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Trial of ursodeoxycholic acid for Parkinson's disease

Submission date
20/11/2018

Recruitment status
No longer recruiting

Registration date
26/11/2018

Overall study status
Completed

Last Edited
13/10/2023

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
This proposal addresses the urgent need for disease modifying drugs in Parkinson's disease (PD), the second most common neurodegenerative condition after Alzheimer's disease.

The aim of this proposal is to explore the potential of UDCA in a randomised, double-blind, placebo-controlled, "proof of concept" study. The primary objective will be to determine its safety and tolerability in PD. We will also use clinical motor rating (MDS-UPDRS/III) as the standard clinical assessment tool to quantify the effect on disease progression.

We will also explore the effect of UDCA on other clinically relevant parameters such as memory impairment and other non-motor symptoms.

Participants will be allocated at random to receive either UDCA or placebo 30 mg/kg daily.

Participants will start by just taking one capsule per day for the first three days. The dose will then be further increased by one capsule every three days until the final dose is reached. This final dose/number of capsules will depend on body weight. Participants will typically reach the final dose within four weeks of the baseline visit and asked to stay on this dose for the subsequent 44 weeks so participants will be taking trial medication for a total of 48 weeks.

At three study visits (baseline visit/visit 1, visit 5 and visit 6), the key assessments need to be conducted in the absence of regular PD medication. This is so that the assessors are able to get a true picture of the disease without it being masked by the participant's medication.

Additional procedures for this study include MR spectroscopy; Gait Analysis; provision of a sensor (to gather data on how people walk and move in their natural home environment), blood tests and ECGs.

Background and study aims
This study aims to address the urgent need for disease modifying drugs in Parkinson's disease (PD), the second most common neurodegenerative condition after Alzheimer's disease. The researchers want to assess the safety and tolerability of a drug called ursodeoxycholic acid (UDCA) in PD. There is strong evidence that UDCA rescues the function of the mitochondria (the

“powerhouse” of the cell) in PD patient tissue and other models of PD. This suggests that UDCA may slow down the worsening of PD. UDCA has been in clinical use for the treatment of liver disease (primary biliary cholangitis) for over 30 years. It is known to be safe and well tolerated in patients with liver disease but it is not yet known whether this is also the case in patients with PD. Furthermore, the dose used for patients with liver disease (15 mg/kg) is not high enough for UDCA to get into the brain. The dose needs to be doubled to 30 mg/kg. This higher dose was also safe in clinical trials for liver disease, but is currently not used routinely in clinical practice. The aim of this study is to explore the potential of UDCA to slow down the progression of PD.

Who can participate?
Patients aged 18-75 who have been diagnosed with PD within the past 3 years

What does the study involve?
Participants are randomly allocated to take either UDCA 30 mg/kg or placebo (dummy drug) daily. Participants start by just taking one capsule per day for the first three days. The dose is then further increased by one capsule every three days until the final dose is reached. This final dose/number of capsules depends on body weight. Participants typically reach the final dose within 4 weeks of the first visit and are asked to stay on this dose for the subsequent 44 weeks so participants take the medication for a total of 48 weeks. At three study visits (baseline visit /visit 1, visit 5 and visit 6), the key assessments need to be conducted in the absence of regular PD medication. This is so that the assessors are able to get a true picture of the disease without it being masked by the participant's medication. Additional procedures for this study include MR spectroscopy, gait analysis, provision of a sensor (to gather data on how people walk and move in their natural home environment), blood tests and ECGs.

What are the possible benefits and risks of participating?
This study will not be of any direct benefit to the participants who take part. However, this study could help to identify mechanisms to slow down the progression of Parkinson's disease in the future. The possible risks of taking part are as follows:
Blood samples: 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. If any relevant genetic changes are detected in the blood the participant will be offered a referral so that they can be formally tested if required. ECG: Rarely, a reaction to the electrode adhesive may cause redness or swelling where the patches were placed. MRS scans: Sometimes people can feel claustrophobic, breathless or generally unwell in the scanner, but they will have a buzzer which they can 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, participants would be informed of the abnormality and referred on to the relevant specialist for further assessment and discussion of treatment options. They should consider carefully this potential risk before you decide whether they wish to take part in this study. All gait analysis techniques are safe and non-invasive and no risks are expected. The gait analysis equipment is manufactured and CE marked to standards for a medical device. The study team will be happy to discuss the results of the depression and memory questionnaires and provide further support if required.

