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Exenatide once weekly over 2 years as a potential disease modifying treatment for Parkinson's disease: protocol for a multi-centre, randomised, double blind, parallel group, placebo controlled, Phase 3 trial, The 'Exenatide-PD3' study

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Exenatide once weekly over 2 years as a potential disease modifying treatment for Parkinson's disease: protocol for a multi-centre, randomised, double blind, parallel group, placebo controlled, Phase 3 trial, The 'Exenatide-PD3' study

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18 Key Words:

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20 Exenatide; Parkinson's disease; randomised control trial.

21 22 23 **Abstract**

24 25 **Introduction**

26
27 Parkinson's disease (PD) is a common neurodegenerative disorder with substantial morbidity. No
28 disease modifying treatments currently exist. The glucagon like peptide-1 receptor agonist exenatide
29 has been associated in single centre studies with reduced motor deterioration over 1 year. The aim
30 of this multicentre UK trial is to confirm whether these previous positive results are maintained in a
31 larger number of participants over two years and if effects accumulate with prolonged drug
32 exposure.
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35 36 **Methods and analysis**

37 This is a phase 3, multi-center, double-blind, randomised, placebo-controlled trial of exenatide at a
38 dose of 2 mg weekly in 200 participants with mild to moderate PD. Treatment duration is 96 weeks.
39 Randomisation is 1:1, drug to placebo. Assessments are performed at baseline, week 12, 24, 36, 48,
40 60, 72, 84, and 96 weeks.
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43 The primary outcome is the comparison of MDS-UPDRS part 3 motor sub-score in the practically
44 defined OFF medication state at 96 weeks between participants according to treatment allocation.
45 Secondary outcomes will compare the change between groups among other motor, non-motor and
46 cognitive scores. The primary outcome will be reported using descriptive statistics and comparisons
47 between treatment groups using a mixed model, adjusting for baseline scores. Secondary outcomes
48 will be summarised between treatment groups using summary statistics and appropriate statistical
49 tests to assess for significant differences.
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52 53 **Ethics and dissemination**

54 This trial has been approved by the Research Ethics Committee and the Health Research Authority.
55 Results will be disseminated in peer-reviewed journals, presented at scientific meetings and to
56 patients in lay-summary format.
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58 59 **Article Summary**

60 **Strengths and Limitations of this Study**

- This is the protocol for the first phase 3 double-blind, randomised, placebo controlled trial of Exenatide in Parkinson's disease (PD).
- This study uses novel secondary outcome measures in sub-studies (cerebrospinal fluid analysis, dopamine transporter imaging, and digital technology measurement devices) which should provide a more sensitive and comprehensive assessment of potential disease modification.
- Although the 2 year follow-up period should provide a more definitive signal on disease modification this will take longer to report findings and has risks for long-term patient retention

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting over 10 million people worldwide and its prevalence is increasing [1]. Symptomatic treatments are available and mainly focus on dopamine replacement strategies [2,3]. Such therapies provide improvements in the core motor features of PD: tremor, limb rigidity and slowness of movement (bradykinesia) [4]. These symptomatic treatments do not impact on the progressive nature of the disease nor the majority of the non-motor symptoms (NMS). Moreover, with time, some patients will develop dopamine-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 with mounting care needs.[3,4]. These complications result in increased dependence, care giver strain, need for 24 hour care and death. Therefore, Parkinson's disease is a growing problem for individuals, healthcare and society making the development of disease modifying treatments imperative.

Exenatide (Exendin-4) is a licensed and effective treatment for patients with type 2 diabetes mellitus (T2DM) [5]. It is an agonist for the Glucagon-like peptide 1 (GLP-1) receptor and in the presence of elevated blood glucose stimulates insulin release. It also increases pancreatic beta islet cell mass and reduces apoptosis. 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 [5].

In parallel with the confirmation of the beneficial effects of exenatide on glucose control, laboratory work has showed that exenatide has beneficial effects on neurons in vitro [6]. Exenatide induces neurite outgrowth, promotes neuronal differentiation and rescues degenerating neuronal cells while also reversing neurotoxin induced damage in animal models [6,7]. These neurotrophic properties have sparked interest regarding its potential use as a neurodegenerative disease modifying agent [8,9].

The specific relevance of exenatide to PD has also been extensively evaluated. Exenatide has been shown to increase transcription of tyrosine hydroxylase (TH) (the rate limiting enzyme in dopamine synthesis) in brainstem catecholaminergic neurons [10]. Furthermore, stimulation of GLP-1 receptors may have beneficial effects on the neurodegenerative processes of PD through downstream cellular pathways [6,11]. These findings are further supported by a recent study suggesting a reduced future risk of developing PD in T2DM patients treated with GLP-1 agents [12].

To investigate the potential effects of exenatide in patients with PD, an investigator-initiated pilot trial was undertaken [13]. This open label, parallel group, randomised controlled trial evaluated the tolerability of exenatide (Byetta 10mcg twice daily) in 45 patients with moderately severe PD (Hoehn and Yahr stage of less than 2.5) over an exposure period of 48 weeks with a subsequent washout

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3 period of 12 weeks. This showed an advantage of 4.9 points in in the Movement Disorders Society
4 Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 (motor sub-score) in exenatide treated
5 patients at 12 months which persisted even after a 12 week washout period. Clinically important
6 differences in cognition were also noted. Serial DaTscan imaging showed no progression between
7 baseline and 48 weeks in the exenatide treated patients [13].
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10 A further Phase 2 double blind randomised controlled trial evaluating the effects of exenatide in 60
11 patients with PD has subsequently been performed [14]. Patients were randomised to self-injection
12 of a long acting form of exenatide, (Bydureon 2mg) once weekly, or matched placebo for 48 weeks.
13 Detailed assessments every 12 weeks for the duration of the treatment and a further assessment at
14 the 60 week time point to explore any lasting effects following washout of the trial medication were
15 performed. Patients receiving exenatide had a mean 3.5 point advantage in their MDS-UPDRS part 3
16 OFF medication scores compared to patients receiving placebo at the 60 week timepoint. Biological
17 specimens collected from trial participants confirmed changes according to treatment with
18 exenatide in downstream cellular effector pathways [15].
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21 The current trial objective (Box 1) is to confirm or refute whether the previous positive results can be
22 reproduced in a multicentre trial design, including a larger number of participants evaluated over
23 twice as long a period as previously. An important secondary objective is to explore if positive effects
24 seen after 48 weeks of exenatide exposure remain static or increase in amplitude by the 96-week
25 time point. The hypothesis is that exenatide will be associated with reduced MDS-UPDRS part 3
26 scores at the 96-week time-point. The overriding priority for this trial is to provide evidence to
27 support or refute any signal of efficacy of exenatide in PD, and thus provide the justification for rapid
28 further investment in this drug if appropriate. In parallel with this, is the aim to explore whether any
29 biological effect(s) of exenatide, relevant to PD, are purely symptomatic effects as opposed to
30 disease modifying effects.
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Box 1 Trial Objectives**Primary**

- 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)

Secondary

- Compare differences at 48 and 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 between scores at 48 and 96 weeks between the exenatide and placebo trial arms in:
 - MDS-UPDRS part 3 Motor subsection OFF medication score

Exploratory

Compare differences between slopes at pre-specified periods between exenatide and placebo trial arms for key outcomes to investigate whether exenatide can be considered disease modifying.

Methods

This trial protocol was designed using the University College London (UCL) Comprehensive Clinical Trials Unit (CCTU) Protocol template. The trial is sponsored by UCL and coordinated by the CCTU. The protocol was designed to provide information about procedures for entering participants into the trial, and 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. All stake holders (research team, sponsor, CCTU and oversight committees) were involved in the design and approval of the protocol. A particular emphasis was given to patient input in the trial design. This patient and public involvement (PPI) approach has proven to be of value in other studies [16] and was harnessed to improve the overall study design. A focus group meeting with patients was organized in the protocol design stages to obtain feedback from patients which led to a number of amendments prior to submission, including the maximum overall trial duration of 96 weeks, and the use of OFF-medication assessments. Two PPI representatives will serve on the trial steering committee (TSC) and will continue to provide regular input throughout recruitment. Patients will also be provided access to the trial website and a link to the protocol and patient information sheets (PIS) on request and will be given the opportunity to continue to provide comments and contact researchers to further discuss their input. The INCLUDE guidance [17] is an NIHR led initiative to improve inclusion of under-served groups. The design of the trial is mindful of the value of the steps outlined in this initiative and aims to incorporate its recommendations into overall trial recruitment with the overarching aim of providing better access and quality care to under-served patient groups.

Patient and Public Involvement:

In the development of this protocol, a formal meeting was held with 6 patients with PD, hosted by the Cure Parkinson's Trust. The aims and the objectives of the trial were discussed including the importance of distinguishing between symptomatic and disease modifying effects of exenatide. Patient feedback was clear that a 2 year period would be the maximal acceptable duration of self-administration of placebo, therefore the trial duration was reduced from the original planned 3 year duration to 96 weeks. The use of weekly self-administered injections, and attendance in the off-medication state to assess PD severity was discussed in detail and considered acceptable. The recruitment strategy has used the patient networks of the Cure Parkinson's Trust and Parkinson's UK to increase the awareness of the trial. Patients and patient representatives are included in the Trial Steering committee. At the end of the study, all participants will be notified of their randomisation allocation and of the main study results. The results will be presented at meetings convened for patient groups and published in open access peer reviewed publications.

Trial design

This is a simple parallel group multicentre phase 3, double-blind, randomised, placebo-controlled 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 (Figure 1). Participants will also attend on a 12

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3 weekly basis to collect supplies of IMP. Participants will be randomly allocated to receive either
4 Exenatide extended release 2mg subcutaneous injection (Bydureon) once weekly for 96 weeks
5 n=100, or Exenatide extended release placebo subcutaneous injection once weekly for 96 weeks
6 n=100. In addition, participants will be randomised using a minimisation algorithm (with a random
7 element incorporated) balancing by research site, participants with greater (Hoehn & Yahr stage 2.5)
8 or lesser (Hoehn & Yahr stage 2.0 or less) PD severity (in the ON medication state), and participation
9 in the sub-studies (Remote Monitoring, Imaging, or not participating).
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14 **Participants & recruitment**

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16 Patients are eligible for screening if they have a clinical diagnosis of PD. The Queen Square brain
17 bank criteria[18] can be also be used to assist in the diagnosis, however, this is not a formal inclusion
18 criterion, and the relevance of a positive family history of PD, or a confirmed genetic basis for an
19 individual's symptoms will be evaluated in the context of other clinical features in determining
20 diagnosis and eligibility. Key inclusion and exclusion criteria are summarised in Box 2.
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23 Participants will typically be recruited through specialist movement disorders clinics at trial sites. The
24 trial will be advertised online by the Parkinson's UK website, the Cure Parkinson's Trust and the NIHR
25 Clinical Research Network websites and will be registered on ClinicalTrials.gov and the ISRCTN
26 registry. Trial advertisements will direct participants to contact teams in order to be provided with a
27 patient information sheet and a reply slip to confirm ongoing interest and to organise a pre-
28 screening telephone call to discuss eligibility and suitability for the study. It is anticipated that
29 recruitment will be completed from six UK sites (National Hospital for Neurology and Neurosurgery
30 (Queen Square, London), King's College Hospital NHS Foundation Trust (London), Oxford University
31 Hospitals NHS Foundation Trust (Oxford), Derriford University Hospital (Plymouth), Salford Royal
32 Hospital (Manchester) and Western General Hospital & Royal Infirmary of Edinburgh (Edinburgh).
33 Recruitment rates will be carefully monitored throughout the trial to inform on the total number of
34 sites required to ensure final recruitment milestones will be reached. If needed, further sites will be
35 set up. All patient assessments will be performed at hospitals in the UK, once sites have confirmed
36 capacity and capability and a site initiation visit has been performed.
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Box 2 Key inclusion and exclusion criteria for study

Key inclusion criteria

- Diagnosis of Parkinson's disease PD based on review of the participant's clinical history, examination findings and response to PD medications. The Queen Square brain bank criteria [18] can be also be used to assist the diagnosis, however this is not a formal inclusion criterion. 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.
- 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.
- Between 25 and 80 years of age.
- 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.
- Ability to self-administer, or to arrange carer administration of trial medication.
- Documented informed consent to participate.

Key exclusion criteria

- 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.
- Patients unable to attend the clinic visits in the practically defined OFF medication state.
- Body mass index < 18.5 . (Exenatide is known to cause weight loss therefore individuals that may not tolerate further weight loss will not be recruited).
- Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol.
- Significant cognitive impairment defined by a score < 21 on the Montreal Cognitive Assessment.
- Concurrent severe depression defined by a score ≥ 16 on the Patient Health Questionnaire (PHQ-9)
- 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.
- 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.
- Participation in another clinical trial of a device, drug or surgical treatment within the last 30 days.
- Previous exposure to exenatide.
- Impaired renal function with creatinine clearance < 50 ml/min.
- History of pancreatitis. Screening serum amylase value must fall within laboratory normal range $\pm 50\%$.
- Type 1 or Type 2 Diabetes mellitus.
- Severe gastrointestinal disease (e.g. gastroparesis)
- Hyperlipidaemia. A lipid profile will be tested at the screening visit. Cholesterol or Triglyceride levels greater than 2 x the upper limit of normal will raise suspicion of a familial or acquired hyperlipidaemia and will prompt referral to a relevant specialist for investigation and treatment.
- History or family history of medullary thyroid cancer (MTC). Undiagnosed neck lump, hoarse voice or difficulty swallowing (not attributable to PD diagnosis).
- Multiple endocrine neoplasia 2 (MEN2) syndrome.
- Hypersensitivity to any of exenatide's excipients.
- Females that are pregnant or breast feeding. There are no safety data regarding exenatide use in pregnancy.
- Women of child bearing potential 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
- Participants who lack the capacity to give informed consent.
- Any medical or psychiatric condition or previous conventional/experimental treatment which in the investigator's opinion compromises the potential participant's ability to participate.

Outcomes

Safety monitoring

Safety and tolerability of exenatide as indicated by changes in vital signs, weight, clinical laboratory measures and adverse events (AEs) will be recorded and monitored throughout. Each patient will have their pulse, blood pressure and weight documented at screening and at each follow up visit. Exenatide is known to cause weight loss. Participants' height will be recorded at screening to enable calculation of body mass index. At each visit, participants are asked to report any AEs that have occurred since the previous visit. AEs may also be detected by the study team reviewing the patient or through notification by the participant's primary care physician. All AEs will be assessed by a study doctor for their severity, likely relationship to study drug and required action by a study doctor not involved in the blinded assessment of the patient. All SAEs will be recorded and reported to the sponsor regardless of relation to trial treatment. Any suspected unexpected serious adverse reactions will be reported to the sponsor immediately to allow facilitation of unblinding as necessary. All AEs reported will be reviewed by the trial management group, trial steering group and monitored by an independent data monitoring committee. Unblinding requests from other clinicians responsible for a patient's care will be handled by the principal investigator (PI) at each site. The PI at each site may also choose to unblind a participant in response to reported AEs as they are reported, if judged to be clinically necessary.

Primary Outcome

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. 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 and adjusted for baseline will be the primary outcome. The scores for these assessments will be collected and recorded by trained clinical trial personnel (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 as part of a MDS-UPDRS automated scoring sub study though the availability of these videos will also enable repeated independent scoring to be performed if there are concerns raised about data quality from a specific site/rater.

Secondary Outcomes

Comparisons at 48 and 96 weeks between participants according to treatment allocation will also be performed for each of the secondary outcomes listed below.

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 48 weeks and also the difference between scores at 48 weeks 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.

