DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Clinical Trial of Investigational Medicinal Product

Full title of trial	A Phase IIa, open label, single-site, 48 week randomised controlled trial evaluating the safety and efficacy of Exenatide once-weekly in the treatment of patients with Multiple System Atrophy.
Short title	Exenatide once-weekly as a treatment for Multiple System Atrophy.
Version and date of protocol	Version 6.0, 13 June 2024
Sponsor:	University College London (UCL)
Sponsor protocol number	125591
Funder (s):	John Black Charitable Foundation, Van Andel Institute, Defeat MSA.]
EudraCT no	2020-000122-26
ISRCTN / Clinicaltrials.gov no:	NCT04431713
ACTIVE IMP(s):	Exenatide
Phase of trial	Phase IIa
Sites(s)	Single site

Chief investigator:
Professor Thomas Foltynie
Box 146,
National Hospital for Neurology & Neurosurgery,
Queen Square, London WC1E 3BG

Sponsor Representative:
Joint Research Office, UCL, 4th Floor, West
250 Euston Road, London, NW1 2PG

Postal address:
Joint Research Office, UCL
Gower Street,
London WC1E 6BT

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
2.0	25/09/2020	Prof Tom Foltynie	Addition of flexibility for remote visits
3.0	01/03/2021	Prof Tom Foltynie	Addition of BCise IMP
4.0	13 Sep 2021	Prof Tom Foltynie	Insertion of 96 week follow-up visit, update to exclusion criterion 12
5.0	3 August 2022	Prof Tom Foltynie	Added in option of home visits if a participant is unable or unwilling to attend site for any of the follow up assessments (weeks 12,24,36,48 and 96)
6.0	13 June 2024	Alison Evans and Prof Tom Foltynie	Section 4 (Objectives) and Section 11.4 (Statistical analysis plan) - removed biomarker analysis as an exploratory outcome. Samples will be analysed under separate REC approved studies

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the current UK Policy Framework for Health and Social Care Research, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Professor Thomas Foltynie

DocuSigned by:
Tom Foltynie
4403A833BA634FD...

19 June 2024 | 11:14 BST

Signature Date

Sponsor

Rajinder Sidhu
UCL

DocuSigned by:
Rajinder Sidhu
D225A0063221469...

19 June 2024 | 13:27 BST

Signature Date

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Contents

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DI	Designated Individual
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVigilance	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMO	Genetically Modified Organisms
HRA	Health Research Authority
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised
MA	Marketing Authorisation

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
MSA	Multiple System Atrophy
PI	Principal Investigator
PIS	Participant Information Sheet
PL	Product License
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person (for release of trial drug)
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UMSARS	Unified Multiple System Atrophy Rating Scale

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

1 Trial personnel

See protocol cover page for Chief Investigator and Sponsor contact details.

Statistician	Dr Gareth Ambler Joint Research Office (Research Support Centre), 1st Floor Maple House B, 149 Tottenham Court Road, London, W1T 7DN Email: g.ambler@ucl.ac.uk Tel: 020 3447 2178
Trial Management	Leonard Wolfson Experimental Neuroscience Centre National Hospital for Neurology & Neurosurgery Queen Square London WC1N 3BG
Central labs	National Hospital for Neurology & Neurosurgery Queen Square London WC1N 3BG
Head of Department	Prof A Schapira National Hospital for Neurology & Neurosurgery Queen Square London WC1N 3BG

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

2 Summary

Objectives:

Primary Objective

To collect pilot data from which to estimate the effectiveness of Exenatide in modifying disease progression of patients with Multiple System Atrophy. The primary endpoint will be the difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 weeks comparing exenatide to best medically treated patients.

Secondary Outcomes

- The proportion of patients with loss of independent ambulation by the end of the study, defined by a score of 4 or more in UMSARS-I item 7 (walking),
- The difference at week 48 in the MSA-QoL scale,
- The difference at week 48 in UMSARS parts III and IV,
- The difference in anti-parkinsonian or anti-orthostatic hypotension drugs,
- The number of falls,
- The proportion of patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling),
- The difference at week 48 in clinical global impression (CGI); difference at week 48 in MoCA scores.

Exploratory Outcomes

- The difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 96 weeks comparing exenatide to best medically treated patients,
- The difference at 96 weeks in the MSA-QoL scale comparing exenatide to best medically treated patients,
- The difference at 96 weeks in UMSARS parts III and IV comparing exenatide to best medically treated patients,
- The difference in anti-parkinsonian or anti-orthostatic hypotension drugs at 96 weeks comparing exenatide to best medically treated patients,
- The difference in the number of falls at 96 weeks comparing exenatide to best medically treated patients,
- The difference in the proportion of patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling) at 96 weeks comparing exenatide to best medically treated patients,

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

- The difference at 96 weeks in clinical global impression (CGI) and MoCA scores comparing exenatide to best medically treated patients.

Type of trial:	Phase IIa, open label, randomised, parallel group, single site trial in Multiple System Atrophy.
Trial design and methods:	Fifty patients with early stage MSA will be recruited and randomised to receive Exenatide injections, or to act as controls in this open label trial. Exenatide will be given as a once weekly subcutaneous injection in addition to participant's regular medication. All patients will continue to receive standard of care treatment for MSA. Detailed assessments will be made of all patients at baseline and periodically for a total of 96 weeks. The primary endpoint will be the difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 weeks comparing Exenatide to best medically treated patients. Secondary measures will include adverse event reports, self-completed questionnaires, and blood test results. Aside from these assessments, all patients will continue any regular MSA medications throughout the trial with adjustments made only according to clinical need.
Estimated total trial duration:	96 weeks per patient 48 months total trial duration.
Planned trial sites:	Single-site- National Hospital for Neurology & Neurosurgery.
Total number of participants planned:	50 participants.
Main inclusion/exclusion criteria:	**Inclusion Criteria** Participants aged 30-80 years old with a diagnosis of Possible or Probable MSA of the parkinsonian subtype (MSA-P) or cerebellar subtype (MSA-C) according to The Gilman Criteria (Gilman et al. 2008) Participants who are less than five years from the time of documented MSA diagnosis or from the time of documented parkinsonian / ataxic neurological condition that later turns out to be MSA. Participants who are able to walk at least 10 metres with or without assistance.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Participants with an anticipated survival of at least three years in the opinion of the investigator.

Participants that are willing to adhere to the study drug regimen.

Participants that are willing and able to perform all protocol-specified assessments and comply with the study visit schedule.

Females of childbearing potential and male participants with partners of childbearing potential agree to use an effective method of contraception from the time consent is signed until 10 weeks after treatment discontinuation.

Females of childbearing potential have a negative pregnancy test within 7 days prior to being randomised.

Willing and able to provide written informed consent. Subjects who are not able to write may give verbal consent in the presence of at least one witness, and the witness should sign the informed consent form.

Exclusion Criteria

Females who are pregnant, planning pregnancy or breastfeeding.

Women of child-bearing potential who do not practice an acceptable method of birth control.

Subjects who meet any of the following criteria which tend to suggest advance disease:

1. Speech impairment as assessed by a score of ≥ 3 on UMSARS question 1
2. Swallowing impairment as assessed by a score of ≥ 3 on UMSARS question 2
3. Impairment in ambulation as assessed by a score of > 3 on UMSARS question 7
4. Falling more frequently than once per week as assessed by a score of ≥ 3 on UMSARS question 8.

Participants with a clinically significant or unstable medical or surgical condition, which in the opinion of the investigator might preclude safe completion of the study.

Participants with active malignant neoplasms or history of malignant neoplasm in the last 5 years.

Participants with movement disorders other than MSA.

Concurrent dementia defined by a score lower than 21 on the MoCA.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Concurrent severe depression defined by a score of ≥30 on the Beck Depression Inventory-II.

History of deep brain stimulation surgery.

Participants who have taken any investigational products within 90 days prior to baseline.

Participants with a BMI < 18.5.

Participants with diabetes, end stage renal disease or severely impaired renal function with creatinine clearance <30ml/min.

History of clinically significant cardiac disease, pancreatitis and/or alcoholism.

Participants with severe gastrointestinal disease including gastroparesis.

Ongoing treatment with sulphonylurea.

Known allergies to the IMP and excipients of IMP.

Statistical methodology and analysis:

The primary endpoint will be the difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 weeks comparing Exenatide to best medically treated patients. The main statistical analysis of the primary endpoint will be based on the intent-to-treat population (ITT). The analysis will use ANCOVA to allow adjustment for baseline severity and MSA subtype.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

3 Background and Rationale

Multiple System Atrophy (MSA) is a rare, progressive neurodegenerative disorder clinically characterized by autonomic dysfunction, parkinsonism and cerebellar impairment. Like Parkinson's disease (PD) and Dementia with Lewy bodies (DLB), MSA is a synucleinopathy and the pathological correlate is the formation of glial cytoplasmic inclusions, composed of accumulated alpha-synuclein. Despite sharing many clinical similarities with PD, unlike PD, there are no effective symptomatic therapies available and no approaches for slowing disease progression, meaning the average survival time from diagnosis is around 6-9 years (Fanciulli and Wenning 2015). There is thus a great unmet need for neuroprotective or disease modifying therapies.

Accumulating data suggest that Exenatide, a glucagon-like peptide-1 (GLP-1) agonist used in the treatment of Type 2 diabetes (T2DM) may offer a novel approach to treating MSA (Bassil et al. 2017). Numerous epidemiological studies have indicated T2DM is a risk factor for developing Alzheimer's disease, PD and other neurodegenerative diseases. Patients with T2DM have 30-40% increased risk of developing PD, while patients with PD and T2DM have a more aggressive disease course, and require increasing amounts of medication (De Pablo-Fernandez et al. 2017; D'Amelio et al. 2009).

Studies have suggested that these age-related diseases share dysfunctional insulin signaling linking diabetes and neurodegeneration. Via insulin receptors found throughout the brain, insulin is responsible for modulating many cellular processes including inflammation, protein aggregation, oxidative stress, autophagy and apoptosis, via the actions of two main downstream pathways Akt and MAPK (Talbot et al. 2012; Athauda and Foltynie 2016). Importantly, these dysregulation of processes are thought to be involved in the pathogenesis of MSA.

Peripheral insulin and insulin-like growth factor levels are increased in the serum of MSA patients and this has been shown to correlate with disease progression, suggesting a link between insulin signalling and MSA (Bassil et al. 2017; Bassil et al. 2017). More recently, a study by Bassil et al. has shown evidence of insulin resistance in the brains of patients with MSA. A measure of insulin resistance is the amount of the downstream messenger insulin receptor substrate-1 (IRS-1) phosphorylated at serine residues 312 (IRS-1pS312) or 616 (IRS-1pS616) and the authors demonstrated increased expression of these markers of insulin resistance that occurred in the context of neuronal cell loss compared to controls. Therefore, if insulin resistance occurs in the brain in MSA, modulating insulin/IGF-1 signalling might provide an effective approach to disease modification.

