UDCA-PD

(The "UP-Study")

A Phase II, Placebo Controlled, Double Blind, Randomised Clinical Trial To Assess The Safety And Tolerability Of 30 mg/KG Daily **U**rsodeoxycholic Acid (UDCA) In Patients With **P**arkinson's Disease (PD).

Version	v5.0
Date	06 January-2020
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Clinical Trials.Gov Number:	NCT03840005

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Authorisation: Chief Investigator

Name: Professor Oliver Bandmann

Role: Chief Investigator

Signature: 

Authorisation: Sponsor/Sheffield Teaching Hospitals NHS Foundation Trust

Name Dr Dipak Patel

Role Research & Innovation Manager

Signature 

Date 03 April 2020

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1 Administrative Information

1.1 Structured trial summary

Primary Registry and Trial Identifying Number	Clinicaltrials.gov: NCT03840005
Source of Monetary or Material Support	The J P Moulton Charitable Foundation
Primary Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Sub-contractor responsibilities	Data Management Service Provision – Sheffield Clinical Trials Research Unit. UDCA drug supply under contractual arrangement with PRO.MED.CS Praha a.s Genetic analysis -National Institute of Health, Bethesda, USA.
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Public Title	Trial of Ursodeoxycholic acid (UDCA) for Parkinson's disease
Scientific Title	A Phase II, Placebo Controlled, Double Blind, Randomised Clinical Trial To Assess The Safety And Tolerability Of 30 mg/KG Daily Ursodeoxycholic Acid (UDCA) In Patients With Parkinson's Disease (PD).
Countries of Recruitment	UK
Health Condition(s) or Problem(s) Studied	Parkinson's disease
Clinical Phase	II

Trial Participants	30 Parkinson's disease patients
Treatment duration	12 months
Follow-up duration	2 months
Planned Trial Period	30 months
Investigational Medicinal Products(s)	Ursodeoxycholic acid (UCDA)
Formulation, Dose, route of Administration	Oral administration 30mg/kg/day
Intervention(s)	UDCA 30 mg/kg/day for 48 weeks. Placebo 30 mg/kg/day for 48 weeks with gradual dose increase by 250 mg every three days until individual total target dose has been reached

Key Inclusion and Exclusion Criteria	**Inclusion Criteria:** • Diagnosis of Parkinson's disease ≤ 5 years ago as defined by the Queen Square Brain Bank criteria (bradykinesia defined as slowness of initiation of voluntary movement with progressive reduction in speed and amplitude on repetitive actions and at least one of the following: • Rigidity, 4-6 Hz rest tremor). • Subjective improvement of motor impairment on dopaminergic medication, confirmed by PI through personal examination and/or review of medical records • Hoehn and Yahr stage ≤ 2.5 in the "ON" medication state. This implies that all patients will be mobile without assistance during their best "ON" medication periods. • Ability to take study drug • Ability to communicate in English • Age 18 - 75 yr. of any gender • Documented informed consent to participate • Able to comply with study protocol and willing to attend necessary study visits
	Exclusion criteria: • Diagnosis or suspicion of other cause of parkinsonism such as Multiple system atrophy (MSA) or progressive supranuclear palsy (PSP), drug induced parkinsonism, dystonic tremor or essential tremor will not be recruited. • Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial/protocol/^{31}P-MR Spectroscopy (^{31}P-MRS) acquisition.

	• Known claustrophobia or other reasons why patient could not tolerate or be suitable for ^{31}P-MRS • Current or previous exposure to UDCA • Current or previous diagnosis of liver disease judged to be significant by the clinical investigator, in particular Primary Biliary Cholangitis (previously referred to as Primary Biliary Cirrhosis, PBC) • Prior intracerebral surgical intervention for PD (including deep-brain stimulation) • Already actively participating in a trial of a device, drug or surgical treatment for PD • History of alcoholism • Women of child-bearing potential (WOCBP) • Participants who lack the capacity to give informed consent • Any medical or psychiatric condition which in the investigator's opinion compromises the potential participant's ability to participate • Concurrent dementia defined by Montreal Cognitive assessment (MoCA) score <25 • Concurrent severe depression defined by a score >16 on the Montgomery-Asberg Depression Rating Scale (MADRS) • Serum transaminases more than 2 times upper limit of normal. • Patients on ciclosporin, nitrendipine or dapsone • Participants with previous or current diagnosis of inflammatory bowel disease (i.e. ulcerative colitis or Crohn's disease)
Study Type	A phase II, placebo controlled, double blind, randomised clinical trial to assess the safety and tolerability of 30mg/kg daily Ursodeoxycholic acid (UDCA) in patients with Parkinson's Disease (PD)

Date of First Planned Enrolment	01. October 2018
Target Sample Size	30
Primary Outcome(s)	Safety and tolerability of UDCA in Parkinson's disease (PD) at a dose of 30 mg/kg Each of the metrics below will be assessed over the whole study period (start of treatment to week 56) and summarised by treatment group. Metrics: • Number of serious adverse events (SAE) • Number of adverse treatment reactions • Number of patients completing the study ***Timepoint: start of treatment to 56 weeks (visit 6)***
Secondary Outcome	<u>For each of the metrics listed below the change from baseline to week 48 will be compared between the randomised treatment groups:</u> Metrics: • Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 motor subsection "OFF" medication score • *In vivo* parameter estimates of high and low energy metabolite levels (ATP, PCr, Pi) , derived from cranial ^{31}P-MRS centered on the basal ganglia and related motor regions • Objective quantification of motor impairment, using motion sensors ***Timepoint: 48 weeks (visit 5)***
Exploratory outcomes	<u>For each of the metrics listed below the change from baseline to week 56 and from week 48 to week 56 will be compared between the randomised treatment groups:</u> <u>Metrics:</u> • Movement Disorders Society Unified Parkinson's

	Disease Rating Scale (MDS-UPDRS) part 3 motor subsection "OFF" medication score • Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 1,2,3 and 4 "ON" medication scores • Levodopa equivalent dose (LED) • Montreal Cognitive assessment (MoCA) score • Non-Motor Symptoms Scale (NMS-QUEST) • Parkinson's Disease 39 item quality of life questionnaire (PDQ-39) • Montgomery-Asberg Depression Rating Scale (MADRS) **Time points: Baseline to week 56 and week 48 to 56 weeks (visit 5 to 6)** <u>Exploratory analyses:</u> <u>Associations between</u> changes of MDS-UPDRS/3 "OFF" motor score and: • Predicted disease progression, calculated using the model of Verseboer et al.[1] • Energy metabolite levels in brain tissue as quantified by ^{31}P MRS • Genetic variants associated with PD

1.2 Roles and responsibilities

1.2.1 Protocol contributors

Name	Affiliation	Role
Professor Oliver Bandmann	Department of Neuroscience, University of Sheffield/STH Department of Neurosciences	Chief Investigator
Mrs. Sarah Moll	NIHR Sheffield Biomedical Research Centre, Sheffield Teaching Hospitals NHS Foundation Trust	Clinical Trial Manager
Ms. Rosie Taylor	Statistical Services Unit, The University of Sheffield	Statistician
Dr. Tom Jenkins/Professor Iain Wilkinson	Department of Neuroscience (TJ)/Radiology (IW), The University of Sheffield	^{31}P-MRS acquisition and analysis
Professor Claudia Mazza/Dr. Alisdair McNeill/ Ms. Ellen Buckley	Department of Engineering (CM)/Neuroscience, The University of Sheffield	Analysis of sensor-based objective quantification of motor impairment
Mrs. Helen Bowler	Sheffield Teaching Hospitals NHS Foundation Trust	Trial Pharmacist

1.2.2 Role of trial sponsor and funders

Name	Affiliation	Role
Dr. Erica Wallis	CRIO Sheffield Teaching Hospitals NHS Foundation Trust	Overall supervision of STH sponsorship. Ultimate authority for writing the report and decision to submit for publication will lie with the Chief Investigator.
Jon Moulton	J P Moulton Charity	Funding

1.2.3 Trial Management Group

Name	Affiliation	Role and responsibilities
Professor Oliver Bandmann	TUoS	Chief Investigator
Dr. Tom Payne	TUoS	Clinical Research Fellow
Mrs. Sarah Moll	STH	BRC Clinical Trials Manager
Dr. Amanda Loban	CTRU	Head of Data Management
Mrs. Helen Bowler	STH	Trial Pharmacist
Clinical Research Facility Lead Nurse	STH	Research Nurse Lead
Miss Sarah Birchall	STH	BRC Data Coordinator

1.2.4 Trial Steering Committee

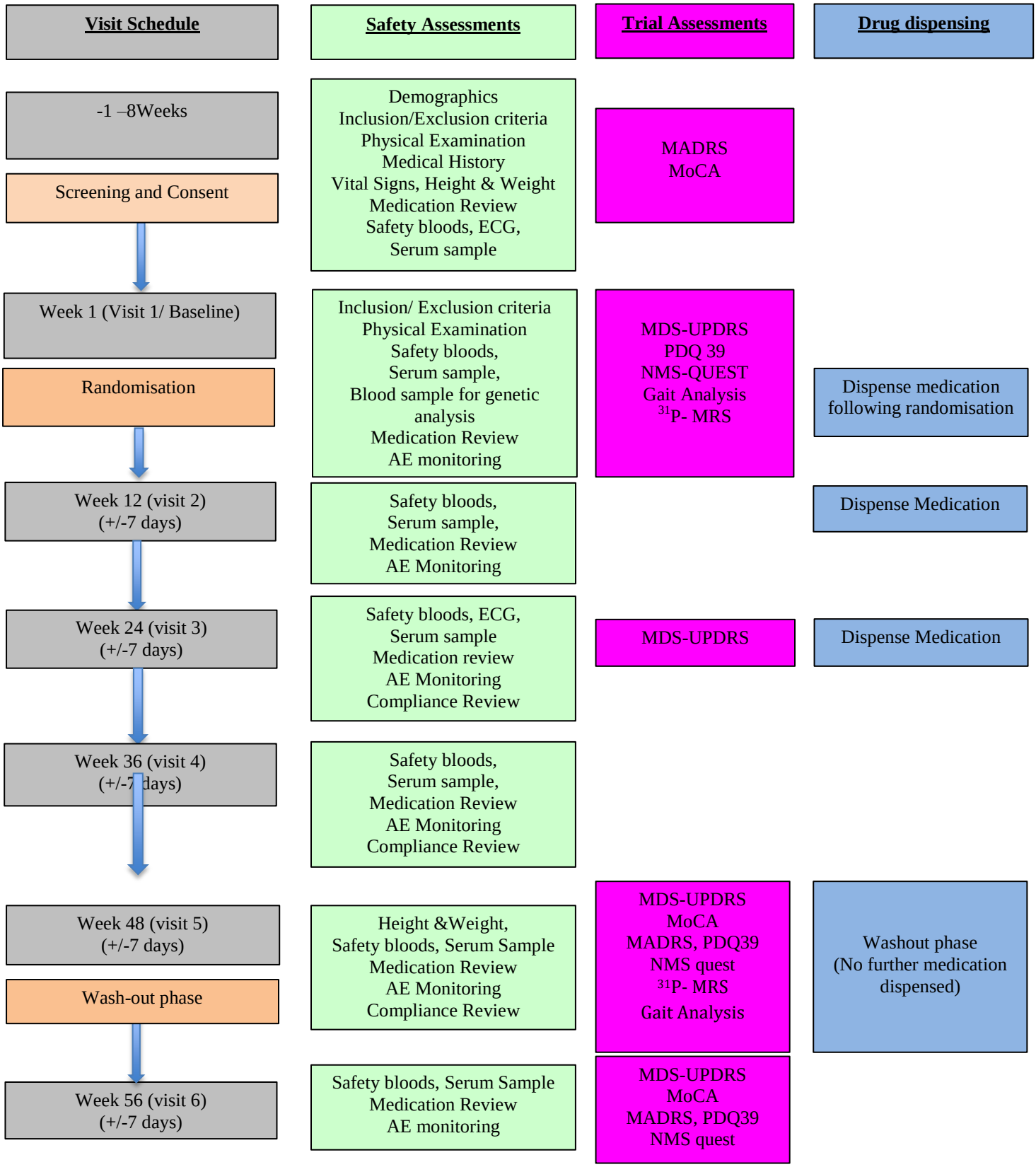
Name	Affiliation	Role and responsibilities
Professor Donald Grosset	University of Glasgow	Independent Chair
Professor Oliver Bandmann	STH	CI
Professor Tom Foltynie	UCLH, London	Co-investigator
Ms. Helen Matthews	Cure Parkinson's Trust	Independent lay representative
Mrs. Sarah Moll	STH	Clinical Trials Manager

Ms. Rosie Taylor	TUoS	Trials Statistician
Miss Sarah Birchall	STH	BRC Data Coordinator

1.2.5 Independent Data Monitoring Committee (IDMC)

Name	Affiliation	Role and responsibilities
Dr. Camille Carroll, Honorary Consultant Neurologist, Plymouth Hospitals NHS Trust	Plymouth Hospitals NHS Foundation Trust	DMC Chair Feedback outcome of DMC meetings to TSC. (PD Academic Clinician)
Professor J Newell-Price	TUoS	DMC Member

2 Trial Flow Chart



3 Abbreviations

AD	Alzheimer's Disease		NMS	Non-Motor Symptoms
AE	Adverse Event		NMS - Quest	Non Motor Symptoms Questionnaire
AR	Adverse Reaction		NRES	National Research Ethics Service
ATP	Adenosine triphosphate		PAM	Physical Activity Monitor
AUC	Area under Curve		PBC	Primary Biliary Cholangitis
BRC	Biomedical Research Centre		PCr	Phosphocreatinine
CI	Chief Investigator		PD	Parkinson's disease
CRF	Case Report Form		PDQ39	Parkinson's disease quality of life questionnaire
CRF	Clinical Research Facility		Pi	Inorganic Phosphate
CRIO	Clinical Research and Innovation Office		PI	Principal Investigator
CRN	Clinical Research Network		PIS	Participant Information Sheet
CSF	Cerebrospinal Fluid		PSC	Primary Sclerosing Cholangitis
CSI	Chemical Shift Imaging		PSP	Progressive Supranuclear Palsy
CT	Computerised Tomography		QA	Quality Assurance
CTA	Clinical Trial Authorisation		QC	Quality Control
CTIMP	Clinical Trials of Investigational Medicinal Products		QL	Quality of Life
CTRU	Clinical Trials Research Unit		QP	Qualified Person
DMC	Data Monitoring Committee		R&D	Research and Development
DSUR	Development Safety Update Report		REC	Research Ethics Committee
ECG	Electrocardiogram		SAE	Serious Adverse Event
e-CRF	Electronic Case Report Form		SAP	Statistical Analysis Plan
EU	European Union		SAR	Serious Adverse Reaction
FDA	(US) Food and Drug Administration		SIV	Site Initiation Visit
FSH	Follicle-stimulating Hormone		SmPC	Summary of Product Characteristics
GCP	Good Clinical Practice		SOP	Standard Operating Procedure
HD	Huntington's Disease		SSA	Site Specific Assessment
ICH	International Conference on Harmonisation		SSAR	Serious Suspected Adverse Reaction

IDMC	Independent Data Monitoring Committee		SUSAR	Suspected Unexpected Serious Adverse Reaction
IMP	Investigational Medicinal Product		STH	Sheffield Teaching Hospitals
ITT	Intention to Treat		TEE	Treatment Emergent Event
LCT	Linked Clinical Trials		TMF	Trial Master File
LED	Levodopa Equivalent Dose		TMG	Trial Management Group
MADRS	Montgomery Asberg Depression Rating Scale		TMT	Trial Management Team
MDS	Movement Disorders Society		ToR	Terms of Reference
MHRA	Medicines and Healthcare products Regulatory Agency		TSC	Trial Steering Committee
MJFF	Michael J Fox Foundation		TUDCA	Taurodeoxycholic Acid
MND	Motor Neurone Disease		UCA	Uroscholanic Acid
MOA	Mode of Action		UDCA	Ursodeoxycholic Acid
MoCA	Montreal Cognitive assessment		TUoS	The University of Sheffield
MRI	Magnetic Resonance Imaging		UPDRS	Unified Parkinson's Disease Rating Scale
MSA	Multiple System Atrophy		UCLH	University College London Hospital
NASH	Non-Alcoholic Steatohepatitis		WOCBP	Women of Child Bearing Potential
NIHR	National Institute of Health Research		^{31}P MRS	^{31}Phosphorous Magnetic Resonance Spectroscopy

4 Glossary

Hoehn & Yahr stage

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

Practically defined "OFF" medication state.

