

Secondary objectives are to

Compare differences at 96 weeks between the exenatide and placebo trial arms in:

- MDS-UPDRS part 1, 2, 3 and 4 ON medication scores
- Timed Walk assessment ON and OFF medication
- Montreal Cognitive Assessment (MoCA)
- Safety and tolerability of exenatide as indicated by changes in vital signs, weight, clinical laboratory measures and adverse events
- Patient Health Questionnaire (PHQ-9)
- Unified Dyskinesia Rating Scale (UDysRS)
- Parkinson’s Disease 39 item Quality of Life questionnaire (PDQ-39)
- Levodopa equivalent doses
- 3 day Hauser diary of PD state (Time-On, Off, Non troublesome Dyskinesia, Troublesome dyskinesia, Asleep)

Compare differences in total values over 96 weeks between the exenatide and placebo trial arms in:

- Health and social care resource use on the modified Client Service Receipt Inventory (CSRI)
- Health and social care costs
- Paid and unpaid carer costs
- Quality adjusted life years (QALYs) calculated using the EQ-5D-5L tariff adjusting for baseline.

Compare differences at 48 weeks and between 48 to 96 weeks between the exenatide and placebo trial arms in:

- MDS-UPDRS part 3 Motor subsection OFF medication score
- MDS-UPDRS part 1, 2, 3 and 4 ON medication scores

5.3 Trial Design

A simple parallel group design as a multicentre phase 3 trial. This will include a 96-week exposure period. Detailed evaluations of all participants will take place at screening, baseline, 24, 48, 72 and 96 weeks.

Participants will be randomly allocated into 2 groups to receive either;

- Exenatide extended release 2mg subcutaneous injection (*Bydureon*) once weekly for 96 weeks n=100, or
- Exenatide extended release placebo subcutaneous injection once weekly for 96 weeks n=100.

Separate randomisation lists will be generated for participants 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 explore whether any biological effect(s) of exenatide, relevant to PD, are purely symptomatic effects as opposed to “disease modifying” effects.

Parallel group designs with a washout period have been used previously in the evaluation of potential neuroprotective agents^{41,42} and this was chosen as the design for the previous phase 2 trial. 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 exercise⁴³).

An alternative approach is to adopt a “Long term simple” design, with longer term follow up to look for a cumulative advantage emerging with prolonged treatment exposure, given the natural history of PD being that of progressive accumulation of motor and non-motor disability. The design of this trial builds on the previous successful clinical trials of exenatide which have introduced a novel, cost effective way of evaluating the potential for disease modifying drugs in PD by recruiting patients already in receipt of conventional dopaminergic treatment, rather than restricting recruitment to incident cases yet to receive dopaminergic treatment. Using this approach, we have successfully demonstrated the potential for rapid recruitment, and improved retention of participants enabling more complete follow up, and a statistically significant advantage in motor scores in people randomised to exenatide over a 48 week period of treatment exposure. We have considered that an exposure period of 96 weeks would allow exploration of long term effects of exenatide exposure, while being the maximum period that participants would tolerate being allocated placebo. Furthermore, this will provide the opportunity to evaluate whether the 48 week data previously published can be replicated and whether effects at 96 weeks are similar to or greater than those seen at 48 weeks.

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the CCTU.

6.1.1 Study Setting

All patient assessments will be performed at hospitals in the UK, once sites have confirmed capacity and capability and a site initiation visit has been performed.

6.1.2 Site/Investigator Eligibility Criteria

It is anticipated that recruitment will be completed from six UK sites (National Hospital for Neurology and Neurosurgery, King's College Hospital, Oxford University Hospital, University Hospitals Plymouth and Manchester and Edinburgh). Recruitment rates will be carefully monitored throughout the trial to inform on the total number of sites required to ensure final recruitment milestones will be reached. If needed, further sites will be set up.

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of the Exenatide-PD3 protocol and investigator brochure (IB).

To participate in the Exenatide-PD3 trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the Exenatide-PD3 Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are available to recruit participants, enter data and collect samples
- The site should be able to store, prepare and dispense the trial medication appropriately

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-PD3 document set so that an assessment of capacity and capability can be made.

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing 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) as agreed in the site agreement. This includes confirmation of appropriate qualifications, by provision of a CV, 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 who 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 (i.e. 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 the CCTU.

6.2 Site approval and activation

On receipt of confirmation of capacity and capability, a signed site agreement, approved delegation of responsibilities log and staff contact details, the Trial Manager or delegate will notify the Principal Investigator (PI) in writing of the plans for site activation. Sites will not be permitted to recruit any participants until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor, by the MHRA and which was given favourable opinion by the Research Ethics Committee (REC) and the Health Research Authority (HRA). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at the CCTU.

A list of activated sites may be obtained from the Trial Manager.

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

1. Diagnosis of Parkinson's disease. PD is a clinical diagnosis and is based on the opinion of the PI or delegate 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.
2. 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.
3. Between 25 and 80 years of age.
4. On dopaminergic treatment for at least 4 weeks before enrolment. All participants must have had previous or ongoing exposure to dopaminergic treatment either as L-dopa or a dopamine agonist. If L-dopa has been stopped due to side effects or lack of response, the local PI should

further confirm that the participant has clinical symptoms and signs and/or radiological investigations consistent with a diagnosis of Parkinson's disease.

5. Ability to self-administer, or to arrange carer administration of trial medication.
6. Documented informed consent to participate.

6.3.1.3 Participant Exclusion Criteria

1. Diagnosis or suspicion of other cause for Parkinsonism. Patients with clinical features indicating a diagnosis of Progressive Supranuclear Palsy, Multiple Systems Atrophy, Drug induced Parkinsonism, Dystonic tremor or Essential tremor will not be recruited.
2. Patients unable to attend the clinic visits in the practically defined OFF medication state.
3. 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).
4. Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol.
5. Significant cognitive impairment defined by a score <21 on the Montreal Cognitive Assessment.
6. Concurrent severe depression defined by a score ≥ 16 on the Patient Health Questionnaire (PHQ-9)
7. 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.
8. Previous participation in one of the following Parkinson's disease trials (Biogen SPARK trial, Prothena Pasadena trial, Sanofi Genzyme MOVES-PD trial, UDCA-PD UP Study or any other trial still considered to involve a potentially PD modifying agent). In the event of any uncertainty, the Chief Investigator will discuss the relevance of exposure to any other specific trials/experimental agents with the local Principal Investigator before recruitment eligibility is confirmed.
9. Participation in another clinical trial of a device, drug or surgical treatment within the last 30 days.
10. Previous exposure to exenatide.
11. Impaired renal function with creatinine clearance <50ml/min.
12. History of pancreatitis. Screening serum amylase value must fall within laboratory normal range +/- 50%.
13. Type 1 or Type 2 Diabetes mellitus.
14. Severe gastrointestinal disease (e.g. gastroparesis)
15. 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.
16. History or family history of medullary thyroid cancer (MTC). Undiagnosed neck lump, hoarse voice or difficulty swallowing (not attributable to PD diagnosis).
17. Multiple endocrine neoplasia 2 (MEN2) syndrome.
18. Hypersensitivity to any of exenatide's excipients.
19. Females that are pregnant or breast feeding. There are no safety data regarding exenatide use in pregnancy.
20. WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire trial period and up to 3 months after the last dose of trial medication. Female participants who are able to become pregnant (defined as women of child bearing potential) 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).

21. Participants who lack the capacity to give informed consent.
22. Any medical or psychiatric condition or previous conventional/experimental treatment which in the investigator's opinion compromises the potential participant's ability to participate.

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

All assessments will be performed by suitably qualified members of the clinical trial team trained in the use of all relevant assessments used as part of the Exenatide-PD3 trial. PI delegated roles and responsibilities for this trial will be documented in the Exenatide-PD3 site delegation of responsibilities log. CVs and GCP certificates of all individuals working on the trial will be collected by the CCTU Exenatide-PD3 trial team to document their qualifications and relevant experience. Protocol specific training will be provided to participating sites prior to site activation. New site staff who start working on the trial after site activation will be provided with protocol specific training prior to performing trial related procedures.

A certificate to confirm training in the use of the MDS-UPDRS will be obtained for all raters.

The clinical trial team will also be trained on the administration of exenatide injection pens using an online teaching video (www.bydureon.com/pen/taking-bydureon/your-first-bydureon-injection) and accompanying product literature and the latest version of the SPC. This knowledge will form the basis of them teaching enrolled participants how to self-administer exenatide, together with the online teaching video.

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 participated in one of the following Parkinson's disease trials (Biogen SPARK trial, Prothena Pasadena trial, Sanofi Genzyme MOVES-PD trial, UDCA-PD UP Study or any other trials of agents **that continue to be considered** to have potential PD disease modifying properties) will also not be permitted to enrol in this trial.

Patients who have previously been involved in other clinical trials of a device, drug or surgical treatment (excluding intra-cerebral surgery for PD) will be permitted to enrol provided that is after 30 days of their end of participation in the trial.

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 routine 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 evaluate patient eligibility:

- MoCA
- PHQ-9
- Blood tests: full blood count (haemoglobin, haematocrit, red blood cell count, white blood cell count, platelets, neutrophils, eosinophils, basophils, lymphocytes and monocytes) urea & electrolytes, liver function tests, HbA1C,c-peptide, coagulation, serum amylase, thyroid function tests, kidney function tests, blood glucose, insulin and lipid profile); Guidance for sample collection and transport can be found in the Laboratory Manual.
- Pregnancy test for women of child bearing potential.
- Lipids & diabetic bloods can be repeated in a fasted state between screening and baseline visits, if required to confirm eligibility.

6.4 Interventions

All investigational medical products (IMPs) will be supplied by AstraZeneca as unlabelled prefilled pens in bulk and in accordance with Good Manufacturing Practice (GMP). Labelling, packaging and release of packed IMPs will be conducted by the sponsor or their designee following GMP. The labels will be prepared in accordance with GMP Annex 13 requirements for labelling and local regulatory guidelines. The IMPs will be QP released in the United Kingdom ahead of trial use.

Site trial staff will be trained on the use of exenatide using the online teaching video, accompanying product literature and the IB. Patients will be taught how to perform the subcutaneous injections by the clinical trial team using the online video, demonstration packs and written literature. They will be told about common adverse reactions 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. 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 patient or confirms their willingness to meet with the PD participant on a weekly basis to administer the injections for the 96 week period of the trial.

6.4.1 Active drug

Exenatide 2.0 mg (powder and solvent for prolonged release, suspension for injection, prefilled pen).

Each dose of exenatide extended release is supplied as a single use injection pen for subcutaneous administration by the patient on a weekly basis.

Refrigerated storage (2-8°C).

6.4.2 Placebo

Placebo exenatide (powder and solvent for prolonged release, suspension for injection, prefilled pen). Each dose of placebo-exenatide extended release is supplied as an identical injection pen for subcutaneous administration by the patient on a weekly basis.

Refrigerated storage (2-8°C).

6.4.3 Treatment Schedule

Patients who meet eligibility criteria at the screening visit will be randomly assigned to receive 96 weeks of double-blind treatment with either exenatide or placebo (2mg once weekly) in a 1:1 ratio.

The first dose will be administered in clinic following injection teaching and subsequent injections given at home every 7 days. Injections will be self-administered by the participants, or administered by their carer, into the participants' abdomen, arm, thigh or buttocks.

To maintain trial blinding, all trial medications will be provided in identically appearing injection pens and packaging.

Patients will receive a telephone call 10 weeks post their last trial medication administration to record any adverse events that may have occurred in this period.

6.4.4 Dispensing

The trial medication will be supplied by Astra Zeneca and sent to the trial medication distributor, who will be responsible for accepting deliveries of the trial medication from AstraZeneca and approving the accompanying paperwork, as well as the refrigerated storage, labelling, QP release, and distribution of the trial medication to the participating site pharmacies as required.

After patients are randomised to receive trial medication, the PI will complete an Exenatide-PD3 prescription and order form (on a 12 weekly basis to coincide with trial follow up visits) which will be screened by the site pharmacist before the trial medication is dispensed.

6.4.5 Dose Modifications, Interruptions and Discontinuations

6.4.5.1 Dose Modifications

No dose modifications are allowed in this trial.

6.4.5.2 Dose Interruptions

Elevation in serum amylase: Participants found to have an elevation in serum amylase (greater than >50% above both baseline level AND above the upper limit of normal) will have their trial medication temporarily stopped until the amylase level falls below 50% above baseline. If a participant has two dose interruptions due to elevations in serum amylase, the TMG will decide (based on their clinical judgement) if the patient needs to be withdrawn from the trial.

Excessive/undesirable weight loss: Participants experiencing excessive/undesirable weight loss (>10% of body mass index during a 12 week interval; who develop a BMI <18.5; or who lose weight to such an extent that there is clinical concern), will have trial medication temporarily interrupted until weight recovers to within 10% of body mass index measured at preceding visit or until weight has risen to a BMI of >18.5 and/or clinical concern has ceased.

6.4.5.3 Dose Discontinuations

Pancreatitis: Participants 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.

Pancreatic or thyroid malignancy: Participants developing clinical suspicion of pancreatic or thyroid malignancy will receive treatment according to NHS standard of care and the trial medication will be permanently stopped.

Decline in renal function: Participants found to have a decline in renal function during the trial (with creatinine clearance <50ml/min) will receive treatment according to NHS standard of care. The PI will use their clinical judgement to decide if the patient needs to temporarily or permanently stop the trial medication.