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3 **Montreal Cognitive assessment (MoCA).** This scale is a validated global measure of cognitive ability.
4 This will be assessed in the ON medication state.
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6 **Timed Tests.** Participants will be asked to perform a **Sit-stand-walk timed test** in both the OFF
7 medication and ON medication state. The timed Sit-stand-walk test will incorporate time taken from
8 seated position to stand and walk 10 metres, turn and return to original seated position.
9

10 **Unified dyskinesia rating scale (UDysRS).** This is considered to be the most useful and objective way
11 of quantifying dyskinesia severity. This will be assessed in the ON medication state.
12

13 **Patient Health Questionnaire-9 (PHQ-9).** This scale allows for self-quantification of depression
14 severity. This will be assessed in the ON medication state.
15

16 **Non-motor symptom scale (NMSS).** This validated scale is a tool to collect data on the frequency and
17 severity of 30 non-motor symptoms sometimes experienced by PD patients. This will be assessed in
18 the ON medication state.
19

20 **The Parkinson's Disease Questionnaire (PDQ-39).** This is the standard disease specific measure of
21 quality of life in PD comprising 39 questions. It has been extensively validated in previous studies.
22

23 **Levodopa equivalent dose (LED).** To facilitate comparisons between patients taking different
24 regimes of conventional PD medications, a set of conversion factors have been used to convert each
25 of the commonly used PD medications to an LED of each of their medications can then be summed
26 for inter-patient / inter-group comparisons.[19]
27

28 **EQ-5D-5L.** This is a simple, 5 question form and visual analogue scale that allows calculation of
29 quality adjusted life years (QALY) to enable health economic analyses to be performed.
30

31 **The Client Service Receipt Inventory (CSRI).** Health and social care resource use. Self-completed
32 health care, social care and paid/unpaid carer resource use questionnaire asking about primary and
33 secondary care resource use relevant to Parkinson's and impact on carers in the past 6 months.
34

35 **3-day Hauser diary** of PD state (Time- On, Off, Troublesome Dyskinesia, Non-troublesome
36 dyskinesia, Asleep). Diary data allows quantification of the amount of time during a 3-day period
37 that patients spend in the varying states of movement ability.
38

39 **Ancillary Studies**

40 There are four optional sub-studies linked to the main trial:
41

42 1. Genetics sub-study: To try to identify genetic markers that may be associated with subtypes of PD
43 or variation in treatment responsiveness.
44

45 2. Cerebrospinal Fluid (CSF) sub-study: To determine whether any CSF changes associated with PD
46 are influenced by exposure to exenatide. These may include alpha synuclein monomers or
47 oligomers, neuroinflammatory markers, and exosomal contents.
48

49 3. Remote Monitoring of PD Symptoms sub-study: To help determine whether measurement of PD
50 symptoms using digital technology may be a more sensitive measure of change with active drug
51 versus placebo compared to the MDS UPDRS 3 in the OFF and ON medication states. This will form
52 two separate measurements comprising 1) home-based smartphone and 2) real-world gait/walking
53 activity monitoring.[20][21][22] This aims to generate precision data, providing person-specific
54 distributions of outcomes and may be able to better delineate baseline clinical features.
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3 4. DaTSCAN (Imaging sub-study): To determine if change in dopamine transporter availability in the
4 caudate and putaminal nuclei as measured by quantitative DaTSCAN signal is influenced by exposure
5 to exenatide compared to placebo.
6

7 **Visits**

8
9 The overall progression of assessments are summarised in figure 1. While we expect to undertake all
10 assessments in respective clinical units, provision has been made in line with INCLUDE guidance for
11 the possibility of home visit assessments to be performed when patient specific situations (e.g.
12 inability to travel due to coronavirus restrictions, worsening 'OFF' state over progression of trial)
13 necessitate this. We hope that this provision will aid overall trial retention while enhancing
14 recruitment of patients from typically less well represented demographics (e.g. rural geographic
15 regions, patients lacking private travel facilities).
16
17

18 **Screening Visit**

19
20 Written informed consent to enter and be randomised into the trial will be obtained from
21 participants, after explanation of the aims, methods, benefits and potential hazards of the trial and
22 before any trial-specific procedures are performed or any blood is taken for the trial. Patients will be
23 screened using the history of their Parkinson's disease, supported by any available clinical
24 correspondence according to usual standard of care.
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26

27 The collection of the following scales will evaluate patient eligibility: MoCA, PHQ-9, as well as blood
28 tests (full blood count, urea & electrolytes, creatinine, liver function tests, HbA1C, C-peptide,
29 coagulation, serum amylase, thyroid function tests, blood glucose, insulin and lipid profile, and a
30 pregnancy test for women of child bearing potential). Tests can be repeated between screening and
31 baseline visits, if required to confirm eligibility.
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33

34 Patients recruited to the DATSCAN substudy will have imaging performing prior to their baseline
35 visit.
36

37 **Baseline visit and randomisation**

38
39 Previously defined primary and secondary outcome measures will be performed in the 'ON' and
40 'OFF' states as outlined below. Patients' LED will be noted. Randomisation to either exenatide or
41 placebo will be administered using a centralised, web-based system (www.sealedenvelope.com). All
42 assessments related to sub-studies will also be performed prior to trial medication administration.
43
44

45 **Assessment Procedures**

46 After the Screening Visit, the named site clinical staff member will call the participant to remind
47 them of the need to stop taking their regular PD medication prior to their next trial visit and to
48 attend in a fasted state (prior to visits 2, 4, 6, 8, 10). The MDS-UPDRS part 3 and Timed Walk
49 assessments will be initially performed in the OFF state. This assessment in both the 'OFF' and 'ON'
50 states will be performed with video recording to facilitate the possibility of a re-review if necessary.
51 Remote monitoring assessments will be conducted at this point at selected sites in patients
52 consenting to participate in this sub-study. While waiting for medications to work, participants will
53 self-complete the MDS-UPDRS parts 1, 2 and 4, PDQ-39, EQ-5D-5L and CSRI. The MDS-UPDRS part 3
54 and Timed Walk assessments will be repeated 1 hour after the participant has taken their routine
55 medications - the ON medication state. After completion of the MDS-UPDRS and Timed Walk
56 assessments in the ON medication state, each participant will be assessed using the MoCA, NMS
57 scale, UDysRS and PHQ-9. This will occur in alternate post-randomisation assessments (at visits 2, 4,
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3 6, 8, 10). At selected centres participants in the CSF sub-study will have a CSF sample taken via
4 lumbar puncture. Ten weeks after the last trial medication administration, a staff member will call
5 the participant to collect details of any adverse events that have occurred after the participant stops
6 taking the trial medication. Participants will complete the 3 Day Hauser Diary prior to visits 2, 6 and
7 10 and return the diary back to the research team at the respective study visits. At each of the visits
8 2, 4, 6, 8, and 10, a blood sample will be collected and processed for storage for future analysis.
9
10

11 The DaTSCAN imaging sub-study will be performed at the UCLH site on all consenting sub-study
12 participants; scans will be performed prior to visit 2 and after visit 10.
13

14 The option for performing a remote assessment will be provided to patients for safety monitoring
15 visits in view of the coronavirus pandemic.
16
17

18 19 **Intervention**

20
21 Each dose of Exenatide 2 mg (powder and solvent for prolonged release, suspension for injection,
22 prefilled pen) is supplied as a single use injection pen for subcutaneous administration by the patient
23 on a weekly basis. The placebo (inactive powder and solvent for prolonged release, suspension for
24 injection, prefilled pen) is supplied as an identical injection pen for subcutaneous administration by
25 the patient on a weekly basis. The trial medication will be refrigerated and stored at 2-8°C. Both
26 exenatide and placebo will be supplied by AstraZeneca as unlabelled prefilled pens in bulk and in
27 accordance with Good Manufacturing Practice (GMP). Labelling, packaging and release of packed
28 trial medications will be managed by the Sponsor's contracted company following GMP. The labels
29 will be prepared in accordance with GMP Annex 13 requirements for labelling and local regulatory
30 guidelines. The trial medications will be released ahead of trial use.
31
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34 Site trial staff will be trained on the use of exenatide using an online teaching video, accompanying
35 product literature and the Investigator's Brochure (IB). Patients will be taught how to perform the
36 subcutaneous injections by the clinical trial team using the online video, demonstration packs and
37 written literature. They will be told about common adverse reactions previously reported e.g.
38 nausea, vomiting, diarrhoea and weight loss by the clinical trial team, and will be advised on the
39 processes for safety reporting. In the event that exenatide injections will be administered by care-
40 givers (e.g. spouse), their willingness to perform this will be documented and they will be trained
41 using the online teaching video. It will also be ascertained that the care-giver either lives with the PD
42 patient or confirms their willingness to meet with the PD participant on a weekly basis to administer
43 the injections for the 96 week period of the trial.
44
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46
47 Patients who meet eligibility criteria at the screening visit will be randomly assigned to receive 96
48 weeks of double-blind treatment with either exenatide or placebo (2mg once weekly) in a 1:1 ratio.
49 The first dose will be administered by the patient in clinic following injection training and
50 subsequent injections will be at home. Injections will be self-administered by the participants, or
51 administered by their carer, into the participants' abdomen, arm, thigh or buttocks every 7 days.
52 Participants will be provided with a link to the injection pen training video and a REC approved
53 injection administration training sheet.
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56 57 **Sample Size**

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3 The sample size is based on the detectable effect size (primary outcome is the MDS-UPDRS motor
4 subsection in the OFF medication state) for a two-arm (exenatide versus placebo) parallel-group trial
5 design. The calculations assume a common standard deviation of 13.5, and a correlation of 0.70
6 between baseline and follow up MDS-UPDRS measurements. These estimates are reasonable based
7 on data from the previous Exenatide-PD trial[14] On this basis, 160 evaluable participants divided
8 equally between the 2 groups is sufficient to detect a difference of 5.0 MDS-UPDRS part 3 points in
9 the OFF medication state between the 2 groups adjusting for baseline MDS-UPDRS part 3 OFF
10 scores, with 90% power and at a significance level of 0.05. Assuming 20% attrition (withdrawal/loss
11 to follow up), 200 participants will be recruited. Participants who withdraw from the trial will not be
12 replaced. Participants who withdraw from trial treatment should remain in the trial for the purpose
13 of follow-up and data analysis. This effect size is a reasonable expectation based on the previously
14 collected pilot data and would represent a clear demonstration of the efficacy of exenatide on the
15 motor severity of PD.
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20 It is also anticipated that the difference in scores in the ON medication state will be greater at 96
21 weeks than at the earlier time points. The expected rate of change in PD severity in the first 5 years
22 after PD diagnosis in the ON medication state is 1 MDS-UPDRS part 3 point per year. A predicted
23 advantage of 2 points in ON scores over 96 weeks would thus equate to an advantage in the rate of
24 disease progression above and beyond that achievable with conventional dopaminergic medication
25 and would be a further clear signal that continued use of exenatide is consistent with not only long-
26 term disease modifying effects, but even demonstration of a small change of 2.5 points in the MDS-
27 UPDRS motor score would constitute a clinically important difference[23] and potentially an
28 advantage in day to day functional impairment and overall improvement in quality of life in the short
29 term.
30
31

32 **Statistical Analysis**

33
34 A full statistical analysis plan (SAP) will be written and approved by the Trial Steering Committee
35 prior to database lock. All analyses will be undertaken according to a modified intention-to-treat
36 (mITT) principle in accordance with the randomised intervention. The analysis population will consist
37 of all subjects who complete 12 weeks on treatment and for whom outcomes are available.
38

39
40 Primary outcome analysis will evaluate the impact of treatment allocation (exenatide or placebo) on
41 the difference between MDS UPDRS part 3 OFF medication scores at 96 weeks follow-up adjusting
42 for baseline. The analysis will use a mixed-model approach incorporating information from all follow-
43 up visits that adjusts for baseline Hoehn & Yahr status and the baseline raw value of each outcome
44 measurement. Site will be included as a random effect to account for variability in outcomes
45 between sites, and a random patient/subject effect will accommodate the correlation between
46 repeated outcome measures on the same patient. A significance level of 5% will be used to judge
47 significance for the primary outcome measure.
48
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50
51 A planned secondary analysis will compare the difference in MDS-UPDRS part 3 OFF medication
52 scores according to randomisation allocation at 96 weeks, with the scores at 48 weeks. An increase
53 in the advantage at 96 weeks compared to 48 weeks would be evidence that the active drug was
54 slowing down disease deterioration rather than having symptomatic effects only. This could
55 translate to a major population advantage in terms of reduction of morbidity and mortality.
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58 Analyses of the remaining secondary/exploratory outcomes will be undertaken similarly for the
59 difference between groups according to treatment allocation at 48 and 96 weeks follow up adjusting
60 for baseline values of each outcome, and confounding factors such as LED.

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3 Further exploratory analyses will consider whether exenatide can be thought of as disease modifying
4 by comparing slopes between groups at pre-specified periods.
5

6 A sensitivity (per protocol) analysis will be performed for the primary outcome measure and will only
7 include those participants who completed the trial in accordance with the approved protocol.
8

9 Results on the primary efficacy outcome will be presented by stratum, according to Hoehn & Yahr
10 stage (≤ 2.0 versus 2.5), and an interaction between Hoehn & Yahr and treatment will be added to
11 the primary analysis model to investigate whether the effect of treatment differs according to the
12 Hoehn & Yahr stage.
13

14 All analyses will be performed by the designated Trial Statistician.
15

16 **Data Management**

17 Data will be entered in the Exenatide-PD3 database by delegated staff at participating sites and
18 members of the Exenatide-PD3 trial team at CCTU. Participants will be given a unique trial PIN
19 (Exnnn). Data will be entered under the PIN onto the central database (InferMed's MACRO stored on
20 the servers based at UCL). The database will be password protected and only accessible to members
21 of the Exenatide-PD3 trial team and external regulators if requested. Video recordings of the MDS-
22 UPDRS will be uploaded onto a secure cloud held by Machine Medicines Technologies (MMT) and
23 used for quality control purposes. Appropriate contractual agreements covering data protection are
24 in place with MMT. All data storage will adhere to GDPR and the Data Protection Act 2018.
25

26 An Independent Data Monitoring Committee (IDMC) will be convened including at least 3 individuals
27 independent from the trial team and sponsor who have experience in the conduct of clinical trials
28 for PD. The IDMC will review the trial results and make a recommendation to the Trial Steering
29 Committee (TSC) regarding continuation/ stopping of the trial based on safety data. A statistician
30 independent of the Exenatide-PD3 Trial Team at CCTU will generate summaries of accumulating trial
31 data for the IDMC to review.
32

33 UCL is the trial sponsor and has delegated the duties as sponsor to CCTU via a signed letter of
34 delegation. The trial sponsor will take on responsibility for securing the arrangements to initiate,
35 manage and finance the trial. Trial oversight is intended to preserve the integrity of the trial by
36 independently verifying processes and prompting corrective action where necessary. In multi-centre
37 trials this oversight is considered and described both overall and for each recruiting centre by
38 exploring the trial dataset or performing site visits. The Trial Team (TT) will assist with developing the
39 design, co-ordination and day to day operational issues in the management of the trial, including
40 budget management. The Trial Management Group (TMG) will assist with developing the design, co-
41 ordination and strategic management of the trial. The Independent Trial Steering Committee (TSC) is
42 the independent group responsible for oversight of the trial in order to safeguard the interests of
43 trial participants. The TSC will provide advice to the Chief Investigator (CI), CCTU, the funder and
44 sponsor on all aspects of the trial through its independent Chair. The Independent Data Monitoring
45 Committee (IDMC) is the only oversight body that has access to unblinded accumulating
46 comparative data. The IDMC will be responsible for safeguarding the interests of trial participants,
47 monitoring the accumulating data and making recommendations to the TSC on whether the trial
48 should continue as planned. The membership, frequency of meetings, activity (including trial
49 conduct and data review) and authority of each committee will be covered in their respective terms
50 of reference.
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52 **Ethics and Dissemination**