The practically defined "OFF" medication state refers to the patient assessment conducted in the absence of their regular medication with the aim of exposing the severity of the underlying PD. Patients will attend the hospital in the morning having not taken any of their prescribed PD medication for 8 hours (overnight) in the case of any drug containing Levodopa (e.g. Sinemet, Madopar, Co-beneldopa, Co-Careldopa), or ≥ 36 hours in the case of longer acting agents such as dopamine agonists (Ropinirole, Pramipexole, Rotigotine) or enzyme inhibitors (Rasagiline, selegiline, safinamide, opicapone). Participants will be asked to attend a clinic visit in the practically defined "OFF" medication state for the baseline visit (v1) and for visit 5 (48 weeks) and visit 6 (56 weeks). To reduce any physical discomfort of stopping medication and to facilitate attendance participants may be provided with some supportive medicines as necessary such as dispersible Madopar, to be taken in the event of severe difficulty with wearing-off symptoms. The time and quantity/dose of Madopar dispersible (or similar) will depend on the clinical needs of the patient. The patients will be asked to document when and how many of these supportive medicines they will have taken. If possible, patients should not take any supportive medication < 90 min prior to the study visit to minimize the possible effect on the respective outcome measures.

Women of child-bearing potential

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

Post-menopause

Women who have had amenorrhea for > 12 consecutive months (without another cause). If required, serum follicle-stimulating hormone (FSH) level can be requested (women with FSH < 35

mIU/mL should be excluded).

Primary biliary cholangitis (PBC)

Primary biliary cholangitis (PBC), also known as primary biliary cirrhosis, is an autoimmune disease of the liver. It results from a slow, progressive destruction of the small bile ducts of the liver, causing bile and other toxins to build up in the liver, a condition called cholestasis.

The Prognostic Model

The Prognostic Model developed by Williams-Gray and co-workers identified the following three parameters as associated with more rapid PD progression: 1. Higher age, 2. Higher UPDRS motor examination axial score (items 27-30), 3. Lower animal naming fluency (participants will be asked to name as many animals as possible in a 1-minute time frame).[1]

5 Introduction

5.1 Background and Rationale

Mitochondrial dysfunction and Parkinson's disease

This clinical trial addresses the urgent need for disease modifying drugs in Parkinson's disease (PD), the second most common neurodegenerative condition after Alzheimer's disease. PD itself is not only a movement disorder but often leads to dementia, neuropsychiatric complications and autonomic dysfunction as well.[2] Unlike other chronic conditions, such as rheumatoid arthritis and multiple sclerosis, there are no disease-modifying treatments for PD. Moreover, symptomatic therapies typically give only partial relief that invariably diminishes over time and is often associated with side effects that can be as disabling as the underlying condition itself. The lack of disease-modifying therapy also has substantial financial implications with costs of £25-60K per patient and year in advanced PD.[3] Disease modifying treatment which would slow down the on-going cell death and PD progression has repeatedly been identified as the most important issue for PD patients and their careers in surveys of the patient self-help organisation Parkinson's UK. Disease-modifying treatment is arguably particularly an important goal in those patients with fast disease progression. Williams-Gray and co-workers have developed a novel ***prognostic model*** with higher age, higher motor examination axial score on the Movement Disorders Society Unified Parkinson's disease rating scale (MDS-UPDRS) and lower animal fluency score (the patient is asked to list as many animals as possible in 60 seconds) all being associated with a higher probability of an unfavourable outcome.[1] Kordower and colleagues undertook a detailed assessment of disease duration and

integrity of the nigrostriatal system in PD.[4] They reported modest loss of dopaminergic neuronal markers in the striatum at year 1-3 after diagnosis but rapid decline through years 4-5 and relatively stable numbers thereafter. This suggests that early intervention with a disease-modifying compound may have a greater chance of exerting a neuroprotective effect in patients with comparatively short disease duration (≤ 5 years).

A recent, high-profile review by leading experts in the field has identified mitochondrial dysfunction as a promising target for neuroprotective strategies in PD.[5] The link between mitochondrial dysfunction and idiopathic (or sporadic) PD was first made after the discovery of mitochondrial complex I deficiency in the substantia nigra.[6] The role of mitochondria in PD has been reinforced by the finding that several familial PD genes encode mitochondrial proteins and that mitochondrial toxins can cause Parkinsonism in animals and humans.[6]

Parkin mutations are the most common identifiable cause of early onset PD, the LRRK2^{G2019S} mutation is the single most common genetic cause of (typically late onset) PD with a mutation prevalence levels of up to 30% in distinct populations.[7] Skin fibroblasts are increasingly used to study these key pathogenic mechanisms in Parkinson's disease.[8] We were the first group worldwide to identify mitochondrial dysfunction in both parkin- and LRRK2^{G2019S} mutant patient tissue.[9, 10] Parkin-mutant fibroblasts displayed marked abnormalities in mitochondrial membrane potential, intracellular ATP production and selective lowering of complex I activity of the mitochondrial respiratory chain, accompanied by changes in mitochondrial morphology.[10] Similar, albeit more mild mitochondrial changes in mitochondrial function and morphology with selective lowering of complex IV activity were identified in LRRK2^{G2019S} mutant fibroblasts from individuals with both clinically manifest Parkinson's disease and currently asymptomatic LRRK2^{G2019S} carriers.[9, 11] We subsequently undertook the first drug screen in genetically stratified PD patient tissue. This novel drug discovery strategy consisted of us undertaking an unbiased drug screen of 2000 compounds directly in PD patient tissue (namely parkin- and LRRK2^{G2019S} mutant fibroblasts) to discover drugs which rescue mitochondrial function in PD.[12] A group of compounds including ursocholanic acid (UCA) was identified which normalised all key aspects of mitochondrial function, namely mitochondrial membrane potential, ATP production and activity of mitochondrial respiratory chain complexes (see Fig 1).

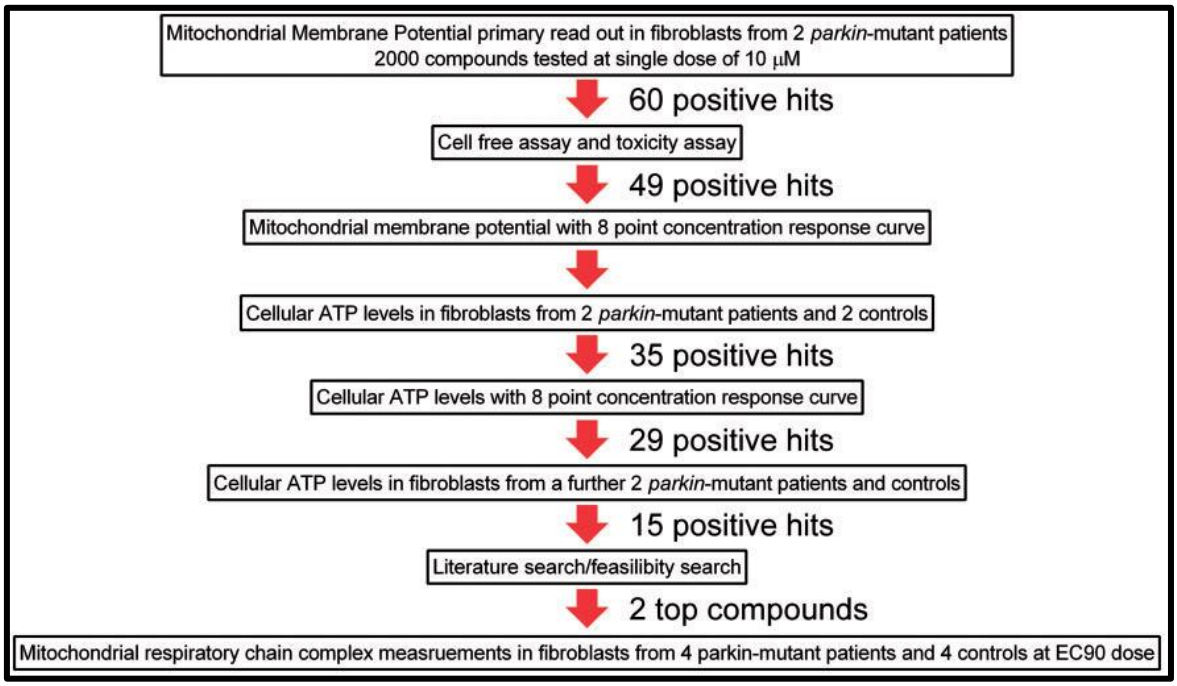


Figure 1: Overview of screening strategy. *Each part of the screen is depicted as is the number of positive hit compounds that were taken to the next stage of the screen (Mortiboys et al, 2013).*

A clear mode of action (MOA), namely activation of the protein kinase Akt with increased phosphorylation at Ser473 was identified for UCA. Subsequent experiments confirmed a similar mitochondrial rescue effect for ursodeoxycholic acid (UDCA) which is chemically closely related to UCA, but – unlike UCA – a licensed drug for human disease (see below). The mitochondrial rescue effect was confirmed in a neuronal model of Parkin deficiency. Others had already reported an Akt-dependent rescue effect of UDCA in a toxin-induced neuronal cell culture model of PD.[13] Impaired function of Akt has been described as the "common denominator" of all forms of PD.[14] Importantly, other groups have independently confirmed the neuroprotective effect of UDCA in the MPTP mouse model and the rotenone rat model of PD.[15, 16] We have also confirmed the beneficial effect of UDCA in LRRK2^{G2019S} transgenic flies.[11] Most recently, we have confirmed its beneficial effect in patient tissue of sporadic PD (unpublished data, see Fig 2).

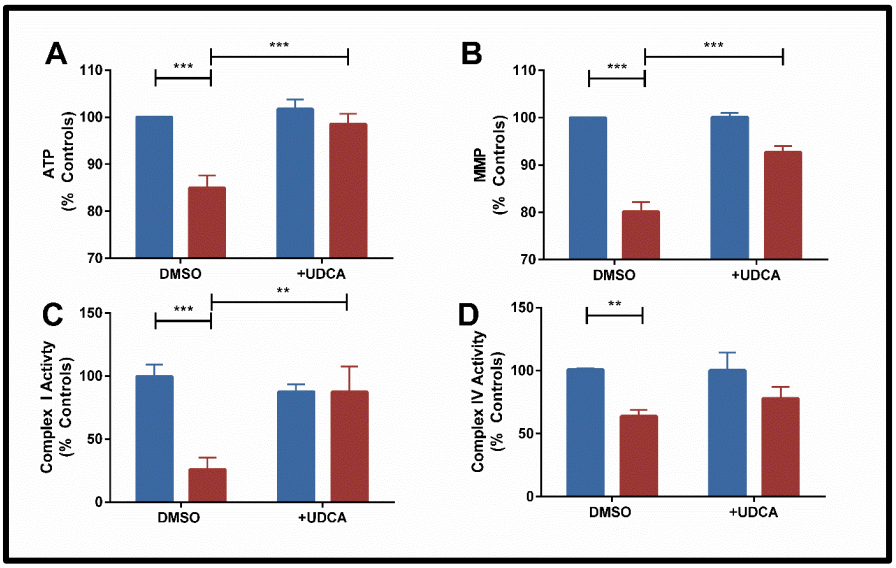


Figure 2: Recovery of mitochondrial deficits after UDCA treatment in sPD patient fibroblasts. *UDCA treatment increases cellular ATP in sPD fibroblasts to 98% of control levels (**A**, *** p < 0.001) and MMP levels to 92% of controls (**B**, *** p < 0.001). Individual respiratory chain measurements found a decrease of 75% in complex I activity in sPD (**C**, *** p < 0.001) and a decrease of 37% in complex IV activity (**D**, ** p < 0.01). Treatment with UDCA increased both complex I (**C**) and complex IV (**D**) activity to 80% of control levels however this was only significant for complex I activity (**C**, ** p < 0.01).*

Pharmacological and safety profile of UDCA

UDCA has been in clinical use for the treatment of primary biliary cholangitis (previously known as primary biliary cirrhosis/PBC) for >30 yr. It is very well tolerated, safe and therefore an ideal candidate for the drug repurposing strategy (see below).

<u>*Basic pharmacological aspects:*</u> UDCA is a naturally occurring bile acid but normally only forms 1-3% of total endogenous human bile acids. When patients with primary biliary cholangitis or healthy volunteers are treated with standard therapeutic doses of UDCA (13-15 mg/kg/day), UDCA may form up to 40% of total bile acids. Intestinal absorption after an oral dose is high with a first-pass clearance of about 50-60%. Plasma levels reach maximum concentrations after 60 minutes after ingestion with another peak at 3 hours.[17] UDCA is rapidly conjugated with glycine and taurine in the liver. In a human adult, the ratio of glycine/taurine conjugates is normally 3:1.[18] UDCA is excreted primarily in the faeces subsequent to initial excretion into the bile.

