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A clinical trial of ambroxol in people with Parkinson's disease

Submission date 20/07/2024	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 22/10/2024	**Overall study status** Ongoing	
Last Edited 26/02/2025	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Parkinson's disease is a condition in which parts of the brain become progressively damaged over many years and is characterised by the core motor symptoms of tremor, limb rigidity, stiffness, and slowness of movement (bradykinesia). Currently, treatment for Parkinson's is limited to symptomatic drugs (treating symptoms) with no treatment available that can slow or prevent disease progression. The purpose of this trial is to investigate whether a drug called ambroxol can slow down the progression of Parkinson's disease and whether it is safe to use over a prolonged period. The researchers want to understand if ambroxol has a beneficial role in Parkinson's disease through its ability to help increase the activity of an enzyme called GCase, which is thought to be defective in people with Parkinson's.

Who can participate?
People who have been diagnosed with Parkinson's disease within the last 7 years and are between 35 and 75 years old

What does the study involve?
Participants will be randomly allocated to one of two groups: one group will receive ambroxol and one group will receive. a matching dummy tablet (placebo) which they will take for 2 years, after this all participants will be given ambroxol for 6 months. Questionnaires and neurological assessments, blood tests, a sebum swab (an oily secretion from the upper back), urine samples and stool samples will be required.

What are the possible benefits and risks of participating?
There is no guarantee that the ambroxol treatment will benefit patients, however, the information we get from the trial will help the trial team find out if ambroxol provides better outcomes for people with Parkinson's disease and therefore, will improve treatment for all Parkinson's patients in the future.
Although research has shown ambroxol is well-tolerated at the dose given in this trial, there is still a potential chance participants will experience adverse effects related to the trial drug. Common side effects include nausea, numbness in the throat and mouth and changes in sense of taste. Uncommon adverse events include dry mouth, vomiting, dyspepsia, diarrhoea and abdominal pain. Rare adverse events include rash and urticaria. Very rare adverse events include

Steven-Johnson syndrome and Lyell's syndrome. The reported frequency of anaphylactic reactions cannot be estimated from the available data. Participants will be informed of all potential adverse events during the informed consent process and they will be advised to monitor and report any side effects in their dosing diaries which will be reviewed by the research team. Participants will undertake a 10-day dose escalation period to mitigate against potential side effects, each stage of the dose escalation period can be extended by further days if adverse events are not tolerable. In addition, telephone calls have been scheduled in between clinic appointments to review any adverse events experienced by participants. All participants will be provided with a patient alert card which details the contact details of the research team in and out of office hours and they will be advised to carry with them at all times.
There is currently no adequate data on the use of ambroxol hydrochloride in pregnant women, however, given that it crosses the placental barrier, its use during pregnancy is not recommended, therefore, pregnant women will be excluded from this trial. In addition, as ambroxol is excreted in breast milk, women participants who are breastfeeding will also be excluded from this trial. Male and female participants will be asked to take highly effective contraceptive measures during the course of the trial starting from the time of informed consent and for 2 weeks after their last administration of the trial drug. Serum pregnancy tests for women of childbearing potential (WOCBP) will be performed at the screening visit and urine pregnancy tests for WOCBP will be performed for all subsequent visits, WOCBP participants will also be posted a pregnancy test to use at home 30 days after the last trial treatment.
Certain medications are prohibited whilst participating in the ASPro-PD trial because of their possible interaction with ambroxol and/or its proposed mechanism of action. These are detailed in the patient information sheet and research teams will review all concomitant medications before trial entry and at each clinic visit. The GP letter will also include the prohibited medication list.
Participants will be required to attend clinic for assessments about every 5 months, three of the visits are in addition to standard-of-care visits. Participants will be reimbursed up to a total of £45 per visit for their travel expenses. For 7 out of the 8 clinic visits, participants will need to attend without having taken their regular PD medication so that they can be assessed in the OFF medication state. Some participants may find this challenging as a result of their symptoms. The trial inclusion criteria have included participants who have a Hoehn Yahr stage of 1 - 2.5 to exclude patients with severe symptoms who may find it extremely challenging to not take their PD medication.
The collection of blood samples can be uncomfortable but rarely results in any serious problems. Reported side effects include feeling light-headed or faint, bruising and/or discomfort around the needle site. Every effort will be made to minimise this. Blood samples will be taken at every visit.
Participants who have consented to the optional CSF sub-study will have a lumbar puncture on two occasions. Although the lumbar puncture procedure is a safe and routine technique, like any procedure there are some risks associated with it. The most common side effect (less than 10% of cases) is a headache usually developing within 24 to 48 hours of the procedure. It is usually relieved by lying down and can be treated with painkillers such as paracetamol and ibuprofen. Some people experience some lower back pain after a lumbar puncture. In most cases, the pain will ease after a few days and it can be treated with painkillers, such as paracetamol and ibuprofen.
A small number (rare) of participants may experience bleeding at the wound site, back discomfort, swelling, rash and itching at the site after the procedure. A very small number (extremely rare) of participants may experience low-pressure headaches, infection, damage to the nerves around the spine and bleeding into the spinal fluid. Participants will be monitored overnight if required.