Exenatide has been a treatment licensed for use in Type 2 diabetes since 2005 and activates the GLP-1 receptor. The GLP-1 receptor is expressed throughout the brain and activates similar pathways to those of insulin (Cork et al. 2015). Previous studies have shown that activation of this receptor by Exenatide has protective effects in models of PD, Alzheimer's disease, stroke, Huntington's disease and multiple sclerosis through positive effects on cell survival, apoptosis, and protein aggregation (Athauda and Foltynie 2016; Greig et al. 2014).

Indeed, a recent study using Exenatide in a transgenic mouse model of MSA showed that Exenatide treatment had positive effects on insulin resistance and monomeric alpha-synuclein

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

levels in the striatum, as well as improving survival of nigral dopamine neurons (Bassil et al. 2017).

Based on these encouraging data, 2 clinical trials of Exenatide in patients with moderate stage PD have been conducted.

A small, "proof-of-concept" open-label phase 2 clinical trial evaluating the safety and efficacy of Exenatide in PD which showed a significant improvement in motor scores and cognitive efficiency at 12 months in patients with PD treated with Exenatide compared to a control group, which persisted following drug withdrawal (Aviles-Olmos et al. 2013, 2014). Despite the open-label design, this study demonstrated that a drug in clinical use for another medical condition could be successfully tested for its disease-modifying effects in patients with PD using standard clinical measures, without the need to include a placebo-controlled arm, in a relatively inexpensive way. The aim of the open label trial was to provide proof of concept of possible efficacy to reassure investment into more formal double blind placebo controlled efficacy trials.

Following on from this, a fully randomised, placebo-controlled trial of Exenatide in patients with moderate stage PD was conducted, which replicated the results of the previous open label trial and showed Exenatide reduced motor severity of PD compared to placebo. Exenatide was well-tolerated in this patient group and it was shown for the first time that peripherally administered Exenatide crossed the blood brain barrier and is detectable in the cerebrospinal fluid at a ratio of around 3% of that detected in serum (Athauda et al. 2017). Post hoc analysis also indicated possible beneficial effects on depression which can be a major contributor to morbidity in both PD and MSA (Athauda et al. 2018). Using patient serum, we isolated and analysed neuronal derived exosomes to assess target engagement and demonstrated that Exenatide appears to normalise brain insulin signalling with subsequent activation of downstream effectors Akt and mTOR (Athauda et al. 2019).

These encouraging results have set the ground for translation into early clinical trials of Exenatide in further neurodegenerative diseases.

Clinical trials in MSA can be conducted with smaller group sizes, due to the marked faster disease progression of MSA compared with that of PD (Fernagut et al. 2014). In addition, previous studies have demonstrated a consistent rate of progression in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part II (Motor examination) (Wenning et al. 2004, 2013; Low et al. 2015; Dodel et al. 2010; Poewe, Hauser, and Lang 2015; Low et al. 2014)

There are no effective treatments that can slow down or modify the course of disease progression. MSA has a prevalence of 4.4 in 100,000 individuals and affects males and females equally. Currently, treatment strategies focus on symptomatic control of parkinsonism, autonomic dysfunction and mood problems. However, despite this, the prognosis remains poor with average survival of eight years. There is thus an urgent unmet need for novel treatments that may slow or halt disease progression in MSA. Patients with MSA require care from a range of services, and as the disease progresses these care needs increase, thus a disease modifying treatment would have a massive impact on caregivers and social services.

Based on prevalence figures of MSA, the estimated annual healthcare costs associated with MSA are estimated to be €1.1–3.0 billion across 27 countries in the European Union. Unpaid care accounts for 68–76%. If an intervention were to reduce the rate of disease progression even by

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

30%, the costs to services would be 9-10% lower and 7-12% lower in unpaid care costs. Preliminary data obtained by this study would provide an urgent impetus for further funding for a larger scale study to assess the effects of Exenatide and other GLP-1 agonists in a wider population of MSA patients.

3.1 Assessment and management of risk

The table below summarises the risks, frequencies and mitigations of the IMP(s)

Name of IMP(s) / NIMP	Potential risk	Risk Frequency	Risk Management
Exenatide	Weight loss	Common	Underweight people will not be recruited. Patients losing weight too rapidly (>10% body weight per month) will temporarily stop the IMP.
Exenatide	Nausea/ Vomiting	Very common	In most cases, nausea is mild and self limiting. In more severe cases, patients will be prescribed a temporary course of Domperidone.
Exenatide	Diarrhoea	Very common	In most cases, diarrhoea is mild and self limiting. Symptomatic and supportive treatment will be given as necessary.
Exenatide	Decreased Appetite	Common	In most cases, loss of appetite is transient and self limiting. Weight will be measured and exenatide will be transiently stopped if weight loss exceeds 10% of body weight per month.
Exenatide	Headache	Common	In most cases, headache is transient and self limiting. Participants will be assessed and given standard of care treatment for persistent headaches.
Exenatide	Dizziness	Common	In most cases, dizziness, is transient and self limiting. Participants will be assessed and given standard of care treatment for persistent dizziness.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Exenatide	Dyspepsia/ Abdominal pain	Common	In most cases, abdominal pain is transient and self limiting. Any suspicion of pancreatitis will lead to temporary discontinuation of exenatide until pancreatitis has been excluded. Participants will be assessed and given standard of care treatment for persistent abdominal pain.
Exenatide	Abdominal Distension/ Flatulence	Common	In most cases, abdominal distension/ flatulence is transient and self limiting. Participants will be assessed and given standard of care treatment for persistent abdominal distension/flatulence.
Exenatide	Constipation	Common	In most cases, constipation is is transient and self limiting. Participants will be assessed and given standard of care treatment for persistent constipation.
Exenatide	Anaphylactic reaction	Rare	Patients will self administer their first Exenatide injection in the trial centre under supervision by the trial team.

The table below summarise the risks and mitigations of all test above standard care that are being performed in a table:

Intervention	Potential risk	Risk Management
Blood tests	Bruising at phlebotomy site	Compression will be applied to minimise bruising.
Lumbar puncture	Post lumbar puncture headache.	Atraumatic needles will be used which have been shown to minimise the risk of post lumbar puncture headache.

In accordance with the MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, this trial is categorised as:

Type B = Somewhat higher than the risk of standard medical care:

This trial is involving a medicinal product licensed in the EU Member State and is being used for a new indication.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

4 Objectives

Primary:

The primary endpoint will be the difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 weeks comparing exenatide to best medically treated patients.

Secondary:

- The proportion of patients with loss of independent ambulation by the end of the study, defined by a score of 4 in UMSARS-I item 7 (walking),
- The difference at week 48 in the MSA-QoL scale,
- The difference at week 48 in UMSARS parts III and IV,
- The difference in anti-parkinsonian or anti-orthostatic hypotension drugs,
- The number of falls,
- The proportion of patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling),
- The difference at week 48 in clinical global impression (CGI)
- The difference at week 48 in MoCA scores.
- Safety of exenatide in MSA based on Adverse event reporting

Exploratory

- The difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 96 weeks comparing exenatide to best medically treated patients,
- The difference at 96 weeks in the MSA-QoL scale comparing exenatide to best medically treated patients,
- The difference at 96 weeks in UMSARS parts III and IV comparing exenatide to best medically treated patients,
- The difference in anti-parkinsonian or anti-orthostatic hypotension drugs at 96 weeks comparing exenatide to best medically treated patients,
- The difference in the number of falls at 96 weeks comparing exenatide to best medically treated patients,
- The difference in the proportion of patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling) at 96 weeks comparing exenatide to best medically treated patients,
- The difference at 96 weeks in clinical global impression (CGI) and MoCA scores comparing exenatide to best medically treated patients.

Data regarding walking will be collected over a week long period at baseline and at week 48 prior to the visit via a CE marked sensor attached to the lower back – Axivity device.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

5 Trial design

5.1 Overall design

This is a non-commercial, open label trial of a licensed drug designed to primarily provide preliminary efficacy and safety data for the use of Exenatide in MSA. This will be a simple parallel group design and include a 48-week exposure period. Detailed evaluations will take place at Screening, Baseline, 12, 24, 36, 48 and 96 weeks.

Patients will be randomly allocated into 2 groups to receive either:

- Exenatide extended release 2mg subcutaneous injection once weekly for 48 weeks together with standard treatment options, n~=25,

or

- Standard treatment options, n~=25

The control arm will attend all the same visits as the Exenatide group. Separate randomisation lists will be generated for patients with MSA-P or MSA-C.