The biological half-life of exogenously administered UDCA in man is 100h.[19] In its conjugated form, the serum half-life of UDCA is approximately 17 hours.[20]

Animal toxicology: Oral administration of UDCA over 5 weeks in rats produced no mortality at doses up to 4g/kg/day.[17] In longer term studies, oral administration of UDCA (500 mg/kg/day) to rats over 26 weeks produced no demonstrable adverse effects. Liver function tests and morphology in rhesus monkeys were unaffected at oral doses up to 100 mg/kg/day over 26 weeks.[17]

Dosing: UDCA is started gradually and generally given in divided doses. Starting the dose at full dose may precipitate pruritus and loose stools. Treatment should therefore be started at a dose of 250 mg per day with an increase in the dose every 3-4 days until the target dose is reached.[19] Serum concentration 1h after dosing and CSF levels 2 hours after dosing correlate (R^2 – 0.7815), indicating that serum UDCA concentration 1h after dosing explains 78% of the variability in CSF UDCA concentration 2 hours after dosing.[20] The mean CSF concentration of UDCA at 15 mg/kg was 86.69 nmol/L (43.1-165.6), at 30 mg/kg the CSF concentration was 114.22 nmol/L (range 57.2-201.4 nmol/l). The EC90 of UDCA was 100 nM in most of our experiments (but even lower in some), making it plausible that UDCA will exert a beneficial effect at 30 mg/kg.[12]

Drug interactions: According to the summary of product characteristics (SmPC) for UDCA, UDCA should not be administered concomitantly with colestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind UDCA in the intestine and thereby inhibit its absorption and efficacy. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 2 hours before or after UDCA.

UDCA can affect the absorption of ciclosporin from the intestine. UDCA has also been shown to reduce the plasma peak concentrations (C_{max}) and the area under the curve (AUC) of the calcium antagonist nitrendipine in healthy volunteers. An interaction with a reduction of the therapeutic effect of dapsone was also reported. Therefore, patients on ciclosporin, nitrendipine or dapsone will not be included in this trial (https://www.medicines.org.uk/emc/product/145/smpc#INTERACTIONS).

Safety, tolerability and side effects: The most frequently reported adverse effects of UDCA at the standard therapeutic dose of 13-15 mg/kg/day include loose stools (2-9%), headache and mild weight gain, these rarely lead to discontinuation.[21] In 2015, a four-year study by and co-workers

demonstrated that the weight gain in patients treated with UDCA was 2.2 +/- 5.1 kg in the first year of treatment which was significantly greater than the average of 0.6 +/- 6.9% kg (0.6 +/- 4.9 kg) gained in the placebo group (P = 0.04). However, there was no further weight gain in the subsequent three years.[22]

Parry and co-workers assessed the safety and tolerability of UDCA in patients with motor neuron disease (MND) at different doses. A total of 18 patients were included with 7 patients on 15 mg/kg, 4 patients on 30 mg/kg and 7 patients on 50 mg/kg for four weeks. The authors comment that UDCA was well tolerated at all doses. The most common adverse side effects were gastrointestinal in nature; 7 subjects complained of constipation, 5 of loose bowel movements, 1 of nausea and 1 of abdominal bloating. Symptoms were rated as mild by all subjects. No other side effect was seen in more than a single individual and they were equally divided amongst the doses. All patients completed the 4 weeks of treatment. There were no significant differences in the incidence of treatment-emergent events (TEE) between dose groups for constipation, diarrhoea/loose stools or gas/nausea/upset stomach. No abnormal laboratory values were seen during the period of the study.[20] Of note, Parry and co-workers escalated the dose daily through the first week up to the maximum target dose per treatment arm of 15 mg/kg, 30 mg/kg or 50 mg/kg respectively rather than escalating the dose every three days only as recommended by others.[19] It is plausible to assume that a slower dose increase may have led to further reduction of the TEE.

Ratziu and co-workers conducted a 12-month, randomised, double-blind, placebo-controlled trial to evaluate efficacy and safety of UDCA at a dose of 28-35 mg/kg/day in 126 patients with non-alcoholic steatohepatitis (NASH) with 62 patients in the UDCA arm and 64 patients in the placebo arm. There was no difference in the incidence of severe adverse events (AE) or intensity of non-severe AE between the two treatment arms. Most AEs were emergent but mild. Three patients in the UDCA arm required dosage changes compared with none in the placebo arm. The most commonly reported AEs were gastrointestinal but only 2/62 patients in the UDCA arm discontinued the treatment because of diarrhoea and abdominal discomfort.[23] Cullen and co-workers compared low (10 mg/kg), medium (20 mg/kg) and high (30 mg/kg) doses of UDCA in 31 patients with primary sclerosing cholangitis (PSC). Patients were taking UDCA at the respective doses for 2 years. Tolerability of the medication was judged by the patients as satisfactory, good or very good in 100%, 81% and 90% at low, standard and high doses, respectively. Diarrhoea was observed in 2/12 patients (17%) on the low dose of UDCA (10 mg/kg) but only in 1/11 (9%) on the medium dose (20 mg/kg) and 0/10 (0%) in the high dose (30 mg/kg) group.[24] Angulo and co-workers compared low (5-7 mg/kg), standard (13-15 mg/kg) and high (23-25 mg/kg) doses of UDCA in a randomised, double-

blind study of 155 patients with primary biliary cirrhosis over one year. No patient discontinued the study because of side effects or toxicity. Possible drug-related side-effects were observed in 12/52 patients on low dose UDCA (23%), 4/49 patients on standard dose (8%) and 6/54 on high dose (11%). With regards to gastrointestinal side effects it is noteworthy that nausea and vomiting were observed in 4/52 patients on low dose UDCA but only 2 on high dose UDCA. Diarrhoea was noted in 1 patient on low dose UDCA, no patient on standard dose UDCA and 2 patients on high dose UDCA. The authors further commented that none of the possible drug-related side effects can be directly attributed to the drug since they disappeared even with continuation of the treatment.[25]

UDCA repurposing strategy

In Sept 2015, the CURE Parkinson's Linked Clinical Trials (LCT) committee, a group of world leading experts, reviewed ~25 promising drugs already in clinical use for their neuroprotective potential. UDCA was rated as the most promising compound for future neuroprotection trials in PD (personal communication from Dr. Richard Wyse, Scientific Director of CURE PD). Repurposing FDA-approved drugs for a new indication may offer an accelerated, cost-saving pathway for new treatments for patients with neurodegenerative diseases.[26] UDCA and its taurine conjugate taurodeoxycholic acid (TUDCA) have also shown promising results in different in both *in vitro* and *in vivo* models of Alzheimer's disease (AD), stroke and Huntington's disease (HD).[27] Thus, positive results from this study may also open up treatment options for other brain diseases.

6 Objectives and Outcome Measures/Endpoints

The primary aim of this study is to generate clinical data to examine the safety, tolerability and potential effectiveness of 48 weeks exposure to UDCA compared to placebo. A definitive study to determine the neuroprotective effect of UDCA using currently available tools would need to involve several hundred patients and cost several million pounds. The proposed pilot study will determine whether such an expensive study would be safe, feasible and justified. Furthermore, it will determine the usefulness of novel objective readouts (namely the objective sensor-based quantification of motor progression and ^{31}P-MRS/imaging-based *in vivo* quantification of ATP) which may allow a reduction of the sample size (and thus cost) of future trials.

6.1 Objectives

Primary objective:

The primary objective is to compare the safety and tolerability of UDCA at 30 mg/kg in PD compared to placebo as indicated by:

- Number of serious adverse events (SAEs)
- Number of adverse Treatment- reactions
- Number of patients completing the study

Secondary objectives

The secondary objectives are to assess the effect of UDCA compared with placebo on disease progression in PD at 48 weeks (assessed as a change from baseline) by:

- Clinical assessment (using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 motor subscale) in the "OFF" medication state
- *In vivo* parameter estimates of high and low energy metabolite levels (ATP, PCr, Pi) , derived from cranial ^{31}P-MRS centered on the basal ganglia and related motor regions (using ^{31}P MRS at 48 weeks)
- Sensor-based, objective quantification of motor impairment, the OPTOgait and Opals systems (Sheffield patients only) as well as the Dynaport Movemonitor (all patients)

6.2 Exploratory objectives

The exploratory objectives are to compare changes from baseline to week 56 and from week 48 to week 56 between UDCA and placebo trial arms in:

- MDS-UPDRS part 3 motor subscale in the practically defined "OFF" medication state
- MDS-UPDRS rating scale part 1,2,3 and 4 "ON" medication scores
- Levodopa equivalent dose (LED)
- Montreal Cognitive assessment (MoCA)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Non-Motor Symptoms Scale (NMS-QUEST)
- Parkinson's Disease 39 item quality of life questionnaire (PDQ-39)

Additional explorative objectives will be:

Associations between treatment response to UDCA as quantified by changes of MDS-UPDRS/3 "OFF" motor score and:

- predicted disease progression, based on the model developed by Velseboer and colleagues[1]
- energy metabolite levels in brain tissue as quantified by ^{31}P-MRS
- genetic variants associated with PD

7 Trial Design

This is double-blind, randomised, placebo-controlled, multi-centre, parallel group trial in patients with PD who have been diagnosed ≤ 5 years ago. 30 patients will be randomised to UDCA at a dose of 30 mg /kg or matched placebo using a 2:1 split (20 patients on UDCA, 10 on placebo). This will include 48 week exposure period and a subsequent 8 week washout period. Detailed evaluations of all patients will take place at Screening, Baseline, 12, 24, 48 and 56 weeks. The trial medication will be taken at three equal doses per day, to be taken orally with food. The dose will be increased gradually by 250 mg (one capsule) every three days until patient reaches a dose of 30 mg/kg.

The overriding priority for this trial is to provide evidence to support or refute the assumption that UDCA is safe and well tolerated at a dose of 30 mg/kg in patients with PD. In addition, we will explore its potential neuroprotective effect.

Parallel group designs with a washout period have been used previously in the evaluation of potential neuroprotective agents.[28] This design is subject to possible long duration symptomatic effects and even a lengthy washout period cannot necessarily distinguish a true neuroprotective effect from a symptomatic effect (in view of preservation of healthy behaviours with long term impacts such as exercise). However more complex trial designs such as the delayed start design are likely useful only in agents known to have a symptomatic effect and they too can be criticised as being unable to reliably distinguish neuroprotective effects from "cumulative" symptomatic effects. An alternative approach is to adopt a "Long term simple" design, using a composite outcome measure with long term follow up to look for response to potential disease modifying therapies being used in -NET-PD LS-1 Creatine in Parkinson's Disease (www.clinicaltrials.gov). This does not address the urgency of the need to confirm or exclude potential agents for study, and again the long term and substantial investment needed requires robust pilot data of efficacy in advance of this approach. We have considered that an exposure period of 48 weeks is the minimum necessary to

allow clinically detectable differences to emerge between the UDCA and placebo groups. Our trial protocol was informed by the protocols and results of the recent exenatide trials which were led by the co-PI Prof Tom Foltynie.[29, 30] The results of these studies can be considered as a bench mark for all future neuroprotective trials in PD due to the promising (but not definitive) results, since they suggested a possible neuroprotective effect of exenatide on disease progression in PD.

7.1 Outcome measures/endpoints

7.1.1 Primary outcome

The primary outcome is the safety and tolerability of UDCA which will be assessed using the measures listed below. Each of these will be assessed over the study period from start of treatment to week 56 and will be summarised by randomised treatment group:

- The number of SAEs,
- The number of adverse treatment reactions and
- The number of patients completing the study.

In addition to descriptive summaries of the active and placebo treatment groups, the safety and tolerability of UDCA in this study will be compared descriptively with that of the recent randomised, double-blind, placebo-controlled exenatide trial.[29]

7.1.2 Secondary outcomes (at 48 weeks)

The secondary outcomes listed below will be assessed as a change from baseline to week 48.

- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 motor subsection "OFF" medication score
- *In vivo* parameter estimates of high and low energy metabolite levels (ATP, PCr, Pi) , derived from cranial ^{31}P-MRS centered on the basal ganglia and related motor regions
- Sensor-based objective quantification of motor impairment, (Dynaport Movemonitor+ (all patients), OPTOgait and Opals (Sheffield patients only). For further information, see appendix 4.

7.1.3 Exploratory outcomes (at 48 and 56 weeks)

The exploratory outcomes listed below will be assessed as the change from baseline to week 56 and from week 48 to week 56:

- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 motor subsection "OFF" medication score

- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 1,2,3 and 4 "ON" medication scores
- Levodopa equivalent dose (LED)
- Montreal Cognitive assessment (MoCA)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Non-Motor Symptoms Scale (NMS-QUEST)
- Parkinson's Disease 39 item quality of life questionnaire (PDQ-39)

Additional detail about the clinical study outcome measures (including calculation of predicted disease progression) is given in Appendix 2. Additional information about ^{31}P MRS is given in Appendix 3. Additional information about the sensor-based objective quantification of motor impairment is given in Appendix 4.

Exploratory analyses will be undertaken from baseline to week 56 and from week 48 to week 56 to investigate associations between changes to MDS-UPDRS part 3 motor score at the practically defined "OFF" medication state and:

- Predicted disease progression, based on the predictive score developed by Velseboer et al. [1]
- Changes in energy metabolite levels in brain tissue as quantified by ^{31}P-MRS at 48 weeks
- Genetic variants

Additional detail about the genetic analysis and the envisaged storage of serum samples for future research is given in Appendix 5.

8 Study Participants

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

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar disease 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 fulfill all the inclusion criteria and none of the exclusion criteria as defined below.

8.1 Participant Inclusion Criteria

Diagnosis of Parkinson's disease: PD is a clinical diagnosis as defined by the Queen Square Brain Bank critieria (bradykinesia defined as slowness of initiation of voluntary movement with progressive reduction in speed and amplitude on repetitive actions and at least one of the following: Rigidity, 4-6 Hz rest tremor). The diagnosis will have been made by the treating clinician and confirmed by the PI on site after review of the clinical history, examination findings and response to PD medication. The Queen Square brain bank criteria MAY be used to help assist in the diagnosis although this need not be a formal inclusion criteria, and the relevance of a positive family history of PD, or a confirmed genetic basis for an individual's symptoms will be evaluated in the context of other clinical features in determining diagnosis and eligibility.

- Diagnosis of Parkinson's disease ≤ 5 years ago by a clinician with particular expertise in the diagnosis and treatment of movement disorders (typically one of the PIs or their consultant colleagues). The date of the diagnosis will be verified by a review of the medical records.
- Subjective improvement of motor impairment on dopaminergic medication, confirmed by PI through personal examination and/or review of medical records
- Hoehn and Yahr stage ≤ 2.5 in the practically defined "ON" medication state. This implies that all patients will be mobile without assistance during their best "ON" medication periods.
- Ability to take the study drug
- Ability to communicate in English
- Age 18-75 yr. of any gender
- Documented informed consent to participate.
- Able to comply with study protocol and willing to attend necessary study visits

8.2 Participant Exclusion criteria

- Diagnosis or suspicion of other cause of parkinsonism. Patients with clinical features indicating a diagnosis of progressive supranuclear palsy (PSP), multiple systems atrophy (MSA), drug induced-parkinsonism, dystonic tremor or essential tremor will not be recruited.

- Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol/^{31}P-MRS acquisition
- Known claustrophobia or other reasons why patient could not tolerate or be suitable for ^{31}P-MRS
- Current or previous exposure to UDCA
- Current or previous diagnosis of liver disease, in particular PBC judged to be significant by the clinical investigator.
- Prior intracerebral surgical intervention for PD (including deep-brain stimulation). Patients who have previously undergone deep brain stimulation, intracerebral administration of growth factors, gene therapies or cell therapies will not be eligible.
- Already actively participating in a trial of a device, drug or surgical treatment for PD
- History of alcoholism
- Women of child-bearing potential (WOCBP)
- Participants who lack the capacity to give informed consent
- Any medical or psychiatric condition which in the investigator's opinion compromises the potential participant's ability to participate
- Concurrent dementia defined by a score lower than 25 on the Montreal Cognitive assessment (MoCA). Dementia may affect the ability of potential research participants to give informed consent or follow the study protocol.
- Concurrent severe depression defined by a score > 16 on the Montgomery-Asberg Depression Rating Scale (MADRS)
- Serum transaminases more than 2 times upper limit of normal
- PD patients who are on ciclosporin, nitrendipine or dapsone for the treatment of concomitant, general medical conditions
- Participants with previous or current diagnosis of inflammatory bowel disease e.g. ulcerative colitis or Crohn's disease.

9 Recruitment and Retention

9.1 Recruitment

Some patients under the care of the PIs have already expressed an interest in participating in this trial. Neurologists in Yorkshire and Humber (relevant for the STH study site) and London (relevant for the UCLH study site) will be informed when the trial is open to recruitment and provided with details of

eligibility criteria, to allow referral of potential candidates to the clinical trial team.

The NRES approved "lay summary of the trial" will be provided to the Cure Parkinson's Trust, Parkinson's UK and Michael J Fox Foundation (MJFF) Fox Trial website managers, the Sheffield National Institute for Health-Related Research (NIHR)-funded Biomedical Research Facility (BRC) webpage as well as the NIHR Clinical Research Network (CRN) portfolio websites. Contact details for the trial team will be included to allow potentially eligible interested patients to make direct enquiries to the trial team.

Patients who have registered an interest in the study via the websites will contact Sheffield Teaching Hospitals directly. They will then be sent a patient information sheet (PIS) and patient reply slip (which will include patient contact details). The study team may follow up with a phone call to the patient if they have not received the patient reply slip within 2 weeks.

Participant Identification Centres (PICs) will also be set up to aid with study recruitment.

It is anticipated that recruitment of 30 patients will be completed within 6 months.

9.2 Retention

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

Appropriate symptomatic treatment for common side effects of UDCA including nausea and diarrhoea will be made available to patients wishing to participate in the trial. Appropriate medical advice and treatment will be made available to any individuals experiencing adverse events from trial participation.

10 Screening and Consent

10.1 Telephone contact 1 (telephone screening)

Subsequent to the site staff having received a reply slip from the patient indicating their interest to participate in the study (see 9.1), a suitable time and date will be arranged with the respective patient to undergo telephone screening by a member of the research team to check potential eligibility, including a brief review of relevant medical history. The CI/PI will check the screening record made after the telephone screening call. Any patients not deemed eligible to be invited for their screening visit will be contacted by a member of the research team to inform them of this

outcome. Patients deemed eligible will be invited to a screening visit. The date of diagnosis and confirmation of the PD diagnosis and any other uncertainties relating to the inclusion/exclusion criteria will be confirmed subsequent to this telephone screening assessment for those patients who seem eligible but are outside the STH/UCLH geographical area by requesting copies of relevant clinic letters or contacting their PD Clinical Consultants directly. The telephone screening call will be repeated if the patient cannot attend visit 0 (screening visit) within 1-8 weeks to ensure that s/he would still fulfil the telephone screening eligibility criteria.

The telephone screening call will not be undertaken for study participants who are already patients of either site.

10.2 Visit 0: Screening (Time -1 -8 weeks prior to baseline visit)

Patients interested in and potentially eligible for the study will be invited to a local screening clinic appointment. At this visit the research team will answer any further questions, check the patient's eligibility for the study as far as possible and, if the patient wishes to participate in the study, obtain written consent (see 10.2.1). A clinical diagnosis of PD is based on the opinion of the Principal Investigator (PI) after review of the participant's clinical history, examination findings and response to PD medication. The Queen Square brain bank criteria MAY be used to help assist in the diagnosis although this need not be a formal inclusion criteria.

10.2.1 Consent

If the patient is deemed potentially eligible and is willing to participate, written consent will be obtained at the screening visit. The written informed consent process will be undertaken by the PI or by an appropriately trained member of the research team as delegated by the PI. Only suitably qualified doctors will receive informed consent from the participants. Doctors undertaking the consent for this study will be authorised by the PI on the site study delegation log Doctors receiving consent will be trained and competent according to the ethically approved protocol, principles of GCP and the Declaration of Helsinki.

A record of the patient's consent to participate should be documented in the hospital notes along with a filed copy of the completed consent form and participant information sheet (PIS). Written informed consent to enter and be randomised into the trial must be obtained from participants, after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed or any blood is taken for the trial. The only procedures that may be performed in advance of written informed consent being obtained are those that would be

performed on all patients in the same situation as usual standard of care. Patients will be screened using the history of their PD, supported by any available clinical correspondence according to usual standard of care. Informed consent will be obtained prior to collection of formal scales necessary to apply to the Inclusion & Exclusion criteria (see below) and ahead of blood tests (see below).

10.2.2 Screening procedures

The PI (or authorised delegate) will complete the following screening assessments/procedures with the participant:

- Obtaining consent
- Inclusion/Exclusion Review
- Demographic information and medical history:
    - Demographic data regarding PD
    - Past medical history
    - Medication History
    - Family history
    - Previous imaging
    - Previous genetic tests
- Confirmation of potential eligibility
- Confirmation of date for diagnosis of PD by PIs or other experts in movement disorders (this may include review of medical records)
- Concomitant medication
- Physical examination (including assessment of modified Hoehn & Yahr stage), including weight, height and vital signs
- Montreal Cognitive Assessment (MoCA)
- Montgomery-Asberg Depression rating scale (MADRS)
- Confirmation of post-menopausal state
- Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile,
- Serum sample stored (approx. 20 ml, stored at -80^{o})
- ECG
- Provision of physical activity monitor and activity diary

10.2.3 Booking the baseline visit and final confirmation of eligibility

Assuming that the patient fulfils the immediate eligibility criteria, arrangements will be made for the patient to attend a baseline appointment approximately two to four weeks after the screening visit.

This interval enables review of the patient's blood results to confirm final eligibility. If more than eight weeks have elapsed since the screening visit, the screening visit and screening assessments should be repeated before proceeding to the baseline visit.

Patients who consent to the study but who are subsequently found not to meet the study eligibility criteria will be contacted by a member of the research team to inform them that they are not eligible to join the study. If any concerns about the patient's health or well-being are identified from out-of-range blood results or abnormal assessment scores, a member of the research team will inform the patient's GP.

11 Randomisation

Final eligibility must be formally signed off by a medically qualified appropriately delegated member of the study team and must be done prior to randomisation taking place. Following final confirmation of eligibility, randomisation will take place at the baseline visit. Randomisation will be administered using a centralised, web-based system hosted by epiGenesys (a wholly owned subsidiary of the University of Sheffield) on behalf of the University Of Sheffield Clinical Trials Research Unit (CTRU). All participants will be assigned a unique participant ID number at screening that will link all of the clinical information collected for them on the study database, these will be in the format Sxx/nnnn; where xx is a unique number assigned to the site by the Trial Manager and "nnnn" is a unique number starting at 0001 and incrementing by 1. These screening numbers will be provided to both sites by the Trials Manager at the SIV. Once the participant ID number has been entered, the system will supply a randomisation number which will identify the treatment pack to be dispensed. The randomisation system will not reveal the actual treatment; although the system can be used to unblind individual participants in cases of emergency (see section 16). The randomisation will be 2:1 in favour of UDCA. The randomisation system will stratify by site.

12 Site Study Teams

The local PI, supported by an appropriate member of the research team, will monitor participant well-being, record adverse events, titrate and prescribe study medication. Since the 'treating' nurse or doctor will review all blood results and be aware of any reported side effects, a separate member of the research team will act as a blinded assessor, undertaking the MDS-UPDRS and other outcome measures after appropriate training. Ideally the blinded assessor will undertake the MDS-UPDRS Part 3 with the participant in the practically defined "OFF" state, followed by the complete MDS-UPDRS, NMS-QUEST and MADRS once the participant is in the practically defined "ON" state. If necessary for

practical or other reasons, the treating nurse or doctor may also undertake the MADRS and the NMS-QUEST. Efforts should be made to ensure that the same outcome assessor is present at all visits but sites should identify back-up personnel to cover staff absences and avoid cross-over of 'assessing' and 'treating' team members.

13 Visit Schedule

13.1 Baseline (Visit 1)

Patients eligible for the study will attend a further clinic visit where baseline assessments will be performed. Results of blood tests and ECG will be reviewed prior to baseline evaluation to ensure patient eligibility. They will be asked to attend in the practically defined "OFF" state (see glossary/section 4).

The baseline visit will need to be re-arranged for participants attending clinic who have forgotten to omit their regular PD medication.

The following assessments will be undertaken in the practically defined "OFF" state:

- Confirmation of eligibility/inclusion/exclusion review
- Medication review
- Physical examination
- Recording of any AEs
- MDS-UPDRS part 3 (motor examination)
- Sensor-based objective quantification of motor impairment: Dynaport Movemonitor+ (all patients), OPTOgait and Opals (Sheffield patients only). They will be invited to take their PD medication following the assessment. The PI or authorised delegate will record any reported serious adverse events and changes to concomitant medications, including PD medication, enabling subsequent calculation of the levodopa–equivalent dose (LED) by the CTRU. In addition, the predicted disease progression will be calculated, following the model developed by Williams-Gray and co-workers (see also glossary/section 4).[1] The assessor will then complete the following procedures with the participant in the practically defined "ON" stage (typically 30-60 min after patient has taken PD symptomatic medication):

- MDS-UPDRS (parts 1A, 3, 4)
- NMS-Quest

Participants will then be asked to complete the following questionnaires:

- MDS-UPRDS (parts 1B and 2)
- PDQ-39

In addition, the following procedures will be undertaken:

- ^{31}P- MRS (see appendix 3)
- Blood sample for genetic analysis
- Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile)
- Serum sample (approx. 20 ml, stored at -80^{o})
- Provision of patient diary
- Return of physical activity monitor and activity diary

See appendices 2-5 for details on the questionnaires and procedures.

13.1.1 Provision of first medication supply

Participants will be randomised at this visit (as detailed in section 11). The PI or appropriately delegated medically qualified member of the study team will complete and sign a study-specific prescription form for presentation to pharmacy by the participant. The prescription form will detail the baseline medication allocation print-out from the randomisation computer system. The randomisation system will also generate an email to all staff at site registered for a SCRAM account and central staff will receive an email notification with the baseline medication allocation information.

13.1.2 Participant diaries

All participants will be provided with a study-specific diary by their local research team at the baseline visit, in which to record any alterations in the dose of trial medication or concomitant medications taken. The study diary is intended to serve as an aide-memoire so participants will be asked to bring their completed diaries to each study visit to aid Case Report Form (CRF) completion. Participants should be advised to contact the study team promptly should they develop loose stools rather than waiting for the next study visit or scheduled telephone call.

13.2 Visit 2: 12 week follow-up clinic

Participants will attend a clinic visit twelve weeks after the baseline visit, having taken all medications as usual. The PI or authorised delegate will complete the following procedures with the participant in conjunction with study diary review:

- Record any AEs and changes to concomitant medications
- Assess compliance with study treatment and collect any unused medication
- Return of unused medication
- Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile)
- Serum sample (approx. 20 ml, stored at -80^{o})
- Diary review

Provided that there are no contra-indications, the participant will be provided with a further 3 month prescription for the trial medication.

13.3 Visit 3: 24 week follow-up clinic

Participants will attend a clinic visit six months after the baseline visit, having taken all medications as usual. The PI or authorised delegate will complete the following procedures with the participant in conjunction with study diary review:

- Record any AEs and changes to concomitant medications
- ECG
- Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile)
- Serum sample (approx. 20 ml, stored at -80^{o})
- Assess compliance with study treatment and collect any unused medication
- Return of unused medication
- MDS-UPDRS/part 3 motor assessment in the practically defined “ON” stage
- Diary review

Provided that there are no contra-indications, the participant will be provided with a further 3 month prescription for the trial medication.

13.4 Visit 4: 36 week follow-up clinic

Participants will attend a clinic visit thirty six weeks after the baseline visit, having taken all medications as usual. The PI or authorised delegate will complete the following procedures with the participant in conjunction with study diary review:

- Record any AEs and changes to concomitant medications
- Assess compliance with study treatment and collect any unused medication
- Return of unused medication
- Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile)
- Serum sample (approx. 20 ml, stored at -80^{o})
- Diary review

Provided that there are no contra-indications, the participant will be provided with a further 3 month prescription for the trial medication.

13.5 Visit 5: 48 week follow-up clinic

Participants will attend a clinic visit 48 weeks after the baseline visit. They will be asked to attend in the practically defined “OFF” state (see glossary/section 4).

This visit will need to be re-arranged for participants attending clinic who have forgotten to omit their regular PD medication.

The assessor will complete the following procedures with the participant in conjunction with study diary review:

- Record any AEs and changes to concomitant medications
- Assess compliance with study treatment and collect any unused medication
- MDS-UPDRS part 3 in the practically defined “OFF” state
- Sensor-based objective quantification of motor impairment: Dynaport Movemonitor+ (all patietns), OPTOgait and Opals (Sheffield patients only)
- Height and Weight

Participants will then be invited to take their routine PD medication. The assessor will then complete the following procedures with the participant in the practically-defined "ON" state (typically 30 – 60 min later):

- MDS-UPDRS (parts 1A, 3, 4)
- NMS-Quest
- Montreal Cognitive Assessment (MoCA)
- Montgomery Asberg Depression Rating Scale (MADRS)

Participants will also be asked to complete the following questionnaires:

- MDS-UPRDS (parts 1B and 2)
- PDQ-39

In addition, the following procedure will be undertaken:

- Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile)
- Serum sample (approx. 20 ml, stored at -80^{o})
- ^{31}P- MRS (see appendix 3)
- Diary review
- Return of the physical activity monitor and activity diary

13.6 Visit 6: 56 week follow-up clinic

Participants will attend a clinic visit 56 weeks after the baseline visit. They will be asked to attend in the practically defined "OFF" state (see glossary/section 4).

This visit will need to be rearranged for participants attending clinic who have forgotten to omit their regular PD medication.