Where is the study run from?
University College London (UK)

When is the study starting and how long is it expected to run for?
July 2024 to December 2030

Who is funding the study?
Cure Parkinson's Trust (UK)

Who is the main contact?
cctu.aspro-pd@ucl.ac.uk

Study website
https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/research-projects/2024/may/aspro-pd

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1008101

ClinicalTrials.gov number
NCT05778617

Secondary identifying numbers
CCTU/2021/372, CPMS 56515

Study information

Scientific Title
Ambroxol to Slow Progression in Parkinson Disease (ASPro-PD): a Phase IIIA multi-centre randomised placebo-controlled trial

Acronym
ASPro-PD

Study objectives
Primary objective:
To assess whether treatment with 1260 mg daily dose of oral ambroxol tablets for 104 weeks (including a 10-day titration period) is associated with an improvement in motor and non-motor function compared with matching placebo.

Secondary objectives:
1. To assess the safety and tolerability of ambroxol
2. To assess the association of ambroxol with an improvement in motor, non-motor and cognitive symptoms of PD
3. To assess the impact of ambroxol on quality of life
4. To investigate whether ambroxol therapy is associated with changes in the natural progression of PD as determined by clinical scales and biochemical biomarkers
5. To investigate ambroxol targeting effect, as determined by its concentration, GCase activity and protein levels and sphingolipids concentration

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 15/10/2024, Wales Research Ethics Committee 2 (Health and Care Research Wales, Castlebridge 5, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0)2920 230 457; Wales.REC2@wales.nhs.uk), ref: 24/WA/0231

Study design
Double-blind randomized placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

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

Interventions
Participants will be recruited and randomly allocated (via an online web-based randomisation service called Sealed Envelope) to one of two treatment arms in a 1:1 ratio:

Arm A (Active):
Oral ambroxol hydrochloride tablets (420 mg), one tablet a day (420 mg/day) for 5 days (Day 1-5) followed by two tablets (840 mg/day) for a further 5 days (Day 6-10), thereafter three tablets (1260 mg/day) from day 11. Participants continue their intake of three tablets (1260 mg/day) for the remainder of the blinded treatment phase (104 weeks).

Arm B (Comparator):
Matching placebo tablets (420 mg), one tablet a day (420 mg/day) for 5 days (Day 1-5) followed by two tablets (840 mg/day) for a further 5 days (Day 6-10), thereafter three tablets (1260 mg /day) from day 11. Participants continue their intake of three tablets (1260 mg/day) for the remainder of the blinded treatment phase (104 weeks).

All participants will then enter the open-label extension phase and will receive oral ambroxol hydrochloride tablets (420 mg), one tablet a day (420 mg/day) for 5 days (Day 1-5) followed by two tablets (840 mg/day) for a further 5 days (Day 6-10), thereafter three tablets (1260 mg/day) from day 11. Participants continue their intake of three tablets (1260 mg/day) for the remainder of the open-label phase.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Ambroxol hydrochloride

Primary outcome measure
Change in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I- III score from baseline to Week 104. The MDS-UPDRS is a comprehensive 50-question

assessment of both motor and non-motor symptoms associated with Parkinson's. A comparison of MDS-UPDRS Parts I-III total score at 104 weeks between participants according to treatment allocation will be made. Parts I and II are measured in the practically defined ON medication state and Part III is measured in the practically defined OFF medication state. Parts I and II are historical data assessed by an examiner and are designed to rate mentation, behaviour and mood; Part III is done as a motor examination at the time of a visit. Participants will undergo MDS-UPDRS assessment at baseline, week 20, week 40, week 60, week 80, and week 104.