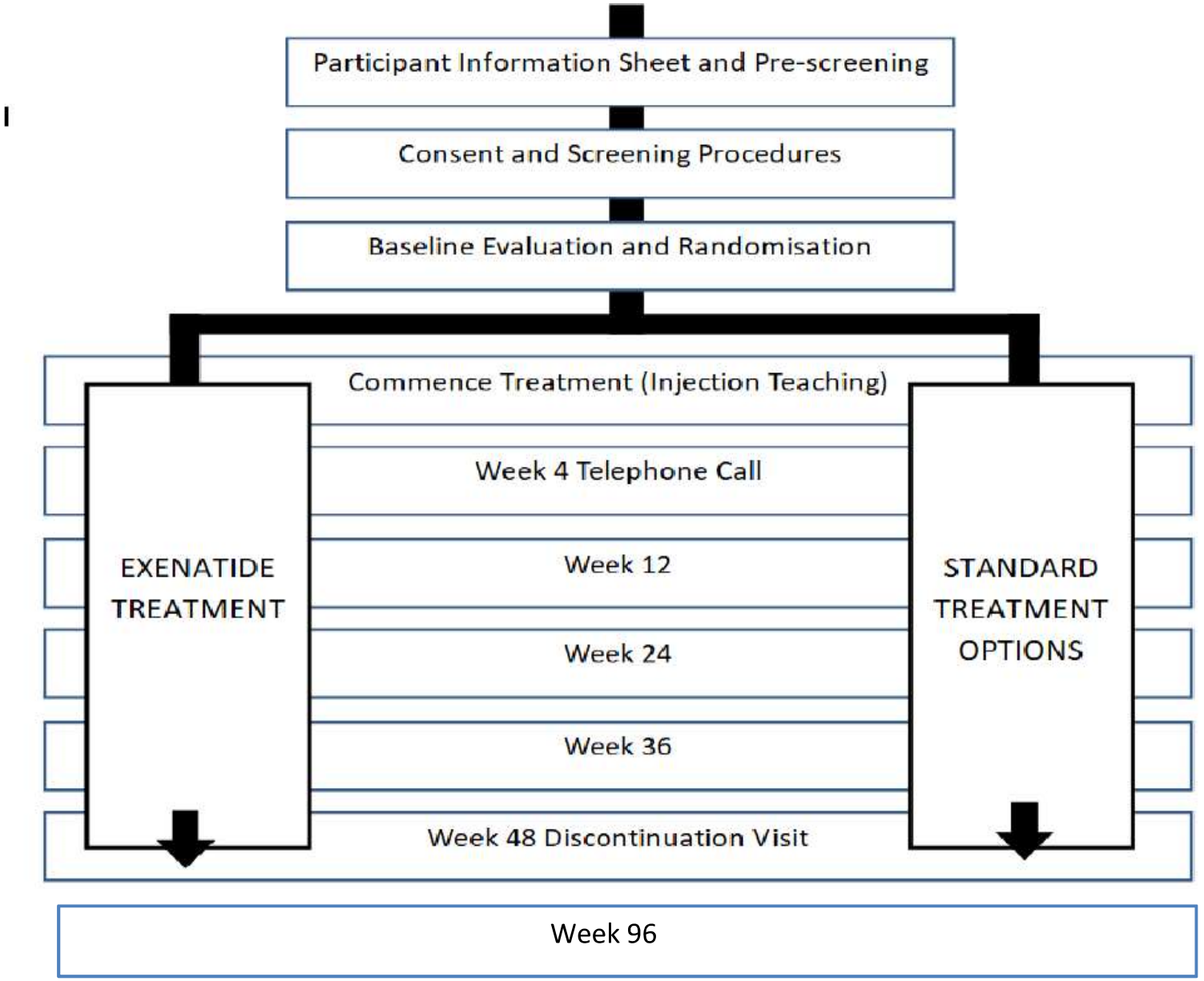
The control group of patients are very important in view of the continued neurodegenerative process of MSA that leads to a mean 7.8 point decline in UMSARS scores per year (Poewe et al. 2015).

All participants will be invited for face to face visits at all timepoints. If a participant is unable or unwilling to attend any of the follow up assessments (12,24,36,48,96 weeks), they may be offered the option of a home visit by 1 or more members of the trial clinical team if staffing levels permit.

This trial will also assess the safety and tolerability of Exenatide when administered to patients with MSA. Encouraging results will be used as a basis for application for funding for a larger double blind placebo controlled RCT and will be used to inform upon sample size calculations for such a trial. This drug already has a license for the treatment of patients with Type II Diabetes and there is extensive safety data from phase 3 trials of its use in this patient group.

.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3



DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

6 Investigational Medicinal Products and Non-Investigational Medicinal Products

6.1 Name and description of IMP(s)

Exenatide (extended-release for injectable suspension) - "Bydureon" 2mg subcutaneous once weekly injection or "Bydureon BCise" 2mg subcutaneous once weekly injection.

Exenatide is a licensed treatment indicated in adults 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose-lowering medicinal products including basal insulin, when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control. This study will investigate Exenatide in a novel indication in Multiple System Atrophy.

The Bydureon dual-chamber pen contains Exenatide powder and solvent in a Type 1 glass cartridge sealed at one end with a chlorobutyl rubber stopper and an aluminium seal, and at the other end with a chlorobutyl rubber piston. The two chambers are separated by a second chlorobutyl rubber piston. There is one needle supplied per pen. Each carton also contains one spare needle. Each pack contains 4 single-dose pre-filled pens and a multipack containing 12 (3 packs of 4) single-dose pre-filled pens.

From 31 March 2021, the Bydureon pen is being replaced by Astra Zeneca by a newer, easier to use device- the Bydureon BCise pen. The discontinuation of Bydureon is not due to quality or manufacturing issues and does not affect trial participants who are currently on Bydureon. The Bydureon BCise pen is a single chamber pen, with a needle already attached, containing the suspension and thus only needs shaking by the user to ensure the suspension is evenly mixed prior to administration. Each pack contains 4 single-dose pre-filled pens.

6.2 Source of IMP, Manufacture and Distribution

Exenatide (Bydureon or Bydureon BCise) will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the pharmacy.

6.3 Storage and handling of IMP(s) at site

All IMP aspects of the trial at participating sites are the responsibility of the PI, who may delegate this duty to the local pharmacist or other appropriately trained personnel. The delegation of duties must be recorded on the Staff Signature and Delegation of Tasks.

Storage and handling (e.g., labelling) of the IMP will be completed in accordance with the relevant SPC and summary of drug arrangements. Exenatide requires refrigerated storage (2-8°C). Once removed from the refrigerator, Exenatide needs to stand at room temperature for at least 15 minutes before administration. All patients will be instructed how to operate the pen device and to perform the injections. They will perform their first injection with supervision of the trial team at the end of the baseline visit.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

For home visits, dispensing of IMP will be performed by trial pharmacy and transported to the patient in an appropriate cool bag with temperature logger by the clinical trial team. The trial team member will check the temperature logger to ensure the temperature has stayed within the range 2-8°C. If the temperature has fallen out of range the IMP must not be dispensed to the patient and should be returned to the trial pharmacy.

Detailed instructions are contained in the summary of drug arrangements.

6.4 Accountability of IMP(s)

The trial pharmacist within the hospital pharmacy will be accountable for trial drug supplies. There will be no additional reconstitution or other preparation required prior to dispensing from hospital stock.

The IMP Drug Accountability Log must be completed to record each dose of IMP dispensed for each trial participant. This log must be retained in the relevant section of the Pharmacy Site File, and a copy must be submitted to the sponsor upon request. It is the responsibility of the Pharmacy Lead to maintain drug accountability records.

The patient will be instructed to return unused IMP to the research facility, which will then be returned to site pharmacy, to be then updated in the drug accountability log in the pharmacy site file. Following authorisation by the sponsor, drug destruction will be conducted in accordance to local practice and this will be documented in the drug destruction log in the hospital pharmacy file.

Detailed instructions are contained in the summary of drug arrangements.

6.5 Concomitant medication

Trial participants will be permitted to use any licensed medication throughout the course of the trial that is recommended by their referring Neurologist and is not contraindicated with trial IMP as per standard practice. Patients will be given advice in any necessary minor adjustments to their pre-existing MSA medications at each of their follow up visits and doses will be recorded and converted to a Levodopa equivalent dose (LED) as appropriate. No routine adjustment of MSA medications will be made by the Investigator(s) unless at the request of the patients. If possible, patients will be invited to attend the trial site at a similar time of day and after a similar duration since they took their usual MSA medications for each of the trial visits.

Patients receiving warfarin or coumarin derivatives may be at risk of increased INR and associated bleeding; therefore INR should be monitored closely at each participant's visit.

Patients on Warfarin will not be able to undergo Lumbar punctures.

There have been rare reported events of altered renal function with Exenatide; therefore patients receiving the following concomitant medications should have their renal function closely monitored using blood tests at every follow up visit:

- angiotensin converting enzyme inhibitors,

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

- angiotensin-II antagonists,
- non-steroidal anti-inflammatory medicinal products
- diuretics

COVID-19 vaccinations that are administered after a patient has signed informed consent should be captured as a concomitant medication. If the vaccination is a multi-dose vaccination, each dose received should be entered as a separate concomitant medication.

Concomitant medications will be recorded in the participant's notes in the local electronic health record system, EPIC.

6.6 Post-trial IMP arrangements

The IMP will not be provided to trial participants' post-trial participation.

7 Selection of Participants

The investigator should only enrol subjects who meet all inclusion and none of the exclusion criteria, are not put at undue risk by participating in the trial and can be expected to comply with the protocol.

There will be NO EXCEPTIONS to eligibility requirements at the time of randomisation. Previous clinical correspondence will be used to confirm eligibility criteria. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

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

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

7.1 Eligibility of trial participants

7.2 Trial participant inclusion criteria

1. Male or female participants aged 30-80 years old with a diagnosis of Possible or Probable MSA of the parkinsonian subtype (MSA-P) or cerebellar subtype (MSA-C) according to The Gilman Criteria (Gilman et al. 2008)
2. Participants who are less than five years from the time of documented MSA diagnosis or from the time of documented parkinsonian / ataxic neurological condition that later turns out to be MSA.
3. Participants who are able to walk at least 10 metres with or without assistance.
4. Participants with an anticipated survival of at least three years in the opinion of the investigator.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

5. Willing to adhere to the study drug regimen.
6. Willing and able to meet all study requirements, including travel to Study Centre, procedures, measurements and visits, including:
    a. Caregiver/trial partner committed to facilitate participants involvement in the study if the participant is unable to attend appointments on their own.
7. Females of childbearing potential and males with partners of childbearing potential agree to use an effective method of double contraception from the time consent is signed until at least 12 weeks after treatment discontinuation.
8. For Females of childbearing potential; they must have had a negative pregnancy test within 7 days prior to being randomised. Participants are considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal
9. Willing and able to provide written informed consent. Subjects who are not able to write may give verbal consent in the presence of at least one witness, and the witness should sign the informed consent form.

7.3 Trial participant exclusion criteria

1. Females who are pregnant, planning pregnancy or breastfeeding
2. Women of child-bearing potential and males with partners of child bearing potential who do not practice an acceptable method of birth control [acceptable methods of birth control in this study are: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy, a double-protection method (condom or diaphragm with spermicide), total abstinence from intercourse with male partners. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), occasional abstinence and withdrawal are not acceptable methods of contraception.
3. Subjects who meet any of the following criteria which tend to suggest advanced disease:

    A) Speech impairment as assessed by a score of ≥ 3 on UMSARS question 1
    B) Swallowing impairment as assessed by a score of ≥ 3 on UMSARS question 2
    C) Impairment in ambulation as assessed by a score of >3 on UMSARS question 7
    D)Falling more frequently than once per week as assessed by a score of ≥ 3 on UMSARS question 8
4. Participants with a clinically significant or unstable medical or surgical condition that, in the opinion of the investigator, might preclude safe completion of the study.
5. Participants with active malignant neoplasms or history of malignant neoplasm in the last 5 years.
6. Movement disorders other than MSA; e.g., Parkinson disease, dementia with Lewy bodies, essential tremor, progressive supranuclear palsy, spinocerebellar ataxia, spastic paraparesis, corticobasal degeneration, or vascular, pharmacological or post-encephalitic parkinsonism.
7. Concurrent dementia defined by a score lower than 21 on the MoCA.
8. Concurrent severe depression defined by a score ≥30 on the Beck Depression Inventory-II

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

9. History of deep brain stimulation surgery.
10. Patients with Body mass index <18.5.
11. Currently active infection that cannot be stabilised before baseline visit.
12. Patients with Diabetes (glycated haemoglobin [HbA1c] ≥ 48mmol/l at screening or random blood glucose >11.1 mmol/L)
13. End stage renal disease or severely impaired renal function with creatinine clearance <30ml/min
14. History of severe cardiac disease (Angina, Myocardial infarction or cardiac surgery in preceding 2 years)
15. History of pancreatitis
16. History of alcoholism

1. Severe gastrointestinal disease including gastroparesis
2. Ongoing treatment with sulphonylurea
3. Concurrent and/or recent involvement in other research or use of another experimental investigational medicinal product within 90 days of study enrolment
4. Known allergies to the IMP and excipients of IMP.