Deep Brain Stimulation (DBS): The local PI will discuss with the TMG and/or TSC whether any participants who undergo DBS during trial participation can be permitted to continue the IMP for the planned duration of the trial.

6.4.6 Accountability

A full accountability trail will be maintained from receipt of trial medication in pharmacy, up to the point of dispensing and destruction of undispensed trial medication. The Trial Pharmacist will remain blind to trial arm and trial medication /placebo kit allocation. As part of a contractual arrangement Astra Zeneca will provide the trial with a sufficient supply to account for lost or damaged kits/ injection pens.

The Trial Pharmacist within each hospital pharmacy department will be delegated oversight of trial medication supplies. No additional reconstitution or other preparation will be required prior to dispensing. All trial medication must be stored in accordance with the manufacturer's instructions and it must be kept in a locked area with restricted access to designated trial personnel. The local Trial Pharmacist will keep accurate records of the quantities of trial medication received, dispensed to each participant and destroyed as unused or expired. CCTU trial personnel will periodically check the supplies of the trial medication held by the local pharmacy departments to ensure accountability of all trial medication used.

All IMP that is dispensed and used will be disposed of at home by the patient or carer, into an incineration bin that will be provided. The participants can return the incineration bins to their GP or to the site trial team for destruction.

Unused IMP will be brought to the final trial visit by the patient and will be checked by the clinical trial team. After accountability and compliance assessments have been completed, the unused IMP will be passed to the site pharmacy team for destruction. Documentation confirming destruction will be provided to the CCTU.

6.4.7 Compliance and Adherence

The importance of compliance with the trial protocol will be explained to the patient during the informed consent process and confirmed again 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. Good relationships will be established with all trial patients to maximise honest reporting of compliance.

6.4.8 Concomitant Care

6.4.8.1 Permitted Concomitant Medications

Any formulations of drugs used for the routine treatment of PD will be permitted including the following:

- Sinemet- Levodopa/Carbidopa
- Madopar- Levodopa/ Benserazide
- Stalevo/Sastravi/Stanek- Levodopa/Carbidopa/Entacapone
- Entacapone
- Tolcapone
- Opicapone
- Ropinirole
- Pramipexole
- Rotigotine
- Apomorphine
- Rasagiline
- Selegiline
- Safinamide
- Domperidone

Participants 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.

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 LED as described in Appendix 1. 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.

6.4.8.2 Concomitant Medications to be used with care

Patients receiving warfarin may be at risk of increased international normalised ratio (INR) and associated bleeding; therefore INR should be monitored closely during initiation of exenatide therapy in patients on warfarin or coumarol derivatives.

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

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

6.4.9 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 overdose will be implemented. Any patient taking a deliberate overdose of trial medication will be interviewed and assessed to consider whether they should exit from the trial and referred for appropriate psychiatric evaluation.

6.4.10 Protocol Treatment Discontinuation

In consenting to the trial, patients are consenting to trial treatments, trial follow-up and data collection. However, an individual patient 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 patients' condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the patient

As participation in the trial is entirely voluntary, the patient 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 patient's rights.

Patients 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 6.4.5.1 to 6.4.5.3 for more information.

6.5 Outcomes

The following assessments will be completed every 24 weeks for a total of 96 weeks. Participants will also attend on a 12 weekly basis to collect supplies of IMP. In addition, the patient will report or be prompted to telephone to report all adverse events.

6.5.1 Primary Outcomes

Comparison of MDS-UPDRS part 3 motor sub-score in the practically defined OFF medication state at 96 weeks between participants according to treatment allocation. The scores for these assessments will be collected and recorded by trained clinical trial personnel as per the delegation log (if possible, the same person will rate these assessments at each site to minimise inter-rater variability). With consent, these assessments will be video recorded to enable repeated independent scoring to be performed if there are concerns raised about data quality from a specific site/rater. Patient weight, concomitant medication and adverse event data will be collected separately by a different individual. This is to minimise the risk of the primary outcome rater being influenced by these data. Together with prior scores, these data will be filed separately in an envelope at the back of each participant folder and primary outcome raters will be encouraged not to review this. Responsible individuals will be listed in the delegation log.

The MDS-UPDRS part 3 motor OFF medication score is a widely accepted measure of the motor disability of PD. The scale is 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 96 weeks between participants according to treatment allocation.

The MDS-UPDRS part 3 motor score in the practically defined OFF medication state at 48 weeks. Whereas the analysis of the 96 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 96 weeks will be important secondary outcomes.

MDS-UPDRS 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.

MoCA. This scale is a validated global measure of cognitive ability. This will be assessed in the ON medication state.

Safety and tolerability of exenatide as indicated by changes in vital signs, weight, clinical laboratory measures and adverse events (recorded and monitored throughout). Each patient will have pulse, blood pressure and weight documented at screening and at each follow up visit. Their height will be recorded at screening to enable calculation of body mass index. Exenatide is known to cause weight loss. Each patient will be questioned about adverse events at each visit using open ended questions and responses documented on their Exenatide-PD3 Adverse Event Log. This will be done by an individual separate from the individual performing the primary outcome measurement to avoid inadvertent potential treatment allocation unblinding of staff performing assessments at each site. In the absence of any such individual being available, the patient will be asked to telephone a clinical staff member centrally to report their weight and adverse events. 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.

Timed Tests:

Participants will be asked to perform a Sit-stand-walk timed test in both the OFF medication and ON medication state. 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.

UDysRS: This is considered to be the most useful and objective way of quantifying dyskinesia severity. This will be assessed in the ON medication state.

PHQ-9: This scale allows for self-quantification of Depression severity. This will be assessed in the ON medication state.

NMSS: 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 state.

PDQ-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.



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 1).

EQ-5D-5L: 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.



CSRI: Health and social care resource use. Self-completed health care, social care and paid/unpaid carer resource use questionnaire asking about primary and secondary care resource use relevant to Parkinson's and impact on carers in the past 6 months

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.



6.6 Participant Timeline

	Screening	Baseline and Randomisation	4 week telephone call	12 week	24 week	36 week	48 week	60 week	72 week ^k	84 week	96 week ^k	106 week Follow-up telephone call ^l
Flexibility of schedule: weeks (w) and days (d)	-28d To -1d	0d	+/- 7 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	- 14 to +7 days	+/- 7 days
Visit number	1	2		3	4	5	6	7	8	9	10	
Informed consent	X											
Review of PD medication history, past medical history, family history, previous imaging, previous genetic tests and clinical examination	X											
Pregnancy test	X											
Hoehn and Yahr staging	X											
Hauser Diary (completed by participant in the week prior to visits 2, 6 and 10) ^m		X					X				X	
Review of concomitant medication	X	X	X	X	X	X	X	X	X	X	X	
ECG	X											
MoCA ^h	X						X				X	
PHQ-9 ^h	X				X		X		X		X	



Exenatide-PD3

	Screening	Baseline and Randomisation	4 week telephone call	12 week	24 week	36 week	48 week	60 week	72 week ^k	84 week	96 week ^k	106 week Follow-up telephone call ^l
Flexibility of schedule: weeks (w) and days (d)	-28d To -1d	0d	+/- 7 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	- 14 to +7 days	+/- 7 days
Visit number	1	2		3	4	5	6	7	8	9	10	
Participant required to arrive fasted		X			X		X		X		X	
Blood tests (FBC, coagulation)	X						X				X	
Non -fasted HbA1c, glucose, insulin, c-peptide, lipid profile ^a	X											
Fasted (HbA1c glucose, insulin, c-peptide, lipid profile) ^a		X					X				X	
Blood tests (U & E, thyroid function tests, kidney & liver function tests, serum amylase)	X			X	X	X	X	X	X	X	X	
Blood sample for gene testing if not previously performed ^a	X											
Height ^b , weight ^c , pulse & blood pressure	X	X		X	X	X	X	X	X	X	X	
Randomisation		X										
Phone call to participant		X			X		X		X		X	

Exenatide-PD3

	Screening	Baseline and Randomisation	4 week telephone call	12 week	24 week	36 week	48 week	60 week	72 week ^k	84 week	96 week ^k	106 week Follow-up telephone call ^l
Flexibility of schedule: weeks (w) and days (d)	-28d To -1d	0d	+/- 7 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	- 14 to +7 days	+/- 7 days
Visit number	1	2		3	4	5	6	7	8	9	10	
immediately prior to visit ^c												
Review of adverse events ^c			X	X	X	X	X	X	X	X	X	X
Review of health resource utilisation (CSRI) ^f		X			X		X		X		X	
MDS-UPDRS part 3 OFF medication ^{d,e}		X			X		X		X		X	
Timed Walk OFF medication ^d		X			X		X		X		X	
MDS-UPDRS parts 1, 2 and 4, PDQ-39, EQ-5D-5L ^f		X			X		X		X		X	
MDS-UPDRS part 3 ON medication ^g		X			X		X		X		X	
Timed Walk ON medication ^g		X			X		X		X		X	
NMS, UDysRS ^h		X			X		X		X		X	
LED		X			X		X		X		X	
Electromagnetic Sensor Readings (selected sites) ^e		X			X		X		X		X	
10ml Plasma samples for storage ⁿ		X			X		X		X		X	
Lumbar Puncture and CSF sampling		X									X	

Exenatide-PD3

	Screening	Baseline and Randomisation	4 week telephone call	12 week	24 week	36 week	48 week	60 week	72 week ^k	84 week	96 week ^k	106 week Follow-up telephone call ^l
Flexibility of schedule: weeks (w) and days (d)	-28d To -1d	0d	+/- 7 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	+/- 14 days	- 14 to +7 days	+/- 7 days
Visit number	1	2		3	4	5	6	7	8	9	10	
(selected centres-optional sub-study) ⁱ												
Dispense 12 week supply of Exenatide / Placebo ^j		X		X	X	X	X	X	X	X		
Instructions/ Education for patient / care-giver regarding injection procedures		X										
DaTSCAN imaging (OPTIONAL). Scans performed at UCLH ^o		X ^p									X ^p	
Axivity Monitor/ Smart phone taken home (optional remote monitoring sub study). Ten minute smart phone test in clinic.		X			X		X		X		X	
Patient IMP Administration Diary (completed by participant after each injection taken) ^r					X	X	X	X	X	X		

- ^a Blood sampling for the Genetics sub-study testing will be taken at the Screening Visit (but can be taken at a later visit if necessary) – further details in Appendix 2.
- ^b Height is ONLY recorded at the Screening Visit.
- ^c After the Screening Visit, the named site clinical staff member calls the participant to remind the participant of the need to stop taking their regular PD medication prior to their next trial visit and to attend in a fasted state (prior to 2,4,6,8,10).
- ^d The MDS-UPDRS part 3 and Timed Walk assessments will be initially performed in the OFF state.
- ^e At selected centres participants will also wear electromagnetic sensors during the assessment of the MDS-UPDRS part 3 motor scores. The primary outcome measure for the main Exenatide-PD3 trial (MDS-UPDRS Part III, OFF) should ideally be completed before the additional EMS measurements are collected in the OFF state. The assessments required for the Exenatide-PD3 trial in the ON state should ideally be collected before the additional EMS measurements are collected in the ON state.
- ^f While waiting for medications to work, participants will self-complete the MDS-UPDRS parts 1, 2 and 4, PD-Q39, EQ-5D-5L and CSRI.
- ^g The MDS-UPDRS part 3 and Timed Walk assessments will be repeated 1 hour after the participant has taken their routine medications - the ON medication state.
- ^h After completion of the MDS-UPDRS and Timed Walk assessments in the ON medication, each participant will be assessed using the MoCA, NMS scale, UDysRS and PHQ-9. This point refers to post randomisation assessments.
- ⁱ At selected centres participants in the Cerebrospinal Fluid sub-study will have a CSF sample taken via lumbar puncture – further details in Appendix 3.
- ^j An additional kit (4 pens) will be dispensed at one of these visits to ensure patient has additional supply in the event of breakages.
- ^k The 72 and 96 week visits may be home visits if the participant is unable to travel to the hospital in the OFF medication state (and if the trial staff at the hospital are able to accommodate home visits).
- ^l 10 weeks post last trial medication administration, the named site clinical staff member will call the participant to collect details of any adverse events that have occurred after the participant stops taking the trial medication. If the participant withdraws from the trial early and stops taking the trial medication, this call does not need to take place if the participant subsequently attends the clinic and adverse events are collected at that clinic visit.
- ^m If a participant forgets to bring a completed copy of the 3 Day Hauser Diary to visits 2, 6 or 10 they should be advised to complete this in the 5 days following the visit and to send the diary back to the research team at their local site.

ⁿ At each of the visits indicated, a 10ml EDTA tube should be centrifuged in order to separate plasma from whole blood. The plasma should then be aliquoted into cryotubes and labelled as per the Exenatide-PD3 Sample Processing Document. Cryotubes and storage boxes/ logs will be provided by the sponsor. Planned analysis detailed in section 7.5.1.

^o Participants will be invited to enrol in a a DaTSCANimaging sub-study performed at the UCLH site – further details in Appendix 5.

^p The baseline DaTSCAN imaging must be acquired prior to the patient's first injection of exenatide/ placebo. This may be on the same day as the baseline visit or up to a maximum of 14 days prior to the baseline visit. Screening bloods confirming eligibility must be obtained prior to the patient undergoing imaging. The 96 week DaTSCAN imaging must be performed -14 to +7 days from the 96 week visit.