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3 The trial protocol, all informed consent forms and any material to be given to the prospective
4 participant have received REC (initial date of approval 15/10/2019, REC reference no.19/SC/0447),
5 and other regulatory approvals (EudraCT 2018-003028-35). Further, the trial was registered in
6 clinictrials.gov NCT004232969 and in ISRCTN (reference 14552789). Subsequent amendments to
7 these documents will be submitted for further approval. The same/amended documents will be
8 submitted for additional local permissions at each clinical site.
9

10
11 This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive
12 2001/20/EC. Therefore, a clinical trial authorisation (CTA) is required in the UK and the trial protocol
13 will therefore be submitted to the UK regulatory authority (MHRA). The progress of the trial, safety
14 issues and reports, including expedited reporting will be reported to the MHRA as required. The
15 protocol, participant information sheet (PIS) and informed consent forms on local headed paper, the
16 REC/HRA and MHRA approvals, schedules of funding and activity (and other trial documentation as
17 needed) have been submitted to the relevant NHS Trust R&D department of each participating site
18 or to other local departments for approval.
19

20
21 Participants will be provided with a PIS and given time to read it fully. Following a discussion with a
22 medical qualified investigator or suitable trained and authorised delegate, any questions will be
23 satisfactorily answered and if the participant is willing to participate, written informed consent will
24 be obtained. During the consent process it will be emphasised that the participant is free to refuse
25 to participate in all or any aspect of the trial, at any time and for any reason, without affecting their
26 treatment. The risk/benefit profile of the trial will be regularly monitored. Consent will be re-sought
27 if new information becomes available that affects the participant's consent in any way.
28

29
30 The rights of the participant to refuse to participate in the trial without giving a reason will be
31 respected and after the participant has entered the trial, the clinician remains free to give
32 alternative treatment to that specified in the protocol, at any stage. The participant remains free to
33 change their mind at any time about the protocol treatment and follow-up without giving a reason
34 and without prejudicing their further treatment. All participants will be made aware of the known
35 adverse reactions.
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40 Discussion

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42 A parallel group design with a washout period has been used previously in the evaluation of
43 potential neuroprotective agents [24,25]. and this was chosen as the design for the previous phase 2
44 trial. This design is subject to possible long duration symptomatic effects and a lengthy washout
45 period potentially impacts on patient retention and cannot necessarily distinguish a true
46 neuroprotective effect from a symptomatic effect (in view of preservation of healthy behaviours
47 with long term impacts such as exercise) [26]. An alternative approach which we have adopted here
48 is a "Long term simple" design, with longer term follow up to look for a cumulative advantage
49 emerging with prolonged treatment exposure, given the natural history of PD being that of
50 progressive accumulation of motor and non-motor disability [27]. This design helps build on the
51 previous successful clinical trials of exenatide which have introduced a novel, cost effective way of
52 evaluating the potential for disease modifying drugs in PD by recruiting patients already in receipt of
53 conventional dopaminergic treatment, rather than restricting recruitment to incident cases yet to
54 receive dopaminergic treatment. Using this approach, we have successfully demonstrated the
55 potential for rapid recruitment, and improved retention of participants enabling more complete
56 follow up, and a statistically significant advantage in motor scores in people randomised to
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3 exenatide over a 48-week period of treatment exposure. We have considered that an exposure
4 period of 96 weeks would allow exploration of long-term effects of exenatide exposure, while being
5 the maximum period that participants would be willing to accept being allocated placebo.
6 Furthermore, this will provide the opportunity to evaluate whether the 48-week data previously
7 published can be replicated and whether effects at 96 weeks are similar to or greater than those
8 seen at 48 weeks and other earlier timepoints.
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11 Many trials have attempted to evaluate the potential for disease modification using drugs with
12 broad mechanisms of action. The majority have either failed to demonstrate clinical efficacy or
13 provided inconclusive results. Some pertinent reasons for this are a failure of the investigated agent
14 to reach and engage its target and lack of objective measures of true clinical disease progression.
15 Clinical endpoints such as the MDS-UPDRS scale are necessary to ultimately confirm relevance;
16 however, these scales lack sensitivity for capturing disease modification unless very long term follow
17 up data are collected. While our approach of following patients for 2 years in this trial will partially
18 mitigate some of this, the addition and to an extent validation of more detailed approaches through
19 a number of sub studies (imaging, CSF analysis for target engagement and drug levels, and device
20 assisted measurements of real-life motor function) could ultimately provide more holistic and
21 definitive metrics for determining if exenatide does in fact deliver disease modification in PD. This
22 more comprehensive approach to approaching assessments and the consistent signal of benefit
23 noted in two earlier trials provide grounds for optimism that the primary outcome will be
24 achievable. The study opened to recruitment in January 2020 and we expect completion of study
25 analysis by Q3 2024.
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33 Author Contributions:

34 The study concept and design was conceived by TF. NV and CG will conduct screening and data
35 collection. GA, MC, KM, KC, SH, PL, DA, CC, MH, MS, JD, RH and VL assisted on drafting the protocol.
36 Analysis will be performed by SS, and data entry by AK. NV prepared the first draft of the
37 manuscript. RG served as a patient adviser for the design of the study protocol. All authors provided
38 edits and revised the manuscript for intellectual content.
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44 Acknowledgement

45 We are grateful to all patients contributing to the design of this study. We thank the Cure
46 Parkinson's Trust and Parkinson's UK for their assistance in the setup and increasing the awareness
47 of this study.
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54 DATScan Imaging substudy grant number BY-TF021 & the Remote Monitoring substudy grant
55 number MH011.
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Competing Interest Statement

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None declared

Data Statement

Not applicable at this stage.

Word Count 5729

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Figure legend

Figure 1: Outline of Trial design

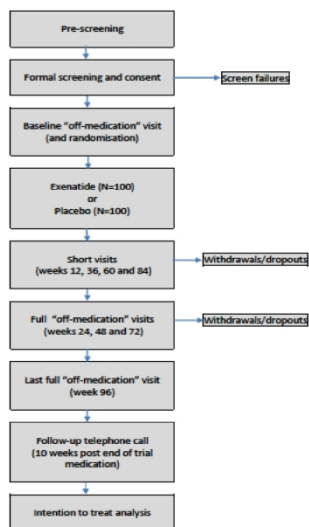


Figure 1: Outline of Trial design

209x296mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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| | | Reporting Item | Page Number |
|---|---------------------|--|-------------|
| Administrative information | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | #3 | Date and version identifier | 16 |
| Funding | #4 | Sources and types of financial, material, and other support | 16 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 16 |

| | | | | |
|----|---------------------------|---------------------|--|-----|
| 1 | Roles and | #5b | Name and contact information for the trial sponsor | 1 |
| 2 | responsibilities: | | | |
| 3 | sponsor contact | | | |
| 4 | information | | | |
| 5 | | | | |
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| 8 | Roles and | #5c | Role of study sponsor and funders, if any, in study design; | 6 |
| 9 | responsibilities: | | collection, management, analysis, and interpretation of data; | |
| 10 | sponsor and funder | | writing of the report; and the decision to submit the report for | |
| 11 | | | publication, including whether they will have ultimate authority | |
| 12 | | | over any of these activities | |
| 13 | | | | |
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| 16 | Roles and | #5d | Composition, roles, and responsibilities of the coordinating centre, | 6 |
| 17 | responsibilities: | | steering committee, endpoint adjudication committee, data | |
| 18 | committees | | management team, and other individuals or groups overseeing the | |
| 19 | | | trial, if applicable (see Item 21a for data monitoring committee) | |
| 20 | | | | |
| 21 | | | | |
| 22 | | | | |
| 23 | Introduction | | | |
| 24 | | | | |
| 25 | Background and | #6a | Description of research question and justification for undertaking | 3-4 |
| 26 | rationale | | the trial, including summary of relevant studies (published and | |
| 27 | | | unpublished) examining benefits and harms for each intervention | |
| 28 | | | | |
| 29 | | | | |
| 30 | Background and | #6b | Explanation for choice of comparators | 3-4 |
| 31 | rationale: choice of | | | |
| 32 | comparators | | | |
| 33 | | | | |
| 34 | | | | |
| 35 | | | | |
| 36 | Objectives | #7 | Specific objectives or hypotheses | 4 |
| 37 | | | | |
| 38 | Trial design | #8 | Description of trial design including type of trial (eg, parallel | 6-7 |
| 39 | | | group, crossover, factorial, single group), allocation ratio, and | |
| 40 | | | framework (eg, superiority, equivalence, non-inferiority, | |
| 41 | | | exploratory) | |
| 42 | | | | |
| 43 | | | | |
| 44 | | | | |
| 45 | Methods: | | | |
| 46 | Participants, | | | |
| 47 | interventions, and | | | |
| 48 | outcomes | | | |
| 49 | | | | |
| 50 | | | | |
| 51 | | | | |
| 52 | Study setting | #9 | Description of study settings (eg, community clinic, academic | 6-7 |
| 53 | | | hospital) and list of countries where data will be collected. | |
| 54 | | | Reference to where list of study sites can be obtained | |
| 55 | | | | |
| 56 | | | | |
| 57 | Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, | 8 |
| 58 | | | eligibility criteria for study centres and individuals who will | |
| 59 | | | | |
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| | | perform the interventions (eg, surgeons, psychotherapists) | |
| 1 | | | |
| 2 | Interventions: | #11a Interventions for each group with sufficient detail to allow | 12 |
| 3 | description | replication, including how and when they will be administered | |
| 4 | | | |
| 5 | | | |
| 6 | Interventions: | #11b Criteria for discontinuing or modifying allocated interventions for a | 12 |
| 7 | modifications | given trial participant (eg, drug dose change in response to harms, | |
| 8 | | participant request, or improving / worsening disease) | |
| 9 | | | |
| 10 | | | |
| 11 | Interventions: | #11c Strategies to improve adherence to intervention protocols, and any | 12 |
| 12 | adherence | procedures for monitoring adherence (eg, drug tablet return; | |
| 13 | | laboratory tests) | |
| 14 | | | |
| 15 | | | |
| 16 | Interventions: | #11d Relevant concomitant care and interventions that are permitted or | 12 |
| 17 | concomitant care | prohibited during the trial | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | Outcomes | #12 Primary, secondary, and other outcomes, including the specific | 9-10 |
| 22 | | measurement variable (eg, systolic blood pressure), analysis metric | |
| 23 | | (eg, change from baseline, final value, time to event), method of | |
| 24 | | aggregation (eg, median, proportion), and time point for each | |
| 25 | | outcome. Explanation of the clinical relevance of chosen efficacy | |
| 26 | | and harm outcomes is strongly recommended | |
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | Participant timeline | #13 Time schedule of enrolment, interventions (including any run-ins | 6-7 |
| 31 | | and washouts), assessments, and visits for participants. A | |
| 32 | | schematic diagram is highly recommended (see Figure) | |
| 33 | | | |
| 34 | | | |
| 35 | | | |
| 36 | Sample size | #14 Estimated number of participants needed to achieve study | 12 |
| 37 | | objectives and how it was determined, including clinical and | |
| 38 | | statistical assumptions supporting any sample size calculations | |
| 39 | | | |
| 40 | | | |
| 41 | Recruitment | #15 Strategies for achieving adequate participant enrolment to reach | 6 |
| 42 | | target sample size | |
| 43 | | | |
| 44 | | | |
| 45 | Methods: Assignment | | |
| 46 | of interventions (for | | |
| 47 | controlled trials) | | |
| 48 | | | |
| 49 | | | |
| 50 | Allocation: sequence | #16a Method of generating the allocation sequence (eg, computer- | 14 |
| 51 | generation | generated random numbers), and list of any factors for | |
| 52 | | stratification. To reduce predictability of a random sequence, | |
| 53 | | details of any planned restriction (eg, blocking) should be provided | |
| 54 | | in a separate document that is unavailable to those who enrol | |
| 55 | | participants or assign interventions | |
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| 1 | Allocation concealment | #16b | Mechanism of implementing the allocation sequence (eg, central | 14 |
| 2 | mechanism | | telephone; sequentially numbered, opaque, sealed envelopes), | |
| 3 | | | describing any steps to conceal the sequence until interventions are | |
| 4 | | | assigned | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |
| 8 | Allocation: | #16c | Who will generate the allocation sequence, who will enrol | 14 |
| 9 | implementation | | participants, and who will assign participants to interventions | |
| 10 | | | | |
| 11 | Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial | 14 |
| 12 | | | participants, care providers, outcome assessors, data analysts), and | |
| 13 | | | how | |
| 14 | | | | |
| 15 | | | | |
| 16 | | | | |
| 17 | Blinding (masking): | #17b | If blinded, circumstances under which unblinding is permissible, | 14 |
| 18 | emergency unblinding | | and procedure for revealing a participant's allocated intervention | |
| 19 | | | during the trial | |
| 20 | | | | |
| 21 | | | | |
| 22 | Methods: Data | | | |
| 23 | collection, | | | |
| 24 | management, and | | | |
| 25 | analysis | | | |
| 26 | | | | |
| 27 | | | | |
| 28 | | | | |
| 29 | Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other | 11 |
| 30 | | | trial data, including any related processes to promote data quality | |
| 31 | | | (eg, duplicate measurements, training of assessors) and a | |
| 32 | | | description of study instruments (eg, questionnaires, laboratory | |
| 33 | | | tests) along with their reliability and validity, if known. Reference | |
| 34 | | | to where data collection forms can be found, if not in the protocol | |
| 35 | | | | |
| 36 | | | | |
| 37 | | | | |
| 38 | | | | |
| 39 | Data collection plan: | #18b | Plans to promote participant retention and complete follow-up, | 11 |
| 40 | retention | | including list of any outcome data to be collected for participants | |
| 41 | | | who discontinue or deviate from intervention protocols | |
| 42 | | | | |
| 43 | | | | |
| 44 | Data management | #19 | Plans for data entry, coding, security, and storage, including any | 11 |
| 45 | | | related processes to promote data quality (eg, double data entry; | |
| 46 | | | range checks for data values). Reference to where details of data | |
| 47 | | | management procedures can be found, if not in the protocol | |
| 48 | | | | |
| 49 | | | | |
| 50 | | | | |
| 51 | Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. | 13-14 |
| 52 | | | Reference to where other details of the statistical analysis plan can | |
| 53 | | | be found, if not in the protocol | |
| 54 | | | | |
| 55 | | | | |
| 56 | Statistics: additional | #20b | Methods for any additional analyses (eg, subgroup and adjusted | 13-14 |
| 57 | analyses | | analyses) | |
| 58 | | | | |
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|----|----------------------------|----------------------|---|-------|
| 1 | Statistics: analysis | #20c | Definition of analysis population relating to protocol non- | 13-14 |
| 2 | population and missing | | adherence (eg, as randomised analysis), and any statistical methods | |
| 3 | data | | to handle missing data (eg, multiple imputation) | |
| 4 | | | | |
| 5 | | | | |
| 6 | Methods: Monitoring | | | |
| 7 | | | | |
| 8 | Data monitoring: | #21a | Composition of data monitoring committee (DMC); summary of its | 7 |
| 9 | formal committee | | role and reporting structure; statement of whether it is independent | |
| 10 | | | from the sponsor and competing interests; and reference to where | |
| 11 | | | further details about its charter can be found, if not in the protocol. | |
| 12 | | | Alternatively, an explanation of why a DMC is not needed | |
| 13 | | | | |
| 14 | Data monitoring: | #21b | Description of any interim analyses and stopping guidelines, | 7 |
| 15 | interim analysis | | including who will have access to these interim results and make | |
| 16 | | | the final decision to terminate the trial | |
| 17 | | | | |
| 18 | Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited | 7 |
| 19 | | | and spontaneously reported adverse events and other unintended | |
| 20 | | | effects of trial interventions or trial conduct | |
| 21 | | | | |
| 22 | Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and | 7 |
| 23 | | | whether the process will be independent from investigators and the | |
| 24 | | | sponsor | |
| 25 | | | | |
| 26 | | | | |
| 27 | | | | |
| 28 | Ethics and | | | |
| 29 | dissemination | | | |
| 30 | | | | |
| 31 | Research ethics | #24 | Plans for seeking research ethics committee / institutional review | 14 |
| 32 | approval | | board (REC / IRB) approval | |
| 33 | | | | |
| 34 | Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, | 14 |
| 35 | | | changes to eligibility criteria, outcomes, analyses) to relevant | |
| 36 | | | parties (eg, investigators, REC / IRBs, trial participants, trial | |
| 37 | | | registries, journals, regulators) | |
| 38 | | | | |
| 39 | Consent or assent | #26a | Who will obtain informed consent or assent from potential trial | 11-13 |
| 40 | | | participants or authorised surrogates, and how (see Item 32) | |
| 41 | | | | |
| 42 | Consent or assent: | #26b | Additional consent provisions for collection and use of participant | 11-13 |
| 43 | ancillary studies | | data and biological specimens in ancillary studies, if applicable | |
| 44 | | | | |
| 45 | Confidentiality | #27 | How personal information about potential and enrolled participants | 11-13 |
| 46 | | | will be collected, shared, and maintained in order to protect | |
| 47 | | | confidentiality before, during, and after the trial | |
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| 1 | Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 16 |
| 2 | | | | |
| 3 | | | | |
| 4 | Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 15 |
| 5 | | | | |
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| 10 | Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 15 |
| 11 | | | | |
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| 13 | | | | |
| 14 | Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 |
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| 21 | Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 15 |
| 22 | | | | |
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| 24 | Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 15 |
| 25 | | | | |
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| 27 | | | | |
| 28 | Appendices | | | |
| 29 | | | | |
| 30 | | | | |
| 31 | Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | 11 |
| 32 | | | | |
| 33 | | | | |
| 34 | Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 11 |
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 41 3.0. This checklist was completed on 14. December 2020 using <https://www.goodreports.org/>, a tool made by
 42 the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Exenatide once weekly over 2 years as a potential disease modifying treatment for Parkinson's disease: protocol for a multi-centre, randomised, double blind, parallel group, placebo controlled, Phase 3 trial, The 'Exenatide-PD3' study