7.4 Recruitment

Initial discussions with patients at scientific and patient support meetings show very high interest in this study. A cohort of patients at the National Hospital for Neurology and Neurosurgery and patients will be utilised for recruitment as well as working with hospitals from surrounding areas. Neurologists in the UK with an interest in MSA will be informed when the trial is open to recruitment and provided with details of eligibility criteria to allow referral of potential recruits to the clinical trial team.

The REC approved "lay summary of the trial" will be provided to the MSA Trust website managers, the UCL Institute of Neurology, UCLH NHS Trust and local National Institute of Health Research Clinical Research Network portfolio websites. Contact details of the trial team will be included to allow potentially eligible interest patients to make direct enquires to the trial team.

All participants will be pre-screened by recognised experts in Movement Disorders to avoid any variability in diagnoses; using the history of their symptoms, supported by all available clinical correspondence according to usual standard of care.

It is anticipated that recruitment of 50 patients will be completed within 15 months of trial commencement.

Participant recruitment at a site will only commence when the trial has

1. Been initiated by the Sponsor (or it's delegated representative), and
2. Issued with the 'Open to Recruitment' letter.

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

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

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

7.5 Informed consent procedure

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The person taking consent will be GCP trained, suitably qualified and experienced, and will have been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks.

"Adequate time" must be given for consideration by the participant before taking part. Consent will be sought at least 24 hours after being given the study documentation. It must be recorded in the participant's notes in the electronic health record system, EPIC, when the participant information sheet (PIS) has been given to the participant.

The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. During the consent process it will be highlighted to the participant by the investigator that they will have a 50% chance of being allocated to randomly to active Exenatide treatment or as a control.

No clinical trial procedures will be conducted prior to the participant giving consent by signing the Consent form. Consent will not denote enrolment into trial. Participants who are unable to write (eg due to severe tremor) will be able to indicate their informed consent verbally and a witness will sign the consent form on their behalf.

A copy of the signed informed consent form will be given to the participant. The original signed form will be retained in the trial file at site and a copy placed in the medical notes.

The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

8 Trial procedures

The trial includes a screening visit (Visit 1), a baseline visit (Visit 2), a 12 week follow up (Visit 3), a 24-week follow-up visit (Visit 4), a 36 week follow up (Visit 5), 48-week follow-up visit (Visit 6), a 58-week telephone review and a final 96-week follow-up visit (Visit 7).

8.1 Pre-treatment Assessments

Screening assessments – Visit 1

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Participants will attend the research centre for informed consent to the trial. The following trial specific procedures will be carried out after consent to assess the participant's eligibility:

- Demographics recorded
- Medical History recorded
- Family History recorded
- All available brain imaging will be recorded
- Any previous genetic tests recorded e.g. if testing has been performed for Spinocerebellar ataxia or Fragile X tremor/ataxia syndrome
- Previous drug compliance issues recorded
- Physical Examination
- Neurological Examination
- 12-Lead ECG
- Routine bloods (FBC, U&E, LFT, glucose, amylase, HbA1c, PT and APTT)
- Height and weight
- Vital signs
- Serum and urine pregnancy test (for women of child bearing potential)
- MoCA
- BDI-II
- Concomitant Medications

At this visit the investigator will also ensure the patient is asked about speech/swallowing and mobility to assess exclusion criteria number 3. Eligible patients will wear a sensor attached by sticking plaster over their lower back for 1 week. They will bring this back to the trial team at the baseline visit or send to the trial team using a Stamped Addressed Envelope.

Participants will be randomised to either the trial drug or control arm.

Week 0 (Baseline assessments) – Visit 2

Patients will attend the research centre for the following trial procedures:

- Physical Examination (if deemed necessary by trial clinician for clinical purposes)
- Neurological Examination (if deemed necessary by trial clinician for clinical purposes)
- Lumbar puncture for CSF collection
- Serum collection
- Fasting blood tests (glucose, insulin, c-peptide and triglycerides)
- Vital signs
- UMSARS
- COMPASS Select
- MSA-QoL scale
- Timed Motor Tests
- The Unified Dystonia Rating scale
- MoCA
- BDI-II

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

- Concomitant Medications review
- Adverse Events review

Participants randomised to the trial drug arm will be dispensed the trial medication and receive teaching on its use.

All pre-treatment procedures will be carried out as specified in the schedule of assessments (appendix 1).

8.2 Randomisation Procedures

All enrolled participants will be entered onto an enrolment log.

Participant randomisation will be undertaken remotely at site using Sealed Envelope, an online service for the randomisation of participants in a clinical trial.

Following participant consent, and confirmation of eligibility (see section 8.1 for pre-treatment assessments) the randomisation procedure described below will be carried out.

Participants will be randomised to receive the trial drug added to their treatment or to continue to receive existing treatment alone. The investigator will enter the patient's initials, gender, date of birth, date of consent, criteria fulfilment and MSA phenotype strata into the Sealed Envelope secure website. A random sequence for study arm allocation will be computer generated by a randomisation service provider (Sealed Envelope.com). Sealed Envelope will provide a unique trial identification code for each recruited participant. Blocking will be used within strata to enable achievement of approximately equal numbers in each group.

Strata 1= Phenotype consistent with MSA-C.

Strata 2= Phenotype consistent with MSA-P

A list of the trial identification codes and treatment allocation will be stored in a secure cabinet with the study team. The randomisation list will be sufficiently long to enable continued randomisation should any patients drop out within the first 9 months. All randomisation procedures will take place during working hours.

Participants are considered to be enrolled into the trial following: consent, pre-treatment assessments (see section 8.1), confirmation of eligibility, completion of the randomisation process, allocation of the participant trial number and treatment by the remote system.

8.3 Treatment Schedule

For participants randomised to receive the trial drug they will receive 2mg Exenatide once-weekly for 48 weeks via subcutaneous injection. Astra-Zeneca announced that they will discontinue manufacturing of Bydureon from March 2021 and that this would be replaced by

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

the Bydureon BCise. There is no difference to the dose of exenatide contained between the devices. Patients who have already started on Bydrureon will be reconsented and given new instructions about how to use the updated device.

The first dose will be administered in clinic following injection teaching and the patient will be given sufficient number of pens to continue injections until their 12 week follow up visit. Each participant will be shown an online video instruction specifically for the Bydureon or Bydureon BCise pen injections, which they can revisit as necessary. Each subsequent injection will be given every 7 days at home by self-administration. Injections will be given into the abdomen, arm, thigh or buttocks. Participants will be given a dosing diary to record the time and day of all injections administered.

The control group of patients are very important in view of the continued but variable rate of the neurodegenerative process of MSA.

Patients will continue to see their treating neurologist at normally scheduled appointments. Adjustment to MSA medications will be permitted based on the clinical judgement of the treating neurologist and/or the clinical trial team to optimise symptom control throughout the duration of the trial. Doses of all medications will be recorded at each trial visit.

8.3.1 *Dose Modifications*

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

Patients found to have an elevation in serum Amylase (>50% above baseline and >50% above the laboratory reference range) will have a clinical assessment and have the test repeated after 1 week. If the amylase remains elevated, a clinical decision will be made whether to temporarily withdraw exenatide until the amylase return to the normal range or permanently withdraw exenatide.

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

Patients experiencing excessive/undesirable weight loss (>10% of body weight during a 12 week interval) or unacceptable adverse effects will have a clinical assessment and a decision regarding temporary withdrawal of study medication will be made.

8.4 Subsequent assessments and procedures

Week 4 (+/-1 week) – telephone call

The study nurse will call the participants to ensure the participants are taking their medication according to the protocol requirements and completing their trial diary as required. They will also perform a concomitant medication and AE check.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Week 12 assessments – Visit 3

At 12 weeks after baseline evaluation, each patient will be telephoned 1 week prior to remind them of their visit

Participants will attend the research centre for the following trial procedures:

- Physical Examination (if deemed necessary by trial clinician for clinical purposes)
- Routine blood tests (FBC, U&E, LFT, glucose, amylase, HbA1c, PT and APTT)
- Serum collection
- Vital signs including weight
- UMSARS Part II (videotaped)
- UMSARS Part I, III and IV
- The Unified Dystonia Rating Scale
- MoCA
- Timed Motor tests
- BDI-II
- Concomitant Medications review
- Adverse Events review
- Dispensing of 12 exenatide (Bydureon or Bydureon BCise) pens (if randomised to receive exenatide).

All participants will be invited for face to face visits at all timepoints. If a participant is unable or unwilling to attend any of the follow up assessments (12,24,36,48,96 weeks), they may be offered the option of a home visit by one or more members of the trial clinical team if staffing levels permit. These participants will be asked to consent to home visits. Assessments will be performed as per protocol. Weight will be measured only if the participant is able to stand, and weighing scales are available. Dispensing of IMP will be performed by trial pharmacy and transported to the patient in an appropriate Cool Bag with temperature logger by the clinical trial team.

Week 24 assessments – Visit 4

At 24 weeks after baseline evaluation, each patient will be telephoned 1 week prior to remind them of their visit. They will be asked not to have eaten and to have drunk water only for 6 hours to enable fasting blood samples to be taken.

Participants will attend the research centre for the following trial procedures:

- Physical Examination (if deemed necessary by trial clinician for clinical purposes)
- Neurological Examination (if deemed necessary by trial clinician for clinical purposes)
- Fasting blood tests (FBC, U&E, LFT, glucose, amylase, insulin, c-peptide, HbA1c)
- Serum collection
- Vital signs including weight
- UMSARS Part II (videotaped)

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

- UMSARS Part I, III and IV
- Timed motor tests
- COMPASS Select
- COMPASS Change
- The Unified Dystonia Rating scale
- BDI-II
- MoCA
- Concomitant Medications review
- Adverse Events review
- Dispensing of 12 exenatide pens (if randomised to receive exenatide).