^q These bloods can be repeated, in a fasted state between screening and baseline visits if required, to confirm eligibility.

^r The Patient IMP Administration Diary will be completed by participants after each injection taken from receipt of the diary up to visit number 10 for all patients remaining on treatment at the time of diary implementation. The diary records the date and time each injection was taken, batch number, expiry date, kit code and confirmation the used injection pen was discarded.

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. CCTU should be informed of the withdrawal in writing using the Exenatide-PD3 Withdrawal Form. Data already collected will be kept and included in analyses according to the intention-to-treat (ITT) principle for all participants who stop follow up early. Participants allocated to a treatment group, but who withdraw prior to receiving any trial medication (verified through the return of unused injection pens), will not be considered to have been randomised as described in ICH E9⁴⁵.

All participants dropping out from the trial will continue to receive treatment for their PD in accordance with NHS Standard of care.

6.6.2 Participant Transfers

If a patient 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 patient's CRFs should be provided to the new centre. Responsibility for the patient remains with the original consenting centre until the new consent process is complete. The original consenting centre will be responsible for resolving any data queries relating to assessments performed up to the point of transfer to the new centre.

6.6.3 Loss to Follow-up

Every effort will be made by the sites 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".

Efforts will be made by the sites to minimise loss to follow-up, such as tracing patients via their NHS number using NHS Digital records which supports the IT infrastructure for health and social care in England once approvals for access have been granted. Consent for this will be sought prior to the patient entering the trial.

6.6.4 Trial Closure

The end of trial for individual patients will be the date of their last visit/follow-up telephone call. Trial closure is defined as the date when all data has been received, cleaned and all priority queries resolved at all sites.

The MHRA and REC will be notified within 90 days of trial completion. A summary report of the research will be sent to the REC and MHRA within 12 months of the end of the trial.

A site may be deemed "closed" once all trial-related activities at that site are reconciled and/or complete, all outstanding data queries have been resolved and a letter confirming that close down is complete has been sent to the site PI from CCTU.

In terms of the funder, the end of the trial is the time of the provision of the final report.

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) trial design. The calculations have been based on a common standard deviation of 13.5, 90% power and an overall type 1 error rate of 5%. In addition, a correlation of 0.70 is assumed between the baseline and follow up MDS-UPDRS measurements. These estimates are reasonable based on data from the previous Exenatide-PD trial.

A sample size of 200 participants divided equally between the 2 groups will have 90% power to detect a difference of 5.0 MDS-UPDRS part 3 points in the OFF medication state between the 2 groups adjusting for baseline MDS-UPDRS part 3 OFF scores, assuming 20% attrition (withdrawal/loss to follow up). This effect size is a reasonable expectation based on the previously collected pilot data and would represent a clear demonstration of the efficacy of exenatide on the motor severity of PD.

It is also anticipated that the difference in scores in the ON medication state will be greater at 96 weeks than at the 48 weeks' time points. The expected rate of change in PD severity in the first 5 years after PD diagnosis in the ON medication state is 1 MDS-UPDRS part 3 point per year. A predicted advantage of 2 points in ON scores over 96 weeks would thus equate to an advantage in the rate of disease progression above and beyond that achievable with conventional dopaminergic medication and would be a further clear signal that continued use of exenatide is consistent with not only long term disease modifying effects, but even an advantage in day to day functional impairment and overall improvement in quality of life in the short term. Given its low costs, this treatment would represent a highly cost effective use of NHS funds for patients with PD.

This sample size is realistically achievable based on previous recruitment of 60³² participants in 8 months from a single centre. For the current proposal, the five sites chosen to start recruitment all have very large patient populations and anticipate to recruit at a similar rate as achieved by NHNN previously. Recruitment will take full advantage of the Clinical Research Networks (CRNs) networks and will exploit the experience of Dr Carroll who is NIHR CRN Neurodegeneration Lead and has set up a network of recruiting centres for an ongoing trial in PD (PD STAT) which will have completed recruitment well before the current proposal commences recruitment. Ten further PD centres have all confirmed willingness to act as recruiting centres using the CRN support infrastructure. Recruitment will be further facilitated by broader inclusion criteria compared with the last trial as well as considerable publicity the surrounded the publication of the last trial. Completeness of follow up will be ensured by the provision of funding to cover the follow up costs of participants at each centre.

The trial will incorporate an internal pilot (6 months) during the recruitment phase to demonstrate our ability to deliver the trial (see further details in section 6.8.1.1).

6.8 Recruitment and Retention

6.8.1 Recruitment

The trial will recruit for an overall period of 21 months, including the 6 month pilot phase, which is discussed in section 6.8.1.1. The aim will be to recruit from sites across the UK. Site selection and number of sites that need to be set up will be informed by the pilot phase results.

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 across the UK 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 at their nearest participating trial site.

The REC approved “lay summary of the trial” will be provided to the Cure Parkinson’s Trust, Parkinson’s UK and Michael J. Fox Foundation 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 200 participants will be completed within 21 months of commencement of recruitment to the trial.

6.8.1.1. Internal Pilot phase: progression criteria

A six internal month pilot phase during recruitment will demonstrate the deliverability of the trial based on anticipated recruitment. Sites will be set up initially at six major PD centres (National Hospital for Neurology and Neurosurgery, King’s College Hospital, John Radcliffe Hospital, Oxford, University Hospitals of Plymouth and Manchester, Western General Hospital, Edinburgh) and recruitment rates will be carefully monitored to inform on the total number of sites required to ensure final recruitment milestones will be reached. Further sites will then be set up if needed.

With anticipated recruitment from six major centres of 1-2 patients/centre/month on average, we would expect >48 patients will have been recruited from the six initial sites in the first six months.

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 patients 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 participants wishing to continue trial participation. Appropriate medical advice and treatment will be made available to any individuals experiencing adverse events from trial participation. Participants 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

An independent online randomisation service provider (Sealed Envelope) will be used to minimise allocation bias within the trial. Sealed Envelope will provide a unique trial participant identification

number (PIN) for each recruited participant who will be randomised 1:1 to receive either exenatide or placebo.

Randomisation will use a minimisation algorithm incorporating a random element, balancing by research site, PD severity defined by Hoehn and Yahr stage and participation in sub-studies:

Balancing factor 1 = Research Site

Balancing factor 2 = Hoehn and Yahr Stage;

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

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

Balancing factor 3 = Participation in Remote Monitoring Sub Study (Yes/No)

Balancing factor 4 = Participation in Imaging Sub Study (Yes/No)

To ensure maximum balance is achieved across the balancing factors, minimisation will be carried out on these factors separately.

At the baseline visit, the clinical investigator will enter the patient’s initials, gender, age, date of consent, criteria fulfilment, PD severity, research site and sub study enrolment into the Sealed Envelope secure database which will then allocate the appropriate PIN (Exnnn) to the patient. Recruitment will continue until a total of 200 participants have been randomised. All participants will be randomly assigned to treatment via the Sealed Envelope randomisation service.

The Trial Statistician at CCTU will generate a sequence of unique 5 digit identifiers for every active/placebo drug kit consisting of 4 single use pens. The drug kit identification codes will be provided to Sealed Envelope and the QP at RFHPMU who will ensure that trial medication and placebo kits are labelled appropriately, and that the trial team and participants remain blind to treatment allocation. A copy of the sequence will be held securely at CCTU.

At baseline 4 kit codes will be given, detailing the kits that should be dispensed. At each follow up visit, the clinical investigator will login and select the patient’s PIN (Exnnn) (previously generated by the Sealed Envelope randomisation service) on the Sealed Envelope website and select the option to assign kits for follow-up visits. Sealed Envelope will then provide the drug kit identification codes to be dispensed (3 kits at Visits 3-9). The trial staff at CCTU along with the site pharmacies will ensure that appropriate amounts of the labelled active/placebo drug kits will be delivered to site pharmacies to allow adequate supplies (of the relevant numbered kits) for pharmacy dispensing.

6.9.1.2 Allocation concealment mechanism

Each trial medication kit will contain a 4 week supply of trial medication (4 pens) and will be identified by the drug kit identification number only. Three trial medication kits, with 3 different codes (sufficient for 12 weeks treatment) will be dispensed at each follow up visit. Due to the possibility of injection pen breakages, at the baseline and randomisation visit (visit 2) an additional kit will be dispensed to

ensure participants have sufficient supply of IMP (4 kits in total given at this visit). This additional kit will be replaced at subsequent trial 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 patient's PIN and date of birth.

6.9.1.3 Allocation Implementation

After the patient has provided written informed consent and their eligibility for the trial has been confirmed, randomisation will be performed by the PI, or delegated member of the clinical investigating team, at local sites using the Sealed Envelope randomisation service stated above. Eligibility and consent will be verified before each patient is randomised. The responsibility for enrolling patients and prescribing trial medication to them lies with the PI at each site. Eligibility decisions will be made in line with the approved protocol. Other physicians employed at the same clinical site may enrol and prescribe trial medication 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 PI.

Trial staff at sites will be given a separate delegation log to request user accounts for access to the Sealed Envelope system (randomise only, randomise and unblind etc.). Individuals at participating sites will be provided with a secure login to the sealedenvelope.com website, according to this delegation of responsibilities log. The users will be required to log into the website and answer eligibility questions before entering balancing data and being permitted to randomise a patient. The randomisation result will be shown directly online as a unique kit identification code, with an email confirmation sent to the user and also to the CCTU trial team.

The investigator will provide details of the allocated unique kit identification number assigned to the participant on prescription and order forms which are then screened by the local site pharmacist before the trial medication is dispensed. A full accountability trail will be maintained from receipt of trial medication by the local site pharmacies, prescribing of the trial medication by the local principal investigators, dispensing of the trial medication by the local sites pharmacies to the point of destruction of undispensed/returned trial medication.

Randomisation will be considered complete when the participant receives their first dose of trial medication. Participants who withdraw before receiving their first dose will be considered withdrawn prior to randomisation on the verification that their pens are untampered.

At subsequent clinic follow up visits, the PI or delegate at each site will enter the patient's PIN into the Sealed Envelope randomisation service which will then provide the kit identification codes for further trial medication to be dispensed.

6.9.2 Blinding

Sealed Envelope will provide the patient PINs at randomisation. The trial medication 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 medication packs occurs appropriately and so as to ensure complete blinding of the IMP to all investigators, participants and the pharmacy staff on the trial. A secure website enables unblinding of a patient in the event of need, and the trial medication kit labelling strategy ensures that the unblinding of one patient will not unblind the entire trial arm.

Detailed information regarding allocation implementation and blinding is provided in the Exenatide-PD3 IMP Management Plan and Exenatide-PD3 Randomisation and Unblinding Plan.

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 A Randomisation and Unblinding Plan will be provided to sites. 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 Principal Investigator (PI) cannot overrule any decision made by a referring clinician. 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.

6.9.4 Unblinding for the submission of SUSAR reports

All SAEs that are related to the trial medication (i.e. SARs) and are suspected to be unexpected i.e. SUSARs, need to be submitted to the regulatory agencies within pre-specified timelines. When SAEs reports are received at the CCTU, if the event is recorded as being a SUSAR then the following procedure will be used to unblind the SUSAR to determine if the participant was receiving active trial medication, and therefore, that the SUSAR needs onward reporting to the regulatory agencies:

- A member of the CCTU trial SUSAR Reporting Team will unblind the patient's trial treatment allocation using the Sealed Envelope randomisation service.
- If the participant is revealed to the CCTU SUSAR Reporting team to be receiving active treatment, the CCTU trial SUSAR Reporting Team member will report the SUSAR on the e-SUSAR database available through the MHRA website or through Eudravigilance (including the unblinded information) and to the MHRA and REC as required.
- This information will not be forwarded to the trial team at the CCTU or at the sites. It will be kept in a separate file by the CCTU SUSAR reporting team.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Each participant will be given a unique trial PIN (Exnnn) to be used in all correspondence. Data will be collected at the time-points indicated in the Participant Timeline (section 6.6) on trial specific paper case report forms (CRFs) which have been designed by the Exenatide-PD3 trial team. The approved Exenatide-PD3 CRFs will be provided to all participating sites. The CRFs will not bear the patient's name, instead the patient's initials, partial date of birth and unique participant identification number will be recorded and used for identification.

Following completion of the Exenatide-PD3 paper CRFs, all information contained within them should be entered onto the Exenatide-PD3 custom designed database. This trial specific electronic database will be designed to capture all relevant clinical data from the paper CRF to allow formal statistical analysis. If capacity at sites allows, the information collected on paper CRFs should be entered onto electronic CRFs (eCRFs) on the database within 10 working days of each trial visit by the site team.

Adverse events, concomitant medications and weight recordings should be recorded on separate CRFs by an independent assessor at the trial visits stated in the Participant Timeline. These paper CRFs should be stored at the back of each participants trial folder in the envelope provided. This information should be entered onto the trial database by the independent assessor to minimise the risk of the primary rater being influenced by these data.

Adverse events should be entered onto the database within 10 working days of information relating to such events being made available. If a site does not have capacity to enter data on the trial database following each trial visit, specific arrangements can be made following discussion with the Exenatide-PD3 trial team.

