Clinical trial results:
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)

Summary

EudraCT number	2018-001887-46
Trial protocol	GB
Global end of trial date	09 November 2020

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	STH18493

Additional study identifiers

ISRCTN number	ISRCTN73371260
ClinicalTrials.gov id (NCT number)	NCT03840005
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sheffield Teaching Hospitals NHS Foundation Trust
Sponsor organisation address	Trust Headquarters of 8 Beech Hill Road, Sheffield, United Kingdom, S10 2SB
Public contact	Dr Dipak Patel, Sheffield Teaching Hospitals NHS Foundation Trust, sth.ResearchAdministration@nhs.net
Scientific contact	Dr Dipak Patel, Sheffield Teaching Hospitals NHS Foundation Trust, sth.ResearchAdministration@nhs.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

There are small risks associated with needle injections. For most people, needle injections do not cause serious problems, however some people experience a small amount of swelling, bleeding or pain at the needle site or some people may feel faint. On very rare occasions infection may occur. Only trained individuals were permitted to take blood samples.
If the team detected any relevant genetic changes in blood they would discuss them with the patient and offer a referral to colleagues in Clinical Genetics so that the patient/family members may be formally tested if required. Any results from the genetic testing would first be received by the Chief Investigator at Sheffield and for participants recruited at UCLH the results would be passed onto Professor Foltynie.

Sometimes people can feel claustrophobic, breathless or generally unwell in the MRI scanner, but patients had a buzzer which they could press at any time to be let out for any reason. There is a small chance that having a scan could result in finding an unexpected abnormality which was causing no major symptoms, for example, an aneurysm or small tumour. If this were to occur, deciding what to do about the abnormality could be difficult. In these circumstances, the patient would be informed of the abnormality and referred on to the relevant specialist for further assessment and discussion of treatment options. Patients asked to consider carefully this potential risk before they decided whether they wished to take part in this study.

The gait analysis equipment is manufactured and CE marked to standards for a medical device.

The study team were happy to discuss the results of the depression and memory questionnaires with patients and provide further support, if required.

Background therapy:

NA

Evidence for comparator:

NA, this is a placebo controlled trial

Actual start date of recruitment	07 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	31
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

30 participants with Parkinson's Disease to be recruited and receive either Ursodeoxycholic Acid (UCDA) or placebo for 12 months, across 2 UK sites (Sheffield and London).

Pre-assignment

Screening details:

Screening of potentially eligible participants was performed over the telephone, where diagnosis, medical history, medications and other relevant inclusion and exclusion criteria were checked (where possible over the telephone) by a member of the study team. If patient deemed eligible then invited for a full screening visit in person.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

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.

Arms

Are arms mutually exclusive?	Yes
Arm title	UDCA

Arm description:

Patients with PD who have been diagnosed ≤ 3 years ago. 20 patients will be randomised to UDCA at a dose of 30 mg /kg . 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.

Arm type	Experimental
Investigational medicinal product name	Ursodeoxycholic Acid
Investigational medicinal product code	PL 12762/0515
Other name	UDCA, Ursonorm
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Research participants will be asked to start taking a single capsule of trial medication (250 mg UDCA) 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). Once the target dose is reached patients advised to remain on the maximum dose if tolerated until their 12 week visit and subsequently throughout weeks 12-48.

Arm title	Placebo

Arm description:

Patients with PD who have been diagnosed ≤ 3 years ago. 10 patients will be randomised to 30 mg /kg matched 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.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	NA
Other name	NA
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Research participants will be asked to start taking a single capsule of trial medication (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 placebo. Once the target dose is reached patients advised to remain on the maximum dose if tolerated until their 12 week visit and subsequently throughout weeks 12-48.

Number of subjects in period 1	UDCA	Placebo
Started	20	11
Randomised	20	11
Withdrawn from treatment	2 [1]	1 [2]
Completed study	18	10
Completed	18	10
Not completed	2	1
Consent withdrawn by subject	2	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: In the UDCA arm there were 20 patients randomised, 20 patients with a full dataset, 18 that completed the study treatment and 2 withdrawn from treatment

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: In the Placebo arm there were 11 patients randomised, 11 patients with a full dataset, 10 that completed the study treatment and 1 withdrawn from treatment

Baseline characteristics

Reporting groups	
Reporting group title	UDCA

Reporting group description:

Patients with PD who have been diagnosed ≤ 3 years ago. 20 patients will be randomised to UDCA at a dose of 30 mg /kg . 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.