Week 36 assessments – Visit 5

At 36 weeks after baseline evaluation, each patient will be telephoned 1 week prior to remind them of their visit.

Participants will attend the research centre for the following trial procedures:

- Physical Examination (if deemed necessary by trial clinician for clinical purposes)
- Routine blood tests (FBC, U&E, LFT, glucose, amylase and HbA1c)
- Serum collection
- Vital signs including weight
- UMSARS Part II (videotaped)
- UMSARS Part I, III and IV
- Timed motor tests
- The Unified Dystonia Rating scale
- BDI-II
- MoCA
- Concomitant Medications review
- Adverse Events review
- Dispensing of 12 exenatide (Bydureon or Bydureon BCise) pens (if randomised to receive exenatide).

Week 48 assessments – Visit 6

At 48 weeks after baseline evaluation, each patient will be telephoned 1 week prior to remind them of their visit. They will be asked not to have eaten and to have drunk water only for 6 hours to enable fasting blood samples to be taken.

Participants will attend the research centre for the following trial procedures:

- Physical Examination (if deemed necessary by trial clinician for clinical purposes)
- Neurological Examination (if deemed necessary by trial clinician for clinical purposes)

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

- Fasting blood tests (glucose, insulin and c-peptide)
- Routine blood tests (FBC, U&E, LFT, glucose, amylase, HbA1c, PT and APTT)
- Serum collection
- Lumbar puncture for CSF collection
- Vital signs including weight
- UMSARS Part II (videotaped)
- UMSARS Part I, III and IV
- Timed motor tests
- COMPASS Select
- COMPASS Change
- MSA-QoL scale
- The Unified Dystonia Rating scale
- BDI-II
- MoCA
- Concomitant Medications review
- Adverse Events review
- Axivity lumbar sensor

If a patient cannot attend the clinical research facility and is being assessed via a home visit, no attempt will be made to perform a lumbar puncture and this missed assessment will be recorded as a protocol deviation.

Week 58 (+/-1 week) telephone call

The study nurse will call the participants to perform an adverse event check.

Week 96 assessments – Visit 7

At 96 weeks after baseline evaluation, each patient will be telephoned 1 week prior to remind them of their visit.

Participants will attend the research centre for the following trial procedures:

- Physical Examination (if deemed necessary by trial clinician for clinical purposes)
- Neurological Examination (if deemed necessary by trial clinician for clinical purposes)
- Serum collection
- Vital signs including weight
- UMSARS Part II (videotaped)
- UMSARS Part I, III and IV
- Timed motor tests
- COMPASS Select
- COMPASS Change
- MSA-QoL scale
- The Unified Dystonia Rating scale
- BDI-II
- MoCA

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

- Concomitant Medications review
- Adverse Events review

8.5 Laboratory Assessments and Procedures

Local laboratories

The following tests will be carried out at Local Laboratories:

- Routine bloods (FBC, U&E, LFT, glucose, amylase, HbA1c, PT and APTT)
- Fasting bloods (glucose, insulin, c-peptide, triglycerides, amylase, FBC, U&E, LFT and HbA1c)
- Urine pregnancy test

These are all standard hospital laboratory tests and will be performed according to standard treatment processes.

Research Samples

Serum samples will be processed, aliquoted and frozen in accordance with laboratory manual. Patients may consent to their samples being kept for future research. Future analyses will be planned as appropriate in accordance with clinical results, future funding application and latest knowledge.

8.6 Clinical Procedures and Data Collection

- Medical history: review of past medical history, family history, previous imaging, previous genetics tests and MSA medication history.
- Physical examination: The following sites will be examined: chest, heart, abdomen, skin, and lymph nodes; and the following systems will be assessed: musculoskeletal and neurological.
- Neurological examination: The following will be examined: mental status, level of consciousness, sensory function, motor function, cranial nerve function and reflexes.
- Electrocardiogram: A standard 12-lead electrocardiogram will be performed.
- Vital signs: For vital signs measurement the participant's position and arm used for the measurement will be noted. Vital signs include systolic and diastolic blood pressure, respiratory rate, oxygen saturation, weight, temperature and pulse rate.
- Concomitant Medication: All over-the-counter or prescription medication, vitamins, and/or herbal supplements will be recorded.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

- The Montreal Cognitive Assessment is a 30-point test that assesses several cognitive domains to detect cognitive impairment.
- The Beck's Depression Inventory-II is a patient rated depression severity scale.
- The Unified MSA Rating Scale (UMSARS) is a multidimensional, reliable, and valid scale for semi quantitative assessment of MSA patients with high internal consistency and substantial-to-excellent interrater agreement and is sensitive to change. It focuses on all aspects of the disorder, including autonomic, cerebellar, and parkinsonism manifestations. USMARS has an Activities of Daily Living score (UMSARS Part 1, 12 questions); a Motor Examination score (UMSARS Part 2, 14 questions); Autonomic examination score (UMSARS Part 3) and a global disability scale (UMSARS Part 4). Part 2 will be videotaped to ensure there is the option to retrospectively score the participants by blinded raters if there are concerns regarding bias in view of this being an open label trial. All videos will be stored in an appropriate secure encrypted storage facility which can only be accessed by members of the research team.
- The Composite Autonomic Symptom (COMPASS) Select is a subset of the full COMPASS consisting of 46 questions in 5 domains (orthostatic intolerance, secretomotor, bladder, constipation, and sleep), leading to a total score between 0 and 125, with a higher score indicating greater impairment
- The COMPASS Change Scale is a derivation of COMPASS-select in which the participants score their change in autonomic symptoms since their last exam. It comprises 26 retrospective questions in which participants scored how much their autonomic symptoms had changed. It is divided into change of 6 autonomic function domains (or 5 in women) [i.e. orthostatic intolerance, sexual failure (erectile dysfunction, male only), bladder disorder, secretomotor disorder, constipation and sleep disorder] with a maximum score of 160 for men and 150 for women (Wenning GK et al., 2007).
- MSA-QoL scale is a validated 40 item self-completed questionnaire in which a participant is asked to record the problems due to their MSA over the preceding 4 weeks.
- Timed Motor Tests include a hand tapping task to evaluate the number of hand taps that an individual can perform within 30 seconds and a timed, sit, stand, walk task.
- The Unified Dystonia Rating scale is an objective assessment of the severity of dystonia in each body region.
- Axivity lumbar sensor device. This CE marked sensor will be worn over the lower back (lumbar region), attached using sticky-backed plastic by the research team at the clinic visit, and worn continuously over 1 week prior to the Baseline visit and after the 48 week visit. The sensor will be posted back to the research team at week 49 using a stamp-addressed envelope given out in clinic with clear written instructions and a telephone contact for problems or queries. All recordings will be stored with the unique participant identification number (PIN) as well as their date of birth and gender. Analysis will be performed by Professor Lynn Rochester's team at Newcastle University (sensor data) according to existing analytic protocols.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

8.7 Assessment of IMP/NIMP compliance

The importance of compliance with the trial protocol will be explained to the participant at baseline and at each follow up visit. Compliance will be optimised by informing all participants of the most commonly experienced side effects and ways of minimising these. Participants will be given adequate instruction regarding administration of injections and will be provided with a diary to record administration of IMP throughout the trial.

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

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

8.8 Discontinuation/withdrawal of participants

In consenting to participate in the trial, participants are consenting to trial treatment, assessments, follow-up and data collection.

Discontinuation of Trial Treatment for clinical reasons

A participant may be withdrawn from trial treatment whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include

- disease progression whilst on therapy
- unacceptable toxicity
- intercurrent illness which prevents further treatment
- patients withdrawing consent to further trial treatment

  Any alterations in the participant's condition which justifies the discontinuation of treatment in the site investigator's opinion
- Persistent non-compliance to protocol requirements

The decision to withdraw a participant from treatment must be recorded in the CRF and medical notes and the sponsor when required should be notified in writing.

In these cases participants remain within the trial for the purposes of follow-up for safety and or data analysis according to the treatment option to which they have been allocated.

Participant withdrawal from trial treatment

If a participant expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up and seek permission to allow use of routine follow-up data to be used for trial purposes. The importance of safety follow-up should be emphasised to the participant in the Participant Information Sheet.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

The decision of the participant to withdraw from treatment must be recorded in the participant's CRF and medical notes in the electronic health record system, EPIC.

The participant may withhold their reason for withdrawal however, if the participant gives a reason for their withdrawal, this should be recorded.

Withdrawal of Consent to Data Collection

If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the participant's notes in the electronic health record system, EPIC.

Loss to follow-up

If a participant is lost to follow-up at a site every effort should be made to contact the participant's GP to obtain information on the participant's status

8.9 Replacements

Participants who withdraw from the trial prior to Week 12 (visit 3) will be replaced and their replacement randomised to maintain adequate numbers of participants reaching the 12 week assessment.

8.10 Stopping rules

The trial may be stopped before completion for the following reasons:

- On the recommendation of the TSC or DMC
- On the recommendation of the sponsor and CI

Individual participant stopping rules include:

- Unacceptable treatment toxicity or adverse event.
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion Justifies the discontinuation of treatment

If a stopping rule is reached safety data will be reviewed and a decision on continuation will be made by the TMG with input from the sponsor.

8.11 Definition of End of Trial

The expected duration of the trial is 4 years from recruitment of the first participant. The end of the trial is the date of the last follow up of the last participant.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

9 Recording and reporting of adverse events and reactions

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the sponsor's SOP (INV/S05).

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *Therefore an AE can be any unfavourable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a participant to whom an IMP or procedural intervention has been administered, including occurrences which are not necessarily caused by or related to that product.*
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which **is related** to any dose administered to that participant. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such **important medical events** should also be considered as serious. *A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	
Suspected Unexpected Serious	A serious adverse reaction, the nature, severity or outcome of which is not consistent with the Reference Safety Information.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Adverse Reaction (SUSAR)	
Reference Safety Information (RSI)	A list of medical events that defines which reactions are expected for the IMP being administered to clinical trial subjects, and so do not require expedited reporting to the Competent Authority. It is contained in a specific section in the Summary of product characteristics (SmPC) or the Investigator Brochure (IB).

9.2 Recording adverse events

All adverse events will be recorded in the in the participant's research consultant navigator in the electronic health record system, EPIC and in the CRF. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate from consent until 10 weeks after they finish IMP (phone call at 58 weeks). From the 58 week phone call and the 96 week visit only AEs related to IMP or other trial intervention need to be recorded in the CRF.

9.3 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality and seriousness as described below.