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| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Medical management, Neurology |
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Exenatide once weekly over 2 years as a potential disease modifying treatment for Parkinson's disease: protocol for a multi-centre, randomised, double blind, parallel group, placebo controlled, Phase 3 trial, The 'Exenatide-PD3' study

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16 Trial Registration Number: Clinicaltrials.gov identifier: NCT04232969, ISRCTN14552789

17
18 Key Words:

19
20 Exenatide; Parkinson's disease; randomised control trial.

21 22 23 24 **Abstract**

25 26 **Introduction**

27
28 Parkinson's disease (PD) is a common neurodegenerative disorder with substantial morbidity. No
29 disease modifying treatments currently exist. The glucagon like peptide-1 receptor agonist exenatide
30 has been associated in single centre studies with reduced motor deterioration over 1 year. The aim
31 of this multicentre UK trial is to confirm whether these previous positive results are maintained in a
32 larger number of participants over two years and if effects accumulate with prolonged drug
33 exposure.

34 35 36 **Methods and analysis**

37
38 This is a phase 3, multi-center, double-blind, randomised, placebo-controlled trial of exenatide at a
39 dose of 2 mg weekly in 200 participants with mild to moderate PD. Treatment duration is 96 weeks.
40 Randomisation is 1:1, drug to placebo. Assessments are performed at baseline, week 12, 24, 36, 48,
41 60, 72, 84, and 96 weeks.

42
43 The primary outcome is the comparison of MDS-UPDRS part 3 motor sub-score in the practically
44 defined OFF medication state at 96 weeks between participants according to treatment allocation.
45 Secondary outcomes will compare the change between groups among other motor, non-motor and
46 cognitive scores. The primary outcome will be reported using descriptive statistics and comparisons
47 between treatment groups using a mixed model, adjusting for baseline scores. Secondary outcomes
48 will be summarised between treatment groups using summary statistics and appropriate statistical
49 tests to assess for significant differences.

50 51 52 **Ethics and dissemination**

53
54 This trial has been approved by the South Central-Berkshire Research Ethics Committee and the
55 Health Research Authority. Results will be disseminated in peer-reviewed journals, presented at
56 scientific meetings and to patients in lay-summary format.

57 58 **Article Summary**

59 60 **Strengths and Limitations of this Study**

- This is the protocol for the first phase 3 double-blind, randomised, placebo controlled trial of exenatide in Parkinson's disease (PD).
- This study uses novel secondary outcome measures in sub-studies (cerebrospinal fluid analysis, dopamine transporter imaging, and digital technology measurement devices) which should provide a more sensitive and comprehensive assessment of potential disease modification.
- Although the 2 year follow-up period should provide a more definitive signal on disease modification this will take longer to report findings and has risks for long-term patient retention

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting over 10 million people worldwide and its prevalence is increasing [1]. Symptomatic treatments are available and mainly focus on dopamine replacement strategies [2,3]. Such therapies provide improvements in the core motor features of PD: tremor, limb rigidity and slowness of movement (bradykinesia) [4]. These symptomatic treatments do not impact on the progressive nature of the disease nor the majority of the non-motor symptoms (NMS). Moreover, with time, some patients will develop dopamine-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 with mounting care needs.[3,4]. These complications result in increased dependence, care giver strain, need for 24 hour care and death. Therefore, Parkinson's disease is a growing problem for individuals, healthcare and society making the development of disease modifying treatments imperative.

Exenatide (Exendin-4) is a licensed and effective treatment for patients with type 2 diabetes mellitus (T2DM) [5]. It is an agonist for the Glucagon-like peptide 1 (GLP-1) receptor and in the presence of elevated blood glucose stimulates insulin release. It also increases pancreatic beta islet cell mass and reduces apoptosis. 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 [5].

In parallel with the confirmation of the beneficial effects of exenatide on glucose control, laboratory work has showed that exenatide has beneficial effects on neurons in vitro [6]. Exenatide induces neurite outgrowth, promotes neuronal differentiation and rescues degenerating neuronal cells while also reversing neurotoxin induced damage in animal models [6,7]. These neurotrophic properties have sparked interest regarding its potential use as a neurodegenerative disease modifying agent [8,9].

The specific relevance of exenatide to PD has also been extensively evaluated. Exenatide has been shown to increase transcription of tyrosine hydroxylase (TH) (the rate limiting enzyme in dopamine synthesis) in brainstem catecholaminergic neurons [10]. Furthermore, stimulation of GLP-1 receptors may have beneficial effects on the neurodegenerative processes of PD through downstream cellular pathways [6,11]. These findings are further supported by a recent study suggesting a reduced future risk of developing PD in T2DM patients treated with GLP-1 agents [12].

To investigate the potential effects of exenatide in patients with PD, an investigator-initiated pilot trial was undertaken [13]. This open label, parallel group, randomised controlled trial evaluated the tolerability of exenatide (Byetta 10mcg twice daily) in 45 patients with moderately severe PD (Hoehn and Yahr stage of less than 2.5) over an exposure period of 48 weeks with a subsequent washout

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3 period of 12 weeks. This showed an advantage of 4.9 points in the Movement Disorders Society
4 Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 (motor sub-score) in exenatide treated
5 patients at 12 months which persisted even after a 12 week washout period. Clinically important
6 differences in cognition were also noted. Serial DaTscan imaging showed no progression between
7 baseline and 48 weeks in the exenatide treated patients [13].
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10 A further Phase 2 double blind randomised controlled trial evaluating the effects of exenatide in 60
11 patients with PD has subsequently been performed [14]. Patients were randomised to self-injection
12 of a long acting form of exenatide, (Bydureon 2mg) once weekly, or matched placebo for 48 weeks.
13 Detailed assessments every 12 weeks for the duration of the treatment and a further assessment at
14 the 60 week time point to explore any lasting effects following washout of the trial medication were
15 performed. Patients receiving exenatide had a mean 3.5 point advantage in their MDS-UPDRS part 3
16 OFF medication scores compared to patients receiving placebo at the 60 week timepoint. Biological
17 specimens collected from trial participants confirmed changes according to treatment with
18 exenatide in downstream cellular effector pathways [15].
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21 The current trial objective (Box 1) is to confirm or refute whether the previous positive results can be
22 reproduced in a multicentre trial design, including a larger number of participants evaluated over
23 twice as long a period as previously. An important secondary objective is to explore if positive effects
24 seen after 48 weeks of exenatide exposure remain static or increase in amplitude by the 96-week
25 time point. The hypothesis is that exenatide will be associated with reduced MDS-UPDRS part 3
26 scores at the 96-week time-point. The overriding priority for this trial is to provide evidence to
27 support or refute any signal of efficacy of exenatide in PD, and thus provide the justification for rapid
28 further investment in this drug if appropriate. In parallel with this, is the aim to explore whether any
29 biological effect(s) of exenatide, relevant to PD, are purely symptomatic effects as opposed to
30 disease modifying effects.
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Box 1 Trial Objectives**Primary**

- 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)

Secondary

- Compare differences at 48 and 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 dose change
 - 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 between scores at 48 and 96 weeks between the exenatide and placebo trial arms in:
 - MDS-UPDRS part 3 Motor subsection OFF medication score

Exploratory

Compare differences between slopes at pre-specified periods between exenatide and placebo trial arms for key outcomes to investigate whether exenatide can be considered disease modifying.

Methods

This trial protocol was designed using the University College London (UCL) Comprehensive Clinical Trials Unit (CCTU) Protocol template. The trial is sponsored by UCL and coordinated by the CCTU. The protocol was designed to provide information about procedures for entering participants into the trial, and 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. All stake holders (research team, sponsor, CCTU and oversight committees) were involved in the design and approval of the protocol. A particular emphasis was given to patient input in the trial design. This patient and public involvement (PPI) approach has proven to be of value in other studies [16] and was harnessed to improve the overall study design. A focus group meeting with patients was organized in the protocol design stages to obtain feedback from patients which led to a number of amendments prior to submission, including the maximum overall trial duration of 96 weeks, and the use of OFF-medication assessments. Two PPI representatives will serve on the trial steering committee (TSC) and will continue to provide regular input throughout recruitment. Patients will also be provided access to the trial website and a link to the protocol and patient information sheets (PIS) on request and will be given the opportunity to continue to provide comments and contact researchers to further discuss their input. The INCLUDE guidance [17] is an NIHR led initiative to improve inclusion of under-served groups. The design of the trial is mindful of the value of the steps outlined in this initiative and aims to incorporate its recommendations into overall trial recruitment with the overarching aim of providing better access and quality care to under-served patient groups.

Patient and Public Involvement:

In the development of this protocol, a formal meeting hosted by the Cure Parkinson's Trust was held with 6 patients with PD to obtain patient feedback on the overall trial design and logistical aspects of the trial that could potentially impede recruitment and retention. The aims and objectives of the trial were discussed including the importance of distinguishing between symptomatic and disease modifying effects of exenatide. Patient feedback was clear that a 2 year period would be the maximal acceptable duration of self-administration of placebo, therefore the trial duration was reduced from the original planned 3 year duration to 96 weeks. The use of weekly self-administered injections, and attendance in the off-medication state to assess PD severity was discussed in detail and considered acceptable. The recruitment strategy has used the patient networks of the Cure Parkinson's Trust and Parkinson's UK to increase the awareness of the trial. Patients and patient representatives are included in the Trial Steering committee. At the end of the study, all participants will be notified of their randomisation allocation and of the main study results. The results will be presented at meetings convened for patient groups and published in open access peer reviewed publications.

Trial design

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3 This is a simple parallel group multicentre phase 3, double-blind, randomised, placebo-controlled
4 trial which includes a 96-week exposure period. Detailed evaluations of all participants will take
5 place at screening, baseline, 24, 48, 72 and 96 weeks (Figure 1). Participants will also attend on a 12
6 weekly basis to collect supplies of Investigational Medicinal Product (IMP). Participants will be
7 randomly allocated to receive either exenatide extended release 2mg subcutaneous injection
8 (Bydureon) once weekly for 96 weeks n=100, or exenatide extended release placebo subcutaneous
9 injection once weekly for 96 weeks n=100. In addition, participants will be randomised using a
10 minimisation algorithm (with a random element incorporated) balancing by research site,
11 participants with greater (Hoehn & Yahr stage 2.5) or lesser (Hoehn & Yahr stage 2.0 or less) PD
12 severity (in the ON medication state), and participation in the sub-studies (Remote Monitoring,
13 Imaging, or not participating).
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19 **Participants & recruitment**

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21 Patients are eligible for screening if they have a clinical diagnosis of PD. The Queen Square brain
22 bank criteria[18] can be also be used to validate the diagnosis and ensure consistency of diagnosis
23 between sites, however, this is not a formal inclusion criterion. The relevance of a positive family
24 history of PD, or a confirmed genetic basis for an individual's symptoms will be evaluated in the
25 context of other clinical features in determining diagnosis and eligibility. Key inclusion and exclusion
26 criteria are summarised in Box 2.
27
28

29 In a post hoc analysis of the Exenatide PD phase 2 trial, younger patients with shorter disease
30 duration had the best outcomes [19]. While aware of this, we feel it is important to collect evidence
31 to determine whether exenatide has beneficial effects on cognition and axial features of PD, and
32 thus took the decision to keep the inclusion criteria broad to improve our chances of detecting
33 effects on these other outcomes and also ensuring that the results will be applicable to the broadest
34 population of PD patients
35

36
37 Participants will typically be recruited through specialist movement disorders clinics at trial sites. The
38 trial will be advertised online by the Parkinson's UK website, the Cure Parkinson's Trust and the NIHR
39 Clinical Research Network websites and will be registered on ClinicalTrials.gov and the ISRCTN
40 registry. Trial advertisements will direct participants to contact teams in order to be provided with a
41 patient information sheet and a reply slip to confirm ongoing interest and to organise a pre-
42 screening telephone call to discuss eligibility and suitability for the study. It is anticipated that
43 recruitment will be completed from six UK sites (National Hospital for Neurology and Neurosurgery
44 (Queen Square, London), King's College Hospital NHS Foundation Trust (London), Oxford University
45 Hospitals NHS Foundation Trust (Oxford), Derriford University Hospital (Plymouth), Salford Royal
46 Hospital (Manchester) and Western General Hospital & Royal Infirmary of Edinburgh (Edinburgh).
47 Recruitment rates will be carefully monitored throughout the trial to inform on the total number of
48 sites required to ensure final recruitment milestones will be reached. All patient assessments will be
49 performed at hospitals in the UK, after a site initiation visit has been performed. The trial began
50 recruitment on January 20th 2020 and will aim to complete all assessments by 30th September 2023.
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Box 2 Key inclusion and exclusion criteria for study

Key inclusion criteria

- Diagnosis of Parkinson's disease PD based on review of the participant's clinical history, examination findings and response to PD medications. The Queen Square brain bank criteria [18] can be also be used to assist the diagnosis, however this is not a formal inclusion criterion. 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.
- 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.
- Between 25 and 80 years of age.
- 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.
- Ability to self-administer, or to arrange carer administration of trial medication.
- Documented informed consent to participate.