Reporting group title	Placebo

Reporting group description:

Patients with PD who have been diagnosed ≤ 3 years ago. 10 patients will be randomised to 30 mg /kg matched 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.

Reporting group values	UDCA	Placebo	Total
Number of subjects	20	11	31
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	56.3	61.9	
standard deviation	± 7.61	± 8.28	-
Gender categorical Units: Subjects			
Female	6	6	12
Male	14	5	19

End points

End points reporting groups

Reporting group title	UDCA

Reporting group description:

Patients with PD who have been diagnosed ≤ 3 years ago. 20 patients will be randomised to UDCA at a dose of 30 mg /kg . 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.

Reporting group title	Placebo

Reporting group description:

Patients with PD who have been diagnosed ≤ 3 years ago. 10 patients will be randomised to 30 mg /kg matched 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.

Primary: The number of Serious Adverse Events (SAEs)

End point title	The number of Serious Adverse Events (SAEs)[1]

End point description:

The primary outcome of the study is safety and tolerability of UDCA which is a assessed using the number of observed SAEs.

End point type	Primary

End point timeframe:

from randomisation to week 56.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: there is no appropriate statistical analysis for these primary endpoints.

End point values	UDCA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: number	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: The number of Adverse Treatment Reactions

End point title	The number of Adverse Treatment Reactions[2]

End point description:

The primary outcome of the study is safety and tolerability of UDCA which is a assessed using the number of observed ATRs.

End point type	Primary

End point timeframe:

from randomisation to week 56.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: there is no appropriate statistical analysis for these primary endpoints.

End point values	UDCA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: number	10	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients still taking the study treatment at any dose at the 48 week visit

End point title	Number of patients still taking the study treatment at any dose at the 48 week visit[3]

End point description:

The primary outcome of the study is safety and tolerability of UDCA which is a assessed using the number of patients till taking the study treatment at any dose at the 48 week visit

End point type	Primary

End point timeframe:

from randomisation to week 48.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: there is no appropriate statistical analysis for these primary endpoints.

End point values	UDCA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: number	18	10		

Statistical analyses

No statistical analyses for this end point

Secondary: The change from baseline to week 48 in Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part 3 motor subsection “OFF” medication score

End point title	The change from baseline to week 48 in Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part 3 motor subsection “OFF” medication score

End point description:

The change from baseline to week 48 (planned end of treatment) in MDS-UPDRS part 3 score to be compared between treatment groups

End point type	Secondary

End point timeframe:
from randomisation to week 48.

End point values	UDCA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	11		
Units: score				
number (not applicable)	-1.68	-5.2		

Statistical analyses

Statistical analysis title	comparison of change in MDS-UPDRS from baseline to
Statistical analysis description: Analysis specification is pre-specified with 19 in UDCA arm and 10 in placebo arm	
Comparison groups	UDCA v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1844
Method	t-test, 2-sided
Parameter estimate	Median difference (net)
Point estimate	3.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	8.86
Variability estimate	Standard error of the mean
Dispersion value	2.55

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs 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 or clinician.

Adverse event reporting additional description:

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	UDCA

Reporting group description:

Patients with PD who have been diagnosed ≤ 3 years ago. 20 patients will be randomised to UDCA at a dose of 30 mg /kg . 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.

Reporting group title	Placebo

Reporting group description:

Patients with PD who have been diagnosed ≤ 3 years ago. 10 patients will be randomised to 30 mg /kg matched 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.

Serious adverse events	UDCA	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	UDCA	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	8 / 11 (72.73%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
General physical health deterioration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Pain			

subjects affected / exposed	1 / 20 (5.00%)	3 / 11 (27.27%)	
occurrences (all)	1	3	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Stress			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Fall			

subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Product use complaint			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dyskinesia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	2	
Loss of consciousness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Parkinson's disease			

subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Syncope			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	2	2	
Dry mouth			

subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	4 / 20 (20.00%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
Salivary hypersecretion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Ligament operation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	2	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Periarthritis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			