9.3.1 *Severity*

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the study specific toxicity grading system and the National Institutes of Health Common Terminology Criteria for

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Adverse Events (CTCAE) version 5.0. SUSARs will be coded via MedDRA for the purpose of expedited reporting to MHRA/REC.

Where the specific event term is not listed in CTCAE please refer to the below table:

Grade	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

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

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

9.3.2 *Causality*

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Related:	A causal relationship between an IMP/investigational treatment and an adverse event is at least a **reasonable possibility**, i.e., the relationship cannot be ruled out.
Not related	There is **no reasonable possibility** of a causal relationship between an IMP/investigational treatment and an adverse event.

9.3.3 *Expectedness*

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Category	Definition
Expected	An adverse event which is consistent with the information about the IMP listed in the current approved Reference Safety Information (RSI) for the trial**.**
Unexpected	An adverse event which is not consistent with the information about the IMP listed in current approved Reference Safety Information (RSI) for the trial**.**

The RSI to be used to assess expectedness against the IMP is:

SmPC for Bydureon (exenatide) 2 mg for prolonged-release suspension for injection in pre-filled pen (BCise) (AstraZeneca UK Limited).

The following events listed below describe expected procedural/disease related AEs: The most frequent adverse reactions were mainly gastrointestinal related (nausea which was the most frequent reaction and associated with the initiation of treatment and decreased over time, and diarrhoea). In addition, injection site reactions (pruritus, nodules, erythema), hypoglycaemia (with a sulphonylurea), and headache occurred. Most adverse reactions associated with prolonged-release exenatide were mild to moderate in intensity.

9.3.4 *Seriousness*

All events are assessed for seriousness as defined for an SAE in section 9.1. Specific adverse events that require expedited reporting as SAEs are detailed in section 9.3.5.

9.3.5 *Other Notifiable Adverse Events*

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

Overdose and potential drug induced liver injury (DILI) events must be handled as SAEs (see section 9.8).

All safety events as described above will be treated as SAEs and reported in line with the procedures set-out in section 9.4 apart from regulatory reporting.

9.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events (SAEs/SARs/SUSARs) will be recorded in the medical records and the CRF, and the sponsor's SAE Recording Log. The SAE Recording Log of SAEs will be reported to the sponsor at least once or twice per year.

All SAEs will be recorded from baseline visit until 10 weeks after completion of IMP (phone call at 58 weeks). From the 58 week phone call and the 96 week visit only SAEs related to IMP or other trial intervention need to be recorded in the CRF.

All SAEs must be recorded on a Serious Adverse Event (SAE) Reporting Form. The CI/PI or designated individual will complete the sponsor's SAE Reporting Form and the form will be

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

emailed to the Sponsor SAE@ucl.ac.uk and within 24 h of his / her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Completed SAE forms must be sent within 24 hours of becoming aware of the event to the Sponsor
Email forms to SAE@ucl.ac.uk

Reporting to the sponsor will be completed as per the sponsor's SOP and using the UCL SAE Reporting Form (INV/S05) as amended for the trial.

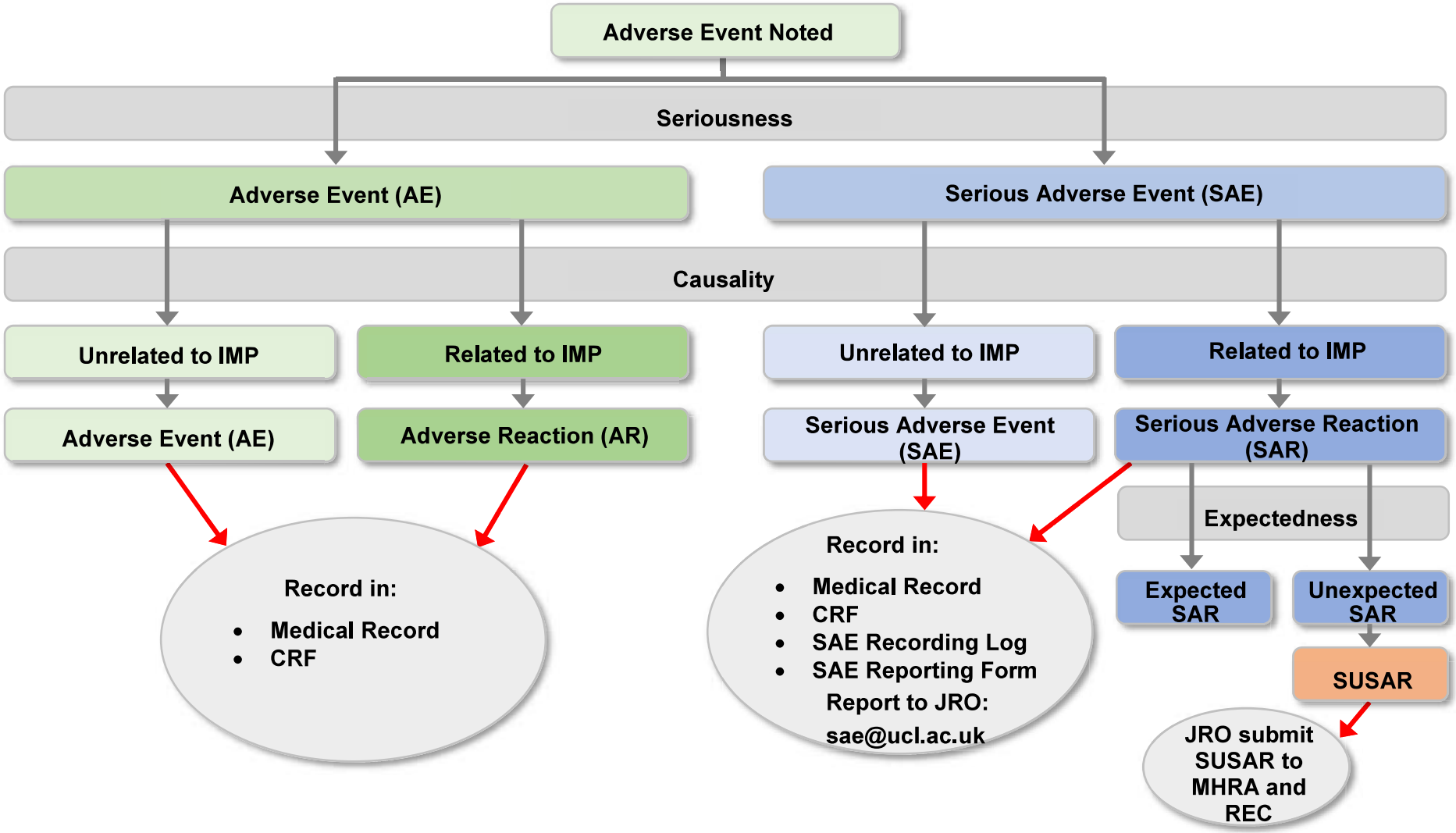
SAEs will be reported to the sponsor until the end of the trial. SAR and SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary.

Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to the JRO as further information becomes available.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Flow Chart for SAE reporting



DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

9.5 Reporting SUSARs

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

9.6 Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the Sponsor's office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

9.7 Pregnancy

There is no safety data to inform on the use of Exenatide during pregnancy. Male participants and female participant of child-bearing potential will be advised to use an effective form of contraception whilst they are on the study. If it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of IMP exposure, including duration of at least 10 weeks after product administration, the IMP will be permanently discontinued in an appropriate manner.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated. Trial follow up assessments will continue as per protocol. The patient's General Practitioner will be informed of the potential unknown risk that may have followed Exenatide exposure during pregnancy.

Pregnancy is not a SAE and should be reported through a Pregnancy Reporting Form. The pregnancy outcome may or may not be considered a SAE.

If a female participant or the female partner of a male participant becomes pregnant at any point during the trial, a completed trial specific Pregnancy Reporting Form will be preferably emailed to the Sponsor **SAE@ucl.ac.uk,** within 24 hours of his / her becoming aware of the event in line with the Sponsors SOP (JRO/INV/S05). The Chief or Principal Investigator will respond to any queries raised by the sponsor as soon as possible.

Completed Pregnancy Reporting Forms must be sent within **24 hours** of becoming aware of the event to the Sponsor
Email forms to SAE@ucl.ac.uk

The Sponsor must be kept informed of any new developments involving the pregnancy through the completion of a follow-up Pregnancy Reporting Form. Any pregnancy that occurs in a female trial subject during a clinical trial should be followed to termination or to term.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Consent to report information regarding the pregnancy must be obtained from the pregnant participant or pregnant partner. A trial-specific pregnancy monitoring information sheet and informed consent form for trial participants or pregnant partners must be used for this purpose.

With consent additional information regarding the pregnancy will be collected and reported to the Sponsor, the Sponsor will advise on the length of follow up of the pregnancy/ child on a case by case basis.

9.8 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important and it must always be reported as a SAE. Overdoses will be fully described in the SAE report form and recorded on the deviation log. Overdoses can be observed from administration diaries, participant and carers comments.

9.9 Reporting Urgent Safety Measures and other safety events

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA, the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

9.10 Notification of Serious Breaches to GCP and/or the protocol (SPON/S15)

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

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

10 Data management and quality assurance

10.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 2018.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

The participant's initials, date of birth and trial identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.

10.2 Data collection tools and source document identification

The majority of study data will be collected from the sites on an electronic CRF and into the participant's electronic health records system, EPIC.

Source data are contained in source documents and must be accurately transcribed on to the electronic CRF. Examples of source documents are electronic medical records which include laboratory and other clinical reports etc.

A source document list will be implemented prior to the start of the trial to identify:

which data is to be recorded directly onto the CRF;

which data is not to be recorded in the CRF but only recorded in source documents, e.g., participant questionnaires and diary cards.

It is the responsibility of the investigator to ensure the accuracy of all data entered in the eCRF. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database. The electronic CRF will be purpose built and tested for completeness before activation of the site.

10.3 Completing Case Report Forms

All CRFs must be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI to perform this duty. The CI is responsible for the accuracy of all data reported in the CRF. Source data verification of a CRF page should be completed and all data queries answered prior to entry into the database where possible.

10.4 Data handling and analysis

A trial specific data management SOP will be in place for the trial. This will contain details of the software to be used for the database, the process of database design, coding, data entry, data quality checks, data queries, data security, database lock and data transfer. Data queries will be resolved by the trial manager through direct discussion with the trial team. A custom designed database will be created to store all trial data. The database will only be available to specified users who will require a username and password for access.

Where data are transferred electronically this will be in accordance with the UK Data Protection Act 2018 as well as UCL Information Security Policy and Trust Information Governance Policy. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer.