The PI or authorised delegate will complete the following procedures with the participant in conjunction with diary collection and review:

- Record any AEs and changes to concomitant medications
- Safety bloods (FBC, U&E, LFTs, blood glucose, HBA1C, Lipid profile)
- Serum sample (approx. 20 ml, stored at -80^{o})

- MDS-UPDRS part 3 motor subscale in the practically defined “OFF medication state

Participants will then be invited to take their routine PD medication. The assessor will then complete the following procedures with the participant in the practically-defined “ON” state (typically 30 – 60 min later):

- MDS-UPDRS (parts 1A, 3, 4)
- NMS-Quest
- Montreal Cognitive Assessment (MoCA)
- Montgomery Asberg Depression Rating Scale (MADRS)

Participants will also be asked to complete the following questionnaires:

- MDS-UPRDS (parts 1B and 2)
- PDQ-39
- Diary review
- Diary collection.

For all visits each procedure is undertaken as part of the study protocol and not part of the participant’s standard care.

13.7 Safety Bloods

The choice of safety bloods is based on the selection of safety bloods in previous clinical trials investigating high dose UDCA (23 – 35 mg/kg) in the context of other (hepatic) disorders.[23, 25]

If participants present with symptoms indicative of suspected liver problems at any point during blinded treatment an unscheduled visit should be arranged for repeat LFTs as required.

In the event of raised LFTs (AST/ALT >2X ULN) at any of the study visits, the LFTs should be repeated and the appropriate action undertaken as outlined in the table below:

Observation	Action required	Repeat Observation	Action required
AST/ ALT>3xULN	Repeat sample within 1 week.	AST/ALT>4xULN	Stop study treatment temporarily*.
		AST/ALT>2xULN but ≤4 x ULN	Repeat again within 3 weeks. If remains >2xULN stop study treatment temporarily*.
AST/ALT>2xULN but ≤3xULN	Repeat again within 3 weeks.	AST/ALT>3xULN	Stop study treatment temporarily*.

		AST/ALT>2xULN but ≤3 x ULN	Repeat again within 3 weeks. If remains >2xULN stop study treatment temporarily*.

**In the event that the study treatment is stopped temporarily, the study team will follow participants up with repeat LFTs, frequency of which to be decided on a case by case basis. The study team will discuss each case with the PI/CI and if appropriate the IDMC with a view to re-starting the blinded treatment under close follow up surveillance by unscheduled visits for repeat LFTs, the frequency will be decided on a case by case basis. Participants may only be re-challenged with study treatment if the AST/ALT has returned to <2XULN.*

If participants are agreeable, and it is felt appropriate to re-challenge with study treatment following the discussions outlined above, participants may be re-started on the blinded treatment by dose escalation as outlined in section 14.6 table 2 of the protocol up to the tolerated dose. Participants will be contacted via weekly telephone calls during the dose escalation period. Some or all weekly telephone calls may be replaced by unscheduled clinic visits for repeat LFTs' . This should be decided on a case by case basis.

The re-start of the medication may be conducted via a telephone visit or clinic visit as appropriate. Tablet counts will be undertaken at each unscheduled clinic visit to record compliance checks in the cases where there is a temporary stop to medication or after a re-start to medication. Unscheduled Contact Form must be completed for all unscheduled visits including repeat LFTs and an unscheduled LFT form must be completed where the visit includes LFT reassessment.

13.8 Unscheduled Visits

An unscheduled visit can be conducted for any reason, which may include assessment of adverse events or restart / titration of medication following a temporary stop of medication for any reason. An Unscheduled Contact Form must be completed for all unscheduled visits including repeat LFTs and an unscheduled LFT form must be completed where the visit includes LFT reassessment.

13.9 Telephone contacts

Following consent, there will be 12 telephone contacts throughout the study, weekly after the baseline visit during the dose escalation period and week 8, week 18, week 30, week 42 and week 52. A 4 day window either side of the scheduled dose escalation calls will allow for calls that would

fall on a weekend or bank holidays, to be undertaken within the working week. Participants will be telephoned to discuss any problems encountered with the study medication, adverse events and compliance as well as any changes to their routine medication. Participants will also be contacted via the telephone 2-4 days prior to their baseline visit, visit 5 and visit 6 to remind participants to attend their next visit in the practically defined "OFF" medication state for their next visit.

13.10 Physical Activity Monitoring

At the screening visit, eligible participants will be given the DynaPort Movemonitor (see appendix 4) to wear for 7 days. A text message will be sent to the participants every morning (during normal office hours) to remind them to wear the device. Participants will then be asked to return the sensor in a pre-paid envelope to their local site or return at their baseline visit. A 2nd DynaPort Movemonitor will be posted to participants 2 weeks (+/4 days, to allow for weekends/ bank holidays) prior to their 48 week visit with instructions to wear the sensor for 7 days prior to their next visit. Participants will then be asked to return this at their 48 week visit.

13.11 Visit Schedule Table

Visit Schedule	Screening (-1-8 wks)	2-4 days prior to baseline[c]	Visit 1	T1 – T4 +/- 4 days	T5 +/- 7 days	Visit 2 +/- 7 days	T6 +/- 7 days	Visit 3 +/- 7 days	T7 +/- 7 days	Visit 4 +/- 7 days	T8 +/- 7 days	2 weeks prior visit 5	2-4 days prior to Visit 5[c]	Visit 5 +/- 7 days	T9 +/- 7 days	2-4 days prior to Visit	Visit 6 +/- 7 days
Procedure			**Baseline**	**1-4[a] wks**	**8 wks**	**12 wks**	**18 wks**	**24 wks**	**30 wks**	**36 wks**	**42 wks**			**48 wks**	**52weeks**		**56 wks**
Inclusion/Exclusion Criteria	X		X														
Confirmation of eligibility	X		X														
Informed Consent	X																
Demographics	X																
Medical History	X																
Concomitant Medication Review	X		X			X		X		X				X			X
Physical Examination (including assessment of modified Hoehn & Yahr stage)	X		X														
Vital signs	X																
Height and Weight	X													X			
Telephone calls		X		X	X		X		X		X		X		X	X	
Randomisation			X														
Administer investigational product (Prescription and dispensing)			X			X		X		X							
Adverse event monitoring/evaluation			X			X		X		X				X			X
Compliance Monitoring						X		X		X				X			
Return unused medication						X		X		X				X			

Visit Schedule	Screening (- 1-8 wks)	2-4 days prior to baseline[c]	Visit 1	T1 – T4 +/- 4 days	T5 +/- 7 days	Visit 2 +/- 7 days	T6 +/- 7 days	Visit 3 +/- 7days	T7 +/- 7 days	Visit 4 +/- 7 days	T8 +/- 7 days	2 weeks prior to visit 5	2-4 days prior to Visit 5[c]	Visit 5 +/- 7days	T9 +/-7 days	2-4 days prior to Visit 6 [c]	Visit 6 +/-7days
Procedure			**Baseline**	**1-4[a] wks**	**8 wks**	**12 wks**	**18 wks**	**24 wks**	**30 wks**	**36 wks**	**42 wks**			**48 wks**	**52wks**		**56 wks**
Assessment of PD, Motor-Function and QL Measures:																	
MDS- UPDRS Rating Scale			X					X						X			X
The predicted disease progression calculation (Williams-Gray and co-workers)[d]			X														
Montreal Cognitive Assessment (MoCA)	X													X			X
Montgomery-Asberg Depression Rating Scale (MADRS)	X													X			X
PD Quality of Life Questionnaire 39 (PDQ 39)			X											X			X
NMS-Quest			X											X			X
Sensor based gait assessment			X											X			
Activity monitor provision	X											X[E]					
Safety Assessments:																	
Safety Bloods	X[b]		X[b]			X[b]		X[b]		X[b]				X[b]			X[b]
Safety ECG	X							X									
Research Assessments:																	
Genetic blood sample			X														
^{31}P-MRS			X											X			
Serum sample	X		X			X		X		X				X			X
Other:																	
Diary provision			X														
Diary review						X		X		X				X			X
Diary collection																	X

a. Participants will be contacted via the telephone weekly during the medication titration period.

b. Full blood count, Urea & Electrolytes, liver function tests, blood glucose, hbA1C, lipid profile.

c. Participants will be contacted 2-4 days prior to their baseline, 48 and 56 week visits to remind them to attend these visits in the practically defined "OFF" medication state.

d. See also Glossary/section 4

e. The activity monitor and activity diary will be posted to participants by the local research team 2 weeks (+/- 4 days) prior to their 48 week visit

Unscheduled visits: Participants may be invited to attend for an unscheduled clinic visit at the discretion of the investigator for example to repeat any out of range blood results. For out of range LFTS please refer to section 13.7 of the protocol.

14 Trial Treatments

All Investigational Medical Products will be supplied by PRO.MED.CS Praha a.s in accordance with Good Manufacturing Practice and will be QP released in the European Union (EU) ahead of trial use. Patients will be taught how to take their medication by dose titration by the clinical trial team (see 14.6 below, treatment schedule) and written literature. They will be told about common side effects, and will be advised on the processes for safety reporting as described in section 15 of the protocol.

14.1 Active and comparator treatments

The name of the medicinal product is **Ursonorm**. Each hard capsule contains 250 mg of **ursodeoxycholic acid (UDCA)** as the active ingredient. The excipients are Maize starch, Maize starch, pregelatinised, Silica, colloidal anhydrous (E551), Magnesium stearate (E470b) Gelatin (E441), Titanium dioxide (E171). The comparator is a matched placebo capsule containing Maize Starch, Maize starch pregelatinised, Silica, Colloidal anhydrous, Magnesium stearate. Each dose of placebo-UDCA is supplied in a hard, white gelatine capsule. There are no differences in taste, appearance and smell of the placebo and the investigational medicinal product only.

14.2 Packaging and labelling

The trial treatment and comparator will be presented identically in packs and labelled in accordance with regulatory requirements. The contents (active or placebo) will not be outwardly identifiable. Trial medication will be prepared and labeled by PRO.MED.CS Praha a.s. The medication is supplied in boxes, each box contains 10 blister strips, each blister strip contains 10 capsules therefore each box has 100 capsules. Blister is formed from transparent PVC/PVdC foil and covering aluminium foil. 10 blister strips are supplied in conventional cardboard suitable for its purpose. The text printed on the label will be in accordance with requirements of the local authorities.

14.3 Provision and storage of trial treatments

All Investigational Medical Products will be supplied by PRO.MED.CS Praha a.s in accordance with Good Manufacturing Practice and will be QP released in the European Union ahead of trial use. Trial medication will be provided on a cost-free basis by Pro.Med.CS Praha a.s Trial medication will be delivered to Sheffield Teaching Hospitals Pharmacy department and University College London Pharmacy department by PRO.MED.CS Praha a.sto be administered to participants following the randomisation schedule as part of the study. Trial medication will be stored at room temperature.

14.4 Prescription and dispensing of trial treatment

At the baseline visit, the participant will be allocated their trial treatment by the study staff using the randomisation system. The PI or a medically qualified and appropriately delegated member of the study team will complete and sign all study-specific prescription forms for the study medication, including the participant's study number, name, hospital number and date of birth. The participant will take the prescription form to the Pharmacy department to enable their trial treatment to be given to the participant for the next 12 weeks. Pharmacy will keep a paper record of the trial treatment for the participant. For visits week 12, 24 and 36 the PI or authorised delegate will write a repeat prescription. At week 12, 24 and 36 the Pharmacy staff will check the prescription against the previous randomisation record to ensure the participant receives the correct trial treatment.

14.5 Drug accountability

Site pharmacists will track receipt, allocation and return of trial medication using a study specific system. Original prescriptions and printed records of box allocations will be kept in a file within each site pharmacy. Participants will be asked to return all empty, full or partially used blister strips at each study visit. Compliance of study medication will be assessed by a member of the research team at each visit. Compliance information will also be recorded on the e-CRF. A repeat compliance check will be undertaken by Pharmacy.

14.6 Treatment schedule and supply to participants

Research participants will be asked to start taking a single capsule of trial medication (250 mg UDCA or placebo) the day after their baseline visit. The medication is to be taken with food. The dose will then be increased every three days by a further capsule of the trial medication until the patient reaches an initial final dose of 30 mg/kg of UDCA (rounded to the nearest possible dose as set out in table 1) or placebo. Once the target dose is reached patients will be advised to remain on the maximum dose if tolerated until their 12 week visit and subsequently throughout weeks 12-48.

Patients will be advised to take each capsule at mealtimes and as the number of capsules increases, patients will be advised to split the number of capsules evenly (or as evenly as possible) between breakfast, lunch and tea times. Patients will be provided with detailed information how to gradually increase the UDCA dose. The titration schedule is set out in table 2.

Table 1: *Target dose based on body weight and number of boxes required to cover this dose at baseline and at subsequent dispensing visits*

UDCA/Placebo 30mg/kg 250mg capsules				
Weight	Target dose/day	Target dose: no of 250mg caps/day	Number of boxes to be supplied at Baseline Visit	Number of boxes to be supplied for visits 2, 3 and 4.
Up to 59.99kg	1750mg	7	6 boxes	7 boxes
60kg-64.99kg	1750mg	7	6 boxes	7 boxes
65kg-74.99kg	2000mg	8	7 boxes	8 boxes
75kg – 79.99kg	2250mg	9	8 boxes	9 boxes
80kg – 89.99kg	2500mg	10	8 boxes	10 boxes
90kg +	2750mg	11	9 boxes	10* boxes

** Supply one extra box (11 boxes in total) if planned visit window is >90 days*. Please note due to trial supplies this additional box can only be dispensed on one occasion out of the four dispensing visits. For any unscheduled changes (e.g. sickness) to the visit appointment which take the visit window to >90 days the study team will post an extra box of medication to those patients whose weight is 90kg+.

Table 2: *Titration schedule following baseline visit (day 0). Titration must stop when the relevant maintenance dose for the patients' body weight is reached (indicated in the final column of this table*

Day	Morning	Midday	Evening	Total daily dose	Optimum dose for weight
	Number of UDCA 250mg / placebo capsules				
1-3			1	250mg	
4-6	1		1	500mg	
7-9	1	1	1	750mg	

10-12	1	1	2	1000mg	
13-15	1	2	2	1250mg	
16-18	2	2	2	1500mg	
19-21	2	2	3	1750mg	Up to 64.99 kg
22-24	2	3	3	2000mg	65 kg - 74.99 kg
25-27	3	3	3	2250mg	75 kg – 79.99 kg
28-30	3	3	4	2500mg	80 kg -89.99 kg
31-33	3	4	4	2750mg	90 kg +

Participants will be provided with twelve weeks' supply of study medication at baseline (visit 1), 12 weeks (visit 2), 24 weeks (visit 3) and 36 weeks (visit 4) according to table 1. Participants will be asked to return any unused medication and all empty boxes and blister strips at the next study visit. Participants will be given written advice about how to take the study medication, and its potential side effects. Participants will be reminded to contact the study team promptly should they develop diarrhoea, constipation or any other potential side effects.

14.7 Monitoring of trial treatment safety and tolerability

Side effects and tolerability of trial medication will be reviewed during clinic visits at 12, 24, 36, 48 and 56 weeks. Telephone calls will be made weekly during the titration period (typically first month, see table 1). Further telephone calls will be made at 8, 18, 30, 42 and 52 weeks. Tolerability will be defined as the ability of participants to remain on the allocated treatment. In the case of unwanted side effects, the defined treatment schedule can be altered as outlined below.