Abnormal loss of weight subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 11 (0.00%) 0	
Vitamin B12 deficiency subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 11 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2019	The IDMC advised that it would be helpful for the protocol to contain further instructions in the event of raised LFTs and when these should be repeated. The re-start of the medication may be conducted via a telephone visit or clinic visit as appropriate. Stopping criteria for permanent discontinuation of trial treatment updated. Temporary Discontinuation of trial treatment updated. Include a further exclusion criterion as follows: 'participants with previous or current diagnosis of inflammatory bowel disease e.g. ulcerative colitis or Crohn's disease'. To ask participants who permanently stop their study medication to continue to attend for the remaining study visits as the data collected at these visits will inform decision to treat analysis. 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'. Protocol updated to remove the 'slow speed test' as this will no longer be undertaken. Participants to be advised not to eat too much protein prior to attending their OFF state visits. updated the participant information sheet To state that regular newsletters will be available at clinic visits so that participants are kept up to date with how the study progresses.
06 March 2019	To open Participant Identification Centres (PICs) at Doncaster and Bassetlaw Teaching Hospitals; Barnsley Hospital NHS Foundation Trust; The Rotherham NHS Foundation Trust; Chesterfield Royal Hospital. To provide a study specific flyer to the local teams at each PIC to hand to potentially eligible participants and again asking these participants to contact the central team at Sheffield Teaching Hospitals, so that the central team can send these participants an invite letter, PIS and reply slip. To amend study team details. Updated the flow chart on P16 to state that the 'wash-out' phase is between week 48 and week 56 and not before week 48. We have clarified that for any unscheduled clinic visits a tablet count will be undertaken to ensure compliance data is captured where there is a temporary stop to medication or after a re-start to medication. Unblinding has been updated to state that members of the local research team who undertake the MoCA and UPDRS questionnaires should not be involved in the monitoring of adverse events. The participant information sheet has been updated to ask participants to wear sensible shoes for the gait analysis tests.

21 June 2019	To ask participants attending UCLH to wear a physical activity monitor (Dynaport Movemonitor+, McRoberts, Netherlands) to undertake gait analysis tests at their clinic baseline visit and week 48. To add an additional exploratory outcome measure to the protocol to assess 'the change from baseline to week 56 between the randomised treatment groups' as this will enable the statistician to analyse this timeline taking into account 8 weeks off study treatment. The updated protocol includes reference to unscheduled visits for reasons other than raised LFTs or temporary stop of medication as participants may be invited to attend unscheduled visits for other reasons e.g. raised potassium levels to be repeated. To amend one of the inclusion criteria 'diagnosis of Parkinson's disease <3 years to <5 years. The Physical Activity diary has been amended to state that the physical activity monitor will be set to record the participant's movements from 12 am rather than 5 am and that participants can either chose to return the activity monitor at their next appointment or using the pre-paid envelope.
15 January 2020	Increased the telephone contact call windows that currently have a +/- 2 day limitation to +/-4 days to allow for weekends and bank holidays. Posting out Sensors prior to week 48 visit. Substantial amendment 03 for this study was submitted to MHRA/NRES/HRA in June 2019. SA03 included the amendment of one of the inclusion criteria 'diagnosis of Parkinson's disease <3 years to <5 years". To ensure the GP Notification Alert Letter is consistent with the above change, the study team have now updated the diagnosis period from "within the past 3 years" to "within the past 5 years". To include: newsletter to be distributed via email, post and relevant websites by the local research team. To include data may be required from the UP study for use in future studies, where relevant. This data would help to develop future algorithms for data analysis. The recruitment end date for this study was 30/09/2019, however as per the protocol (version 4.1 22 Aug 2019) any participant withdrawing prior to Week 12 will be replaced. We therefore may replace participants between 30th September and 31st December 2019. The study team wish to thank participants upon completion of the study, to thank them for their time and participation. The study team will also inform the participants that the study team will update them with the progress of the study and inform them of the outcome of the study as soon as the study teams are able.
20 May 2020	To change from postal consent to verbal consent and do not intend to provide information to participants ahead of the phone call. Due to the impact of COVID-19 face to face appointments for the study have changed to virtual visits either by telephone or utilising video conferencing facilities. Due to these changes, participants are posted a sensor to wear for 7 days prior to visit 5 and are also posted questionnaires to complete for visit 5 and visit 6. Therefore to not overburden participants further with an additional cover letter and consent form relating to the gait data, we propose that during the telephone call visits we seek verbal consent from the participant that they are willing for their gait data to be used for future research. To telephone participants who are not due a virtual clinic visit to seek verbal consent from the participant that their gait data can be used for future research.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

NA

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32759251