11 Statistical Considerations

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

11.1 Outcomes

11.1.1 *Primary outcomes*

The primary outcome will be the difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 week comparing Exenatide to best medically treated patients. The analysis will use ANCOVA to allow adjustment for baseline severity and MSA sub-type.

11.1.2 *Secondary & Exploratory outcomes*

Key secondary outcomes would include proportion of patients with loss of independent ambulation by the end of week 48 and 96, defined by a score of 4 or more in UMSARS-I item 7 (walking); difference at Week 48 and 96 in the MSA-QoL scale; difference at Week 48 and 96 in UMSARS Part I, II, III and IV; difference in anti-parkinsonian or anti-orthostatic hypotension drugs; number of falls; and the proportion of patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling); difference in Week 48 and 96 in clinical global impression (CGI); difference at Week 48 and 96 in MoCA scores.

11.2 Sample size and recruitment

11.2.1 *Sample size calculation*

The recent rasagiline for MSA (MSA-Ras) trial evaluated rasagiline versus placebo using the UMSARS total (Parts 1 and II) as the primary efficacy measure after 48 weeks treatment. Patients in the placebo group declined by mean 7.8 points (SD 10.4 – Werner et al. 2015).

Therefore, on the basis of this previously collected data and with a two-sided 5% significance level, we estimated that a sample size of 40 patients (20 per group) would be required to detect a difference of 5 total UMSARS points between the two groups, assuming a correlation between baseline and final disease severity of 0.85. These calculations were based on a common SD of 10.4, 80% power and an overall type 1 error rate of 5%. A 5 point difference between groups would be a clinically important effect size. Based on a 20% dropout rate as reported from previous trials, the sample size would be 50 (25 per arm).

11.2.2 *Planned recruitment rate*

The estimate recruitment period for the trial is 15 months.

11.3 Randomisation methods

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

Strata 1 = MSA of parkinsonian sub-type (MSA-P)

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Strata 2 = MSA of cerebellar sub-type (MSA-C)

At the baseline visit, the clinical investigator will enter the patient's initials, gender, date of birth, date of consent, criteria fulfilment and MSA sub-type strata into the SealedEnvelope.com secure website which will then allocate the appropriate trial identification code to the patient.

11.4 Statistical analysis plan

11.4.1 *Summary of baseline data and flow of participants*

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

11.4.2 *Primary outcome analysis*

The primary outcome will be the difference in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (Parts I and II) at 48 weeks. The primary analysis will compare exenatide patients to be best medically treated patients using a regression (ANCOVA) model that adjusts for baseline severity and MSA subtype. All modelling assumptions will be checked. The statistical analysis will be based on all participants as randomised, irrespective of subsequent compliance with allocated treatment (intention to treat analysis). The impact of missing data and non-compliance will be investigated as appropriate.

11.4.3 *Secondary outcome analysis*

Key secondary outcomes would include loss of independent ambulation by end of study, defined by a score of 4 or more in UMSARS-I item 7 (walking); MSA-QoL scale UMSARS parts I, II, III and IV at week 48 and 96; use of anti-parkinsonian or anti-orthostatic hypotension drugs; number of falls; and the proportion of patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling) ; clinical global impression (CGI) at week 48 and 96; MoCA scores at week 48 and 96. These outcomes will be analysed using appropriate statistical methods, adjusting for baseline values where possible. Again, all assumptions will be checked.

11.4.4 *Sensitivity and other planned analyses*

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

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

11.5 Other statistical considerations

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

12 Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI and trial sites for a minimum of 25 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

13 Oversight Committees

13.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet to discuss trial progress every 3 months as stated in the TMG terms of reference.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC and/or MHRA.

13.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and Sponsor.

13.3 Data Monitoring Committee (DMC)

The role of the DMC is to provide advice on data and safety aspects of the trial but where all members are independent. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the DMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

14 Direct Access to Source Data/Documents

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

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

15 Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and an appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

Before the site may be opened to recruit participants, the Chief Investigator or designee must have HRA approval and capacity and capability confirmed in writing from their Trust Research & Development (R&D). It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including HRA approvals (where required) at the site. It is the responsibility of the CI or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including NHS Permission (where required) at the site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants (see section 9.9 for reporting urgent safety measures).

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

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a report of the clinical trial which complies with the format as defined by the EMA. This will then be uploaded to EudraCT for availability to the MHRA and a copy of the report will be submitted to the main REC, within 1 year after the end of the trial.

16 Monitoring requirement for the trial

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly. The degree of monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, blinding, endpoints and risks associated with the trial. A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

17 Finance

The trial is being funded by the John Black Charitable Foundation and the Van Andel Research Institute. It also has financial support from the Defeat MSA Alliance from the USA. The trial will benefit from support for recruitment via the MSA Trust in the UK.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

18 Insurance

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

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

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

19 Publication policy

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

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

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

All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings."

20 References

Athauda, D., and T. Foltynie. 2016. "Insulin Resistance and Parkinson's Disease: A New Target for Disease Modification?" Progress in Neurobiology.

Athauda, Dilan, and Thomas Foltynie. 2016. "The Glucagon-like Peptide 1 (GLP) Receptor as a Therapeutic Target in Parkinson's Disease: Mechanisms of Action." Drug Discovery Today 21 (5): 802–18.

Athauda, Dilan, Seema Gulyani, Hanuma Karnati, Yazhou Li, David Tweedie, Maja Mustapic, Sahil Chawla, et al. 2019. "Utility of Neuronal-Derived Exosomes to Examine Molecular Mechanisms That Affect Motor Function in Patients With Parkinson Disease: A Secondary Analysis of the Exenatide-PD Trial." JAMA Neurology, January.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Athauda, Dilan, Kate Maclagan, Natalia Budnik, Luca Zampedri, Steve Hibbert, Simon S. Skene, Kashfia Chowdhury, Iciar Aviles-Olmos, Patricia Limousin, and Thomas Foltynie. 2018. “What Effects Might Exenatide Have on Non-Motor Symptoms in Parkinson’s Disease: A Post Hoc Analysis.” Journal of Parkinson’s Disease 8 (2): 247–58.

Athauda, Dilan, Kate Maclagan, Simon S Skene, Martha Bajwa-joseph, Dawn Letchford, Kashfi Chowdhury, Steve Hibbert, et al. 2017. “A Randomised, Double-Blind, Placebo Controlled Trial of Exenatide Once-Weekly in Parkinson’s Disease.” Lancet.

Aviles-Olmos, Iciar, John Dickson, Zinovia Kefalopoulou, Atbin Djamshidian, Peter Ell, Therese Soderlund, Peter Whitton, et al. 2013. “Exenatide and the Treatment of Patients with Parkinson ’ S Disease” 123 (6).

Aviles-Olmos, Iciar, John Dickson, Zinovia Kefalopoulou, Atbin Djamshidian, Joshua Kahan, Peter Ell Fmedsci, Peter Whitton, et al. 2014. “Motor and Cognitive Advantages Persist 12 Months After Exenatide Exposure in Parkinson’s Disease.” Journal of Parkinson’s Disease, March.

Bassil, Fares, Marie-Hélène Canron, Anne Vital, Erwan Bezard, Pierre-Olivier Fernagut, and Wassilios G. Meissner. 2017. “Brain Insulin Resistance in Parkinson’s Disease [MDS Abstracts].” Movement Disorders 32 (suppl.

Bassil, Fares, Marie-Hélène Canron, Anne Vital, Erwan Bezard, Yazhou Li, Nigel H. Greig, Seema Gulyani, Dimitrios Kapogiannis, Pierre-Olivier Fernagut, and Wassilios G. Meissner. 2017. “Insulin Resistance and Exendin-4 Treatment for Multiple System Atrophy.” Brain 140 (5). Oxford University Press: 1420–36.

Bergenstal, Richard M, Carol Wysham, Leigh Macconell, Jaret Malloy, Brandon Walsh, Ping Yan, Ken Wilhelm, Jim Malone, and Lisa E Porter. 2010. “Efficacy and Safety of Exenatide Once Weekly versus Sitagliptin or Pioglitazone as an Adjunct to Metformin for Treatment of Type 2 Diabetes (DURATION-2): A Randomised Trial.” Lancet 376 (9739): 431–39.

Blevins, Thomas, John Pullman, Jaret Malloy, Ping Yan, Kristin Taylor, Christine Schulteis, Michael Trautmann, and Lisa Porter. 2011. “DURATION-5: Exenatide Once Weekly Resulted in Greater Improvements in Glycemic Control Compared with Exenatide Twice Daily in Patients with Type 2 Diabetes.” The Journal of Clinical Endocrinology & Metabolism 96 (5): 1301–10.

Consoli, Agostino, and Gloria Formoso. 2015. “Potential Side Effects to GLP-1 Agonists: Understanding Their Safety and Tolerability.” Expert Opinion on Drug Safety 14 (2). Informa UK, Ltd.London: 207–18.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Cork, Simon C., James E. Richards, Marie K. Holt, Fiona M. Gribble, Frank Reimann, and Stefan Trapp. 2015. “Distribution and Characterisation of Glucagon-like Peptide-1 Receptor Expressing Cells in the Mouse Brain.” Molecular Metabolism 4 (10): 718–31.

D’Amelio, Marco, Paolo Ragonese, Graziella Callari, Norma Di Benedetto, Barbara Palmeri, Valeria Terruso, Giuseppe Salemi, Giorgia Famoso, Paolo Aridon, and Giovanni Savettieri. 2009. “Diabetes Preceding Parkinson’s Disease Onset. A Case-Control Study.” Parkinsonism & Related Disorders 15 (9): 660–64.

Dodel, Richard, Annika Spottke, Alexander Gerhard, Alexander Reuss, Sylvia Reinecker, Nicole Schimke, Claudia Trenkwalder, et al. 2010. “Minocycline 1-Year Therapy in Multiple-System-Atrophy: Effect on Clinical Symptoms and [11 C] (R) -PK11195 PET (MEMSA-Trial).” Movement Disorders 25 (1): 97–107.

Drucker, Daniel J, John B Buse, Kristin Taylor, David M Kendall, Michael Trautmann, Dongliang Zhuang, Lisa Porter, and DURATION-1 Study Group. 2008. “Exenatide Once Weekly versus Twice Daily for the Treatment of Type 2 Diabetes: A Randomised, Open-Label, Non-Inferiority Study.” The Lancet 372 (9645): 1240–50.

Egan, Amy G, Eberhard Blind, Kristina Dunder, Pieter A de Graeff, B Timothy Hummer, Todd Bourcier, and Curtis Rosebraugh. 2014. “Pancreatic Safety of Incretin-Based Drugs--FDA and EMA Assessment.” The New England Journal of Medicine 370 (9): 794–97.