Where is the study run from?
The study is running from two sites; the Royal Hallamshire Hospital in Sheffield, which will be the lead centre, and the University College London Hospital in London (UK)

When is the study starting and how long is it expected to run for?
April 2018 to November 2020

Who is funding the study?
J P Moulton Charitable Foundation

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2018-001887-46

ClinicalTrials.gov (NCT)

NCT03840005

Protocol serial number
39616

Study information

Scientific Title
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

Acronym
The UP study

Study objectives
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 31P-MRS/imaging-based in vivo quantification of ATP) which may allow a reduction of the sample size (and thus cost) of future trials.

Ethics approval required
Old ethics approval format

Ethics approval(s)
East of England – Cambridgeshire and Hertfordshire Research Ethics Committee, 08/11/2018, ref: 18/EE/0280

Study design
Randomised; Both; Design type: Treatment, Drug, Genetic epidemiology

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Parkinson's disease

Interventions
Participants will be allocated at random in a 2:1 ratio to receive either ursodeoxycholic acid (UDCA) or a placebo.
Participants will start by just taking one capsule per day for the first 3 days, with a dosage of 30 mg/kg per capsule. The dose will then be further increased by one capsule every 3 days until the final dose is reached. This final dose/number of capsules will depend on body weight.
Participants will typically reach the final dose within 4 weeks of the baseline visit and asked to

stay on this dose for the subsequent 44 weeks, therefore participants will be taking trial medication for a total of 48 weeks.
At three study visits (baseline visit/visit 1, visit 5 and visit 6), the key assessments need to be conducted in the absence of regular PD medication. This is so that the assessors are able to get a true picture of the disease without it being masked by the participant's medication.
Additional procedures for this study include MR spectroscopy; Gait Analysis; provision of a sensor (to gather data on how people walk and move in their natural home environment), blood tests and ECGs.

Visit 0: Screening (Time -1 – 8 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. 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.

Screening procedures
The PI (or authorised delegate) will complete the following screening assessments/procedures with the participant:
1. Obtaining consent
2. Inclusion/exclusion review
3. Demographic information and medical history:
4. Demographic data regarding PD
5. Past medical history
6. Medication history
7. Family history
8. Previous imaging
9. Previous genetic tests
10. Confirmation of potential eligibility
11. Confirmation of date for diagnosis of PD by PIs or other experts in movement disorders (this may include review of medical records)
12. Concomitant medication
13. Physical examination (including assessment of modified Hoehn & Yahr stage), including weight, height and vital signs
14. Montreal Cognitive Assessment (MoCA)
15. Montgomery-Asberg Depression rating scale (MADRS)
16. Confirmation of post-menopausal state
17. Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile,
18. Serum sample stored (approx. 20 ml, stored at -80o)
19. ECG
20. Provision of physical activity monitor and activity diary

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.

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.

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.

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:
1. Confirmation of eligibility/inclusion/exclusion review
2. Medication review
3. Physical examination
4. Recording of any AEs
5. MDS-UPDRS part 3 (motor examination)
6. Optogait and Opals sensor-based objective quantification of motor impairment (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. 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):
1. MDS-UPDRS (parts 1A, 3, 4)
2. NMS-Quest

Participants will then be asked to complete the following questionnaires:
1. MDS-UPRDS (parts 1B and 2)
2. PDQ-39

In addition, the following procedures will be undertaken:
1. 31P- MRS (see appendix 3)
2. Blood sample for genetic analysis
3. Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile)
4. Serum sample (approx. 20 ml, stored at -80o)
5. Provision of patient diary
6. Return of physical activity monitor and activity diary
7. Provision of first medication supply

Participants will be randomised at this visit. 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.

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.

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

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

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

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

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:
1. Record any AEs and changes to concomitant medications

2. Assess compliance with study treatment and collect any unused medication
3. Return of unused medication
4. Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile)
5. Serum sample (approx. 20 ml, stored at -80oC)
6. Diary review

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

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.