Training on paper CRF completion and storage will be provided for site staff listed on the delegation of responsibilities log at the site initiation meetings. Staff will also receive training on data collection and use of the Exenatide-PD3 database. This database is stored on secure servers based at UCL. Clinical trial team members will be taught on the use of the PD assessment scales including certification from the MDS on the use of the MDS-UPDRS. The MDS-UPDRS part 3 will be video-recorded on a tablet device. Patients will be asked to consent to being videoed and the data from videos will be uploaded and stored on a GDPR compliant, secure Machine Medicines Technology (MMT) server. These videos will be used for quality control purposes and to improve how Parkinson's Disease is monitored. If the participant does not consent to video recording being performed during the MDS-UPDRS, the data from this assessment will be entered onto the paper CRF only. For patients who do consent to being videoed, data should be collected on both the video tablet and the paper CRF and uploaded to the trial database.

At selected centres participants will also wear electromagnetic (EM) sensors during the assessment of the MDS-UPDRS part 3 motor scores. These sensors will allow objective quantification of movement speed/fluidity and will be uploaded to a secure server to allow central analysis for e.g. speed and rhythmicity in an automated fashion. Participants will wear the EM sensors (Polhemus Inc.) on the index finger and thumb when they perform the assessments. The EM sensors are commercially available and carry a CE mark for conventional use.

The EM assessments will give sufficient data to plan further studies to investigate the properties of the finger tapping measurement and, we hope, improve the future conduct of research in Parkinson's disease. Patients at selected sites will be asked to consent to having Electromagnetic Sensor assessments performed and to their data being securely transferred and analysed by The University of York.

Medical notes will be used as the source data unless the data required on the CRF is not normally entered in patients' medical notes. In these cases, the CRFs will be used as the source data for monitoring purposes. The paper CRF will be used as the source data for the MDS-UPDRS therefore a paper CRF should be completed as well as the video recording for all participants (with consent). All data will be handled in accordance with the Data Protection Act 2018 and the General Data Protection Regulation (2016). Source data at each site will be defined in Source Data Agreements which will be in place with all participating sites.

Data collection, data entry and queries raised by a member of the Exenatide-PD3 trial team will be conducted in line with the Exenatide-PD3 Data Management Plan.

Identification logs, screening logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room.

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- pseudonymised, coded and dated
- ECG printout- anonymised, coded and dated
- MDS-UPDRS - The MDS-UPDRS training program & exercise are obtainable from; www.movementdisorders.org/updrs/
- UDysRS obtainable from www.movementdisorders.org/publications/rating_scales/udysrs.pdf
- PHQ-9 available from <https://patient.info/doctor/patient-health-questionnaire-phq-9>
- MoCA obtainable from <https://www.mocatest.org/>
- PDQ 39 obtainable from <https://www.ndph.ox.ac.uk/research/health-services-research-unit-hsru/outcome-measures>
- EQ-5D-5L obtainable from www.euroqol.org
- NMS obtainable from [Chaudhuri et al. Movement Disorders 2007. 22\(13\) p1901-11.](#)
- Client Services Receipt Inventory (CSRI) - see section 6.10.5.1
- Hauser Diary obtainable from [Hauser et al. A Home Diary to Assess Functional Status in Patients with Parkinson's Disease with Motor Fluctuations and Dyskinesia 2000. Clin. Neuropharmacol., 23\(2\) p79-81.](#)

6.10.2 Data Management

Data will be entered in the approved Exenatide-PD3 database by delegated staff at participating sites and members of the Exenatide-PD3 trial team at CCTU. Data will be protected using established CCTU procedures. Delegated research staff at participating sites will be given access to the database by the Exenatide trial team at the CCTU. Initially researchers will be given access to a training account within the database. The Trial Team will provide dummy data to be entered by staff at participating sites for training purposes. Following completion of this training, evidence should be sent to the Exenatide trial

team who will review the quality of data entered during training. If satisfactory, staff at research sites will then be given appropriate access to the live database at their specific site and can enter the information from paper CRFs onto the database.

Coded data: Participants will be given a unique trial PIN (Exnnn). Data will be entered under the PIN onto the central database (InferMed's MACRO stored on the servers based at UCL). The database will be password protected and only accessible to members of the Exenatide-PD3 trial team at CCTU, delegated members of research teams at participating sites and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

The database and coding frames will be developed by the programmer based at the CCTU. The database will only be available to specified users who will require a username and password for access. MACRO supports a role based security model, granting different users different database privileges. MACRO 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.

After completion of the trial the database will be retained on the servers of UCL for on-going analysis of secondary outcomes.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudonymised PIN (Exnnn), will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by CCTU.

Data resulting from the EMS and Video recordings of MDS-UPDRS assessments will be initially stored on password protected computer-tablets/ laptops. At regular intervals, the data will be encrypted and backed-up to cloud-based storage.

The EMS assessments will be uploaded to Google Drive, as recommended by the University of York as this institution has agreements in place with Google ensuring the security and physical location of the data. Once received, the data will be decrypted by the team at York University and kept on password-protected secure systems within the University of York's firewall. Only authorised members of the research team will have access to the data for processing and analysis. Participants will be asked to consent to this.

Video recordings of the MSD-UPDRS will be uploaded onto a secure cloud held by Machine Medicines Technologies (MMT) and used for quality control purposes.

Participants will be asked to consent to both EMS and Video recordings prior to them being undertaken. If consent is not given, these assessments will not take place. Appropriate contractual agreements covering data protection are in place with The University of York and MMT.

All data storage will adhere to Data Protection Act 2018.

6.10.3 Non-Adherence and Non-Retention

The number of subcutaneous injections successfully self-administered will be estimated at each visit based on noting the amount of trial product dispensed at previous visit, the interval between visits and asking the participant to state the number of unused injections remaining. Reasons for non-adherence to protocol will be noted in the relevant CRF. Outcome data will continue to be collected on all contactable participants continuing to provide informed consent.

6.10.4 Statistical Methods

6.10.4.1 Statistical Analysis Plan

All trial analyses will be according to the Statistical Analysis Plan (SAP), 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.

A CONSORT diagram will be used to describe the course of participants 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 OFF medication scores at 96 weeks follow up. All analyses will be performed by the Trial Statistician at UCL CCTU.

The analysis will use a mixed model approach incorporating information from all follow up visits that adjusts for Hoehn & Yahr status and the baseline raw value of each outcome measurement. Site will be included as a random effect to account for variability in outcomes between sites, and a fixed patient/subject effect will accommodate the correlation between repeated outcome measures on the same patient. The model will be fully specified in the SAP. A significance level of 5% will be used to judge significance for the primary outcome measure.

A planned secondary analysis will compare the difference in MDS-UPDRS part 3 OFF medication scores according to randomisation allocation at 96 weeks, with the scores at 48 weeks. An increase in the advantage at 96 weeks compared to 48 weeks would be evidence that the active drug was halting deterioration of the disease rather than having symptomatic effects only. This would translate to a major population advantage in terms of reduction of morbidity and mortality.

Analyses of the remaining secondary/exploratory outcomes will be undertaken similarly for the difference between groups according to treatment allocation at 96 weeks follow up adjusting for baseline values of each outcome, and confounding factors such as LED. A planned comparison between MDS UPDRS part 3 OFF scores at 48 and 96 weeks will also be performed.

An exploratory analysis will consider whether exenatide can be thought of as disease modifying by comparing slopes between groups following a pre-specified period.

Participants that discontinue trial medication will continue to be followed up in accordance with the trial protocol and their data included in accordance with the modified intention-to-treat analyses, see section 6.10.5.

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

EMS analysis: The proposed analyses will be conducted by the team at York University and will be concerned only with the properties of the EMS assessment compared to those of other measures in the trial, and will not use the main trial's analysis approach. Analyses will use data for the centres where the EMS assessment is used and for participants for whom both variables being compared are available only.

The effect sizes for the EMS measures and the MDS-UPDRS part III (OFF and ON) scores will be estimated. The difference between the effect sizes for the EMS measures and MDS-UPDRS part III (OFF and ON) scores will be used to evaluate the superiority (or otherwise) of the finger tapping measure.

6.10.4.3 Additional Analyses - Subgroup

Results on the primary efficacy outcome will be presented by stratum, according to Hoehn & Yahr stage (≤ 2.0 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

Since randomisation will be balanced by site and Hoehn & Yahr stage (≤ 2.0 versus 2.5), all analyses of outcomes will adjust for these factors. Where appropriate, analyses will additionally adjust for baseline values of each outcome.

6.10.5 Analysis Population and Missing Data

The main analysis will be conducted following a modified intention-to-treat (mITT) principle in accordance with the randomised intervention. The analysis population will consist of all subjects who complete 12 weeks on treatment and for whom outcomes are available.

Any participants that undergo Deep Brain Stimulation (DBS) during trial participation will not contribute further outcome data after the DBS surgery has been performed. The data recorded up to and including the participant's last pre-operative trial visit will however contribute to the mixed model for the final analysis.

A per protocol sensitivity analysis will be performed for the primary outcome measure including only those participants who completed the trial in accordance with the approved protocol.

Missing covariate data are not anticipated since covariates must be recorded to allocate treatment. Missing outcome data will be assumed to be missing-at-random (MAR) conditional on any variable included in the analysis model and so independent of the values of the unobserved data themselves. The primary analysis is likelihood based and is therefore robust to the MAR assumption. Reasons for missingness may be important and these will be investigated using logistic regression of covariates on

an indicator of missingness. Sensitivity analyses will investigate the validity of the MAR assumption of the primary analysis as detailed in the SAP.

6.10.5.1 Economic evaluations

Health and social care resource utilization, impact on paid and unpaid carers and EQ-5D-5L (for calculation of QALYs) data will be collected to support a future funding application for formal cost effectiveness of exenatide in PD to be performed.

Participant resource use will be assessed using a shortened version of the Client Services Receipt Inventory (CSRI) and using the Concomitant Medications Log. The CSRI will be modified according to the needs of people with Parkinson's disease and will be administered at baseline (asking about the previous six months), 24, 48, 72 and 96 weeks (each time collecting information on resources used since the last visit). These questionnaires will ask participants for details of primary, secondary and social care resource use related to PD and impact on paid and unpaid carers.

We anticipate that the primary analysis will be from a health and social care cost perspective and will report the incremental cost per QALY gained of exenatide compared to treatment as usual (placebo arm CSRI and QALYs, but with medication monitoring costs that reflect current practice) over 96 weeks using trial data. A secondary analysis will include paid and unpaid carer costs. QALYs will be calculated as the area under the curve using EQ-5D-5L responses and the UK tariff, adjusting for baseline. A full health economics analysis plan will be developed as part of the future funding application and include covariates for adjustment and handling of uncertainty and missing data. We will consider the suitability of a decision model over a longer time horizon to project costs and QALYs into the future.

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 Exenatide-PD3 Trial Statistician at CCTU will generate regular summaries of accumulating trial data for the IDMC to review.

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 any interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the Exenatide-PD3 IDMC Terms of Reference (ToR).

6.11.2 Interim Analyses

No formal interim analyses are planned however, IDMC members will convene at scheduled time points throughout the duration of the trial to review interim trial data and safety data.

The IDMC may request an interim analysis of the PD severity measures if there are concerns with respect to patient safety but no interim efficacy analyses will be performed. This will avoid the issue of multiple comparisons or any compromise of the study's power to detect statistically significant effects.

6.11.3 Data Monitoring for Harm

All adverse events (AEs) and SAEs occurring during the trial observed by the investigator or reported by the patient, whether or not attributed to the investigational drug, trial interventions or other trial-specific procedure will be recorded in the patient's medical records, and on the appropriate Exenatide-PD3 CRFs. CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

The period for reporting of AEs directly related to the participant will be from the time of first dose of trial medication until 10 weeks post final trial medication administration.

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.

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: <ul style="list-style-type: none"> • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***
<p>* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction)</p> <p>** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE</p> <p>*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).</p>	

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the trial medication is an SAE.

All SAEs should be reported to the AZ Safety Team. 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 trial. 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

Adverse events include:

- an exacerbation (i.e. increase in the frequency or intensity) of a pre-existing illness, episodic event or symptom (initially recorded at the screening visit), that is detected after trial medication administration/intervention
- occurrence of a **NEW** illness, episodic event or symptom, that is detected after trial medication administration/intervention

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Overdose of medication that is not considered both excessive and medically important

6.11.3.3 Laboratory test abnormalities

The following laboratory test result abnormalities should be captured on the Exenatide-PD3 Adverse Event Log and Serious Adverse Event 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 trial medication 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).

6.11.3.4 *Other Notifiable Adverse Events*

6.11.3.4.1 Pancreatitis

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.

6.11.3.4.2 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.

6.11.3.4.3 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 (also known as potential Hy's Law) event as a SAE. Potential drug induced liver injury is defined as:

- Alanine transaminase (ALT) or aspartate transaminase (AST) elevation ≥ 3 times upper limit of normal (ULN)

AND

- Total bilirubin ≥ 2 times ULN, irrespective of initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of ALT or AST 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.

6.11.3.5 *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. Female patients with a positive pregnancy test at screening are not eligible for inclusion in this trial and should not be randomised. Women on exenatide should not breastfeed. Male participants and female participants of child-bearing potential will be advised to use an effective form of contraception whilst they are in the trial. If, following initiation of the investigational product, it is subsequently discovered that a trial 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 trial 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.

