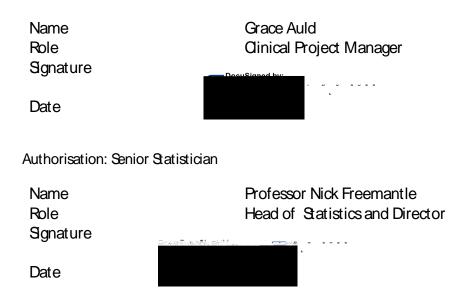


A randomised, double blind, parallel group, placebo controlled, Phase 3 trial of Exenatide once weekly over 2 years as a potential disease modifying treatment for Parkinson's disease.

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Date	22 Feb 2022
Sponsor	University College London (UCL)
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Authorisation: Senior Operations Staff





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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.

Primary	Registry	and	Trial	Clinicaltrials.gov: NCT04232969
Identifying	g Number			
Date of	Registration	in	Primary	ISRCTN: 08 Oct 2019
Registry				Clinicaltrials.gov: 16 Jan 2020
Secondary Identifying Numbers			bers	ISRCTN: ISRCTN14552789

Primary Outcome(s)	Outcome name - Motor score
Primary Outcome(s)	
	medication state.
	Matria Mayament Disorder Opticity Unified
	Metric - Movement Disorder Society Unified
	Disease Rating Scale part 3 Motor subsection score.
	Timenaint OC weeks
	Timepoint - 96 weeks
Key Secondary Outcomes	Difference between 96 week scores for each of the
	secondary outcomes listed below will be compared between
	groups according to treatment allocation:
	Disease Deting Orden and 4.0.0 and 4.0N as a first inc
	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)
	questionnaire
	Non-Motor Symptoms scale
	Levodopa equivalent dose
	3 day Hauser diary of PD state (Time-On, Off, Non
	troublesome Dyskinesia, Troublesome dyskinesia,
	Asleep)
	Difference between total values over 96 week for each of the
	secondary outcomes listed below will be compared between
	groups according to treatment allocation:
	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-5LUK tariff and adjusting for baseline.
	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
	Disease Rating Scale part 3 Motor subsection OFF
	medication score
	Movement Disorder Soci
	Disease Rating Scale part 1,2,3 and 4 ON medication
	scores

Name

Pre-screening

Terms of Reference Tropomyosin receptor kinase B Trial Steering Committee

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

points over the course of the trial. Serial DaTscan showed no progression between baseline and 48 weeks in the exenatide

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 Bashoff 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)

Exenatide-PD3

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

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

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.

It is anticipated that recruitment will be completed from six UK sites (National Hospital for Neurology and Neurosurgery, K 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.

Bigibility criteria:

A named dinician 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 GOP, 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.

Stes 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.

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. Stes 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 OCTU.

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

6.3.1.1 Participant selection

further confirm that the participant has clinical symptoms and signs and/or radiological investigations consistent with a diagnosis of Park

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

6.3.1.3 Participant Exclusion Criteria

- 1. <u>Diagnosis or suspicion of other cause for Parkinsonism.</u> 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. <u>Body mass index <18.5.</u> (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. <u>Concurrent severe depression</u> defined by a score 16 on the Patient Health Questionnaire (PHQ-9)
- 7. <u>Prior intra-cerebral s</u> undergone Deep Brain Stimulation, intra-cerebral administration of growth factors, gene therapy or cell therapies will not be eligible.
- 8. <u>Previous participation in one of the followin</u> (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. <u>Participation in another clinical trial of a device, drug or surgical treatment within the last 30 days</u>.
- 10. Previous exposure to exenatide.
- 11. Impaired renal function with creatinine clearance <50ml/min.
- 12. History of pancreatit4ll4h

21. Participants who lack the capacity to give informed consent.

22.

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

<u>Deep Brain Stimulation (DBS)</u>: 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.

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

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

<u>EQ-5D-5L</u>: 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.

<u>CSRI</u>: 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

<u>3 day Hauser diary of PD state</u> (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.

	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	
Rexibility 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											

^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 CSR.

⁹The MDS-UPDRSpart 3

^p The baseline DaTSCAN imaging

. 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.

The sample size calculations have been based on the detectable effect size

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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 (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 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

Exenatide

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 trialspecific proce dical 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

summary of product characteristics (SPC) for an authorised

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

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 dosure.

The Exenatide-PD3 Serious Adverse Event form must be completed by the investigator (the consultant named on) 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 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 dinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue

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 respons 0 11.9867.00000mhe independe

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 astrocy

trial 2, Or GCIa GO 2003-56<0102-12<017D-5<0100-4<015D011A-5<011E-9<0003-56<0102-12<0003-56

Exenatide-PD3 is fully funded by the Efficacy and Mechanism Evaluation (EME)

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 whet e] TJETQq0.000008871

documented at screening and at each follow up visit. Their height will be recorded at screening to enable calculation of

6.4.5.2 Dose Interruptions replaced by

6.6 Participant Timeline Hauser Diary

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.

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

6.9.1.1 Sequence generation

Balancing factors added (research site and sub studies)

unique 3 digit identifiers for every active/placebo drug kit

Changed to

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

11.5 Appendix 5 Proof-of-concept imaging sub-study- added.

This study will be run through Prof. Marios Politis at the Maurice Wohl Clinical Neuroscience Institute, Institute of

London (KCL). KCL will apply for separate ethical approval for this study and provide all study documentation.

wording removed

İS″

Exenatide-PD3

Exenatide-

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.



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- (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. BMJ2013; 346:e7586.
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Exenatide

(46) Hauser RA

et al. A Home Diary

Drug	Conversion factor	
Immediate release L-dopa	X1	j
Controlled release L-dopa	X0.75	1
Entacapone (or Stalevo®)	LD X 0.33	1
Tolcapone	LD X 0.5	1
Opicapone	LD X 0.5	j
Duodopa®	X1.11	j
Pramipexole (as salt)	X100	j
Ropinirole	X 2072.5041 0 0 1 4 Tf Tm0 G[()] TJETQQ EMOF1	11.0415 580.66

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 visitThese blood samples will be collected in EDTA sample tubes for the extraction of DNA by University College London Hospitals/ UCL Neurogenetics Laboratory.

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

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 Roor, 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 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 sease 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.

11.2.3.1 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 dinical 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.

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 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 amples with those of other patients

11.3.1

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:

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.

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

. Baseline CSF samples

11.4.1

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.

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.

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

During five of the dinic visits, consenting participants will have their voice and movement measured using a 10 minute smartphone test - 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.

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 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 lodide 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.

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.

(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 lodide 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 subsequ088r reW* nq0.000008871 0s-110(f)10(c)-2

Certificate Of Completion

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UCL

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prof

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