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:
1. Record any AEs and changes to concomitant medications
2. Assess compliance with study treatment and collect any unused medication
3. MDS-UPDRS part 3 in the practically defined "OFF" state
4. Opticals/Sensor based objective quantification of motor impairment (Sheffield patients only)
5. 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):
1. MDS-UPDRS (parts 1A, 3, 4)
2. NMS-Quest
3. Montreal Cognitive Assessment (MoCA)
4. Montgomery Asberg Depression Rating Scale (MADRS)

Participants will also be asked to complete the following questionnaires:
1. MDS-UPRDS (parts 1B and 2)
2. PDQ-39

In addition, the following procedure will be undertaken:
1. Safety bloods (full blood count, urea & electrolytes, liver function tests, blood glucose, HbA1C, lipid profile)
2. Serum sample (approx. 20 ml, stored at -80o)
3. 31P- MRS (see appendix 3)
4. Diary review
5. Return of the physical activity monitor and activity diary

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:
1. Record any AEs and changes to concomitant medications
2. Safety bloods (FBC, U&E, LFTs, blood glucose, HBA1C, Lipid profile)
3. Serum sample (approx. 20 ml, stored at -80o)
4. 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):
1. MDS-UPDRS (parts 1A, 3, 4)
2. NMS-Quest
3. Montreal Cognitive Assessment (MoCA)
4. Montgomery Asberg Depression Rating Scale (MADRS)

Participants will also be asked to complete the following questionnaires:
1. MDS-UPRDS (parts 1B and 2)
2. PDQ-39
3. Diary review
4. Diary collection

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

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. 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 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.

Sensors
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 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. A 2nd DynaPort Movemonitor will be posted to participants 2 weeks 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.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Ursodeoxycholic acid

Primary outcome(s)

The safety and tolerability of UDCA in Parkinson’s disease (PD) at a dose of 30 mg/kg, assessed by:
1. Number of serious adverse events (SAEs)
2. Number of adverse treatment reactions
3. Number of patients completing the study
Assessed over the study period from start of treatment to week 56

Key secondary outcome(s))
Assessed as a change from baseline to week 48:
1. Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part 3 motor subsection “OFF” medication score
2. In vivo parameter estimates of high and low energy metabolite levels (ATP, PCr, Pi), derived from cranial 31P-MRS centered on the basal ganglia and related motor regions
3. Objective quantification of motor impairment using motion sensors (Optogait and Opal sensor-based assessment: Sheffield patients only; Dynaport Movemonitor: all patients)

Completion date
01/11/2020

Eligibility

Key inclusion criteria
1. Diagnosis of Parkinson’s disease ≤3 years ago by a clinician with particular expertise in the diagnosis and treatment of movement disorders
2. Subjective improvement of motor impairment on dopaminergic medication, confirmed by PI through personal examination and/or review of medical records
3. 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.
4. Ability to take the study drug
5. Ability to communicate in English
6. Aged 18-75 years
7. Documented informed consent to participate
8. Able to comply with study protocol and willing to attend necessary study visits

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex

All

Total final enrolment
30

Key exclusion criteria
1. 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.
2. Known abnormality on CT or MRI brain imaging considered likely to compromise compliance with trial protocol/31P-MRS acquisition
3. Known claustrophobia or other reasons why patient could not tolerate or be suitable for 31P-MRS
4. Current or previous exposure to UDCA
5. Current or previous diagnosis of liver disease, in particular PBC judged to be significant by the clinical investigator
6. 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.
7. Already actively participating in a trial of a device, drug or surgical treatment for PD
8. History of alcoholism
9. Women of child-bearing potential (WOCBP)
10. Participants who lack the capacity to give informed consent
11. Any medical or psychiatric condition which in the investigator's opinion compromises the potential participant's ability to participate
12. Concurrent dementia defined by a score lower than 25 on the Montreal Cognitive assessment (MoCA)
13. Concurrent severe depression defined by a score > 16 on the Montgomery-Asberg Depression Rating Scale (MADRS)
14. Serum transaminases more than 2 times upper limit of normal
15. Using ciclosporin, nitrendipine or dapsone for the treatment of concomitant, general medical conditions

Date of first enrolment
17/12/2018

Date of final enrolment
01/05/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Hallamshire Hospital
Sheffield Teaching Hospitals NHS Foundation Trust

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Study participating centre
University College Hospital
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Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Charity

Funder Name
J P Moulton Charitable Foundation

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/08/2023	13/10/2023	Yes	No

Protocol article	05/08/2020	27/04/2021	Yes	No
HRA research summary		28/06/2023	No	No
Other unpublished results	25/05/2022	13/06/2022	No	No