Pregnancy is not a SAE. Following initiation of the trial medication, if a female participant becomes pregnant, the Pregnancy Notification & Follow-Up Form should be completed by the investigator at the site and forwarded to the Exenatide-PD3 trial team at CCTU. CCTU notification should take place immediately, but no longer than 24 hours of the investigator becoming aware of the pregnancy. The pregnancy outcome may or may not be considered a SAE. Participants will be given a copy of the Exenatide-PD3 Pregnancy Monitoring Information Sheet and will be asked to sign the Exenatide-PD3 Pregnancy Monitoring Consent Form agreeing for data on the pregnancy to be collected. Pregnancy

should be followed until the outcome is known (including any premature termination of the pregnancy) and information on the status of the mother and child. Pregnant participants will be followed up until birth, the Exenatide-PD3 Pregnancy Notification & Follow-Up Form (capturing information for up to 6 to 8 weeks after birth) should be completed and forwarded to the trial team at CCTU. Any congenital malformations and/or birth defects are reportable as an SAE.

The CCTU will forward the Pregnancy Notification & Follow-Up Form to AstraZeneca according to pregnancy procedures described in the Exenatide-PD3 Safety Management Plan.

6.11.3.6 *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 non-serious or serious AE, as appropriate, and reported accordingly on Exenatide-PD3 Adverse Event Log and/or Serious Adverse Event form.

6.11.3.7 *Investigator responsibilities relating to safety reporting*

All AEs and ARs, whether expected or not, should be recorded in the participant's medical notes and on the Exenatide-PD3 Adverse Event Log. SAEs and SARs should be notified to CCTU immediately, using the Exenatide-PD3 Serious Adverse Event form, when the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours). The SAEs and SARs should also be recorded in the participant's medical notes.

6.11.3.7.1 *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 Exenatide-PD3 Serious Adverse Event Form must be completed and CCTU notified immediately (no longer than 24 hours after the investigator becomes aware of the event). CCTU will report the SAE to AstraZeneca (see section 6.11.3.8.2).

6.11.3.7.2 *Severity or grading of Adverse Events*

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be reported and graded using the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Grade 1: Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

Grade 3: Severe or medically significant but not life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE or AR.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.

**Self-care AD refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

6.11.3.7.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

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.

6.11.3.7.4 Expectedness

If there is at least a possible involvement of the trial medications (including any comparators), the sponsor will assess the expectedness of the event. If information on the expectedness is provided by the investigator this should be taken into consideration by the sponsor. An unexpected adverse reaction is one that is not reported in the current approved IB or SPC for exenatide, or one that is more frequently reported or more severe than previously reported. See the reference safety information (RSI) in section 5.6 of the current approved IB for the trial 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 the MHRA and REC reporting guidelines apply (see Notifications sections of the protocol).

6.11.3.8 Notifications

6.11.3.8.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAEs immediately (within 24 hours) of the investigator becoming aware of the event.

Investigators should notify CCTU of any SAEs and other Notifiable Adverse Events (NAEs) occurring from the time of randomisation until 10 weeks after the last protocol treatment administration, including SARs and SUSARs. From this point forward the site will not actively monitor SAEs or NAEs but will notify the CCTU of any SARs and SUSARs if they become aware of them until trial closure.

The Exenatide-PD3 Serious Adverse Event form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) who will provide the grading and causality for the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the Exenatide-PD3 Serious Adverse Event form at the earliest opportunity, make any changes necessary, sign and then email to CCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the participant's PIN, 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.

The SAE form must be scanned and sent by email to the trial team at CCTU on cctu.exenatidepd3@ucl.ac.uk.

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. Follow-up Exenatide-PD3 Serious Adverse Event forms (clearly marked as follow-up) should be completed and emailed to CCTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by trial PIN, initials and month and year of birth only. The participant's name should not be used on any correspondence and should be blacked out and replaced with the participant's PIN on any test results (if applicable).

6.11.3.8.2 CCTU responsibilities

A medically qualified member of staff will be appointed as the sponsor clinical reviewer (usually the Chief Investigator (CI) or a medically qualified delegate) and will perform a clinical review of all SAE reports received. The sponsor clinical reviewer will complete the assessment of expectedness in light of the RSI.

CCTU will notify the AstraZeneca Safety Team within 24 hours of becoming aware of the event. SAEs, whether related or not related to the trial medication, and pregnancies will be reported in the Exenatide-PD3 Serious Adverse Event form and Exenatide-PD3 Pregnancy Notification & Follow-Up Form, respectively. Follow up forms will be sent using the same procedure and timelines used for transmitting the initial report to AstraZeneca through their ESR System: http://az_medi.envisionpharma.com/vt_az_medi.

CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authority (MHRA) and the ECs as appropriate. An independent SUSAR Reporting team will be responsible for unblinding SAEs and the onward reporting of SUSARs. Fatal and

life threatening SUSARs must be reported to the competent authorities within 7 days of CCTU becoming aware of the event; other SUSARs must be reported within 15 days.

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

The Trial Manager or delegate at CCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

This trial is defined as risk Category B according to the MHRA Risk Assessment (i.e. somewhat higher than that of standard medical care).

The Quality Assurance (QA) and Quality Control (QC) considerations for the Exenatide-PD3 trial are based on the standard 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 CCTU

CCTU staff will review 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-PD3 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-PD3 Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority CCTU must be notified as soon as possible.

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 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-PD3 QMMP.

6.11.4.4.1 Trial Team

The Trial Team (TT) 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. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TT terms of reference.

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, 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.

6.11.4.4.4 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 TSC 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.

6.11.4.4.5 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 CCTU via a signed letter of delegation.

7 Ethics and Dissemination

7.1 Ethics Committee 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 and the Health Research Authority (HRA) 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 permissions.

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 participants will be minimal. All participants will be made aware of the known adverse reactions 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. Participants will be assessed first thing in the morning to minimise 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 is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a clinical trial authorisation (CTA) is required in the UK. This protocol will be submitted to the UK regulatory authority (MHRA) where the trial will be conducted.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the MHRA as required.

7.3 Other Approvals

The protocol, participant information sheet (PIS) and informed consent forms on local headed paper, the REC/HRA and MHRA approvals, schedules of funding and activity (and other trial documentation as needed) will be submitted by those delegated to do so to the relevant NHS Trust R&D department of each participating site or to other local departments for approval as required in each country. The NHS Trust R&D department will conduct a local feasibility assessment to determine whether the NHS Trust has the capacity and capability to participate in the trial. No trial conduct can take place at a participating site until all approvals including the local capacity and capability approval are in place.

The protocol has received formal review and methodological, statistical, clinical and operational input from the 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), REC and HRA prior to any patient recruitment. The protocol and all agreed substantial amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

7.5 Consent or Assent

Participants will be provided with a patient information sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. 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.

In accordance with the UK Clinical Trial Regulations, the risk/benefit profile of the trial will be regularly monitored. 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 REC prior to their use.

Capacity to consent will be kept under review throughout the trial. If a participant is judged to have lost capacity to consent then he/she will be withdrawn from the trial.

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

7.5.1 Consent or Assent in Ancillary Studies

Participants can take part in either one, or a combination of sub-studies depending on which of these is being undertaken at their participating centre. Separate Informed Consent Forms and Patient Information Sheets will be used for each of these sub studies. These documents will be fully approved by the REC and HRA prior to use.

The 4 sub-studies are:

1. Genetics sub-study (Appendix 2)
2. Cerebrospinal Fluid sub-study (Appendix 3).
3. Remote Monitoring of PD Symptoms sub-study (Appendix 4).
4. DaTSCAN imaging sub-study (Appendix 5).

Participants interested in the Genetics sub-study will be asked to consent to storage of biological specimens for future research purposes to enable the investigation of emerging biomarkers in PD. All stored biological specimens will be retained under the participant's identification number.

Withdrawal of participant from the trial or any of the associated sub-studies will not be accompanied by withdrawal of previously collected specimens. No individual information derived from this aspect of the research will be communicated to the participants.

Additional details relating to the sub-studies is outlined in Section 8 and in Appendices 2,3,4 and 5.

Participants at all 6 trial sites consent to give 1x 10ml EDTA tube at each of the long trial visits (as detailed in section 6.6) for research purposes. These samples are being centrifuged by research teams at sites and labelled/ stored as per the Sample Management Plan prior to be safely transported to research labs at UCL (and others if approved) for exploratory analyses. Participants at UCL are offered the opportunity for CSF collection (Appendix 3).

The analyses on these samples will include exploring the molecular features in CSF and plasma that reflect the underlying pathophysiology Parkinson's disease with the aim of using these to demonstrate the certainty of the diagnosis in comparison to other atypical parkinsonian conditions, prediction of patient's progression profiles over the course of the trial and exploring markers ability to capture therapeutic effects from exenatide over the 6 month intervals in the trial. To explore these different aspects the levels and activity profile of a number of molecules will be studied with a variety of laboratory techniques including serum neuronal exosomal studies, enzyme linked immunoassays, Real-time quaking induced conversion and electron microscopy. Potential molecules that will be studied include alpha synuclein and its phosphorylated and oligomeric subtypes, tau and its phosphorylated subtypes, markers of insulin resistance including IRS-1 pSer312, markers of neurodegeneration such as neurofilament light chain and markers of inflammatory response and astrocyte activation including interleukin levels, NDRG2, GFAP, and S100β.

7.6 Confidentiality

Each participant's data will be collected and kept secure. SealedEnvelope.com will provide a unique trial PIN for each participant (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 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 Indemnity

University College London holds insurance against claims from 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 of the clinical trial. UCL 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.

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 UCL 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 UCL'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 UCL, upon request.

7.9 Finance

Exenatide-PD3 is fully funded by the Efficacy and Mechanism Evaluation (EME) Programme grant number 16/167/19. It is not expected that any further external funding will be sought, aside to allow for the conduct of specific sub studies to be conducted in parallel with the main trial.

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of Exenatide-PD3 trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by the CCTU.

7.11 Access to Data

The CI, CPM, Trial Manager, Data Manager, Statistician and Trial Management Team will have full access to the trial data. Following the predefined analyses on response to treatment, requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TSC. Considerations for approving access are documented in the TSC Terms of Reference.

7.12 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 PIS.

7.13 Publication Policy

7.13.1 Trial Results

The results of this trial will be submitted for publication in peer reviewed journals as well as in the NIHR EME journal, in addition to reports at appropriate specialist conferences. The results of the trial will be disseminated regardless of the direction of effect.

The trial will be registered with international trials databases such as clinicaltrials.gov, and reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement for the results (<http://www.consortstatement.org/>).

The participants will all be invited to a lay presentation of the trial results and provided with an opportunity to ask questions about the implications of the results for their own treatment. The trial results will be the subject of formal press releases to the mainstream media and will be disseminated to charitable organisations so that public and patients have the opportunity for further information about the results. The results will also be presented at International Scientific Conferences on PD.

7.13.2 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.

7.13.3 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

There are four optional sub-studies linked to the main trial:

1. Genetics sub-study (Appendix 2) – to try to identify genetic markers that may be associated with subtypes of PD or variation in treatment responsiveness.
2. Cerebrospinal Fluid sub-study (Appendix 3) – to determine whether any CSF changes associated with PD are influenced by exposure to exenatide. These may include alpha synuclein monomers or oligomers, Neuroinflammatory markers, Exosomal contents
3. Remote Monitoring of PD Symptoms sub-study (Appendix 4) - to help determine whether the assessment of voice and movement symptoms in patients with PD may be better performed using a smartphone than by conventional clinical assessments.
4. DaTSCAN Imaging sub-study (Appendix 5)- to determine if change in dopamine transporter availability in the caudate and putaminal nuclei as measured by quantitative DaTSCAN signal is influenced by exposure to exenatide.