Key exclusion criteria

- 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.
- Patients unable to attend the clinic visits in the practically defined OFF medication state.
- Body mass index < 18.5 . (Exenatide is known to cause weight loss therefore individuals that may not tolerate further weight loss will not be recruited).
- Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol.
- Significant cognitive impairment defined by a score < 21 on the Montreal Cognitive Assessment.
- Concurrent severe depression defined by a score ≥ 16 on the Patient Health Questionnaire (PHQ-9)
- 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.
- 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.
- Participation in another clinical trial of a device, drug or surgical treatment within the last 30 days.
- Previous exposure to exenatide.
- Impaired renal function with creatinine clearance < 50 ml/min.
- History of pancreatitis. Screening serum amylase value must fall within laboratory normal range $\pm 50\%$.
- Type 1 or Type 2 Diabetes mellitus.
- Severe gastrointestinal disease (e.g. gastroparesis)
- Hyperlipidaemia. A lipid profile will be tested at the screening visit. Cholesterol or Triglyceride levels greater than 2 x the upper limit of normal will raise suspicion of a familial or acquired hyperlipidaemia and will prompt referral to a relevant specialist for investigation and treatment.
- History or family history of medullary thyroid cancer (MTC). Undiagnosed neck lump, hoarse voice or difficulty swallowing (not attributable to PD diagnosis).
- Multiple endocrine neoplasia 2 (MEN2) syndrome.
- Hypersensitivity to any of exenatide's excipients.
- Females that are pregnant or breast feeding. There are no safety data regarding exenatide use in pregnancy.
- Women of child bearing potential 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
- Participants who lack the capacity to give informed consent.
- Any medical or psychiatric condition or previous conventional/experimental treatment which in the investigator's opinion compromises the potential participant's ability to participate.

Outcomes

Safety monitoring

Safety and tolerability of exenatide as indicated by changes in vital signs, weight, clinical laboratory measures and adverse events (AEs) will be recorded and monitored throughout. Each patient will have their pulse, blood pressure and weight documented at screening and at each follow up visit. Exenatide is known to cause weight loss. Participants' height will be recorded at screening to enable calculation of body mass index. At each visit, participants are asked to report any AEs that have occurred since the previous visit. AEs may also be detected by the study team reviewing the patient or through notification by the participant's primary care physician. All AEs will be assessed by a study doctor for their severity, likely relationship to study drug and required action by a study doctor not involved in the blinded assessment of the patient. All SAEs will be recorded and reported to the sponsor regardless of relation to trial treatment. Any suspected unexpected serious adverse reactions will be reported to the sponsor immediately to allow facilitation of unblinding as necessary. All AEs reported will be reviewed by the trial management group, trial steering group and monitored by an independent data monitoring committee. Unblinding requests from other clinicians responsible for a patient's care will be handled by the principal investigator (PI) at each site. The PI at each site may also choose to unblind a participant in response to reported AEs as they are reported, if judged to be clinically necessary.

Primary Outcome

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. 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 and adjusted for baseline will be the primary outcome. The scores for these assessments will be collected and recorded by trained clinical trial personnel (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 as part of a MDS-UPDRS automated scoring sub study though the availability of these videos will also enable repeated independent scoring to be performed if there are concerns raised about data quality from a specific site/rater.

Secondary Outcomes

Comparisons at 48 and 96 weeks between participants according to treatment allocation will also be performed for each of the secondary outcomes listed below.

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 48 weeks and also the difference between scores at 48 weeks 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.

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3 **Montreal Cognitive assessment (MoCA).** This scale is a validated global measure of cognitive ability.
4 This will be assessed in the ON medication state.
5

6 **Timed Tests.** Participants will be asked to perform a **Sit-stand-walk timed test** in both the OFF
7 medication and ON medication state. The timed Sit-stand-walk test will incorporate time taken from
8 seated position to stand and walk 10 metres, turn and return to original seated position.
9

10 **Unified dyskinesia rating scale (UDysRS).** This is considered to be the most useful and objective way
11 of quantifying dyskinesia severity. This will be assessed in the ON medication state.
12

13 **Patient Health Questionnaire-9 (PHQ-9).** This scale allows for self-quantification of depression
14 severity. This will be assessed in the ON medication state.
15

16 **Non-motor symptom scale (NMSS).** This validated scale is a tool to collect data on the frequency and
17 severity of 30 non-motor symptoms sometimes experienced by PD patients. This will be assessed in
18 the ON medication state.
19

20 **The Parkinson's Disease Questionnaire (PDQ-39).** This is the standard disease specific measure of
21 quality of life in PD comprising 39 questions. It has been extensively validated in previous studies.
22

23 **Levodopa equivalent dose (LED).** To facilitate comparisons between patients taking different
24 regimes of conventional PD medications, a set of conversion factors have been used to convert each
25 of the commonly used PD medications to an LED of each of their medications can then be summed
26 for inter-patient / inter-group comparisons.[20]
27

28 **EQ-5D-5L.** This is a simple, 5 question form and visual analogue scale that allows calculation of
29 quality adjusted life years (QALY) to enable health economic analyses to be performed.
30

31 **The Client Service Receipt Inventory (CSRI).** Health and social care resource use. Self-completed
32 health care, social care and paid/unpaid carer resource use questionnaire asking about primary and
33 secondary care resource use relevant to Parkinson's and impact on carers in the past 6 months.
34

35 **3-day Hauser diary** of PD state (Time- On, Off, Troublesome Dyskinesia, Non-troublesome
36 dyskinesia, Asleep). Diary data allows quantification of the amount of time during a 3-day period
37 that patients spend in the varying states of movement ability.
38

39 **Ancillary Studies**

40 There are four optional sub-studies linked to the main trial:
41

- 42 1. Genetics sub-study: To try to identify genetic markers that may be associated with subtypes of PD
43 or variation in treatment responsiveness.
44
- 45 2. Cerebrospinal Fluid (CSF) sub-study: To determine whether any CSF changes associated with PD
46 are influenced by exposure to exenatide. These may include alpha synuclein monomers or
47 oligomers, neuroinflammatory markers, and exosomal contents.
48
- 49 3. Remote Monitoring of PD Symptoms sub-study: To help determine whether measurement of PD
50 symptoms using digital technology may be a more sensitive measure of change with active drug
51 versus placebo compared to the MDS UPDRS 3 in the OFF and ON medication states. This will form
52 two separate measurements comprising 1) home-based smartphone and 2) real-world gait/walking
53 activity monitoring.[21][22][23] This aims to generate precision data, providing person-specific
54 distributions of outcomes and may be able to better delineate baseline clinical features.
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3 4. DaTSCAN (Imaging sub-study): To determine if change in dopamine transporter availability in the
4 caudate and putaminal nuclei as measured by quantitative DaTSCAN signal is influenced by exposure
5 to exenatide compared to placebo.
6

7 **Visits**

8
9 The overall progression of assessments are summarised in figure 1. While we expect to undertake all
10 assessments in respective clinical units, provision has been made in line with INCLUDE guidance for
11 the possibility of home visit assessments to be performed when patient specific situations (e.g.
12 inability to travel due to coronavirus restrictions, worsening 'OFF' state over progression of trial)
13 necessitate this. We hope that this provision will aid overall trial retention while enhancing
14 recruitment of patients from typically less well represented demographics (e.g. rural geographic
15 regions, patients lacking private travel facilities).
16
17

18 **Screening Visit**

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20 Written informed consent to enter and be randomised into the trial will be obtained from
21 participants, after explanation of the aims, methods, benefits and potential hazards of the trial and
22 before any trial-specific procedures are performed or any blood is taken for the trial. Patients will be
23 screened using the history of their Parkinson's disease, supported by any available clinical
24 correspondence according to usual standard of care.
25
26

27 The collection of the following scales will evaluate patient eligibility: MoCA, PHQ-9, as well as blood
28 tests (full blood count, urea & electrolytes, creatinine, liver function tests, HbA1C, C-peptide,
29 coagulation, serum amylase, thyroid function tests, blood glucose, insulin and lipid profile, and a
30 pregnancy test for women of child bearing potential). Tests can be repeated between screening and
31 baseline visits, if required to confirm eligibility. Abnormalities detected that warrant further
32 management e.g. newly diagnosed diabetes will be referred for appropriate medical
33 evaluation.
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36 Patients recruited to the DATSCAN substudy will have imaging performing prior to their baseline
37 visit.
38

39 **Baseline visit and randomisation**

40
41 Previously defined primary and secondary outcome measures will be performed in the 'ON' and
42 'OFF' states as outlined below. Patients' LED will be noted. Randomisation to either exenatide or
43 placebo will be administered using a centralised, web-based system (www.sealedenvelope.com). All
44 assessments related to sub-studies will also be performed prior to trial medication administration.
45
46

47 **Assessment Procedures**

48
49 After the Screening Visit, the named site clinical staff member will call the participant to remind
50 them of the need to stop taking their regular PD medication prior to their next trial visit and to
51 attend in a fasted state (prior to visits 2, 4, 6, 8, 10). The MDS-UPDRS part 3 and Timed Walk
52 assessments will be initially performed in the OFF state. This assessment in both the 'OFF' and 'ON'
53 states will be performed with video recording to facilitate the possibility of a re-review if necessary.
54 Remote monitoring assessments will be conducted at this point at selected sites in patients
55 consenting to participate in this sub-study. While waiting for medications to work, participants will
56 self-complete the MDS-UPDRS parts 1, 2 and 4, PDQ-39, EQ-5D-5L and CSRI. The MDS-UPDRS part 3
57 and Timed Walk assessments will be repeated 1 hour after the participant has taken their routine
58 medications - the ON medication state. After completion of the MDS-UPDRS and Timed Walk
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3 assessments in the ON medication state, each participant will be assessed using the MoCA, NMS
4 scale, UDysRS and PHQ-9. This will occur in alternate post-randomisation assessments (at visits 2, 4,
5 6, 8, 10). At selected centres participants in the CSF sub-study will have a CSF sample taken via
6 lumbar puncture. Ten weeks after the last trial medication administration, a staff member will call
7 the participant to collect details of any adverse events that have occurred after the participant stops
8 taking the trial medication. Participants will complete the 3 Day Hauser Diary prior to visits 2, 6 and
9 10 and return the diary back to the research team at the respective study visits. At each of the visits
10 2, 4, 6, 8, and 10, a blood sample will be collected and processed for storage for future analysis.

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13 The DaTSCAN imaging sub-study will be performed at the UCLH site on all consenting sub-study
14 participants; scans will be performed prior to visit 2 and after visit 10.

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16 The option for performing a remote assessment will be provided to patients for safety monitoring
17 visits in view of the coronavirus pandemic.
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20 21 **Intervention**

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23 Each dose of exenatide 2 mg (powder and solvent for prolonged release, suspension for injection,
24 prefilled pen) is supplied as a single use injection pen for subcutaneous administration by the patient
25 on a weekly basis. The placebo (inactive powder and solvent for prolonged release, suspension for
26 injection, prefilled pen) is supplied as an identical injection pen for subcutaneous administration by
27 the patient on a weekly basis. The trial medication will be refrigerated and stored at 2-8°C. Both
28 exenatide and placebo will be supplied by AstraZeneca as unlabelled prefilled pens in bulk and in
29 accordance with Good Manufacturing Practice (GMP). Labelling, packaging and release of packed
30 trial medications will be managed by the Sponsor's contracted company following GMP. The labels
31 will be prepared in accordance with GMP Annex 13 (Supplementary Materials 1) requirements for
32 labelling and local regulatory guidelines. The trial medications will be released ahead of trial use.
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36 Site trial staff will be trained on the use of exenatide using an online teaching video, accompanying
37 product literature and the Investigator's Brochure (IB). Patients will be taught how to perform the
38 subcutaneous injections by the clinical trial team using the online video, demonstration packs and
39 written literature. They will be told about common adverse reactions previously reported e.g.
40 nausea, vomiting, diarrhoea and weight loss by the clinical trial team, and will be advised on the
41 processes for safety reporting. In the event that exenatide injections will be administered by care-
42 givers (e.g. spouse), their willingness to perform this will be documented and they will be trained
43 using the online teaching video. It will also be ascertained that the care-giver either lives with the PD
44 patient or confirms their willingness to meet with the PD participant on a weekly basis to administer
45 the injections for the 96 week period of the trial.
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49 Patients who meet eligibility criteria at the screening visit will be randomly assigned to receive 96
50 weeks of double-blind treatment with either exenatide or placebo (2mg once weekly) in a 1:1 ratio.
51 The first dose will be administered by the patient in clinic following injection training and
52 subsequent injections will be at home. Injections will be self-administered by the participants, or
53 administered by their carer, into the participants' abdomen, arm, thigh or buttocks every 7 days.
54 Participants will be provided with a link to the injection pen training video and a REC approved
55 injection administration training sheet.
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60 **Sample Size**

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3 The sample size is based on the detectable effect size (primary outcome is the MDS-UPDRS motor
4 subsection in the OFF medication state) for a two-arm (exenatide versus placebo) parallel-group trial
5 design. The calculations assume a common standard deviation of 13.5, and a correlation of 0.70
6 between baseline and follow up MDS-UPDRS measurements. These estimates are reasonable based
7 on data from the previous exenatide-PD trial[14]. On this basis, 160 evaluable participants divided
8 equally between the 2 groups is sufficient to detect a difference of 5.0 MDS-UPDRS part 3 points in
9 the OFF medication state between the 2 groups adjusting for baseline MDS-UPDRS part 3 OFF
10 scores, with 90% power and at a significance level of 0.05. Assuming 20% attrition (withdrawal/loss
11 to follow up), 200 participants will be recruited. Participants who withdraw from the trial will not be
12 replaced. Participants who withdraw from trial treatment should remain in the trial for the purpose
13 of follow-up and data analysis. This effect size is a reasonable expectation based on the previously
14 collected pilot data and would represent a clear demonstration of the efficacy of exenatide on the
15 motor severity of PD.
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20 It is also anticipated that the difference in scores in the ON medication state will be greater at 96
21 weeks than at the earlier time points. The expected rate of change in PD severity in the first 5 years
22 after PD diagnosis in the ON medication state is 1 MDS-UPDRS part 3 point per year. A predicted
23 advantage of 2 points in ON scores over 96 weeks would thus equate to an advantage in the rate of
24 disease progression above and beyond that achievable with conventional dopaminergic medication
25 and would be a further clear signal that continued use of exenatide is consistent with not only long-
26 term disease modifying effects, but even demonstration of a small change of 2.5 points in the MDS-
27 UPDRS motor score would constitute a clinically important difference[24] and potentially an
28 advantage in day to day functional impairment and overall improvement in quality of life in the short
29 term.
30
31

32 **Statistical Analysis**

33
34 A full statistical analysis plan (SAP) will be written and approved by the Trial Steering Committee
35 prior to database lock. All analyses will be undertaken according to a modified intention-to-treat
36 (mITT) principle in accordance with the randomised intervention. The threshold for the analysis
37 population will be participants who complete 12 weeks on treatment and for whom outcomes are
38 available.
39

40
41 Primary outcome analysis will evaluate the impact of treatment allocation (exenatide or placebo) on
42 the difference between MDS UPDRS part 3 OFF medication scores at 96 weeks follow-up adjusting
43 for baseline. The analysis will use a mixed-model approach incorporating information from all follow-
44 up visits that adjusts for baseline Hoehn & Yahr status and the baseline raw value of each outcome
45 measurement. Site will be included as a random effect to account for variability in outcomes
46 between sites, and a random patient/subject effect will accommodate the correlation between
47 repeated outcome measures on the same patient. A significance level of 5% will be used to judge
48 significance for the primary outcome measure.
49

50
51 A planned secondary analysis will compare the difference in MDS-UPDRS part 3 OFF medication
52 scores according to randomisation allocation at 96 weeks, with the scores at 48 weeks. An increase
53 in the advantage at 96 weeks compared to 48 weeks would be evidence that the active drug was
54 slowing down disease deterioration rather than having symptomatic effects only. This could
55 translate to a major population advantage in terms of reduction of morbidity and mortality.
56
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58 Analyses of the remaining secondary/exploratory outcomes will be undertaken similarly for the
59 difference between groups according to treatment allocation at 48 and 96 weeks follow up adjusting
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3 for baseline values of each outcome, and confounding factors such as LED differences between
4 groups.
5

6 Further exploratory analyses will consider whether exenatide can be thought of as disease modifying
7 by comparing slopes between groups at pre-specified periods.
8