Fanciulli, Alessandra, and Gregor K. Wenning. 2015. “Multiple-System Atrophy.” Edited by Dan L. Longo. New England Journal of Medicine 372 (3): 249–63.

Fernagut, Pierre-Olivier, Benjamin Dehay, Aline Maillard, Erwan Bezard, Paul Perez, Anne Pavy-Le Traon, Olivier Rascol, Alexandra Foubert-Samier, François Tison, and Wassilios G. Meissner. 2014. “Multiple System Atrophy: A Prototypical Synucleinopathy for Disease-Modifying Therapeutic Strategies.” Neurobiology of Disease 67 (July). Academic Press: 133–39.

Fineman, Mark S, K F Mace, M Diamant, T Darsow, B B Cirincione, T K Booker Porter, L a Kinninger, and M E Trautmann. 2012. “Clinical Relevance of Anti-Exenatide Antibodies: Safety, Efficacy and Cross-Reactivity with Long-Term Treatment.” Diabetes, Obesity & Metabolism 14 (6): 546–54. https://doi.org/10.1111/j.1463-1326.2012.01561.x.

Gilman, S., G. K. Wenning, P. A. Low, D. J. Brooks, C. J. Mathias, J. Q. Trojanowski, N. W. Wood, et al. 2008. “Second Consensus Statement on the Diagnosis of Multiple System Atrophy.” Neurology 71 (9): 670–76.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Greig, Nigel H, David Tweedie, Lital Rachmany, Yazhou Li, Vardit Rubovitch, Shaul Schreiber, Yung-Hsiao Chiang, et al. 2014. “Incretin Mimetics as Pharmacologic Tools to Elucidate and as a New Drug Strategy to Treat Traumatic Brain Injury.” Alzheimer’s & Dementia : The Journal of the Alzheimer’s Association 10 (1 Suppl). Elsevier: S62-75.

Low, Phillip A, Stephen G Reich, Joseph Jankovic, Clifford W Shults, Matthew B Stern, Peter Novak, Caroline M Tanner, et al. 2015. “Natural History of Multiple System Atrophy in the USA: A Prospective Cohort Study.” The Lancet Neurology 14 (7): 710–19.

Low, Phillip A, David Robertson, Sid Gilman, Horacio Kaufmann, Wolfgang Singer, Italo Biaggioni, Roy Freeman, et al. 2014. “Efficacy and Safety of Rifampicin for Multiple System Atrophy: A Randomised, Double-Blind, Placebo-Controlled Trial.” The Lancet Neurology 13 (3): 268–75. https://doi.org/10.1016/S1474-4422(13)70301-6.

Madsbad, Sten. 2016. “Review of Head-to-Head Comparisons of Glucagon-like Peptide-1 Receptor Agonists.” Diabetes, Obesity & Metabolism 18 (4). Wiley-Blackwell: 317–32.

Pablo-Fernandez, E. De, F. Sierra-Hidalgo, J. Benito-León, and F. Bermejo-Pareja. 2017. “Association between Parkinson’s Disease and Diabetes: Data from NEDICES Study.” Acta Neurologica Scandinavica 136 (6): 732–36.

Poewe, Werner, Robert A. Hauser, and Anthony Lang. 2015. “Effects of Rasagiline on the Progression of Nonmotor Scores of the MDS-UPDRS.” Movement Disorders 30 (4): 589–92.

Poewe, Werner, Klaus Seppi, Cheryl J Fitzer-Attas, Gregor K Wenning, Sid Gilman, Phillip A Low, Nir Giladi, et al. 2015. “Efficacy of Rasagiline in Patients with the Parkinsonian Variant of Multiple System Atrophy: A Randomised, Placebo-Controlled Trial.” The Lancet Neurology 14 (2): 145–52.

Talbot, Konrad, Hoau-Yan Wang, Hala Kazi, Li-Ying Han, Kalindi P Bakshi, Andres Stucky, Robert L Fuino, et al. 2012. “Demonstrated Brain Insulin Resistance in Alzheimer’s Disease Patients Is Associated with IGF-1 Resistance, IRS-1 Dysregulation, and Cognitive Decline.” The Journal of Clinical Investigation 122 (4). American Society for Clinical Investigation: 1316–38.

Wenning, Gregor K., Francois Tison, Klaus Seppi, Cristina Sampaio, Anja Diem, Farid Yekhlef, Imad Ghorayeb, et al. 2004. “Development and Validation of the Unified Multiple System Atrophy Rating Scale (UMSARS).” Movement Disorders 19 (12): 1391–1402.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

Wenning GK et al. Progression of dysautonomia in multiple system atrophy: a prospective study of self-perceived impairment.Eur J Neurol. 2007 Jan;14(1):66-72.

Wenning, Gregor K, Felix Geser, Florian Krismer, Klaus Seppi, Susanne Duerr, Sylvia Boesch, Martin Köllensperger, et al. 2013. “The Natural History of Multiple System Atrophy: A Prospective European Cohort Study.” The Lancet Neurology 12 (3): 264–74.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

	Screening (Pre-treatment assessment)	**Treatment Phase**							**Final visit**
Visit No:	1	2	Telephone call	3	4	5	6	Telephone call	7
	Day – 28 to Day -1	Week 0	Week 4[6]	Week 12	Week 24	Week 36	Week 48 / Discontinuation visit	Week 58[7]	Week 96
Window of flexibility for timing of visits:			+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days +/- 7 days	+/- 7 days	+/- 7 days
Informed Consent	X								
Demographics	X								
Medical History[1]	X								
Height	X								
Weight	X	X		X	X	X	X		X
Physical Examination	X	X*		X*	X*	X*	X*		X*
Neurological Examination	X	X*			X*		X*		X*
Vital Signs[2]	X	X		X	X	X	X		X
12-Lead ECG	X								
Routine blood test[3]	X			X	X	X	X		
Fasting blood tests[4]		X			X		X		
Lumbar puncture + 10ml serum sample		X					X		X[10]
MoCA	X	X		X	X	X	X		X
BDI-II	X	X		X	X	X	X		X

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

UMSARS Part 1, 3 and 4		X		X	X	X	X		X
UMSARS Part 2 (videotaped)		X		X	X	X	X		X
COMPASS Select		X			X		X		X
COMPASS Change					X		X		X
MSA-QoL scale		X					X		X
Timed Motor Tests		X		X	X	X	X		X
The Unified Dystonia Rating		X		X	X	X	X		X
Eligibility confirmation	X	X							
Randomisation		X[8]							
IMP administration[5]		X		X	X	X			
Adverse Events/SAEs review	X	X	X	X	X	X	X X	X	X
Concomitant Medication review	X	X	X	X	X	X	X X		X

Appendix 1 - Schedule of assessments

1. Medical History: including MSA history, family history, medication history, previous imaging, previous genetic tests and previous drug compliance issues.
2. Vital signs: blood pressure, respiratory rate, heart rate, temperature, oxygen saturation and weight.
3. Routine blood tests: FBC, U&E, LFT, glucose, amylase, HbA1c, PT and APTT (PT and APTT not done at weeks 24 and 36).
4. Fasting blood tests
    - Baseline visit: glucose, insulin, c-peptide, and triglycerides.
    - Week 24 visit: glucose, insulin, c-peptide.
    - Week 48 visit: glucose, insulin, c-peptide.
5. 5 IMP administration: Participants will be randomly allocated into 2 groups to receive either Exenatide (n~=25) or best medical treatment (n~=25). Only participants randomised to the Exenatide arm will receive the IMP.
6. At Week 4 the study nurse will call the participants to provide support and optimise compliance.
7. At Week 58 the study nurse will call the participants to perform an adverse event check.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

8. Randomisation will occur once eligibility has been confirmed prior to Visit 2 to allow Pharmacy team time to prepare IMP for dispensing.
9. * Clinical and Neurological examinations will be performed with deemed relevant/necessary by trial clinician for clinical purposes.
10. Only a serum sample will be collected for research purposes at week 96.

Appendix 2

COVID19 mitigation plans

The objective of this Appendix is to set out a plan detailing the proposed continuation of the Exenatide-MSA trial if a restriction in trial Face to Face visits should occur as a result of a resurgence of COVID19 infections.

CONTINUATION OF IMP DISPENSING FOR EXISITNG TRIAL RECRUITS

1. Patient consent required. Each patient will be contacted by the research team, at site. Consent to ship IMP to the patients home to be fully documented in source notes
2. Patient will be assessed via telephone by Chief Investigator (or appropriate delegated trial team member) to decipher whether suitable to dispense IMP. Specific questions to be asked in relation to abdominal pain/ weight/ AEs/ new con-meds etc.
3. NB Scheduled blood tests will not be performed. Given that Exenatide is licensed for the treatment of Type 2 Diabetes that does not routinely require regular monitoring of patient safety using blood tests, these will not be performed unless a patient describes symptoms potentially indicating an adverse effect of the IMP. In the event of a clinically significant adverse reaction to the IMP, dispensing will be paused until a face to face evaluation of the participant can be completed.
4. If a patient describes adverse events that require urgent medical treatment, appropriate clinical advice will be given to patient regarding all/any necessary precautions/investigations/ treatment options through trial team/ GP/ local hospital facilities.

DocuSign Envelope ID: 8E59A475-2ED0-4161-B371-6E26D476D7C3

If it is deemed suitable to dispense IMP:

A) Consent for telephone follow-up and IMP delivery obtained verbally and documented (as per MHRA/ HRA advice)

B) IMP prescribed by trial team (as normal)

C) Courier collects IMP from NHNN Pharmacy

D) Upon arrival at participants address courier has agreed to unpack the IMP from cooler, wipe them down (alcohol wipe), place at the patients door and ring and then step back (to minimise COVID-19 transmission risk). Patients will be informed by site team when to expect the delivery.

E) The site team shall then call the patient and confirm and document delivery.

REMOTE ASSESSMENTS

To minimise disruption to the scientific integrity of the trial, for patients who remain well but who are unable to attend a scheduled trial visit due to National guidelines/ patient concerns regarding risk of travel, face to face evaluation will be replaced by remote evaluation. Questionnaires will be completed remotely and a Video examination of UMSARS part 2 will be performed with the exception that Rigidity will not be rated (Item 6), and the Pull test will not be performed (Item 13) . These remote measures will be appropriately labelled to ensure that any necessary adjustments for remote/ face to face assessments are incorporated in the final statistical analysis of the trial.

Visit CRFs will otherwise be completed in full. The fact that this visit has taken place by video/telephone will be documented on paper CRF and source notes along with all relevant visit information.