9 Protocol Amendments

Protocol version number	Protocol date	List of Substantial Amendments (for full description, please refer to the "Summary of changes to the protocol" document)
1.0	25 June 2019	Version initially submitted to REC/ MHRA
1.1	26 July 2019 Approved by MHRA 15th Aug 2019	<p>Changes requested by the MHRA following initial submission;</p> <p>SECTION 4- Glossary- Updated meaning of Abstinence</p> <p>SECTION 6.4.5.3 and 6.10.5- DBS- "during trial follow-up" changed to "during trial participation".</p> <p>SECTION 6.11.3.7.4- Reference to SmPC has been removed. Changed to reference RSI section of IB.</p> <p>SECTION 6.11.3.8.1- sentence regarding MHRA yellow card reporting system removed.</p> <p>REC Reference Number- updated as original REC had to cancel meeting due to not being quorate.</p>
2.0	16 Oct 2019 2019	<p>1.3 Structured Trial Summary <u>ISRCTN number added</u></p> <p>1.4.5 Trial Steering Committee Two members added to the Trial Steering Committee and one removed. Trial Statistician changed to Kashfia Chowdhury</p> <p>6.3.1.3 Participant Exclusion Criteria 12. "Baseline serum amylase" changed to "Screening serum amylase"</p> <p>6.4.6 Accountability "Unused IMP will be brought to the next trial visit by the patient and checked by the clinical trial team." Changed to "Unused IMP will be brought to the final trial visit by the patient and will be checked by the clinical trial team."</p> <p>6.5.1 Primary Outcomes "amylase" removed and replaced with "concomitant medication"</p> <p>Wording updated to: "This is to minimise the risk of the primary outcome rater being influenced by these data. Together with prior scores, these data will be filed separately in an envelope at the back of each participant folder and primary outcome raters will be encouraged not to review this. Responsible individuals will be listed in the delegation log."</p> <p>6.5.2 Secondary Outcomes "Baseline" changed to "Screening"</p>

		<p>“Each patient will have pulse, blood pressure and weight documented at screening and at each follow up visit. Their height will be recorded at screening to enable calculation of body mass index”</p> <p>6.4.5.2 Dose Interruptions ‘Baseline’ replaced by ‘screening’.</p> <p>6.6 Participant Timeline Hauser Diary</p> <p>Timing of first Hauser diary changed from after visit 2 to prior to visit 2 as the first Hauser should be documented prior to administration of IMP/placebo.</p> <p>Additional Point added “m If a participant forgets to bring a completed copy of the 3 Day Hauser Diary to visits 2, 6 or 10 they should be advised to complete this in the 5 days following the visit and to send the diary back to the research team at their local site”</p> <p>“This point refers to post randomisation assessments” The above wording added to state to point ^h to highlight that this point refers to post randomisation.</p> <p>Weight, pulse and blood pressure will also be collected at baseline & randomisation - an X has been added to the table to highlight this.</p> <p><u>Months changed to weeks</u></p> <p>1 month telephone call has been changed to “4 week telephone call”</p> <p>10 week follow up telephone call has been changed to “106 week follow up telephone call”</p> <p><u>Serum changed to plasma and additional subtext added</u></p> <p>Serum changed to Plasma to be taken at 5 time points. Subtest added to highlight how this sample should be processed, as below:</p> <p>“n At each of the visits indicated, a 10ml EDTA tube should be centrifuged in order to separate plasma and whole blood. The plasma should then be aliquoted into cryotubes and labelled as per the Exenatide-PD3 Sample Processing Document. Both cryotubes and labels will be provided by the sponsor”</p>
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		<p>6.9.1.1 Sequence generation</p> <p>“Stratification” changed to “Balancing” throughout</p> <p>Balancing factors added (research site and sub studies)</p> <p>“The Trial Statistician at CCTU will generate a sequence of unique 3 digit identifiers for every active/placebo drug kit consisting of 4 single use pens”</p> <p>Changed to</p> <p>The Trial Statistician at CCTU will generate a sequence of unique 5 digit identifiers for every active/placebo drug kit consisting of 4 single use pens.</p> <p>6.10.1 Data Collection Methods</p> <p>Wording updated to reflect remote data entry.</p> <p>“Blood Tests” removed and replaced with “Concomitant Medications”</p> <p>6.10.2 Data Management</p> <p>Wording updated to reflect remote data entry.</p> <p>6.10.3- Non-Adherence and Non-Retention</p> <p>“asking the participant to state” has been added</p> <p>6.10.4.2 Statistical Methods- Outcomes</p> <p>Sentence added; “An exploratory analysis will consider whether exenatide can be thought of as disease modifying by comparing slopes between groups following a pre-specified period”.</p> <p>6.11.3.7.2 Severity or grading of Adverse Events</p> <p>The following sentence has been removed. “SUSARs will be coded via MedDRA for the purpose of expedited reporting to MHRA/REC”</p> <p>6.11.3.8.1 Notifications by the Investigator to CCTU</p> <p>“30 days” changed to “10 weeks”</p> <p>7.5.1 and 8.0</p> <p>Sub study added</p> <p>11.1 Appendix 1</p> <p>“Opicapone” added to table</p> <p>11.3.5 Outcomes and Analysis</p>
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	<p>Sentence added- “Baseline serum and CSF samples will be made available for comparison with serum and CSF samples taken from patients participating in other ethically approved studies”</p> <p>11.5 Appendix 5 Proof-of-concept imaging sub-study- added.</p> <p>This study will be run through Prof. Marios Politis at the Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King’s College London (KCL). KCL will apply for separate ethical approval for this study and provide all study documentation.</p>
3.0	<p>1.3 Structured Trial Summary</p> <p>ISRCTN and Clinicaltrial.gov registration numbers added to table</p> <p>Source of Monetary or Material Support: Wording updated as per funder advice.</p> <p>1.4 Roles and Responsibilities</p> <p>Protocol contributors- additions Professor Politis replaced by Professor Chaudhuri Dr John Dixon</p> <p>Trial Team- additions Dr Girges and Dr Vijiaratnam</p> <p>Trial Management Group- additions Dr Gordon Duncan (Edinburgh) and Prof Ray Chaudhuri</p> <p>Role of trial Sponsor and funders Wording updated as per funder advice.</p> <p>6.3.1.6 Screening Procedures and Pre-randomisation Investigations</p> <ul style="list-style-type: none"> - “Kidney Function” added as wording missed in error in v2.0 - “fasting tests” removed at screening - c-peptide added - “Lipids & diabetic bloods can be repeated in a fasted state between screening and baseline visits if required to confirm eligibility” <p>6.4.5.2 Dose Interruptions (greater than >50% above both baseline level AND above the upper limit of normal) Wording in bold added</p> <p>6.5 Outcomes</p>

		<p>“at which time data will be collected regarding health resource utilisation” – wording removed</p> <p>6.5.1 “with consent” added for clarity</p> <p>The scale “can be” replaced by “the scale is”</p> <p>6.5.2 EMS wording removed</p> <p>“recorded and monitored throughout”</p> <p>6.6 Participant Timeline</p> <ul style="list-style-type: none"> - Non fasted HbA1c, glucose, insulin, c-peptide, lipid profile at screening - Fasted HbA1c, glucose, insulin, c-peptide, lipid profile at baseline - DaTSCAN and Remote Monitoring sub-studies added to table. - Electromagnetic Sensor added to table (corresponding sub text in point e updated) - Sub text points o and p added in relation to DaTSCAN - Subtext point q- added <ul style="list-style-type: none"> - Subtext c - “If a site does not have a separate clinician to record weight/other adverse events to preserve blinding of the rating clinician then these calls will be made to the central trial Research team.” Removed as all sites have separate clinician. - Subtext c wording updated to “After the Screening Visit, the named site clinical staff member calls the participant to remind the participant of the need to stop taking their regular PD medication prior to their next trial visit and fasted (prior to 2,4,6,8,10). Prior to visits 2, 6 and 10 the participant will also be reminded to attend these visits in a fasted state” <p>6.6.4 Trial closure</p> <p>“priority” added</p> <p>6.8.1.1 Internal Pilot phase: progression criteria</p> <p>Sixth site added- Western General Hospital- Edinburgh</p> <p>6.9.1.1 Sequence generation</p> <p>Updated wording to add clarify (e.g PIN (Exnnn) and kit dispensing)</p> <p>6.9.1.2 Allocation concealment mechanism</p> <ul style="list-style-type: none"> • “initial visit” replaced by “baseline and randomisation visit (visit 2)” • “(4 kits in total given at this visit)” added for clarity <p>6.9.3 Emergency Unblinding</p>
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		<p>“A Randomisation and Unblinding Plan will be provided to sites” wording added</p> <p>6.10.1 Data Collection Methods</p> <ul style="list-style-type: none"> - “PIN (Exnnn) added - “with Consent” added - Wording added to clarify that videos will go to MMT for QC purposes - Electromagnetic Sensor Paragraphs added - “Source data at each site will be defined in Source Data Agreements which will be in place with all participating sites” – wording added. <p>Wording removed “The following standard data will be entered into the medical records (source) and then onto the CRFs:</p> <ul style="list-style-type: none"> • Informed consent • PIN • Demographic data regarding 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 • LED • Vital signs- pulse, BP, weight • Biological specimens collected” <p>Wording removed due to source data variation at sites.</p> <p>6.10.2 Data Management</p> <p>Wording added to clarify how data from the video recording of the MDS-UPDRS part III and electromagnetic sensor will be managed.</p> <p>6.10.3 Non-Adherence and Non-Retention Bold wording removed “Reasons for non-adherence to protocol will be noted in the medical notes and the relevant CRF”</p> <p>6.10.4.2 Statistical Methods – Outcomes Electromagnetic Sensor analysis added</p> <p>6.11.3.7.2 Severity or grading of Adverse Events</p> <ul style="list-style-type: none"> • “repeated and ” added • “Exenatide-PD3 Adverse Event Grading System (trial specific)” removed <p>6.11.3.1 Safety reporting</p>
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		<p>“baseline” removed</p> <p>7.5.1 Consent or Assent in Ancillary Studies</p> <p>“Participants can take part in either one, or a combination of sub-studies depending on which of these is being undertaken at their participating centre. Separate Informed Consent Forms and Patient Information Sheets will be used for each of these sub studies. These documents will be fully approved by the REC and HRA prior to use”</p> <p>Replaced by</p> <p>“The main trial consent form will include taking consent from all eligible Exenatide-PD3 patients at the sites participating in the sub-studies (in addition to main trial) to partake in either one, or a combination of the sub-studies”</p> <p>“Appendix 5- Proof of Concept” replaced by “DaTSCAN imaging sub-study (Appendix 5)</p> <p>“and in Appendices 2,3,4 and 5” wording added</p> <p>7.9 Finance</p> <p>“to be subject to separate consent and ethics approvals” replaced by “to be conducted in parallel with the main trial”</p> <p>8 Ancillary Studies</p> <p>“three” replaced by “four”</p> <p>Wording added “DaTSCAN Imaging sub-study (Appendix 5)- to determine if change in dopamine transporter availability in the caudate and putaminal nuclei as measured by quantitative DaTSCAN signal is influenced by exposure to exenatide”</p> <p><u>Appendices</u></p> <p>11.2 Appendix 2 Genetics Sub-Study</p> <p>11.2.2.1 Wording updated to reflect that consent form will be sent to Professor Morris securely separately to blood samples. Wording updated: “Professor Huw Morris and his research team at UCL” from “ the team at UCLH Neurogenetics Laboratory</p> <p>Wording removed- “in accordance with the analytical plan agreed by the Exenatide-PD3 genetic sub-study investigators (Professor Tom Foltynie and Professor Huw Morris) and their teams”.</p> <p>11.2.2.2 Removed ECACC removed</p> <p>11.2.3.1 Wording Updated:</p>
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		<p>Genetic analysis will include high throughput genotyping with SNP chip; and may include targeted genotyping and DNA sequencing.</p> <p>This will enable the identification of known single gene causes of PD (e.g. LRRK2) and low frequency risk factors (e.g. polygenic risk scores for PD, DM etc). This genetic variation may affect clinical disease course, treatment response and be important for trial outcomes.</p> <p>It will also enable the identification of primary candidate variants that influence the response to exenatide e.g. GLP1 receptor variants.</p> <p>11.2.5 wording added “by Professor Huw Morris and Professor Tom Foltynie and their teams at UCL”</p> <p>11.2.3.2 Wording added “ Professor Huw Morris and his team”</p> <p>11.2.6 Wording added</p> <p>In some circumstances the research analyses may indicate that existing or future NHS-based genetic or chemical testing may be useful in accurately diagnosing PD and in determining the risk of disease to other members of the participant’s family, or selecting treatments.</p> <p>Participants can choose whether they wish to be informed about this, in advance. If they do choose to be informed of future test development, the genetics sub-study team will arrange for them to be given appropriate genetic advice and counselling.</p> <p>11.3 Appendix 3 Cerebrospinal Fluid Sub-Study</p> <ul style="list-style-type: none"> - Blood samples removed from the CSF Sub Study. These will not be obtained. <p>11.4 Appendix 4 Remote Monitoring of PD symptoms Sub-Study</p> <p>Two small wording clarifications:</p> <ul style="list-style-type: none"> - “five times (1 week at a time” - “and/or the lumbar sensor will be completed/ worn”- bold wording added <p>11.5 Appendix 5 DaTSCAN Proof-of-concept imaging sub-study</p> <ul style="list-style-type: none"> - Imaging sub study added in full. King’s are no longer leading on this sub study and the funding has been transferred to UCL- Professor Foltynie.
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4.0		<p>NSA 03. Information added to 7.5.1 regarding exploratory analyses of plasma samples taken at long trial visits. Similar text also added to Appendix 3 – CSF sub-study.</p> <p>“Planned analysis detailed in section 7.5.1.” added under table 6.6 beside reference to these samples.</p> <p>Clinical Project Manager and Data Manager, names changed. TM name delated and TBC added.</p>
5.0	11 Nov 2022	<p>6.6 Participant Timeline</p> <p>Row added to table for “Patient IMP Administration Diary”. Table footnote r added which provides further information and wording added “The Patient IMP Administration Diary will be completed by participants after each injection taken from receipt of the diary up to visit number 10 for all patients remaining on treatment at the time of diary implementation. The diary records the date and time each injection was taken, batch number, expiry date, kit code and confirmation the used injection pen was discarded.”</p> <p>Change in name of Sponsor/CCTU Director Representative (Head of Clinical Trials Operations) on protocol authorisation page and Section 1.4.3 Trial Team “TBC” removed as Trial Manager and name added.</p>

10 References

- (1) Chan AW, Tetzlaff JM, Altman DG, laupacis A, Berlin JA, Rennie D et al. SPIRIT 2013 Statement: Defining Protocol Items for Clinical Trials. *Ann Intern Med* 2013; 158:200-207.
- (2) Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, laupacis A et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346:e7586.
- (3) Perry T, Lahiri DK, Chen D, Zhou J, Shaw KT, Egan JM et al. A novel neurotrophic property of glucagon-like peptide 1: a promoter of nerve growth factor-mediated differentiation in PC12 cells. *J Pharmacol Exp Ther* 2002; 300(3):958-966.
- (4) Perry T, Haughey NJ, Mattson MP, Egan JM, Greig NH. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. *J Pharmacol Exp Ther* 2002; 302(3):881-888.
- (5) Drucker DJ, Philippe J, Mojsov S, Chick WL, Habener JF. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. *Proc Natl Acad Sci U S A* 1987; 84(10):3434-3438.
- (6) Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; 368(9548):1696-1705.
- (7) Aviles-Olmos I, Limousin P, Lees A, Foltynie T. Parkinson's disease, Insulin resistance and novel routes to neuroprotection. *Brain* 2012; Epub ahead of print.
- (8) Perry T, Lahiri DK, Sambamurti K, Chen D, Mattson MP, Egan JM et al. Glucagon-like peptide-1 decreases endogenous amyloid-beta peptide (A β) levels and protects hippocampal neurons from death induced by A β and iron. *J Neurosci Res* 2003; 72(5):603-612.
- (9) During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. *Nat Med* 2003; 9(9):1173-1179.
- (10) Perry TA, Greig NH. A new Alzheimer's disease interventional strategy: GLP-1. *Curr Drug Targets* 2004; 5(6):565-571.
- (11) Yamamoto H, Lee CE, Marcus JN, Williams TD, Overton JM, Lopez ME et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. *J Clin Invest* 2002; 110(1):43-52.
- (12) Tansey MG, Frank-Cannon TC, McCoy MK, Lee JK, Martinez TN, McAlpine FE et al. Neuroinflammation in Parkinson's disease: is there sufficient evidence for mechanism-based interventional therapy? *Front Biosci* 2008; 13:709-713.
- (13) Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. *Neurology* 2011; 76(10):863-869.
- (14) International Parkinson's disease Genetics Consortium. A two-stage meta-analysis identifies several new loci for Parkinson's disease. *PLoS Genet* 2011; 7(6):e1002142.
- (15) Gerhard A, Pavese N, Hotton G, Turkheimer F, Es M, Hammers A et al. In vivo imaging of microglial activation with [11 C](R)-PK11195 PET in idiopathic Parkinson's disease.