14.8 Stopping criteria for permanent discontinuation of trial treatment

The defined stopping criteria for the permanent discontinuation of trial medication are:

- Subjects **MUST** discontinue the investigational product in the event of accelerated disease progression at the opinion of the PI and to be discussed with the CI, which cannot be explained by the natural progression of the disease or by other general medical issues such as intercurrent infection.

- Persistent intolerable gastrointestinal symptoms, in particular diarrhoea even after dose adjustment
- Onset of a clinical condition (in particular primary biliary cholangitis) for which the prescription of UDCA is indicated

14.9 Dose adjustments

Dose adjustments may be made at clinic visits (e.g. in the event of reported unwanted side effects) or at an interim point (e.g. following review of blood results or clinical discussion). In the latter situation, a member of the research team should contact the participant (preferably by telephone but followed by written confirmation) with instructions about any dose change or need to stop trial medication. The trial dose can be reduced to the previous highest tolerable trial dose if trial subjects experience new onset side effects or an intolerable worsening of previous side effects after a dose increase, provided the dose (UDCA or placebo) is equivalent to or higher than 15 mg/kg (standard dose of UDCA for the treatment of PBC).

14.10 Temporary discontinuation of trial treatment

In certain cases where it is clinically deemed necessary to temporarily stop the study medication for any reason, and if participants are agreeable, participants may be re-started on the blinded treatment by dose escalation as outlined in section 14.6 Table 2 of the protocol, up to the tolerated dose. Participants will be contacted via weekly telephone calls during the dose escalation period. Such scenarios will be considered on a case by case basis by the local PI.

The re-start of the medication may be conducted via a telephone visit or clinic visit as appropriate. Tablet counts will be undertaken at each unscheduled clinic visit to record compliance checks in the cases where there is a temporary stop to medication or after a re-start to medication.

Please also refer to section 13.0 of the protocol in the event of blinded treatment being stopped temporarily due to raised LFTs.

14.11 Concomitant Care

The Pharmacy database at Sheffield Teaching Hospitals, the summary of product characteristics for UDCA (https://www.medicines.org.uk/emc/product/145/smpc#INTERACTIONS) and 'Stockley's Drug Interactions' as the standard reference source for drug interactions (http://www.pharmpress.com/product/9780857112705/stockley) were interrogated by the CI, no contraindications regarding concomitant care were identified. However, UDCA can affect the

absorption of ciclosporin from the intestine. UDCA has also been shown to reduce the plasma peak concentrations (C_{max}) and the area under the curve (AUC) of the calcium antagonist nitrendipine in healthy volunteers. An interaction with a reduction of the therapeutic effect of dapsone was also reported. Therefore, patients on ciclosporin, nitrendipine or dapsone will not be included in this trial (https://www.medicines.org.uk/emc/product/145/smpc#INTERACTIONS).

14.12 Permitted Concomitant Medications

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

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

Any UK licensed oral L-dopa treatments, dopamine agonists, monoamine oxidase inhibitors or catechol-O-methyl transferase inhibitors used by patients in the treatment of their PD will be considered concomitant medication.

Adjustment to PD medications will be permitted based on the clinical judgment of the treating neurologist and/or the clinical trial team to optimise PD symptom control throughout the duration of the trial. Doses of PD medication will be recorded at each trial visit and converted to a Levodopa equivalent dose (LED)-see Appendix 1.

14.13 Concomitant Medications to be used with care

Study medication capsules should not be administered concomitantly with colestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind UDCA in the intestine and thereby inhibit its absorption and efficacy. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 2

hours before or after UDCA,
(https://www.medicines.org.uk/emc/product/145/smpc#INTERACTIONS).

15 Pharmacovigilance

15.1 Definitions

An adverse event (AE) is defined as any unfavourable and unintended sign, symptom or illness that develops or worsens during the period of the trial, whether or not it is considered to be related to the trial intervention. AEs include unwanted side effects, injury or intercurrent illnesses and abnormal blood results and may be expected or unexpected. An AE that is considered to have a suspected causal relationship to the trial intervention is defined as an **adverse reaction (AR)**.

An AE is classified as a **Serious Adverse Event (SAE)** if it:

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- or is considered by the investigator to be an important medical event

15.2 Reporting non-serious adverse events

AEs will be recorded by a member of the research team or other member of the research team in the CRF and also in the participant's hospital case notes. AEs should be recorded from the baseline visit until the date the participant completes follow-up or withdraws from the study. AEs may be identified during follow-up visits, telephone contacts or as a result of direct reporting by the participant, non-study clinician or other informant at any time during the study. Multiple symptoms should be recorded as separate events. The PI or authorised delegate is responsible for assessing the relationship between each adverse event and the trial treatment. Completed AE forms will be entered onto the Prospect database by a member of the research team and paper copies filed in the site file. In the event that a participant reports an adverse event necessitating discontinuation of study medication, the local research team should maintain regular telephone follow-up with the participant to monitor resolution of the adverse event.

15.3 Reporting serious adverse events

Any serious adverse events (**SAE),** whether thought to be related to trial treatment or not, must be reported to the sponsor by the local PI or another member of the research team. The SAE form must be sent via email to the sponsor and clinical trial manager on **sth.sae@nhs.net** **and** **sarah.moll2@nhs.net** within 24 hours of the research team becoming aware of it. The CTRU will provide monthly reports to the Trial Management Group and quarterly reports for the Data Monitoring Committee and Sponsor on all reported SAEs. If incomplete information is available at the time of reporting, all appropriate information relating to the SAE should be forwarded to the Sponsor as soon as possible. Completion of the SAE form must include the PI's assessment of causality i.e. whether there is a reasonable causal relationship between the SAE and trial treatment.

In order for the follow up of any SAE to be considered complete the event needs to have a final diagnosis, a causality assessment, and expectedness assessment where the causality is related and either an end date or, in the case of long-term SAEs or SAEs on-going when the study ends, a confirmation that the SAE stable.

The CRTU will report organ system listings of all SAEs to the Data Monitoring Committee (DMC) and Sponsor on a quarterly basis.

15.4 Suspected Unexpected Serious Adverse Reaction

All suspected adverse reactions that are serious,unexpected and related (SUSARs) are subject to expedited reporting.

Current European guidelines require that the individual participant's treatment code be broken by the study Sponsor before a SUSAR is reported to the relevant authorities. In the case of a potential SUSAR, the Sponsor will have the facility to unblind the treatment allocation.

The Sponsor will report any SUSAR which is **fatal or life-threatening** to the Medicines and Healthcare products Regulatory Agency (MHRA) and relevant ethics committee **not later than 7 days** after the Sponsor is first made aware of the reaction. The Sponsor is responsible for forwarding relevant follow-up information to the MHRA and Research Ethics Committee (REC) within an additional eight days.

SUSARs which are **not** fatal or life-threatening will be reported by the Sponsor to the MHRA and relevant REC as soon as possible and not later than 15 days after the Sponsor first becomes aware of

the reaction. The Sponsor will forward follow-up information to the MHRA and REC as soon as possible.

All potential SUSARs will be reported to the DMC as they occur and all events will be followed until resolution. In the event of a potential SUSAR at any participating site, the PIs at all sites will be notified of the event in a blinded manner. There is no routine requirement for the study Sponsor to report SAEs other than SUSARs to the MHRA and REC. However, the Sponsor is obliged to submit an annual safety report (DSUR - Development Safety Update Report) to the MHRA and REC, including listings of all suspected serious adverse reactions. The DSUR will be submitted within 60 days of the anniversary of regulatory approvals.

15.5 Overdose of Trial Medication

Participants will be counselled on the importance of taking the study medications as prescribed. In the event that an overdose of study medication does occur, the participant will contact the local study team as soon as possible to receive appropriate advice. Accidental or deliberate overdose of trial medication will be treated as necessary according to clinical indices and haematological and biochemical parameters. Reintroduction of scheduled trial medication dosing following accidental over-dosage will be according to the best judgment of the investigator to maintain appropriate serum dosage throughout the trial period. All possible measures to reduce the risk of further over-dosage will be implemented.

Participants will be provided with an out of hours contact number but will be advised to attend A&E in the case of an emergency. Any patient taking a deliberate overdose of trial medication will exit from the trial and will be referred for appropriate psychiatric evaluation.

16 Unblinding

Participants will be blinded to treatment allocation throughout the trial, as will the trial management team, investigator site teams and site pharmacy staff. To preserve blinding as far as possible, members of site research teams assigned to undertake the MoCA and UPDRS questionnaires should not be involved in monitoring adverse events or titration of study medication dose. In the event of a potential SUSAR, unblinding will be undertaken by the Sponsor in accordance with the regulatory requirements for safety reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs). Unblinding may also be performed at the request of a senior clinician responsible for the care of a trial participant but such requests are likely to occur only in the case of a serious adverse clinical

event and are expected to be rare. Both sites will have the facility to unblind by either accessing SCRAM or by opening sealed envelopes held securely at each site. The participant's treatment allocation will be reported directly to the relevant clinician according to the agreed procedure outlined in the study specific SOP for unblinding. The CI and CTRU will be kept informed of all instances of unblinding but remain blind to treatment allocations themselves wherever possible.

17 Subject Withdrawal

Participants will normally complete the study after the 56 week follow-up clinic. The trial itself will end on the date that the last participant attends his/her last study visit. A participant may, at any time, withdraw from trial treatment and/or follow-up without giving a reason and without it affecting their relationship with the clinical team, their future treatment or care. Participants that wish to permanently stop the study medication will be invited to continue to attend for the remaining study visits as this will inform intention to treat analysis.

Efforts will be made to replace participants who permanently discontinue treatment during the first twelve weeks of the study, regardless of whether these patients continue to attend for study follow up visits or completely withdraw from the study.

Participants who permanently discontinue treatment or completely withdraw from the study any later (after visit 2), will not be replaced. Participants who completely withdraw from the trial for any reason will be asked to attend the next scheduled study visit to return the remaining study medication and ensure optimal documentation of the reasons leading to withdrawal, in particular possible side effects of the study medication.

17.1 Withdrawal from treatment

Participants may also have their trial treatment permanently discontinued by the PI or authorised delegate for safety reasons, as described in section 14.8. These participants will also be invited to continue to attend for study visits to inform intention to treat analysis. Withdrawal from trial treatment, and the reason, if known, should be clearly documented in the participant's clinical records and reported to the CTU according to the agreed procedure.

17.2 Withdrawal from follow-up

Although all participants will be encouraged to complete study follow-up, participants may withdraw from follow-up at any time without it affecting their care. Participants should be asked to explain

their reason for withdrawing, but are under no obligation to do so. Withdrawal from trial follow-up, and the reason, if known, should be clearly documented in the participant's clinical records and recorded in the eCRF. Data collected prior to withdrawal from follow-up will be included in the study analysis.

17.3 Premature termination of study

In the event that the Trial Steering Committee (TSC), Data Monitoring Committee (DMC) or Sponsor recommends early termination of the study for any reason, the Clinical Trials Manager will notify the REC and MHRA. The PI will be responsible for informing participants of the premature termination of the study.

18 Data Collection

All patient data will be collected by members of the clinical trial team as described in the Delegation log. Clinical trial team members will receive protocol training and will be taught on the use of the PD assessment scales including certification from the MDS on the use of the MDS UPDRS.

Where this data is generated during a study visit it may be recorded as source data either in the medical notes or in the paper CRF. Site staff will then transcribe this data from the source into the eCRF. Source data should not be recorded directly into the eCRF.

Data already available in source notes can be directly transcribed into Prospect, the bespoke clinical data management system (CDMS) used for the capture of electronic Case Report Forms (eCRF). However paper CRFs (proformas) are also provided should this not be feasible or practical. All data will be handled in accordance with the appropriate regulations.

The Case Report Forms (CRFs) will not bear the subject's name. The subject's unique participant ID number will be used for identification.

Case report forms will be designed and produced by the Sheffield CTRU, Chief investigator and trial team. The final version will be approved by the Data Manager, CI, Clinical Trials Manager, Statistician and Sponsor representative. All data entered in the paper CRFs will be entered legibly in black ink with a ball-point pen. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialed and dated by the person making the alteration. Overwriting or use of correction fluid will not be permitted.

Data points to be entered onto the electronic Case Report Form (CRF) from source data include:

- Informed consent
- Trial identification code number
- Demographic data regarding PD
- Past medical history (including documentation of all previous/ ongoing medical problems)
- Medication history
- Family history-including age at onset of all affected relatives
- Clinical examination
- Adverse events
- Predicted disease progression score
- Levodopa Equivalent Dose
- Vital signs-pulse, BP, weight
- Biological specimens collected.

The following data are from standardised tools that have been extensively validated in previous clinical trials. The printed questionnaires completed at each visit will be the source documents which will be filed in the patient research file. Each site will be provided with paper copies of the questionnaires listed below:

- MDS-UPDRS. The MDS-UPDRS training program & exercise are obtainable from:
  - www.movementdisorders.org/updrs/
- NMS-Quest. The NMS-Quest can be obtained from:
  - https://www.movementdisorders.org/MDS/Education/Rating-Scales.htm
- Montgomery-Asberg Depression Rating scale (MADRS) obtainable from:
  - https://psychology-tools.com/montgomery-asberg-depression-rating-scale/
- Montreal Cognitive Assessment (MoCA) obtainable from:
  - https://baynav.bopdhb.govt.nz/media/1127/moca.pdf
- PDQ39 obtainable from; University of Oxford, Health Services Research Unit. https://innovation.ox.ac.uk/outcome-measures/parkinsons-disease-questionnaire-pdq-39-pdq-8/

Prospect will be designed to capture all clinical data to allow for formal statistical analysis.

18.1 Non-Adherence and Non-Retention

The number of tablets successfully self-administered will be estimated at each visit based on directly questioning the patient/ their carer, as well as noting the amount of trial product dispensed at previous

visit, the interval between visits and the number of unused tablets remaining. Reasons for non-adherence to the protocol will be noted in the medical notes and eCRF. Outcome data will continue to be collected on all contactable patients continuing to provide informed consent.

18.2 Data Management

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

All data will be entered remotely on to a centralised database held within the CTRU (Prospect) by a research study member at the study site. Access to Prospect is controlled by usernames and encrypted passwords.

All participants will be assigned a unique participant ID number at screening that will link all of the clinical information held about them on the study database. It will also be used in all correspondence between CTRU and participating centres.

18.3 Access to Data

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature will be used to ensure that users have access to only the minimum amount of data required to complete their tasks.

The study staff at each site will enter data from source documents into the study specific Prospect database when available. After data have been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. No contact details will be entered on the database. All data will be identifiable by participant ID number and no direct identifiers will be transferred from the database to the statistician. All data will be stored and processed in accordance with the General Data Protection Regulation (GDPR).

19 Statistical Considerations

Statistical analysis will be carried out University of Sheffield Statistical Services Unit (SSU) at the end of the study (following last participant's last visit).