9 A sensitivity (per protocol) analysis will be performed for the primary outcome measure and will only
10 include those participants who completed the trial in accordance with the approved protocol.
11

12 Results on the primary efficacy outcome will be presented by stratum, according to Hoehn & Yahr
13 stage (≤ 2.0 versus 2.5), and an interaction between Hoehn & Yahr and treatment will be added to
14 the primary analysis model to investigate whether the effect of treatment differs according to the
15 Hoehn & Yahr stage.
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17

18 All analyses will be performed by the designated Trial Statistician.
19

20 **Data Management**

21 Data will be entered in the Exenatide-PD3 database by delegated staff at participating sites and
22 members of the Exenatide-PD3 trial team at CCTU. Participants will be given a unique trial PIN
23 (Exnnn). Data will be entered under the PIN onto the central database (InferMed's MACRO stored on
24 the servers based at UCL). The database will be password protected and only accessible to members
25 of the Exenatide-PD3 trial team and external regulators if requested. Video recordings of the MDS-
26 UPDRS will be uploaded onto a secure cloud held by Machine Medicines Technologies (MMT) and
27 used for quality control purposes. Appropriate contractual agreements covering data protection are
28 in place with MMT. All data storage will adhere to GDPR and the Data Protection Act 2018.
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32 An Independent Data Monitoring Committee (IDMC) will be convened including at least 3 individuals
33 independent from the trial team and sponsor who have experience in the conduct of clinical trials
34 for PD. The IDMC will review the trial results and make a recommendation to the Trial Steering
35 Committee (TSC) regarding continuation/ stopping of the trial based on safety data. A statistician
36 independent of the Exenatide-PD3 Trial Team at CCTU will generate summaries of accumulating trial
37 data for the IDMC to review.
38
39

40 UCL is the trial sponsor and has delegated the duties as sponsor to CCTU via a signed letter of
41 delegation. The trial sponsor will take on responsibility for securing the arrangements to initiate,
42 manage and finance the trial. Trial oversight is intended to preserve the integrity of the trial by
43 independently verifying processes and prompting corrective action where necessary. In multi-centre
44 trials this oversight is considered and described both overall and for each recruiting centre by
45 exploring the trial dataset or performing site visits. The Trial Team (TT) will assist with developing the
46 design, co-ordination and day to day operational issues in the management of the trial, including
47 budget management. The Trial Management Group (TMG) will assist with developing the design, co-
48 ordination and strategic management of the trial. The Independent Trial Steering Committee (TSC) is
49 the independent group responsible for oversight of the trial in order to safeguard the interests of
50 trial participants. The TSC will provide advice to the Chief Investigator (CI), CCTU, the funder and
51 sponsor on all aspects of the trial through its independent Chair. The Independent Data Monitoring
52 Committee (IDMC) is the only oversight body that has access to unblinded accumulating
53 comparative data. The IDMC will be responsible for safeguarding the interests of trial participants,
54 monitoring the accumulating data and making recommendations to the TSC on whether the trial
55 should continue as planned. The membership, frequency of meetings, activity (including trial
56 conduct and data review) and authority of each committee will be covered in their respective terms
57 of reference.
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Ethics and Dissemination

The trial protocol, all informed consent forms and any material to be given to the prospective participant have received REC (initial date of approval 15/10/2019, REC reference no.19/SC/0447), and other regulatory approvals (EudraCT 2018-003028-35). Further, the trial was registered in clinictrials.gov NCT004232969 and in ISRCTN (reference 14552789). Subsequent amendments to these documents will be submitted for further approval. The same/amended documents will be submitted for additional local permissions at each clinical site.

This is a Clinical Trial of an IMP as defined by the EU Directive 2001/20/EC. Therefore, a clinical trial authorisation (CTA) is required in the UK and the trial protocol will therefore be submitted to the UK regulatory authority (MHRA). The progress of the trial, safety issues and reports, including expedited reporting will be reported to the MHRA as required. 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) have been submitted to the relevant NHS Trust R&D department of each participating site or to other local departments for approval.

Participants will be provided with a 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 (Supplementary Materials 2). During the consent process it will be emphasised 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 affecting their treatment. 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.

The rights of the participant to refuse to participate in the trial without giving a reason will be respected and after the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage. 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. All participants will be made aware of the known adverse reactions.

Discussion

A parallel group design with a washout period has been used previously in the evaluation of potential neuroprotective agents [25,26]. and this was chosen as the design for the previous phase 2 trial. This design is subject to possible long duration symptomatic effects and a lengthy washout period potentially impacts on patient retention and cannot necessarily distinguish a true neuroprotective effect from a symptomatic effect (in view of preservation of healthy behaviours with long term impacts such as exercise) [27]. An alternative approach which we have adopted here is 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 [28]. This design helps build 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

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3 potential for rapid recruitment, and improved retention of participants enabling more complete
4 follow up, and a statistically significant advantage in motor scores in people randomised to
5 exenatide over a 48-week period of treatment exposure. We have considered that an exposure
6 period of 96 weeks would allow exploration of long-term effects of exenatide exposure, while being
7 the maximum period that participants would be willing to accept being allocated placebo.
8 Furthermore, this will provide the opportunity to evaluate whether the 48-week data previously
9 published can be replicated and whether effects at 96 weeks are similar to or greater than those
10 seen at 48 weeks and other earlier timepoints.
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13 Many trials have attempted to evaluate the potential for disease modification using drugs with
14 broad mechanisms of action. The majority have either failed to demonstrate clinical efficacy or
15 provided inconclusive results. Some pertinent reasons for this are a failure of the investigated agent
16 to reach and engage its target and lack of objective measures of true clinical disease progression.
17 Clinical endpoints such as the MDS-UPDRS scale are necessary to ultimately confirm relevance;
18 however, these scales lack sensitivity for capturing disease modification unless very long term follow
19 up data are collected. While our approach of following patients for 2 years in this trial will partially
20 mitigate some of this, the addition and to an extent validation of more detailed approaches through
21 a number of sub studies (imaging, CSF analysis for target engagement and drug levels, and device
22 assisted measurements of real-life motor function) could ultimately provide more holistic and
23 definitive metrics for determining if exenatide does in fact deliver disease modification in PD. This
24 more comprehensive approach to approaching assessments and the consistent signal of benefit
25 noted in two earlier trials provide grounds for optimism that the primary outcome will be
26 achievable. The study opened to recruitment in January 2020 and we expect completion of study
27 analysis by Q3 2024.
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36 Author Contributions:

37
38 The study concept and design was conceived by TF. NV and CG will conduct screening and data
39 collection. GA, MC, KM, KC, HM, SH, PL, DA, CC, MH, MS, GD, RC, CL, SDD, AY, LR, RG, JD, RH and VL
40 assisted on drafting the protocol. Analysis will be performed by SS, and data entry by AK. NV
41 prepared the first draft of the manuscript. RG served as a patient adviser for the design of the study
42 protocol. All authors provided edits and revised the manuscript for intellectual content.
43
44

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46 We are grateful to all patients contributing to the design of this study. We thank the Cure
47 Parkinson's Trust and Parkinson's UK for their assistance in the setup and increasing the awareness
48 of this study.
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55 number MH011.
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Competing Interest Statement

None declared

Data Statement

Not applicable at this stage.

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51 Figure legend

52 Figure 1: Outline of Trial design
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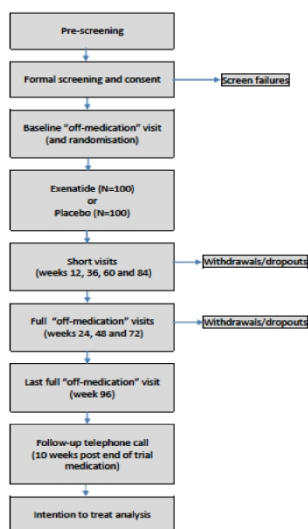


Figure 1: Outline of Trial design

209x296mm (400 x 400 DPI)



EUROPEAN COMMISSION
 ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 03 February 2010
 ENTR/F/2/AM/an D(2010) 3374

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4

EU Guidelines to

Good Manufacturing Practice

Medicinal Products for Human and Veterinary Use

Annex 13

Investigational Medicinal Products

| Document History | |
|---|--|
| <p>Revision to reinforce the principle of independence between production and quality control functions in cases where the number of personnel involved is small.</p> <p>Changes to sections 36 and 37 to supplement, for investigational medicinal products, the guidance for reference and retention samples given in Annex 19.</p> <p>An additional note has been introduced to clarify the meaning of “reconstitution” as referred to in article 9.2 of Directive 2005/28/EC.</p> <p>The content of the Batch Certificate referred to in Art. 13(3) of Directive 2001/20/EC, agreed following a separate public consultation, has been added as an attachment.</p> <p>A few editorial changes have been made to sections not consulted upon in the interests of updating references and consistency with terminology used throughout the GMP Guide.</p> | <p>February 2008</p> |
| <p>Public consultation</p> | <p>April 2008 until January 2009</p> |
| <p>Adopted by the European Commission</p> | <p>31 January 2010</p> |
| <p>Deadline for coming into operation</p> | <p>31 July 2010</p> |

PRINCIPLE

Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products (The Rules Governing Medicinal Products in The European Community, Volume IV). Other guidelines published by the European Commission should be taken into account where relevant and as appropriate to the stage of development of the product. Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.

In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products. The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified.

The production of investigational medicinal products involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, and the need, often, for randomisation and blinding and increased risk of product cross-contamination and mix up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation, or, marketed products may be used which have been re-packaged or modified in some way. These challenges require personnel with a thorough understanding of, and training in, the application of GMP to investigational medicinal products. Co-operation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products. The increased complexity in manufacturing operations requires a highly effective quality system.

The Annex also includes guidance on ordering, shipping, and returning clinical supplies, which are at the interface with, and complementary to, guidelines on Good Clinical Practice.

Notes

Non-investigational medicinal product¹

Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial. Such products may be used as support or escape medication for preventative, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator. The sponsor should ensure that they are in accordance with the notification/request for authorisation to conduct the trial and that they are of appropriate quality for the purposes of the trial taking into account the source of the materials, whether or not they are the subject of

¹ Further information can be found in the European Commission's Guidance on Investigational Medicinal Products (IMPs) and other Medicinal Products used in Clinical Trials

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2 a marketing authorisation and whether they have been repackaged. The advice and
3 involvement of a Qualified Person is recommended in this task.
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5 *Manufacturing authorisation and reconstitution*

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7 Both the total and partial manufacture of investigational medicinal products, as well as the
8 various processes of dividing up, packaging or presentation, is subject to the authorisation
9 referred to in Article 13(1) Directive 2001/20/EC, cf. Article 9(1) Directive 2005/28/EC. This
10 authorisation, however, shall not be required for reconstitution under the conditions set out in
11 Article 9(2) Directive 2005/28/EC. For the purpose of this provision, reconstitution shall be
12 understood as a simple process of:
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- 15 • dissolving or dispersing the investigational medicinal product for administration of the
16 product to a trial subject,
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- 18 • or, diluting or mixing the investigational medicinal product(s) with some other
19 substance(s) used as a vehicle for the purposes of administering it,
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21

22 Reconstitution is not mixing several ingredients, including the active substance, together to
23 produce the investigational medicinal product.
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25 An investigational medicinal product must exist before a process can be defined as
26 reconstitution.
27

28 The process of reconstitution has to be undertaken as soon as practicable before
29 administration.
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32 This process has to be defined in the clinical trial application / IMP dossier and clinical trial
33 protocol, or related document, available at the site.
34
35

36 **GLOSSARY**

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38 **Blinding**

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40 A procedure in which one or more parties to the trial are kept unaware of the treatment
41 assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-
42 blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data
43 analyst(s) being unaware of the treatment assignment(s). In relation to an investigational
44 medicinal product, blinding shall mean the deliberate disguising of the identity of the product
45 in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of
46 the identity of blinded products.
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50 **Clinical trial**

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52 Any investigation in human subjects intended to discover or verify the clinical,
53 pharmacological and/or other pharmacodynamic effects of an investigational product(s)
54 and/or to identify any adverse reactions to an investigational product(s), and/or to study
55 absorption, distribution, metabolism, and excretion of one or more investigational medicinal
56 product(s) with the object of ascertaining its/their safety and/or efficacy.
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Comparator product

An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Investigational medicinal product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Manufacturer/importer of Investigational Medicinal Products

Any person engaged in activities for which the authorisation referred to in Article 13(1) of Directive 2001/20/EC is required.

Order

Instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).

Product Specification File

A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

Randomisation

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomisation Code

A listing in which the treatment assigned to each subject from the randomisation process is identified.

Shipping

The operation of packaging for shipment and sending of ordered medicinal products for clinical trials.

Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

QUALITY MANAGEMENT

1. The Quality System, designed, set up and verified by the manufacturer or importer, should be described in written procedures available to the sponsor, taking into account the GMP principles and guidelines applicable to investigational medicinal products.
2. The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained.

PERSONNEL

3. All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.

Even in cases where the number of staff involved is small, there should be, for each batch, separate people responsible for production and quality control.

4. The Qualified Person should ensure that there are systems in place that meet the requirements of GMP and should have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Qualified Person in connection with the certification of investigational medicinal products is given in paragraphs 38 to 41.

PREMISES AND EQUIPMENT

5. The toxicity, potency and sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection / test methods and acceptance limits to be used after cleaning should reflect the nature of these risks. Consideration should be given to campaign working where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

DOCUMENTATION

Specifications and instructions

6. Specifications (for starting materials, primary packaging materials, intermediate, bulk products and finished products), manufacturing formulae and processing and packaging instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial requirements, and should allow traceability to the previous document. Any changes should be carried out according to a written procedure, which should address any implications for product quality such as stability and bio equivalence.

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7. Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and documented².

Order

8. The order should request the processing and/or packaging of a certain number of units and/or their shipping and be given by or on behalf of the sponsor to the manufacturer. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorised and refer to the Product Specification File and the relevant clinical trial protocol as appropriate.

Product Specification File

9. The Product Specification File (see glossary) should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, the following documents:

- Specifications and analytical methods for starting materials, packaging materials;
- Intermediate, bulk and finished product;
- Manufacturing methods;
- In-process testing and methods;
- Approved label copy;
- Relevant clinical trial protocols and randomisation codes, as appropriate;
- Relevant technical agreements with contract givers, as appropriate;
- Stability data;
- Storage and shipment conditions.

The above listing is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development. The information should form the basis for assessment of the suitability for certification and release of a particular batch by the Qualified Person and should therefore be accessible to him/her. Where different manufacturing steps are carried out at different locations under the responsibility of different Qualified Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

Manufacturing Formulae and Processing Instructions

10. For every manufacturing operation or supply there should be clear and adequate written instructions and written records. Where an operation is not repetitive it may not be

² Guidance on changes that require the request of a substantial amendment to the IMP dossier submitted to the Competent Authorities is given in the CHMP guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials

necessary to produce Master Formulae and Processing Instructions. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorisation is granted.

11. The information in the Product Specification File should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping.

Packaging Instructions

12. Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and any retention samples to be kept. Sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.

Processing, testing and packaging batch records

13. Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify the procedures used and any changes made, enhance knowledge of the product and develop the manufacturing operations.
14. Batch manufacturing records should be retained at least for the periods specified in Directive 2003/94/EC.

PRODUCTION

Packaging materials

15. Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.