- (16) Lee JK, Tran T, Tansey MG. Neuroinflammation in Parkinson's disease. *J Neuroimmune Pharmacol* 2009; 4(4):419-429.
- (17) Kim S, Moon M, Park S. Exendin-4 protects dopaminergic neurons by inhibition of microglial activation and matrix metalloproteinase-3 expression in an animal model of Parkinson's disease. *J Endocrinol* 2009; 202(3):431-439.
- (18) Bomfim TR, Fornhy-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Aβ oligomers. *J Clin Invest* 2012; 122(4):1339-1353.
- (19) Shiraishi D, Fujiwara Y, Komohara Y, Mizuta H, Takeya M. Glucagon-like peptide-1 (GLP-1) induces M2 polarization of human macrophages via STAT3 activation. *Biochem Biophys Res Commun* 2012; 425(2):304-308.
- (20) Fan R, Li X, Gu X, Chan JC, Xu G. Exendin-4 protects pancreatic beta cells from human islet amyloid polypeptide-induced cell damage: potential involvement of AKT and mitochondria biogenesis. *Diabetes Obes Metab* 2010; 12(9):815-824.
- (21) Bertilsson G, Patrone C, Zachrisson O, Andersson A, Dannaeus K, Heidrich J et al. Peptide hormone exendin-4 stimulates subventricular zone neurogenesis in the adult rodent brain and induces recovery in an animal model of Parkinson's disease. *J Neurosci Res* 2008; 86(2):326-338.
- (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.
- (23) Esposito G, Ana CF, Verstreken P. Synaptic vesicle trafficking and Parkinson's disease. *Dev Neurobiol* 2012; 72(1):134-144.
- (24) Belluzzi E, Greggio E, Piccoli G. Presynaptic dysfunction in Parkinson's disease: a focus on LRRK2. *Biochem Soc Trans* 2012; 40(5):1111-1116.
- (25) Kitada T, Pisani A, Karouani M, Haburcak M, Martella G, Tschertner A et al. Impaired dopamine release and synaptic plasticity in the striatum of parkin^{-/-} mice. *J Neurochem* 2009; 110(2):613-621.
- (26) Kitada T, Pisani A, Porter DR, Yamaguchi H, Tschertner A, Martella G et al. Impaired dopamine release and synaptic plasticity in the striatum of PINK1-deficient mice. *Proc Natl Acad Sci U S A* 2007; 104(27):11441-11446.
- (27) McClean PL, Gault VA, Harriott P, Holscher C. Glucagon-like peptide-1 analogues enhance synaptic plasticity in the brain: a link between diabetes and Alzheimer's disease. *Eur J Pharmacol* 2010; 630(1-3):158-162.
- (28) Yun et al. *Nature Medicine* 2018. <https://doi.org/10.1038/s41591-018-0051-5>.
- (29) Harkavyi A, Abuirmeileh A, Lever R, Kingsbury AE, Biggs CS, Whitton PS. Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. *J Neuroinflammation* 2008; 5:19.
- (30) Li Y, Perry T, Kindy MS, Harvey BK, Tweedie D, Holloway HW et al. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. *Proc Natl Acad Sci U S A* 2009; 106(4):1285-1290.

- (31) Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T et al. Exenatide and the treatment of patients with Parkinson's disease. *J Clin Invest* 2013.
- (32) Athauda D, Maclagan K, Skene SS et al: Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2017; 390: 1664-75.
- (33) Athauda et al. *Jam Neurology* 2019. doi: 10.1001/jamaneurol.2018.4304
- (34) Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res Clin Pract* 2012; 98(2):271-284.
- (35) Wenten M, Gaebler JA, Hussein M, Pelletier EM, Smith DB, Girase P et al. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. *Diabet Med* 2012; 29(11):1412-1418.
- (36) Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; 141(1):150-156.
- (37) Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med* 2013; 173(7):534-539.
- (38) Butler PC, Elashoff M, Elashoff R, Gale EA. A Critical Analysis of the Clinical Use of Incretin-Based Therapies: Are the GLP-1 therapies safe? *Diabetes Care* 2013; 36(7):2118-2125.
- (39) Nauck MA. A Critical Analysis of the Clinical Use of Incretin-Based Therapies: The benefits by far outweigh the potential risks. *Diabetes Care* 2013; 36(7):2126-2132.
- (40) FDA: Bydureon Drug Safety [Internet]. Available from: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190406.htm [accessed 2/Jan/2014].
- (41) Parkinson's Disease Study Group. DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. *Parkinson Study Group. Arch Neurol* 1989; 46(10):1052-1060.
- (42) Olanow CW, Schapira AH, LeWitt PA, Kieburtz K, Sauer D, Olivieri G et al. TCH346 as a neuroprotective drug in Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol* 2006; 5(12):1013-1020.
- (43) Ward CD. Does selegiline delay progression of Parkinson's disease? A critical re-evaluation of the DATATOP study. *J Neurol Neurosurg Psychiatry* 1994; 57(2):217-220.
- (44) ICH Harmonised Tripartite Guideline Statistical Principles for Clinical Trials E9, Current *Step 4* version dated 5 February 1998.
- (45) Smith C. Levodopa Dose Equivalency - A Systematic Review [Internet]. 2010 [updated 2010 Jun 8; cited 2013 Nov 07]. Available from: <http://www.birmingham.ac.uk/Documents/college-mds/trials/bctu/PDRehab/Investigators/meetings/2010-2/CSmithLEDReview.pdf>.

(46) Hauser RA, Friedlander J, Zesiexicz TA, Adler CH, Seeberger LC, O'Brien CF et al. A Home Diary to Assess Functional Status in Patients with Parkinson's Disease with Motor Fluctuations and Dyskinesia 2000. Clin. Neuropharmacol., 23(2) p79-81.

11 Appendices

11.1 Appendix 1: Conversion factors used to convert each of the commonly used PD medications to a Levodopa equivalent dose (LED)⁴⁵

Drug	Conversion factor
Immediate release L-dopa	X 1
Controlled release L-dopa	X 0.75
Entacapone (or Stalevo®)	LD X 0.33
Tolcapone	LD X 0.5
Opicapone	LD X 0.5
Duodopa®	X 1.11
Pramipexole (as salt)	X 100
Ropinirole	X 20
Rotigotine	X 30
Selegiline-Oral	X 10
Selegiline-Sublingual	X 80
Rasagiline	X 100
Amantadine	X 1
Apomorphine	X 10

11.2 Appendix 2 Genetics Sub-Study

The participation information sheet for the Exenatide-PD genetics sub-study includes information on this optional genetic sub-study. The sub-study requires a blood sample to be taken (for genetic analysis) at screening or at any study visit. Participants will be given an opportunity to discuss the genetic sub-study with the local study team and to have any questions answered. Participants who do not wish to participate in the genetic sub-study will not be excluded from the main trial.

Two 10ml blood samples (approximately 2 tablespoon) will be taken, usually at the screening visit. These blood samples will be collected in EDTA sample tubes for the extraction of DNA by University College London Hospitals/ UCL Neurogenetics Laboratory.

11.2.1 Aims of genetic sub-study

The aim of this sampling is to try to identify genetic markers that may be associated with subtypes of PD or variation in treatment responsiveness and variation in the clinical phenotype. The primary aim of this resource and of future work will be to enable targeting of the best treatments to specific patient groups.

Secondary outcomes will include:

- Correlation of high quality clinical data with genotype
- Investigation of pharmacokinetic variables linked to absorption, distribution, metabolism and excretion of therapeutic agents (ADME).
- Identification of research-engaged patients carrying specific genetic variants for future studies

11.2.2 Sample collection

Instructions for collection, packing and dispatching samples are included in the Exenatide-PD3 Laboratory Manual.

11.2.2.1 UCLH Neurogenetics laboratory sample

One sample will be collected in an EDTA tube, appropriately packaged and sent (along with a copy of the UCL Neurogenetics Request Form) by post at room temperature from individual study sites to UCLH Neurogenetics Laboratory, 6th Floor, Queen Square House, Queen Square, London WC1N 3BG, to be stored with other samples in a biobank within the UCL Institute of Neurology. A copy of the consent form for this sub study will be sent securely to Professor Huw Morris and team. If the participant has consented to being contacted in the future, the participant's contact details will be forwarded to Professor Huw Morris and his research team at UCL. The inherited material (DNA and genes) will be extracted from the whole blood. The inherited material will be stored in The Cure Parkinson's Trust DNA bank, a subset of the Clinical Neurological Disease Biobank and Neurogenetics Research Study (CANDAS) DNA bank, and used for genetic investigations into PD. The UCL Neurogenetics laboratory will process, store and dispose of blood samples in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act, 2004 and any amendments thereto. Professor Huw Morris will be the custodian of the samples and any accompanying data.

11.2.3 Analyses

11.2.3.1 Genetic analysis

Genetic analysis will include high throughput genotyping with SNP chip; and may include targeted genotyping and DNA sequencing.

This will enable the identification of known single gene causes of PD (e.g. LRRK2) and low frequency risk factors (e.g. polygenic risk scores for PD, DM etc). This genetic variation may affect clinical disease course, treatment response and be important for trial outcomes.

It will also enable the identification of primary candidate variants that influence the response to exenatide e.g. GLP1 receptor variants.

11.2.3.2 Pharmacogenomic analysis

In collaboration with the Exenatide-PD3 trial team and The Cure Parkinson's Trust, Professor Huw Morris and his team will investigate whether specific major genetic sub-groups of PD or specific variants in candidate genes influence the outcome of PD drug trials in a preliminary pilot analysis. This will initially be a post-hoc analysis on a very small number of subjects.

11.2.3.3 Other analyses

Other analyses may include:

- Screening and analysis of potential pathogenic and anonymous genetic variations in sporadic and familial patients, with comparison to control samples. This will include DNA variants such as point mutations, gene re-arrangements, deletions/duplications, non-coding sequence change and DNA expansions. Analysis will include large-scale SNP analysis and sequence analysis.
- Analysis of phenotype modifiers i.e. analysis of gene variants which modify the disease by altering age at onset, or other disease phenotypes such as drug responsiveness, or secondary characteristics such as cognitive impairment and specific psychiatric features.

11.2.4 Sample and data sharing

All samples will be treated as a gift for research. UCL Neurogenetics department samples will be stored and used in ongoing and future projects by the Exenatide-PD3 genetic sub-study investigators (Professor Tom Foltynie and Professor Huw Morris) and their teams. Samples will form part of The Cure Parkinson's Trust DNA bank (currently within the CANDAS biobank) which will be made available as a resource for the Parkinson's research community through a vetted application process. A committee including core investigators, scientific, lay and charity representatives will review requests for data and sample access. These samples will be made available to responsible investigators in the UK and around the world for use in research, teaching, therapeutics and diagnostic purpose in collaborative research programs.

11.2.5 Confidentiality

Blood samples for the genetic sub-study will be labelled with the Exenatide-PD3 participant identification number ensuring the pseudonymity of the participants who have provided the samples. Brief clinical details will be stored with the genotype data including the full date of birth, gender, age at onset of PD, family history and ethnicity by Professor Huw Morris and Professor Tom Foltynie and

their teams at UCL. Genotype results will be stored on a web-based, secure confidential database, including after completion of the Exenatide-PD3 trial. Participants may ask for their information to be removed from this database at any time, in accordance with the Data Protection Act 2018.