19.1 Sample size

The primary outcome of interest for this study is the safety and tolerability of UDCA which will be assessed using the rate of SAEs in both the UDCA and placebo groups, alongside the review of adverse treatment reactions, and study completion. As the study is a pilot it is not powered to compare the SAE rate between the groups statistically, but any SAEs in either group will be presented descriptively, the placebo group providing a baseline against which to view any SAEs in the UDCA group.

Should this small study result in no SAEs then it would be of interest to determine how likely it is that a larger study would find an intolerable rate of SAEs. For this purpose, we will consider the rate of SAEs reported by Aviles-Olmos et al. in their Exenatide trial to be tolerable and acceptable (i.e. 20%) [22]. It is estimated that, in this study, should no SAEs be found in the group receiving UDCA (n=20) then the likelihood that the true SAE rate is less than 20% is 0.990778 (i.e. there is a less than 1% chance that the true SAE rate is intolerable).

19.2 Planned recruitment rate

Over a 6 month recruitment period it is estimated that 5 participants per month will be recruited over two sites until the recruitment target of 30 is reached.

19.3 Statistical analysis plan

A detailed statistical analysis plan (SAP) will be finalised before the database is locked and data is unblinded; the keys points of the analysis are detailed below:

Summary of baseline data and flow of patients

Baseline data will be summarised by random treatment group list. This will include:

- Demographic data such as age and gender
- Baseline characteristics including physical examination
- MDS-UPDRS part 3 motor subsection off medication score
- Predicted disease progression score
- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 1,2,3 and 4 "ON" medication scores
- Levodopa equivalent dose (LED)

- Montreal Cognitive Assessment Score (MoCA)
- Montgomery-Asberg Depression rating scale (MADRS)
- Non-Motor Symptoms Scale (NMS-QUEST)
- Parkinson's Disease 39 item quality of life questionnaire (PDQ-39)
- ^{31}P-MRS parameters of high and low energy metabolites
- Sensor-based objective quantification of motor impairment

The number of patients at each stage of the study, including the number randomised, the number completing the study and details of any drop outs will be summarised by treatment group.

19.3.1 Primary outcome analysis

The primary outcome is safety and tolerability of UDCA which will be assessed by summarising each of the following:

- Serious adverse event rate
- Summary of SAEs
- Summaries of adverse treatment reactions
- Number of patients still taking the study treatment at any dose at the 48 week visit

These measures will be summarised by treatment group and descriptive comparisons will be made. Note that as the study is not powered for a formal analysis no formal analysis of these outcomes will be carried out.

All patients randomised and receiving at least one dose of treatment (UDCA or placebo) will be included in this analysis.

19.3.2 Secondary outcome analysis

The secondary outcome measures are listed below. For each of these the change from baseline to week 48 will be compared between the randomised treatment groups:

- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 motor subsection "OFF" medication score
- *In vivo* parameter estimates of high and low energy metabolite levels (ATP, PCr, Pi) , derived from cranial ^{31}P-MRS centered on the basal ganglia and related motor regions
- Objective quantification of spatio-temporal gait parameters (OPTOgait), postural stability (APDM Opals) and continuous activity monitory (McRoberts Movemonitor+)

For each of the secondary outcomes the change from baseline will be summarised within treatment groups using standard summary statistics (n, mean, standard deviation, median, minimum and maximum). The change from baseline will then be compared between treatment groups using a t-test. If there is an imbalance in baseline characteristics between randomised groups further analysis will be explored within the constraints of the small sample size, this may include an analysis of covariance. Scores will be suitably transformed if necessary. If the distributional assumptions for a t-test are not fulfilled an alternative analysis will be performed. Further details will be given in the SAP and final analysis decisions will be made prior to unblinding of the data.

This study is not powered to show statistically significant differences in the secondary objectives, therefore the interpretation will concentrate on observed trends and confidence intervals for estimated differences. The results will be presented in such a way (effect size estimates, standard errors and confidence intervals) that this data can be used to inform the design of any future study, including the assessment of sample size and power.

These analyses will include all randomised patients (an intention to treat (ITT) analysis population), and patients will be analysed according to their randomised treatment unless it can be shown that any mis-allocation was due to a purely administrative error.

19.3.3 Exploratory outcome analysis

Exploratory outcome measures are listed below, for each of these the change from baseline to week 56 and from week 48 to week 56 weeks will be compared between randomised treatment groups

- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 motor subsection "OFF" medication score
- Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 1,2,3 and 4 "ON" medication scores
- Levodopa equivalent dose (LED)
- Montreal Cognitive Assessment Score (MoCA)
- Non-Motor Symptoms Scale (NMS-QUEST)
- Parkinson's Disease 39 item quality of life questionnaire (PDQ-39)
- Montgomery-Asberg Depression Rating Scale (MADRS)

The change from week 48 to week 56 will be summarised within treatment groups using standard summary statistics (n, mean, standard deviation, median, minimum and maximum). Further analysis

will follow as for the secondary outcomes described previously. These analyses will include all randomised patients (an intention to treat analysis population), and patients will be analysed according to their randomised treatment. For the analysis of the MDS-UPDRS "ON" medication scores an analysis including an adjustment for Levodopa equivalent dose will be investigated.

In addition, exploratory analyses will be undertaken from baseline to week 56 and from week 48 to week 56 to investigate any associations between changes to MDS-UPDRS/part 3 motor score in the practically defined "OFF" medication state and:

- Disease progression score (Velseboer) at baseline
- Changes in energy metabolite levels (ATP, PCr, Pi) in brain tissue as quantified by ^{31}P-MRS
- Genetic variants

This analysis will utilise regression and correlation techniques, including variables for treatment group, centre and other baseline covariates as appropriate.

19.3.4 Subgroup analyses

Subgroup analysis of the primary and secondary endpoints will be undertaken for all those patients who stayed on the target dose of 30 mg/kg for > 24 weeks (>50% of total treatment duration of 48 weeks). The analysis will follow the same analysis plan as described above.

19.3.5 Adjusted analysis

Due to the relatively small sample size and pilot nature of the study it is unlikely that an adjusted analysis will be appropriate, however, as described above if there appears to be a significant imbalance between the randomised groups consideration will be given to adjusting for this in the analysis. Further details will be given in the SAP and final analysis decisions will be made prior to unblinding of the data.

19.3.6 Interim analysis and criteria for the premature termination of the trial

No formal interim analyses are planned. Safety data will be reviewed by the Data Monitoring committee (see section 20.4) who will be able to recommend the premature closing of the trial if safety concerns arise. In addition if the investigators have any safety concerns they are able to request an unscheduled meeting of the DMC.

19.4 Participant population

The study analysis will use a modified intention to treat population whereby patients must have taken at least one dose of trial medication to be included in the analysis.

19.5 Procedure(s) to account for missing or spurious data

If there are noteworthy amounts of missing patient data the reason for this will be investigated, e.g. if there is a missed visit was this because the patient was too ill to attend. Where possible safety data from missed visits will be completed at future visits, e.g. adverse events.

Visit compliance will be summarised and if appropriate described and compared between treatment groups.

Missing clinical assessments (MDS-UPDRS, NMS-QUEST, and PDQ39) will be noted in the interpretation but no attempt will be made to impute any missing data.

20 Data Monitoring and Quality Assurance

Data will be monitored centrally for quality and completeness by the CTRU and every effort will be made to recover incomplete where possible. The CTRU data manager will oversee data tracking and data entry and initiate processes to resolve data queries where necessary. The Sponsor and Trial manager will devise a risk-based monitoring plan specific to the study which will include both central monitoring strategies and study site visits as appropriate.

All trial procedures will be conducted in compliance with the protocol and according to the principles of Good Clinical Practice. Procedures specifically conducted by the CTRU team will be conducted in compliance with CTRU standard operating procedures (SOPs).

20.1 Trial Oversight

The CI will be responsible for the overall running of the trial and for the local conduct of the trial at the STH site. The PI at the UCLH site will be responsible for the conduct of the study at his trial site. The CTRU will organise the web-based randomisation, prepare the database and oversee safety reporting activities.

20.2 Trial Management Group (TMG)

A trial management group (TMG) including the CI, the trial manager, the trial statistician and other personnel relevant to the study (e.g. clinicians, clinical trials pharmacist, CTU data manager, patient and Sponsor representatives) will meet regularly (usually monthly) throughout the duration of the trial to monitor progress, resolve day-to-day problems, oversee development of study documentation, monitor participant recruitment and retention, assess data quality, review budgetary issues, discuss analysis, interpret study findings, draft reports and plan dissemination of results.

20.3 Trial Steering Committee (TSC)

The TSC will oversee the conduct and safety of the trial, ensuring that milestones are achieved and general scientific probity is maintained. The Committee will include an independent chair (Prof Donald Grosset, neurologist), the trial statistician (Ms Rosie Taylor), the CI (Prof Oliver Bandmann), the co-investigator (Prof Tom Foltynie) and a lay representative (Ms Helen Matthews). Terms of reference for the TSC will be agreed before the start of the study and updated from time to time as required. The TSC will meet once before the start of the study (either in person or via Skype or similar) and approximately 3 monthly until completion of the study.

20.4 Data Monitoring Committee (DMC)

An independent DMC will monitor the safety and ethics of the trial by overseeing recruitment, primary outcome data completeness and AEs. Terms of reference will be agreed before the start of the study and updated from time to time as required. The committee will be chaired by Dr Camille Carroll (PD Academic Clinician) and the other member will be Prof John Newell-Price (academic physician at STH/UoS with considerable trial experience). The committee will meet once before the start of the trial and then 6 monthly thereafter. The DMC will typically meet by teleconference, but may also meet face-to-face. The data monitoring committee will be provided with unblinded summaries of safety data (SAEs, AEs, relevant safety labs). The study team will remain blinded and the DMC should not communicate any unblinded information to the study team.

21 Ethics and Regulatory Approvals

21.1 Sponsor

The study Sponsor is Sheffield Teaching Hospitals (STH) although financial oversight will be the responsibility of the University of Sheffield. Selected sponsorship tasks will be formally delegated to the University of Sheffield CTRU according to the collaboration agreement with both parties.

21.2 Research governance

The study will be undertaken at STH and UCLH, subject to appropriate REC approval, local NHS Research & Development confirmation of capacity and capability, HRA approval and a Clinical Trials Authorisation (CTA) issued by the Medicines and Healthcare products Regulatory Agency (MHRA). The trial will be conducted in accordance with the study protocol, the principles of the Declaration of Helsinki, International Conference on Harmonisation of Good Clinical Practice (ICH GCP) and the Medicines for Human Use (Clinical Trials) Regulations, 2004. Any amendments of the protocol will be submitted to the REC and regulatory authority for approval. On request, the CI/PI should make

available relevant trial-related documents for monitoring and audit by the Sponsor, the relevant REC or the MHRA.

21.3 Statement of Indemnity

This is an NHS-sponsored research trial. If an individual suffers negligent harm as a result of participating in the trial, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an ex-gratia payment may be considered in the event of a claim.

22 Publication Policy

The study team will prepare a plain English summary of the study results which will be sent to the study participants as soon as possible after the end of the trial. Results of the study may also be presented at meetings of PD support groups or to other relevant lay audiences.

The Chief Investigator will establish a writing committee comprising co-applicants, relevant members of the trial management group and/or others connected with the trial. The committee will be responsible for establishing authorship rules and preparing scientific reports of the study findings. The study results will be submitted for publication in international, high impact, peer reviewed journals relating to neurology and PD. Names of key collaborators and groups who have contributed to the trial will be clearly stated in all publications. The study findings will be presented at regional, national and international meetings as appropriate.

23 Finance

The trial is funded by a grant from the JP Moulton Charitable Foundation. The University of Sheffield is responsible for managing the study budget.

24 References

1. Velseboer DC, de Bie RM, Wieske L, et al. Development and external validation of a prognostic model in newly diagnosed Parkinson disease. Neurology 2016;86:986-993.

2. Kalia LV, Lang AE. Parkinson's disease. Lancet 2015.

3. Findley LJ, Wood E, Lowin J, Roeder C, Bergman A, Schifflers M. The economic burden of advanced Parkinson's disease: an analysis of a UK patient dataset. J Med Econ 2011;14:130-139.

4. Kordower JH, Olanow CW, Dodiya HB, et al. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. Brain : a journal of neurology 2013;136:2419-2431.

5. Schapira AH, Olanow CW, Greenamyre JT, Bezard E. Slowing of neurodegeneration in Parkinson's disease and Huntington's disease: future therapeutic perspectives. Lancet 2014;384:545-555.

6. Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. The EMBO journal 2012;31:3038-3062.

7. Gasser T. Usefulness of Genetic Testing in PD and PD Trials: A Balanced Review. Journal of Parkinson's disease 2015;5:209-215.

8. Auburger G, Klinkenberg M, Drost J, et al. Primary skin fibroblasts as a model of Parkinson's disease. Molecular neurobiology 2012;46:20-27.

9. Mortiboys H, Johansen KK, Aasly JO, Bandmann O. Mitochondrial impairment in patients with Parkinson disease with the G2019S mutation in LRRK2. Neurology 2010;75:2017-2020.

10. Mortiboys H, Thomas KJ, Koopman WJ, et al. Mitochondrial function and morphology are impaired in parkin-mutant fibroblasts. Annals of neurology 2008;64:555-565.

11. Mortiboys H, Furmston R, Bronstad G, Aasly J, Elliott C, Bandmann O. UDCA exerts beneficial effect on mitochondrial dysfunction in LRRK2(G2019S) carriers and in vivo. Neurology 2015;85:846-852.

12. Mortiboys H, Aasly J, Bandmann O. Ursocholanic acid rescues mitochondrial function in common forms of familial Parkinson's disease. Brain : a journal of neurology 2013;136:3038-3050.

13. Chun HS, Low WC. Ursodeoxycholic acid suppresses mitochondria-dependent programmed cell death induced by sodium nitroprusside in SH-SY5Y cells. Toxicology 2012;292:105-112.

14. Greene LA, Levy O, Malagelada C. Akt as a victim, villain and potential hero in Parkinson's disease pathophysiology and treatment. Cell Mol Neurobiol 2011;31:969-978.

15. Abdelkader NF, Safar MM, Salem HA. Ursodeoxycholic Acid Ameliorates Apoptotic Cascade in the Rotenone Model of Parkinson's Disease: Modulation of Mitochondrial Perturbations. Molecular neurobiology 2016;53:810-817.

16. Castro-Caldas M, Carvalho AN, Rodrigues E, et al. Tauroursodeoxycholic acid prevents MPTP-induced dopaminergic cell death in a mouse model of Parkinson's disease. Molecular neurobiology 2012;46:475-486.

17. Ward A, Brogden RN, Heel RC, Speight TM, Avery GS. Ursodeoxycholic acid: a review of its pharmacological properties and therapeutic efficacy. Drugs 1984;27:95-131.

18. Crosignani A, Setchell KD, Invernizzi P, Larghi A, Rodrigues CM, Podda M. Clinical pharmacokinetics of therapeutic bile acids. Clin Pharmacokinet 1996;30:333-358.