Secondary outcome measures

1. The rate of change of MDS-UPDRS parts I-III (parts I and II measured in the practically defined ON medication state and part III measured in the practically defined OFF medication state) from baseline to 104 weeks (assessed at baseline, week 20, week 40, week 60, week 80, week 104)
2. Motor signs of PD are measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III score, which assesses the motor signs of PD and will involve a motor examination in the OFF-medication state from baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, week 104)
3. The rate of change of MDS-UPDRS part III score in the OFF-medication state from baseline to 104 weeks (assessed at baseline, week 20, week 40, week 60, week 80, week 104)
4. MDS-UPDRS part I score in the ON medication state at 104 weeks. The non-motor impact of PD on patients is measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I score, which assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living, in the ON medication state baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
5. MDS-UPDRS part II score in the ON medication state at 104 weeks. The motor aspect impact of PD patients' experiences of daily living is measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II score, which assesses the motor aspect impact of Parkinson's disease (PD) on patients' experiences of daily living, in the ON medication state from baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
6. MDS-UPDRS part IV score in the ON medication state at 104 weeks. Motor complications of PD are measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part IV score, which assesses two motor complications, dyskinesias and motor fluctuations using historical and objective information, in the ON medication state from baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
7. MDS-UPDRS Tremor score at 104 weeks. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) tremor component score from baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
8. MDS-UPDRS Non-tremor score at 104 weeks. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) non-tremor component score from baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
9. Montreal Cognitive Assessment (MoCA) at 104 weeks. Cognitive impairment is measured using the Montreal Cognitive Assessment, a 30-question test, which assesses mild cognitive impairment by checking participant orientation, short-term memory, executive function, language, abstraction, naming of animals, attention and a clock drawing test, from baseline to Week 104 (assessed at screening and week 104).
10. Trial Making Test (Part A &B) at 104 weeks (assessed at baseline and week 104). A neuropsychological test that involves assessing visual scanning and working memory.
11. The Hooper Visual Organization Test (VOT) at 104 weeks (assessed at baseline and week 104). A neurological test which measures the individual's ability to organize visual stimuli.
12. Parkinson’s disease 39-item Quality of Life questionnaire (PDQ-39) at 104 weeks. Patient-reported health status and quality of life are measured using the Parkinson's disease 39-item

Quality of Life questionnaire from baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
13. Patient Global Impression (PGI) Severity and Change at 104 weeks. Symptom improvement from baseline to Week 104 is measured using the Patient Global Impression of Change from baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, and week 104).
14. EuroQol Eq-5D 5-Level Health Related Quality of Life Questionnaire at 104 weeks. Quality of life outcome differences between the two treatment groups from baseline to Week 104, as measured by the descriptive system for health-related quality of life, EQ-5D-5L (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
15. Non-Motor Symptoms Scale (NMSS) at 104 weeks. Non-motor symptoms of PD from baseline to Week 104, as measured by the Non-Motor Symptoms Scale (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
16. PD progression measured using Parkinson's Disease Comprehensive Response (PD CORE), a composite approach integrating three standard outcome measures PDCORE = (1 × change in OFF state motor score) + (2 × change in OFF state ADL score) - (10 × change in total good-quality ON time per day) at 104 weeks (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
17. Dresden Falls Questionnaire (DREFAQ) at 104 weeks. Assessment of postural instability and falls from baseline to Week 104 using the Dresden Falls Questionnaire (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
18. Clinical Global Impression (CGI) Severity and Improvement at 104 weeks. Symptom severity, treatment response and the efficacy of treatment from baseline to Week 104 measured using the Clinical Global Impression of symptom severity and improvement scales (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
19. Safety and tolerability of Ambroxol as indicated by changes in vital signs, weight, clinical laboratory measures and adverse events (recorded and monitored throughout).
20. Time to initiation of rescue medication as measured by use of rescue medication from baseline to Week 104 (assessed at baseline, week 20, week 40, week 60, week 80, week 104).
21. Change in levodopa equivalent dose at 104 weeks (recorded at baseline, week 20, week 40, week 60, week 80, week 104).