Genetic sub-study samples will be linked to the main trial data held by Professor Foltynie's team at the end of the trial via the unique Exenatide-PD3 participant identification number to integrate genetic, clinical and trial outcome data as secondary analyses following the main trial. This is essential for analysis of phenotype modifiers - analysis of genes which modify the disease by altering age at onset or other disease phenotypes such as drug responsiveness, or secondary characteristics such as age at onset, response to therapy, and motor and psychiatric phenotype. Participants will be informed of this in the information sheet. Any information collected during the study will be kept confidential, aside from enabling the research team to inform participants about the development of new tests if participants have agreed to this as part of the consent process.

Pseudonymised (de-identified) information and DNA collected during the study may be transferred both within and outside the European Economic Area as part of ongoing collaboration with other researchers. This may include combining data from participants' samples with those of other patients in order to determine important factors related to Parkinson's. This information may be made available to other researchers to enable large-scale analysis and new discoveries. Pseudonymised (de-identified) data will be hosted centrally through a secure web-based database holding research data without personal details. This will meet high security standards and safety measures, including ISO27001 certification, and will enable sharing of data to approved groups. Participants are informed of this in the Exenatide-PD3 patient information sheet and will consent to these specific aspects. Personal data will be held separately from research data on a separate, secure web-based database meeting the same security standards. Written records linking participant identification numbers with personal identifiable information (e.g. contact details for future communication) will be stored securely in locked filing cabinets.

11.2.6 Follow-up and future contact

During the consent process for the sub-study, participants will be asked if they would be happy to be contacted in the future to provide further samples or details about their Parkinson's or to learn about new tests or research studies for which they may be eligible. In some circumstances the research analyses may indicate that existing or future NHS-based genetic or chemical testing may be useful in accurately diagnosing PD and in determining the risk of disease to other members of the participant's family, or selecting treatments.

Participants can choose whether they wish to be informed about this, in advance. If they do choose to be informed of future test development, the genetics sub-study team will arrange for them to be given appropriate genetic advice and counselling.

11.2.7 Withdrawal

Participation in the genetic sub-study is voluntary and participants can choose to withdraw at any time. If participants decide not to take part or to withdraw from the genetic sub-study, participation and treatment in the main study will not be affected. If participants withdraw from the main study (withdrawal from treatment and/or withdrawal from follow-up), their data and samples will be retained for further use as described in the sub-study participant information sheet. If participants request that their samples and data be withdrawn from the genetic sub-study, every effort will be

made to destroy samples and data that have been provided but in some cases this may not be possible, e.g. when further analyses have been carried out by collaborators.

11.3 Appendix 3 Cerebrospinal Fluid Sub-Study

11.3.1 Eligibility Criteria

The eligibility criteria for the cerebrospinal fluid sub-study are identical to the inclusion and exclusion criteria of the main Exenatide-PD3 trial with the addition of an extra exclusion criterion as follows:

- Patients with a bleeding tendency or low platelet count or who are currently receiving warfarin treatment or any other anticoagulant.

The cerebrospinal fluid sub-study is only being conducted at a restricted number of sites participating in the main Exenatide-PD3 trial.

11.3.2 Aim

To determine whether any CSF changes associated with PD are influenced by exposure to exenatide. These may include alpha synuclein monomers or oligomers, Neuroinflammatory markers, Exosomal contents.

11.3.3 Rationale & Risks/Benefits

The sampling of the cerebrospinal fluid (via lumbar puncture) will help to determine the mechanism(s) of action of exenatide. This will support the clinician-led and patient-reported outcome measures of the Exenatide-PD3 trial.

Lumbar punctures are generally very low-risk procedures. However, they sometimes cause short-lived side effects. Some people experience some lower back pain after a lumbar puncture. This is usually felt in and around the area where the needle was inserted, but it can also be felt in the backs of the legs. In most cases, the pain will ease after a few days and it can be treated with painkillers, such as paracetamol.

A headache is a common side effect usually developing within 24 to 48 hours of the procedure. Most people describe a dull or throbbing pain at the front of their head, sometimes spreading to the neck and shoulders. The pain is usually worse while standing or sitting up and is usually relieved by lying down and can be treated with oral fluids, caffeine or painkillers.

Patients may experience some bruising and minor swelling in the lower back. The swelling is caused by a small amount of fluid leaking and collecting under the skin. This should go down naturally.

If patients develop a temperature or sensitivity to bright lights, if the lumbar puncture site becomes painful and swollen, they notice blood or clear fluid around the site, they experience tingling and numbness in legs, hearing loss and double vision they should seek medical advice.

11.3.4 Assessments

Consenting participants will have a 15ml sample of CSF taken via a lumbar puncture test at baseline (Visit 2) and at week 96 (Visit 10) and stored until the end of the trial.

The lumbar punctures will be carried out under local anaesthetic with the patient lying on their side, with their legs pulled up and their chin tucked in (sometimes the procedure is carried out whilst the patient is seated and leaning forwards). A hollow needle will be very carefully inserted into the base of the spine which contains the nerves coming from the spinal cord. The pressure within the spinal

canal is measured and a sample of CSF is slowly removed and sent for testing. It usually takes around 15-20 minutes to complete. Patients will be instructed to lie flat for at least 1 hour after the procedure to minimise post lumbar puncture headache.

11.3.5 Outcomes and analysis

All samples will be centrifuged and stored in 1ml aliquots with the unique trial participant identification number (PIN) and visit number. Analysis will be performed by the research team who will be blinded to the status or identity of the sample. Formal analyses plans for all CSF samples will include exploring the molecular features in CSF that reflect the underlying pathophysiology Parkinson's disease with the aim of using these to demonstrate the certainty of the diagnosis in comparison to other atypical parkinsonian conditions, prediction of patient's progression profiles over the course of the trial and exploring markers ability to capture therapeutic effects from exenatide over the 6 month intervals in the trial. To explore these different aspects the levels and activity profile of a number of molecules will be studied with a variety of laboratory techniques including serum neuronal exosomal studies, enzyme linked immunoassays, Real-time quaking induced conversion and electron microscopy. Potential molecules that will be studied include alpha synuclein and its phosphorylated and oligomeric subtypes, tau and its phosphorylated subtypes, markers of insulin resistance including IRS-1 pSer312, markers of neurodegeneration such as neurofilament light chain and markers of inflammatory response and astrocyte activation including interleukin levels, NDRG2, GFAP, and S100 β . . Baseline CSF samples will be made available for comparison with CSF samples taken from patients participating in other ethically approved studies.

Pseudonymised (de-identified) information during the sub-study may be transferred both within and outside the European Economic Area as part of ongoing collaboration with other researchers. This information may be made available to other researchers to enable large-scale analysis and new discoveries. Pseudonymised (de-identified) data will be hosted centrally through a secure web-based database holding research data without personal details. This will meet high security standards and safety measures, including ISO27001 certification, and will enable sharing of data to approved groups. Participants are informed of this in the sub-study patient information sheet and will consent to these specific aspects. Personal data will be held separately from research data on a separate, secure web-based database meeting the same security standards. Written records linking participant identification numbers with personal identifiable information (e.g. contact details for future communication) will be stored securely in locked filing cabinets.

11.4 Appendix 4 Remote Monitoring of PD symptoms Sub-Study

11.4.1 Eligibility Criteria

The eligibility criteria for the Remote Monitoring of PD Symptoms Sub-Study are identical to the inclusion and exclusion criteria of the main Exenatide-PD3 trial. The Remote Monitoring of PD Symptoms Sub-Study is being conducted at a restricted number of sites participating in the main Exenatide-PD3 trial.

11.4.2 Aim

The Remote Monitoring of PD symptoms sub-study has the aim to help determine whether the assessment of voice and movement symptoms in patients with PD is better performed using a smartphone or by conventional clinical methods used by a doctor or nurse.

11.4.3 Rationale & Risks/Benefits

The application of the 10 minute mobile phone test will provide an objective measure of participant's voice and movements. This will support the clinician-led and patient-reported outcome measures of the Exenatide-PD3 trial.

11.4.4 Assessments

During five of the clinic visits, consenting participants will have their voice and movement measured using a 10 minute smartphone test (before and after they take their Parkinson's medication)- the phone being used to assess voice, balance, gait, resting and postural tremor, finger tapping and reaction time with the phone held in the participant's hand, on a flat surface, in their trouser pocket or briefly strapped onto their lower back.

We will also invite participants to record their voice and movement symptoms at home five times (1 week at a time, 3 times daily) using a recycled loaned research consumer grade phone, and/or a wearable lumbar sensor. The small sensor worn over the lower back (lumbar region) will be attached using sticky-backed plastic by the research team at the clinic visit, and worn continuously over 1 week.

Both the loaned research phone and lumbar back sensor (CE marked) will be posted back to the research team using stamp-addressed envelopes given out in clinic with clear written instructions and a telephone contact for problems or queries.

The smartphone test and/or the lumbar sensor will be completed/worn at the following time points:

- Baseline (Visit 2)
- Week 24 (Visit 4)
- Week 48 (Visit 6)
- Week 72 (Visit 8)
- Week 96 (Visit 10)

Patients will be asked to complete a questionnaire at baseline and at the end of the study.

11.4.5 Outcomes and analysis

All recordings will be stored with the unique participant identification number (PIN) as well as their date of birth and gender. When the lumbar sensors are returned to site, data will be downloaded by the research team and uploaded to a secure GDPR compliant cloud held by Newcastle University.

Data from the smartphones will be automatically uploaded to a secure GDPR compliant cloud held by the University of Oxford, upon the patient completing their assessment, if the device is connected to WiFi. Analysis will be performed by Professor Hu, at University of Oxford and Professor Lynn Rochester's team at Newcastle University according to existing analytic protocols. Contractual agreements will be in place with both institutions.

11.5 Appendix 5 DaTSCAN imaging sub-study

11.5.1 Eligibility Criteria

The eligibility criteria for the imaging sub-study are identical to the inclusion and exclusion criteria of the main Exenatide-PD3 trial with the addition of an extra exclusion criterion as follows:

- Known or suspected intolerance of DaTSCAN or Potassium Iodide administration.

The imaging will be being conducted at the UCLH site and will be limited to 80 consenting participants (balanced equally between the exenatide and placebo groups). Participants recruited at other sites who are able to travel to the ULCH site will be eligible to participate.

11.5.2 Aim

To determine if any differences in dopamine transporter availability in the caudate and putaminal nuclei as measured by quantitative DaTSCAN signal is influenced by exposure to exenatide.

11.5.3 Rationale & Risks/Benefits

“DaTSCAN” (ioflupane (I-123)) is a SPECT ligand which can precisely quantify the presence of dopamine transporters, present on surviving pre-synaptic dopaminergic terminals. A reduced rate of decline of DaTSCAN binding in the exenatide group was noted in the Exenatide-PD2 trial on statistical parametric mapping analysis. In the Exenatide-PD3 trial, DaTSCAN imaging will be utilised to further explore these findings over two years. This will support the clinician-led and patient-reported outcome measures.

These scans are acquired at the Department of Nuclear Medicine at UCLH. Patients are given Potassium Iodide by the Department of Nuclear Medicine with instructions to take two doses of this in the 24 hours before the scan to minimise ligand uptake by the thyroid gland. DaTSCAN is then given as a single injection via the intravenous route. The recommended radioactivity given by injection is between 111 to 185 MBq (megabequerel). The image scanning is subsequently performed 3 to 6 hours after the injection.

DaTSCAN imaging is a very low-risk procedure. However, it can cause short-lived side effects. Some people experience a mild headache (1 in 10) for a brief period and less common side effects (1 in 100) include increased appetite, dizziness, taste disturbance, nausea, dry mouth, vertigo, formication (a sensation of insects crawling under the skin) and burning pain at the injection site. Other rare side effects of uncertain frequency include hypersensitivity, shortness of breath, hypotension, rash and urticaria. All scans will be extra to those that participants would have if they did not take part in the trial. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. The chances of this happening to participants as a consequence of taking part in this study are 0.04%. The dose of radioactivity in the body from the scan is very small and is passed out of the body within a few days without the need for special precautions. As the injection will contain 5% ethanol by volume (197 mg), patients will be informed of this at consenting. The use of contraception will be reinforced in view of the risk of radioactivity to the child and caution against breastfeeding for 3 days after the scan will be advised if relevant in cases.

11.5.4 Assessments

Consenting participants will have DaTSCAN imaging performed prior to their baseline (Visit 2) (-14 days maximum) and at week 96 (Visit 10) -14 /+ 7 days. DaTSCAN imaging will not be undertaken until

eligibility has been confirmed by assessments carried out at screening visits and adequate screening blood results. This is to ensure patients are not scanned and exposed to radiation unnecessarily.

11.5.5 Outcomes and analysis

Statistical parametric mapping will be utilized to quantitatively analyse DaTSCAN data. Baseline and delayed images for each participant will be smoothed and co-registered before spatial normalisation into Montreal Neurological Institute space via a DaTSCAN template. We will utilise a fully flexible model after image scaling to assess between-group differences in loss of DaTSCAN uptake between baseline and 96-week scans by ANCOVA, adjusting for baseline differences in DaTSCAN signal, Hoehn and Yahr stage, and change in LED at 96 weeks. Further analysis will also be done to assess the differences in the changes between the two allocations. The resulting statistical parametric maps will be masked to restrict differences to bilateral caudate and putamen regions at a height threshold of p less than 0.01, uncorrected for multiple comparisons, and for an extent threshold of ten voxels.

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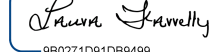
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Professor & Director

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