19. Abbas G, Lindor KD. Pharmacological treatment of biliary cirrhosis with ursodeoxycholic acid. Expert opinion on pharmacotherapy 2010;11:387-392.
20. Parry GJ, Rodrigues CM, Aranha MM, et al. Safety, tolerability, and cerebrospinal fluid penetration of ursodeoxycholic Acid in patients with amyotrophic lateral sclerosis. Clinical neuropharmacology 2010;33:17-21
21. Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. Lancet 2015;386:1565-1575.
22. Siegel JL, Jorgensen R, Angulo P, Lindor KD. Treatment with ursodeoxycholic acid is associated with weight gain in patients with primary biliary cirrhosis. J Clin Gastroenterol 2003;37:183-185.
23. Ratziu V, de Ledinghen V, Oberti F, et al. A randomised controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol 2011;54:1011-1019.
24. Cullen SN, Rust C, Fleming K, Edwards C, Beuers U, Chapman RW. High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis is safe and effective. J Hepatol 2008;48:792-800.
25. Angulo P, Dickson ER, Therneau TM, et al. Comparison of three doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis: a randomised trial. J Hepatol 1999;30:830-835.
26. Shineman DW, Alam J, Anderson M, et al. Overcoming obstacles to repurposing for neurodegenerative disease. Ann Clin Transl Neurol 2014;1:512-518.
27. Ackerman HD, Gerhard GS. Bile Acids in Neurodegenerative Disorders. Front Aging Neurosci 2016;8:263.
28. Olanow CW, Schapira AH, LeWitt PA, et al. TCH346 as a neuroprotective drug in Parkinson's disease: a double-blind, randomised, controlled trial. Lancet Neurol 2006;5:1013-1020.
29. Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:1664-1675.
30. Aviles-Olmos I, Dickson J, Kefalopoulou Z, et al. Exenatide and the treatment of patients with Parkinson's disease. The Journal of clinical investigation 2013;123:2730-2736.
31. Chaudhuri KR, Sauerbier A, Rojo JM, et al. The burden of non-motor symptoms in Parkinson's disease using a self-completed non-motor questionnaire: a simple grading system. Parkinsonism & related disorders 2015;21:287-291.
32. Chou KL, Amick MM, Brandt J, et al. A recommended scale for cognitive screening in clinical trials of Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2010;25:2501-2507.
33. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology 2009;73:1738-1745.
34. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Movement disorders : official journal of the Movement Disorder Society 2007;22:1077-1092.
35. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res 1995;4:241-248.

36. Blauwendraat C, Faghri F, Pihlstrom L, et al. NeuroChip, an updated version of the NeuroX genotyping platform to rapidly screen for variants associated with neurological diseases. Neurobiol Aging 2017;57:247 e249-247 e213.

25 Appendices

25.1 Appendix 1 – Conversion Factors

Conversion factors used to convert each of the commonly used PD medications to a Levodopa equivalent dose (LED). The LED is calculated in mg for all drugs listed below, the total daily dose of all Parkinson's disease medication taken by the patient listed below is then added together to calculate the overall total daily LED.

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

25.2 Appendix 2 – Clinical rating scales

- The **MDS-UPDRS** is the standard validated tool for the assessment of patients with PD (Goetz et al., 2008). This scale includes subsections collecting data regarding the impact of PD on a patient's mood and mental state, (UPDRS part 1), their activities of daily living (UPDRS part 2) an examination of the motor features of PD (UPDRS part 3), and complications arising from the use of dopamine replacement (part 4). The MDS-UPDRS/part 3 score has to be ascertained in the practically defined "OFF" (see glossary/section 4) at baseline (visit 1), visit 5 (48 weeks) and visit 6 (56 weeks) to ensure that the obtained motor score reflects the severity of the underlying neurodegenerative disease process which can be partially or completely masked by the effect of the symptomatic Parkinson's disease medication. Assessment in the practically defined "OFF" is standard procedure in all neuroprotection trials for Parkinson's disease.

- The **Non-Motor Symptom Questionnaire (NMSQuest)** is a validated 30-item self-assessment instrument designed to capture the presence of the non-motor features of PD.[31] It generates a score from 0- 30, where a score of under 10 is considered mild, 10-20 moderate and over 20 severe.

- The Montreal Cognitive Assessment **(MoCA)** test is a widely used screening assessment for detecting cognitive impairment. The MoCA test is a one-page 30-point test administered in 30 minutes. It has been validated for PD and is the recommended minimum cognitive screening measure in clinical trials of PD where cognitive performance is not the primary outcome measure. [32] The recommended cut-off when screening for dementia is 24/25, individuals with a MoCA score < 25 at screening will be excluded.[33]

- The **Montgomery and Asberg Depression Rating Scale (MADRS)** is a 10 item physician rated depression severity scale previously used in the assessment of PD. Its usefulness for screening purposes was confirmed by a MDS Task Force.[34] The appropriate cut-off in PD for screening purposes is 14/15; individuals with a MADRS score of > 16 at screening will be excluded.

- The **PDQ39** is a PD-specific health status questionnaire used both clinically and within research since its publication > 20 years ago.[35] It consists of 39 items covering eight discrete dimensions: mobility, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. The scores from each dimension are computed into a scale ranging from 0 (best, i.e. no problem at all) to 100 (worst, i.e. maximum level of problem). In addition a summary score, the PDQ-39SI (summary index) can be calculated by averaging the scores of the eight dimensions.

- The **Prognostic Model** developed by Williams-Gray and co-workers identified the following three parameters as associated with more rapid PD progression: 1. Higher age, 2. Higher UPDRS motor examination axial score (items 27-30), 3. Lower animal naming fluency (participants will be asked to name as many animals as possible in a 1-minute time frame).[1]

25.3 Appendix 3 – 31P MR Spectroscopy (31P-MRS)

^{31}Phosphorus magnetic resonance spectroscopy (31P-MRS) is a non-invasive technique that is experienced by patients in an identical manner to a conventional MRI scan, without requirement for any injection of contrast agent. 31P-MRS is ideally suited to the study of energy metabolism and mitochondrial function because measurement of spectral resonances due to adenosine triphosphate (ATP) and other phosphorylated energy substrates is possible. 31P-MRS will be undertaken in all research participants at baseline, using locally established protocols at 3 Tesla in a clinical-research dedicated multinuclear scanner (Ingenia 3.0T, Philips Healthcare, Best, and NL). Participants will lie supine within a dedicated radiofrequency head-coil, dual-tuned for 1H and 31P capability (Rapid Biomedical GmbH, Rimpar, Germany). Spectroscopic acquisition parameters (flip angle, sampling bandwidth, proton-decoupling parameters etc.) have been optimised and implemented locally (Prof I. Wilkinson). Two-dimensional Chemical Shift Imaging will be used for spectral spatial localisation. From the resulting spectra, estimates of relative beta-ATP, phosphocreatine (PCr) and inorganic phosphate (Pi) levels from nigrostriatal areas will be obtained (Fig. 3). This investigation will be undertaken in Sheffield only. Sheffield participants should ideally have the 31P-MRS on the same day as all other assessments on the respective study visit day but can have the scan up to 1 week before or after visit 1 (baseline visit) and visit 5 (48 weeks). Trial participants otherwise assessed at UCLH will be invited to travel to Sheffield for 31P-MRS up to 1 week before or after visit 1 (baseline visit) and visit 5 but participation is not compulsory. Travel expenses will be covered. Prior to UCLH participants attending Sheffield, a member of the Sheffield Research team will phone the participant to complete the clinical screening form to ensure the participants are suitable for the MRSpectroscopy before travelling to Sheffield.

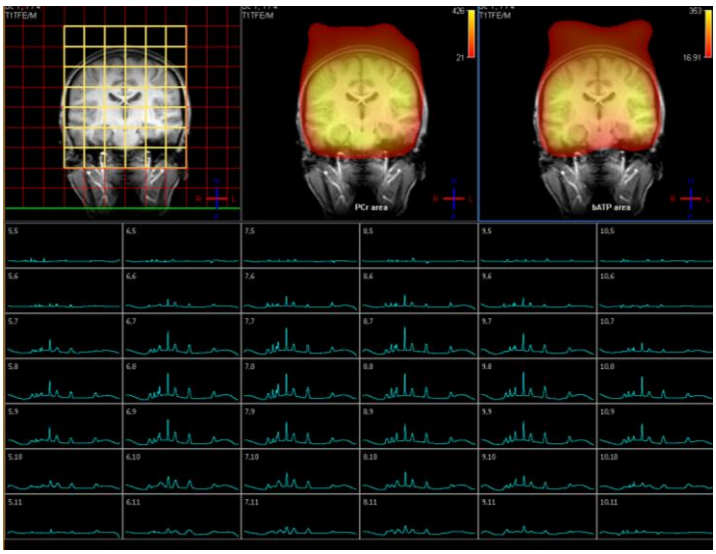


Figure 3: *Example intracranial ^{31}P-MRS recently obtained from a healthy volunteer using the Sheffield 3T multinuclear MR system. A coronal chemical shift imaging (CSI) slice grid is shown overlaid on a proton scout image (top left). Within each phosphorous spectrum (main panel), the main peaks refer to phosphomonesters, inorganic phosphate, phosphocreatine, and the gamma-, alpha- and beta-subpeaks of adenosine triphosphate (ATP). Top middle and top right panels show phosphocreatine and beta-adenosine triphosphate quantitative heat maps, respectively.*

25.4 Appendix 4 – Sensor-based objective quantification of motor impairment

For at-home physical activity monitoring (all patients), we will use the DynaPort Movemonitor+ (McRoberts, The Hague, the Netherlands). It is a light physical activity monitor (PAM) containing a triaxial accelerometer, gyroscope, a digital memory card and a battery. According to the manufacturer guidelines, the device will be placed on the lower back using an elastic belt. The subjects will be asked to wear the PAM for 7 consecutive days and remove it only during swimming or bathing. The BRC Clinical Trials team will provide telephone support during the assessment period. The PAMs are safe to use. They are commercially available CE marked devices. The participant will be asked to maintain daily activity diary and not to alter their normal weekly routine. In addition, a text message will be sent to them every morning (during normal office hours) to remind them to wear the device. After seven days, the subject will return to the local research team, data from the device will be stored in a computer for further analysis and the PAM will be collected back. This will provide data on the participants gait and movement in the home environment to provide a measure of their gait in a "natural" setting (see Figure 3).

Figure 3 *- The picture above shows the patient activity monitor to be worn by study participants*

For clinic-based gait analysis, all participants (Sheffield and London) will complete three gait tasks while wearing the Dynaport Movemonitor+: Timed-Up and Go test, self-selected preferred speed walking test and self-selected fast speed walking test. For research participants recruited at Sheffield, the gait analysis will additionally involve using the OPTOgait 5m system of photoelectric bars (Microgate S.r.l, Italy) and the Opals triaxial inertial sensors (APDM Inc.). This will assess participant mobility in a controlled setting compared with their at-home monitoring.

The OPTOgait (http://www.algeos.com/OPTOgait_5_metre_kit.html) is a system of floor mounted bars embedded with LED sensors one of which emits an infrared signal which is detected by the other sensor. During walking, these signals are broken by the movement of the research subject's feet. When placed in a two-dimensional configuration it creates a 10m long walkway with a 4m x 1m assessment area to measure spatiotemporal gait parameters. This system has a spatial resolution of

1cm and a temporal resolution of milliseconds. It captures information on 25 spatio-temporal gait characteristics such as stride and step length, stride width and stance time. It records all of these data automatically for offline storage and analysis (see Figure 4).

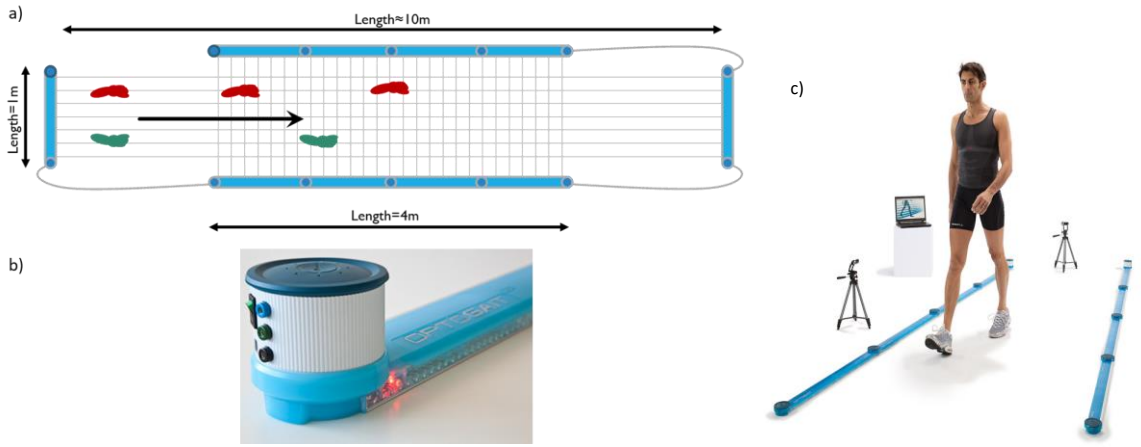


Figure 4 *– a) The layout of the OPTOgait system in a 2D configuration b) LEDs embedded in an OPTOgait bar c) A man walking through the OPTOgait 5m system.*

The Opals system will also be used to monitor truncal sway during walking. This consists of body worn sensors (attached with Velcro scrap) at the lower back, both ankles, lower neck and forehead. The sensors are small (around 3cm by 3cm) and not onerous to wear. The sensors contain an accelerometer, gyroscope and magnetometer. Data is collected in real time wirelessly and captured on the study laptop (see Figure 5).

Figure 5 *– A man wearing the small Opal sensors which are worn by study participants during the gait analysis.*

25.5 Appendix 5 - Genetic analysis and serum sample for storage

EDTA blood will be taken for DNA extraction and stored at 80^{-} at the STH or UCLH CRFs. The frozen EDTA blood sample will then be transferred on dry ice in batches (typically 5-10 samples) to SITraN. At SITraN, DNA will be extracted using a high yield phenol-chloroform based system. The DNA samples will be anonymised and then sent in one batch on dry ice to the laboratory of Dr A Singleton (National Institute of Health, Bethesda, USA) for analysis on the NeuroChip.[36] The NeuroChip is a low-cost, custom-designed array containing a tagging variant backbone of about 306,670 variants complemented with a manually curated custom content comprised of 179,467 variants implicated in neurodegenerative diseases. The analysis will be undertaken as part of a scientific collaboration with Dr Singleton.

Additional serum samples for storage will be taken at screening, visit 1, 2, 3, 4, 5 and 6 and stored at 80^{-} at both sites. All serum samples will be transferred to SITraN in batches (typically 5-10 samples) on dry ice. It is envisaged that these additional serum samples may be of use for future analyses such as wet biomarker studies. However, these samples would only be used for such future studies subsequent to a successful application to the regulatory authorities as appropriate.