Manufacturing operations

16. During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continually to the experience gained in production. Parameters identified and controlled should be justifiable based on knowledge available at the time.
17. Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified. For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing. Likewise, when required, virus inactivation/removal and that of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived

1
2 products, by following the scientific principles and techniques defined in the available
3 guidance in this area.
4

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6 18. Validation of aseptic processes presents special problems when the batch size is small; in
7 these cases the number of units filled may be the maximum number filled in production.
8 If practicable, and otherwise consistent with simulating the process, a larger number of
9 units should be filled with media to provide greater confidence in the results obtained.
10 Filling and sealing is often a manual or semi-automated operation presenting great
11 challenges to sterility so enhanced attention should be given to operator training, and
12 validating the aseptic technique of individual operators.
13

14 **Principles applicable to comparator product**

- 15
16 19. If a product is modified, data should be available (e.g. stability, comparative dissolution,
17 bioavailability) to demonstrate that these changes do not significantly alter the original
18 quality characteristics of the product.
19
20 20. The expiry date stated for the comparator product in its original packaging might not be
21 applicable to the product where it has been repackaged in a different container that may
22 not offer equivalent protection, or be compatible with the product. A suitable use-by
23 date, taking into account the nature of the product, the characteristics of the container
24 and the storage conditions to which the article may be subjected, should be determined
25 by or on behalf of the sponsor. Such a date should be justified and must not be later than
26 the expiry date of the original package. There should be compatibility of expiry dating
27 and clinical trial duration.
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31 **Blinding operations**

- 32
33 21. Where products are blinded, systems should be in place to ensure that the blind is
34 achieved and maintained while allowing for identification of “blinded” products when
35 necessary, including the batch numbers of the products before the blinding operation.
36 Rapid identification of product should also be possible in an emergency.
37
38

39 **Randomisation code**

- 40
41 22. Procedures should describe the generation, security, distribution, handling and retention
42 of any randomisation code used for packaging investigational products, and code-break
43 mechanisms. Appropriate records should be maintained.
44
45

46 **Packaging**

- 47
48 23. During packaging of investigational medicinal products, it may be necessary to handle
49 different products on the same packaging line at the same time. The risk of product mix
50 up must be minimised by using appropriate procedures and/or, specialised equipment as
51 appropriate and relevant staff training.
52
53 24. Packaging and labelling of investigational medicinal products are likely to be more
54 complex and more liable to errors (which are also harder to detect) than for marketed
55 products, particularly when “blinded” products with similar appearance are used.
56 Precautions against mis-labelling such as label reconciliation, line clearance, in process
57 control checks by appropriately trained staff should accordingly be intensified.
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25. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

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Labelling

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26. Table 1 summarises the contents of Articles 26-30 that follow. Labelling should comply with the requirements of Directive 2003/94/EC. The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system:
- 14 (a) name, address and telephone number of the sponsor, contract research
15 organisation or investigator (the main contact for information on the product,
16 clinical trial and emergency unblinding);
 - 17 (b) pharmaceutical dosage form, route of administration, quantity of dosage units,
18 and in the case of open trials, the name/identifier and strength/potency;
 - 19 (c) the batch and/or code number to identify the contents and packaging operation;
 - 20 (d) a trial reference code allowing identification of the trial, site, investigator and
21 sponsor if not given elsewhere;
 - 22 (e) the trial subject identification number/treatment number and where relevant,
23 the visit number;
 - 24 (f) the name of the investigator (if not included in (a) or (d));
 - 25 (g) directions for use (reference may be made to a leaflet or other explanatory
26 document intended for the trial subject or person administering the product);
 - 27 (h) “For clinical trial use only” or similar wording;
 - 28 (i) the storage conditions;
 - 29 (j) period of use (use-by date, expiry date or re-test date as applicable), in
30 month/year format and in a manner that avoids any ambiguity.
 - 31 (k) “keep out of reach of children” except when the product is for use in trials
32 where the product is not taken home by subjects.
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27. The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.
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28. Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in Article 26 should appear on the primary packaging and on the secondary packaging (except for the cases described in Articles 29 and 30). The requirements with respect to the contents of the label on the primary and outer packaging are summarised in Table 1. Other languages may be included.
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29. When the product is to be provided to the trial subject or the person administering the medication within a primary package together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in Paragraph 26, the following information shall be included on the label of the primary package (or any sealed dosing device that contains the primary packaging):
- (a) name of sponsor, contract research organisation or investigator;
 - (b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;
 - (c) batch and/or code number to identify the contents and packaging operation;
 - (d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
 - (e) the trial subject identification number/treatment number and where relevant, the visit number.
30. If the primary packaging takes the form of blister packs or small units such as ampoules on which the particulars required in Paragraph 26 cannot be displayed, secondary packaging should be provided bearing a label with those particulars. The primary packaging should nevertheless contain the following:
- (a) name of sponsor, contract research organisation or investigator;
 - (b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;
 - (c) batch and/or code number to identify the contents and packaging operation;
 - (d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
 - (e) the trial subject identification number/treatment number and where relevant, the visit number;
31. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.
32. For clinical trials with the characteristics identified in Article 14 of Directive 2001/20/EC, the following particulars should be added to the original container but should not obscure the original labelling:
- i) name of sponsor, contract research organisation or investigator;
 - ii) trial reference code allowing identification of the trial site, investigator and trial subject.
33. If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be

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2 performed at an appropriately authorised manufacturing site. However, when justified, it
3 may be performed at the investigational site by or under the supervision of the clinical
4 trial site pharmacist, or other health care professional in accordance with national
5 regulations. Where this is not possible, it may be performed by the clinical trial
6 monitor(s) who should be appropriately trained. The operation should be performed in
7 accordance with GMP principles, specific and standard operating procedures and under
8 contract, if applicable, and should be checked by a second person. This additional
9 labelling should be properly documented in both the trial documentation and in the batch
10 records.
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14 **QUALITY CONTROL**

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16 34. As processes may not be standardised or fully validated, testing takes on more
17 importance in ensuring that each batch meets its specification.
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19 35. Quality control should be performed in accordance with the Product Specification File
20 and in accordance with the information notified pursuant to Article 9(2) of Directive
21 2001/20/EC. Verification of the effectiveness of blinding should be performed and
22 recorded.
23
24 36. Samples are retained to fulfill two purposes; firstly to provide a sample for analytical
25 testing and secondly to provide a specimen of the finished product. Samples may
26 therefore fall into two categories:
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30 *Reference sample:* a sample of a batch of starting material, packaging material, product
31 contained in its primary packaging or finished product which is stored for the purpose of
32 being analysed should the need arise. Where stability permits, reference samples from
33 critical intermediate stages (e.g. those requiring analytical testing and release) or
34 intermediates, which are transported outside of the manufacturer's control, should be
35 kept.
36
37

38 *Retention sample:* a sample of a packaged unit from a batch of finished product for each
39 packaging run/trial period. It is stored for identification purposes. For example,
40 presentation, packaging, labeling, leaflet, batch number, expiry date should the need
41 arise.
42
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44 In many instances the reference and retention samples will be presented identically, i.e.
45 as fully packaged units. In such circumstances, reference and retention samples may be
46 regarded as interchangeable. Reference and retention samples of investigational
47 medicinal product, including blinded product should be kept for at least two years after
48 completion or formal discontinuation of the last clinical trial in which the batch was
49 used, whichever period is the longer.
50

51 Consideration should be given to keeping retention samples until the clinical report has
52 been prepared to enable confirmation of product identity in the event of, and as part of an
53 investigation into inconsistent trial results.
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- 56 37. The storage location of Reference and Retention samples should be defined in a
57 Technical Agreement between the sponsor and manufacturer(s) and should allow timely
58 access by the competent authorities.
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2 *Reference samples* of finished product should be stored within the EEA or in a third
3 country where appropriate arrangements have been made by the Community with the
4 exporting country to ensure that the manufacturer of the investigational medicinal
5 product applies standards of good manufacturing practice at least equivalent to those laid
6 down by the Community. In exceptional circumstances the reference samples of the
7 finished product may be stored by the manufacturer in another third country, in which
8 case this should be justified, and documented in a technical agreement between the
9 sponsor, importer in the EEA and that third country manufacturer.

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12 The reference sample should be of sufficient size to permit the carrying out, on, at least,
13 two occasions, of the full analytical controls on the batch in accordance with the IMP
14 dossier submitted for authorisation to conduct the clinical trial.

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17 In the case of *retention samples*, it is acceptable to store information related to the final
18 packaging as written or electronic records if such records provide sufficient information.
19 In the case of the latter, the system should comply with the requirements of Annex 11.

20 21 22 **RELEASE OF BATCHES**

- 23
24
25 38. Release of investigational medicinal products (see paragraph 43) should not occur until
26 after the Qualified Person has certified that the requirements of Article 13.3 of Directive
27 2001/20/EC have been met (see paragraph 39). The Qualified Person should take into
28 account the elements listed in paragraph 40 as appropriate.
- 29
30 39. The duties of the Qualified Person in relation to investigational medicinal products are
31 affected by the different circumstances that can arise and are referred to below. Table 2
32 summarises the elements that need to be considered for the most common circumstances:
- 33
34 (a) i) Product manufactured within EU but not subject to an EU marketing
35 authorisation: the duties are laid down in article 13.3(a) of Directive
36 2001/20/EC.
- 37
38 (b) ii) Product sourced from the open market within EU in accordance with Article
39 80(b) of Directive 2001/83/EC and subject to an EU marketing authorisation,
40 regardless of manufacturing origin: the duties are as described above, however,
41 the scope of certification can be limited to assuring that the products are in
42 accordance with the notification/request for authorisation to conduct the trial
43 and any subsequent processing for the purpose of blinding, trial-specific
44 packaging and labelling. The Product Specification File will be similarly
45 restricted in scope (see 9).
- 46
47 (c) Product imported directly from a 3rd country: the duties are laid down in
48 article 13.3(b) of Directive 2001/20/EC. Where investigational medicinal
49 products are imported from a 3rd country and they are subject to arrangements
50 concluded between the Community and that country, such as a Mutual
51 Recognition Agreement (MRA), equivalent standards of Good Manufacturing
52 Practice apply provided any such agreement is relevant to the product in
53 question. In the absence of an MRA, the Qualified Person should determine
54 that equivalent standards of Good Manufacturing Practice apply through
55 knowledge of the quality system employed at the manufacturer. This
56 knowledge is normally acquired through audit of the manufacturer's quality
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2 systems. In either case, the Qualified Person may then certify on the basis of
3 documentation supplied by the 3rd country manufacturer (see 40).
4

- 5 (d) For imported comparator products where adequate assurance cannot be
6 obtained in order to certify that each batch has been manufactured to
7 equivalent standards of Good Manufacturing Practice, the duty of the Qualified
8 Person is defined in article 13.3(c) of Directive 2001/20/EC.
9

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11 40. Assessment of each batch for certification prior to release may include as appropriate:
12

- 13 • batch records, including control reports, in-process test reports and release reports
14 demonstrating compliance with the product specification file, the order, protocol and
15 randomisation code. These records should include all deviations or planned changes,
16 and any consequent additional checks or tests, and should be completed and endorsed
17 by the staff authorised to do so according to the quality system;
18
- 19 • production conditions;
20
- 21 • the validation status of facilities, processes and methods;
22
- 23 • examination of finished packs;
24
- 25 • where relevant, the results of any analyses or tests performed after importation;
26
- 27 • stability reports;
28
- 29 • the source and verification of conditions of storage and shipment;
30
- 31 • audit reports concerning the quality system of the manufacturer;
32
- 33 • Documents certifying that the manufacturer is authorised to manufacture
34 investigational medicinal products or comparators for export by the appropriate
35 authorities in the country of export;
36
- 37 • where relevant, regulatory requirements for marketing authorisation, GMP standards
38 applicable and any official verification of GMP compliance;
39
- 40 • all other factors of which the QP is aware that are relevant to the quality of the batch.
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45 The relevance of the above elements is affected by the country of origin of the product,
46 the manufacturer, and the marketed status of the product (with or without a marketing
47 authorisation, in the EU or in a third country) and its phase of development. The sponsor
48 should ensure that the elements taken into account by the qualified person when
49 certifying the batch are consistent with the information notified pursuant to Article 9(2)
50 of Directive 2001/20/EC. See also section 44.
51
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- 53
54 41. Where investigational medicinal products are manufactured and packaged at different
55 sites under the supervision of different Qualified Persons, the recommendations listed in
56 Annex 16 to the GMP Guide should be followed as applicable.
57
- 58 42. Where, permitted in accordance with local regulations, packaging or labelling is carried
59 out at the investigator site by, or under the supervision of a clinical trials pharmacist, or
60 other health care professional as allowed in those regulations, the Qualified Person is not

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2 required to certify the activity in question. The sponsor is nevertheless responsible for
3 ensuring that the activity is adequately documented and carried out in accordance with
4 the principles of GMP and should seek the advice of the Qualified Person in this regard.
5
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7 **SHIPPING**

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10 43. Investigational medicinal products should remain under the control of the sponsor until
11 after completion of a two-step procedure: certification by the Qualified Person; and
12 release by the sponsor for use in a clinical trial following fulfillment of the requirements
13 of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. Both steps
14 should be recorded³ and retained in the relevant trial files held by or on behalf of the
15 sponsor. The Sponsor should ensure that the details set out in the clinical trial application
16 and considered by the Qualified Person are consistent with what is finally accepted by
17 the Competent Authorities. Suitable arrangements to meet this requirement should be
18 established. In practical terms, this can best be achieved through a change control
19 process for the Product Specification File and defined in a Technical Agreement between
20 the QP and the Sponsor.
21
22
23 44. Shipping of investigational products should be conducted according to instructions given
24 by or on behalf of the sponsor in the shipping order.
25
26 45. De-coding arrangements should be available to the appropriate responsible personnel
27 before investigational medicinal products are shipped to the investigator site.
28
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30 46. A detailed inventory of the shipments made by the manufacturer or importer should be
31 maintained. It should particularly mention the addressees' identification.
32
33 47. Transfers of investigational medicinal products from one trial site to another should
34 remain the exception. Such transfers should be covered by standard operating
35 procedures. The product history while outside of the control of the manufacturer,
36 through for example, trial monitoring reports and records of storage conditions at the
37 original trial site should be reviewed as part of the assessment of the product's suitability
38 for transfer and the advice of the Qualified person should be sought. The product should
39 be returned to the manufacturer, or another authorised manufacturer, for re-labelling, if
40 necessary, and certification by a Qualified Person. Records should be retained and full
41 traceability ensured.
42
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46 **COMPLAINTS**

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48 48. The conclusions of any investigation carried out in relation to a complaint which could
49 arise from the quality of the product should be discussed between the manufacturer or
50 importer and the sponsor (if different). This should involve the Qualified Person and
51 those responsible for the relevant clinical trial in order to assess any potential impact on
52 the trial, product development and on subjects.
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59 ³ A harmonised format for batch certification to facilitate movement between Member States is provided in
60 attachment 3.

RECALLS AND RETURNS

Recalls

49. Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator and monitor need to understand their obligations under the retrieval procedure.
50. The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.

Returns

51. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.
52. Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.

DESTRUCTION

53. The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorisation by the Sponsor.
54. The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor.
55. When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

TABLE 1:SUMMARY OF LABELLING DETAILS (§26 TO 30)

a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);

GENERAL CASE

For both the primary and secondary packaging (§26)

(b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;

Particulars a⁴ to k

(c) the batch and/or code number to identify the contents and packaging operation;

(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

PRIMARY PACKAGE

Where primary and secondary packaging remain together throughout (§29)⁵

(e) the trial subject identification number/treatment number and where relevant, the visit number;

a⁶ b⁷ c d e

(f) the name of the investigator (if not included in (a) or (d));

(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product

PRIMARY PACKAGE

Blisters or small packaging units (§30)⁵

(h) "for clinical trial use only" or similar wording;

a⁶ b^{7,8} c d e

(i) the storage conditions;

(j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.

(k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

⁴ The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times (§ 27).

⁵ When the outer packaging carries the particulars listed in Article 26.

⁶ The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not be included.

⁷ Route of administration may be excluded for oral solid dose forms.

⁸ The pharmaceutical dosage form and quantity of dosage units may be omitted.