Overall study start date
18/07/2024

Completion date
01/12/2030

Eligibility

Key inclusion criteria
1. A diagnosis of Parkinson's disease (in accordance with the MDS diagnostic criteria) within 7 years of the screening visit confirmed by year of diagnosis
2. Adults aged ≥35 and ≤75 years
3. Hoehn and Yahr stage between 1-2.5, inclusive (in ON state) at screening visit
4. Known glucocerebrosidase gene (GBA1) status, mutant, or wildtype, confirmed prior to the screening visit
5. On stable dopaminergic treatment for at least 3 months before enrolment
6. Able and willing to provide informed consent prior to any study related assessments and/or procedures

7. Able and willing to attend trial visits and comply with all study procedures for the duration of the trial
8. Willing and able to self-administer oral ambroxol medication or placebo

Participant type(s)
Patient

Age group
Adult

Lower age limit
35 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
330

Key exclusion criteria
1. Participation in another interventional clinical trial of an Investigational Medicinal Product (IMP) within 90 days prior to the first dose of trial treatment.
2. Use of an Investigational Medicinal Product (IMP) within 90 days prior to the first dose of trial treatment.
3. Participation in another clinical trial of an Investigational New Drug being tested for PD disease modifying potential within 12 months prior to the first dose of trial treatment.
4. Past surgical history of deep brain stimulation.
5. Use of ambroxol in the past 12 months.
6. Exposure to Exenatide within 12 months prior to the first dose in this current trial.
7. Concomitant medications that in the opinion of the Investigator would preclude participation in the study e.g., exenatide or other GLP1 agonist for diabetes.
8. Confirmed dysphagia that would preclude self-administration of ambroxol.
9. History of known sensitivity to the study medication, ambroxol or its excipients (lactose monohydrate, granulated microcrystalline cellulose, copovidone and magnesium stearate) in the opinion of the investigator that contraindicates their participation.
10. History of known rare hereditary disorders of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
11. Presence of the LRRK2 G2019S mutation
12. History of drug abuse or alcoholism in the opinion of the Investigator that would preclude participation in the trial.
13. Pregnant (or planned pregnancy during the trial) and/or breastfeeding.
14. Women of childbearing potential (WOCBP) and male participants with a partner of childbearing potential not willing to use highly effective contraception or abstinence for the duration of the trial treatment and for 2 weeks following the last dose of the study drug.
15. Any clinically significant or unstable medical or surgical condition that in the opinion of the Investigator may; put the participant at risk when participating in the study, influence the results of the study or affect the participants ability to take part in the study, as determined by medical history, physical examinations, electrocardiogram (ECG) or laboratory tests. Such conditions may

include:
15.1. Impaired renal function with creatinine clearance <50ml/min at screening visit.
15.2. Moderate or severe hepatic impairment
15.3. A major cardiovascular event (e.g., myocardial infarction, acute coronary syndrome, compensated congestive heart failure, pulmonary embolism, coronary revascularisation) that occurred within 6 months prior to the screening visit.
16. Severe depression defined by a score >20 on the Beck Depression Inventory-II (BDI-II) at screening.
17. Significant cognitive impairment defined by a score <20 on the Montreal Cognitive Assessment (MoCA) at screening.
18. Use of trihexyphenidyl or benztropine within 30 days prior to the first dose of trial treatment.
19. Only applicable for those patients consenting to the optional CSF sub-study: Evidence or history of hypersensitivity to lidocaine or its derivatives.
20. Only applicable for those patients consenting to the optional CSF sub-study: Current treatment with anti-coagulants (e.g., warfarin) that might preclude safe completion of the lumbar puncture in the opinion of the Investigator. Aspirin will be permitted.
21. Only applicable for those patients consenting to the optional CSF sub-study: Significant known lower spinal malformations or other spinal abnormalities that would preclude a lumbar puncture.

Date of first enrolment
25/02/2025

Date of final enrolment
01/10/2026

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Uclh
250 Euston Road
London
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Study participating centre
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Sponsor type

University/education

Website
http://www.ucl.ac.uk/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Cure Parkinson's Trust

Alternative Name(s)
The Cure Parkinson's Trust, CPT

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Submission to regulatory authorities

The latest version of the protocol will be made available as supplementary material upon publication of the final clinical investigation report. Applications for access to the trial dataset at the end of the trial, can be submitted formally in writing to UCL CCTU and will be considered, and approved in writing after formal consideration by the trial oversight committees and the chief investigator. Data, including genetic data, collected may be shared with regulators, other researchers either at academic sites nationally or internationally, or academic, commercial or charitable organisations approved by the Sponsor, in other future ethically approved research or regulatory approval process.

Intention to publish date
01/12/2031

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