Table 2: BATCH RELEASE OF PRODUCTS

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ELEMENTS TO BE TAKEN INTO ACCOUNT(3)

PRODUCT AVAILABLE IN THE EU

PRODUCT IMPORTED FROM THIRD COUNTRIES

Product manufactured in EU without MA

Product with MA and available on EU market

Product without any EU MA

Product with a EU MA

Comparator where documentation certifying that each batch has been manufactured in conditions at least equivalent to those laid down in Directive 2003/94/EC cannot be obtained

BEFORE CLINICAL TRIAL PROCESSING

a) Shipping and storage conditions

Yes

b) All relevant factors (1) showing that each batch has been manufactured and released in accordance with:
Directive 2003/94/EC, or
GMP standards at least equivalent to those laid down in Directive 2003/94/EC.

Yes

Yes (2)

c) Documentation showing that each batch has been released within the EU according to EU GMP requirements (see Directive 2001/83/EC, article 51), or documentation showing that the product is available on the EU market and has been procured in accordance with article 80(b) of Directive 2001/83/EC.

Yes

d) Documentation showing that the product is available on the local market and documentation to establish confidence in the local regulatory requirements for marketing authorisation and release for local use.

Yes

e) Results of all analysis, tests and checks performed to assess the quality of the imported batch according to:
the requirements of the MA (see Directive 2001/83/EC, article 51b), or
the Product Specification File, the Order, article 9.2 submission to the regulatory authorities.

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Yes

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Yes

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Where these analyses and tests are not performed in the EU, this should be justified and the QP must certify that they have been carried out in accordance with GMP standards at least equivalent to those laid down in Directive 2003/94/EC.

Yes

Yes

Yes

AFTER CLINICAL TRIAL PROCESSING

f) In addition to the assessment before clinical trial processing, all further relevant factors (1) showing that each batch has been processed for the purposes of blinding, trial-specific packaging, labelling and testing in accordance with:
Directive 2003/94/EC, or
GMP standards at least equivalent to those laid down in Directive 2003/94/EC.

Yes

Yes (2)

ATTACHMENT 3

[LETTERHEAD OF MANUFACTURER]

Content of the Batch Certificate**Referred to in Art. 13.3 Directive 2001/20/EC**

- (1) Name(s) of product(s)/product identifier(s) as referred to in the clinical trial application, where applicable.
- (2) EudraCT No(s) and sponsor protocol code number, when available.
- (3) Strength
Identity (name) and amount per unit dose for all active substance(s) for each IMP (including placebo). The manner in which this information is provided should not unblind the study.
- (4) Dosage form (pharmaceutical form)
- (5) Package size (contents of container) and type (e.g. vials, bottles, blisters).
- (6) Lot/batch number
- (7) Expiry/retest/use by date
- (8) Name and address of manufacturer where the Qualified Person issuing the certificate is located.
- (9) Manufacturing Authorisation number for the site listed under item 8.
- (10) Comments/remarks
- (11) Any additional information considered relevant by the QP.
- (12) Certification statement.
- (13) “I hereby certify that this batch complies with the requirements of Article 13.3 of Directive 2001/20/EC “
- (14) Name of the QP signing the certificate
- (15) Signature
- (16) Date of signature

Explanatory Note

Investigational medicinal products may not be used in a clinical trial in a member state of the European Economic Area until the completion of the two-step procedure referred to in section 43 of this Annex. The first step is the certification of each batch by the Qualified Person of the manufacturer or importer that the provisions of Article 13.3(a),

1
2 (b) or (c) of Directive 2001/20/EC have been complied with and documented in
3 accordance with Art. 13.4 of the same Directive. According to Directive 2001/20/EC a
4 batch of investigational medicinal product shall not have to undergo further checks in
5 relation to the provisions of article 13.3(a), (b) or (c) of the same directive when it moves
6 between Member States accompanied by batch certification signed by the Qualified
7 Person. In order to facilitate the free movement of investigational medicinal products
8 between Member States the content of these certificates should be in accordance with the
9 above harmonised format. This format may also be used to certify batches destined for
10 use within the Member State of the manufacturer or importer.
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For peer review only



Exenatide-PD3 Site Number: _____ Exenatide-PD3 Patient Identifiers:
 Screening ID: _____ - _____
 Trial ID (Exnnn): _____

Sponsor R&D Number: 18/0320 Chief Investigator: Professor Tom Foltynie

Exenatide-PD3 Informed Consent Form

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.

This Informed Consent Form is intended for consenting patients to take part in the Exenatide-PD3 trial.

| CONSENT FORM | | Please initial |
|--------------|--|----------------|
| 1 | I have read the Exenatide-PD3 information sheet version (X.X)_____dated (DD/MMM/YYYY) _____ for this trial. I have had the opportunity to consider the information and ask questions that have been answered satisfactorily. | |
| 2 | I understand that my participation in the Exenatide-PD3 is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. | |
| 3 | I understand that I may not benefit directly by participating in this trial. However, the research may help others in the future. | |
| 4 | I understand that relevant sections of my medical notes and data collected during the trial may be looked at by individuals from the sponsors' office (University College London), regulatory authorities, or from the NHS Trust or drug manufacturer, where it is relevant to my taking part in this research. I understand that these individuals have a duty of confidentiality towards me. | |
| 5 | I understand that one of my assessments at five of my visits will be video recorded, stored securely on a GDPR compliant server and securely transferred to Machine Medicines Technologies (MMT) for analysis. I understand that they will be used for quality control purposes, and to help improve PD assessments. | |
| 6 | I understand that I am required to attend five of my visits off of my normal PD medication, as stated in the Patient Information Sheet. | |

| | | |
|----|--|--|
| 7 | If the trial research team are unable to contact me at any time during the trial, I agree to the relevant sections of my medical records on NHS Digital (Spine) being accessed to obtain my contact details. | |
| 8 | I agree to my General Practitioner (GP) being informed of my participation in the Exenatide-PD3 trial. | |
| 9 | I agree that my data gathered in this trial will be stored in a secure facility (with limited access by individual from the sponsor's office (University College London) for 10 years after the completion of the trial as set out by the UK Medicines & Healthcare products Regulatory Agency. | |
| 10 | I give consent for my data and blood samples collected as part of the trial to be shared with other researchers and used in other ethically approved research following legal requirements to conceal my identity. | |
| 11 | I agree to take part in the Exenatide-PD3 Trial. | |
| 12 | I understand that one of my assessments at five of my visits will be recorded using an Electromagnetic Sensor (placed on my hand) and the information collected will be stored securely on a GDPR compliant server and securely transferred to The University Of York for analysis. <i>(Participating sites only).</i> | |

| | | |
|-------------------------|--------------------------------------|--------------------|
| Participant Name | Date (DD-MMM-YYYY) __ / __ / ____ | Signature _____ |
| Person taking Consent | Date (DD-MMM-YYYY) __ / __ / ____ | Signature _____ |
| Witness (if applicable) | Date (DD-MMM-YYYY) __ / __ / ____ | Signature _____ |

Once completed, please give 1 copy to the participant, keep 1 copy in the participant's medical records and file the original in the investigator site file.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

| | | Reporting Item | Page Number |
|---|---------------------|--|-------------|
| Administrative information | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | #3 | Date and version identifier | 16 |
| Funding | #4 | Sources and types of financial, material, and other support | 16 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 16 |

| | | | | |
|----|---------------------------|---------------------|--|-----|
| 1 | Roles and | #5b | Name and contact information for the trial sponsor | 1 |
| 2 | responsibilities: | | | |
| 3 | sponsor contact | | | |
| 4 | information | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | Roles and | #5c | Role of study sponsor and funders, if any, in study design; | 6 |
| 8 | responsibilities: | | collection, management, analysis, and interpretation of data; | |
| 9 | sponsor and funder | | writing of the report; and the decision to submit the report for | |
| 10 | | | publication, including whether they will have ultimate authority | |
| 11 | | | over any of these activities | |
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| 15 | Roles and | #5d | Composition, roles, and responsibilities of the coordinating centre, | 6 |
| 16 | responsibilities: | | steering committee, endpoint adjudication committee, data | |
| 17 | committees | | management team, and other individuals or groups overseeing the | |
| 18 | | | trial, if applicable (see Item 21a for data monitoring committee) | |
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| 21 | | | | |
| 22 | | | | |
| 23 | Introduction | | | |
| 24 | | | | |
| 25 | Background and | #6a | Description of research question and justification for undertaking | 3-4 |
| 26 | rationale | | the trial, including summary of relevant studies (published and | |
| 27 | | | unpublished) examining benefits and harms for each intervention | |
| 28 | | | | |
| 29 | | | | |
| 30 | Background and | #6b | Explanation for choice of comparators | 3-4 |
| 31 | rationale: choice of | | | |
| 32 | comparators | | | |
| 33 | | | | |
| 34 | | | | |
| 35 | Objectives | #7 | Specific objectives or hypotheses | 4 |
| 36 | | | | |
| 37 | | | | |
| 38 | Trial design | #8 | Description of trial design including type of trial (eg, parallel | 6-7 |
| 39 | | | group, crossover, factorial, single group), allocation ratio, and | |
| 40 | | | framework (eg, superiority, equivalence, non-inferiority, | |
| 41 | | | exploratory) | |
| 42 | | | | |
| 43 | | | | |
| 44 | | | | |
| 45 | Methods: | | | |
| 46 | Participants, | | | |
| 47 | interventions, and | | | |
| 48 | outcomes | | | |
| 49 | | | | |
| 50 | | | | |
| 51 | Study setting | #9 | Description of study settings (eg, community clinic, academic | 6-7 |
| 52 | | | hospital) and list of countries where data will be collected. | |
| 53 | | | Reference to where list of study sites can be obtained | |
| 54 | | | | |
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| 57 | Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, | 8 |
| 58 | | | eligibility criteria for study centres and individuals who will | |
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| | | perform the interventions (eg, surgeons, psychotherapists) | |
| 1 | | | |
| 2 | Interventions: | #11a Interventions for each group with sufficient detail to allow | 12 |
| 3 | description | replication, including how and when they will be administered | |
| 4 | | | |
| 5 | Interventions: | #11b Criteria for discontinuing or modifying allocated interventions for a | 12 |
| 6 | modifications | given trial participant (eg, drug dose change in response to harms, | |
| 7 | | participant request, or improving / worsening disease) | |
| 8 | | | |
| 9 | Interventions: | #11c Strategies to improve adherence to intervention protocols, and any | 12 |
| 10 | adherence | procedures for monitoring adherence (eg, drug tablet return; | |
| 11 | | laboratory tests) | |
| 12 | Interventions: | #11d Relevant concomitant care and interventions that are permitted or | 12 |
| 13 | concomitant care | prohibited during the trial | |
| 14 | | | |
| 15 | Outcomes | #12 Primary, secondary, and other outcomes, including the specific | 9-10 |
| 16 | | measurement variable (eg, systolic blood pressure), analysis metric | |
| 17 | | (eg, change from baseline, final value, time to event), method of | |
| 18 | | aggregation (eg, median, proportion), and time point for each | |
| 19 | | outcome. Explanation of the clinical relevance of chosen efficacy | |
| 20 | | and harm outcomes is strongly recommended | |
| 21 | Participant timeline | #13 Time schedule of enrolment, interventions (including any run-ins | 6-7 |
| 22 | | and washouts), assessments, and visits for participants. A | |
| 23 | | schematic diagram is highly recommended (see Figure) | |
| 24 | | | |
| 25 | Sample size | #14 Estimated number of participants needed to achieve study | 12 |
| 26 | | objectives and how it was determined, including clinical and | |
| 27 | | statistical assumptions supporting any sample size calculations | |
| 28 | | | |
| 29 | Recruitment | #15 Strategies for achieving adequate participant enrolment to reach | 6 |
| 30 | | target sample size | |
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| 45 | Methods: Assignment | | |
| 46 | of interventions (for | | |
| 47 | controlled trials) | | |
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| 50 | Allocation: sequence | #16a Method of generating the allocation sequence (eg, computer- | 14 |
| 51 | generation | generated random numbers), and list of any factors for | |
| 52 | | stratification. To reduce predictability of a random sequence, | |
| 53 | | details of any planned restriction (eg, blocking) should be provided | |
| 54 | | in a separate document that is unavailable to those who enrol | |
| 55 | | participants or assign interventions | |
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| 1 | Allocation concealment | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 14 |
| 2 | mechanism | | | |
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| 8 | Allocation: | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 14 |
| 9 | implementation | | | |
| 10 | | | | |
| 11 | Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 14 |
| 12 | | | | |
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| 17 | Blinding (masking): | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 14 |
| 18 | emergency unblinding | | | |
| 19 | | | | |
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| 21 | | | | |
| 22 | Methods: Data | | | |
| 23 | collection, | | | |
| 24 | management, and | | | |
| 25 | analysis | | | |
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| 29 | Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11 |
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| 39 | Data collection plan: | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 11 |
| 40 | retention | | | |
| 41 | | | | |
| 42 | | | | |
| 43 | | | | |
| 44 | Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 11 |
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| 51 | Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 13-14 |
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| 56 | Statistics: additional | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13-14 |
| 57 | analyses | | | |
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| 1 | Statistics: analysis | #20c | Definition of analysis population relating to protocol non- | 13-14 |
| 2 | population and missing | | adherence (eg, as randomised analysis), and any statistical methods | |
| 3 | data | | to handle missing data (eg, multiple imputation) | |
| 4 | | | | |
| 5 | | | | |
| 6 | Methods: Monitoring | | | |
| 7 | | | | |
| 8 | Data monitoring: | #21a | Composition of data monitoring committee (DMC); summary of its | 7 |
| 9 | formal committee | | role and reporting structure; statement of whether it is independent | |
| 10 | | | from the sponsor and competing interests; and reference to where | |
| 11 | | | further details about its charter can be found, if not in the protocol. | |
| 12 | | | Alternatively, an explanation of why a DMC is not needed | |
| 13 | | | | |
| 14 | Data monitoring: | #21b | Description of any interim analyses and stopping guidelines, | 7 |
| 15 | interim analysis | | including who will have access to these interim results and make | |
| 16 | | | the final decision to terminate the trial | |
| 17 | | | | |
| 18 | Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited | 7 |
| 19 | | | and spontaneously reported adverse events and other unintended | |
| 20 | | | effects of trial interventions or trial conduct | |
| 21 | | | | |
| 22 | Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and | 7 |
| 23 | | | whether the process will be independent from investigators and the | |
| 24 | | | sponsor | |
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| 33 | Ethics and | | | |
| 34 | dissemination | | | |
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| 36 | Research ethics | #24 | Plans for seeking research ethics committee / institutional review | 14 |
| 37 | approval | | board (REC / IRB) approval | |
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| 40 | Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, | 14 |
| 41 | | | changes to eligibility criteria, outcomes, analyses) to relevant | |
| 42 | | | parties (eg, investigators, REC / IRBs, trial participants, trial | |
| 43 | | | registries, journals, regulators) | |
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| 47 | Consent or assent | #26a | Who will obtain informed consent or assent from potential trial | 11-13 |
| 48 | | | participants or authorised surrogates, and how (see Item 32) | |
| 49 | | | | |
| 50 | | | | |
| 51 | Consent or assent: | #26b | Additional consent provisions for collection and use of participant | 11-13 |
| 52 | ancillary studies | | data and biological specimens in ancillary studies, if applicable | |
| 53 | | | | |
| 54 | | | | |
| 55 | Confidentiality | #27 | How personal information about potential and enrolled participants | 11-13 |
| 56 | | | will be collected, shared, and maintained in order to protect | |
| 57 | | | confidentiality before, during, and after the trial | |
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| 1 | Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 16 |
| 2 | | | | |
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| 4 | Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 15 |
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| 10 | Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 15 |
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| 14 | Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 |
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| 21 | Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 15 |
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| 24 | Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 15 |
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| 28 | Appendices | | | |
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| 31 | Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | 11 |
| 32 | | | | |
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| 34 | Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 11 |
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