The Dutch Parkinson GBA Ambroxol trial (DUPARG-AMBROXOL): A randomised, double-blind, placebo-controlled, single-center trial with Ambroxol in Parkinson patients with a GBA mutation

Published: 13-03-2023
Last updated: 05-04-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON52316

Source
ToetsingOnline

Brief title
The Dutch Parkinson GBA Ambroxol trial

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson, Parkinson's disease

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Two private gifts.

Intervention

Keyword: Ambroxol, GBA variations, Parkinson's disease, Physiological Effects of Drugs

Outcome measures

Primary outcome

The primary endpoint is the comparison of MDS-UPDRS part III motor subscale in

the practically defined OFF medication state at 60 weeks after a 12 week

washout period.

Secondary outcome

Secondary endpoints are:

- Safety and tolerability by examine adverse events

- F-DOPA PET

- MRI

- Montreal Cognitive Assessment (MoCA)

- Non-Motor Symptoms scale (NMSS)

- Parkinson*s Disease 39 item Quality of life questionnaire (PDQ-39)

- GCase activity measured using a flow cytometry based assay of peripheral

blood mononuclear cells (PBMCs)

Study description

Background summary

The pathological cause of Parkinson*s disease (PD) is related to aggregation of the protein alpha-synuclein (aSyn) in the nervous system. Currently, there are no therapies available that slow down disease progression, which is the most important unmet need in PD treatment. The most common genetic risk factor for PD is a heterozygous mutation of the GBA1 (GBA) gene, encoding the lysosomal enzyme glucocerebrosidase (GCase). Reduced GCase activity in the brain is associated with increased levels of aSyn. Ambroxol is mucolytic molecule and appears to facilitate the refolding of misfolded mutant GCase protein at the endoplasmatic reticulum, allowing effective trafficking to the lysosome. Because of these chaperon properties, ambroxol can act as a potential disease-modifying strategy enhancing the GBA-mediated pathway of aSyn degradation. Non-clinical studies support the potential for using ambroxol as a disease-modifying treatment for synucleinopathies such as PD. Studies with ambroxol in humans so far showed that ambroxol can be safely given in higher dosages for a longer period. This prospective placebo-controlled trial aims to determine the effect of ambroxol on the clinical PD motor symptoms of patients carrying a GBA mutation.

Study objective

The primary objective is to compare the effectiveness of ambroxol versus placebo on the MDS-UPDRS part III motor sub-score in the *practically defined OFF-medication state* in patients with moderate PD, carrying a GBA mutation. The hypothesis is that ambroxol will be associated with reduced MDS-UPDRS part III scores at the 60 week time-point after a 12 week washout period.
Secondary objectives will compare the differences at 60 weeks between the ambroxol and placebo trial arms with respect to:
- Safety and tolerability
- Participant*s prediction of their treatment (ambroxol or placebo) to asses adequate blinding
- Glucocerebrosidase (GCase) activity in blood mononuclear cells
- Striatal F-DOPA uptake as measured by [18] F-DOPA PET scan
- Relationship between resting-state functional and structural connectivity as measured by MR imaging and dopaminergic innervation (PET scan)
- Integrity of the nigrostriatal fibers, connecting the substantia nigra and putamen, using diffusion tensor imaging (DTI) tractography
- Quality of Life (PDQ-39 questionnaire)
- Non Motor Symptoms (NMSS scale)
- Cognition, using the Montreal Cognitive Assessment (MoCA)
- Levodopa dose (LED, Ldopa Equivalent Dose)

Study design

This study is designed as a prospective placebo-controlled trial with a washout design of PD patients carrying a GBA mutation. During a 48 weeks exposure period, patients will self-administer ambroxol or placebo. At 48 weeks the

ambroxol patients are switched to placebo. Patients however will be kept blinded during this period. At 60 weeks, baseline measurements will be repeated followed by study drug withdrawal and a final motor assessment 12 weeks later. Measurements at baseline, and at 60 weeks consist of: motor assessment in OFF-medication state, non-motor assessments including neuropsychological assessment and a quality of life assessment, GCase activity in peripheral blood mononuclear cells (PBMCs), F-DOPA PET and MRI. Motor assessments will also take place at 12, 24, 36, 48 and 72 weeks in a defined dopaminergic OFF-state. GCase activity in PBMCs is also measured at 48 weeks.

Intervention

Patients will start with oral tablets of Ambroxol 600mg or placebo, which will increase with 600mg per week, to a maximum of 3 times 600mg a day for a period of 48 weeks. At 48 weeks all participants will switch to placebo during the last 12 weeks.

Study burden and risks

Before inclusion an electrocardiogram (ECG) and a laboratory blood test will be collected. In total 8 visits will take place in a time period of 72 weeks. Subjects will undergo 2 longer visits of 5 hours (at baseline and after 60 weeks) including a F-DOPA PET scan, MRI, a blood draw (40 mL), motor assessment (MDS-UPDRS III), cognitive assessment (MoCA) and two questionnaires. At 12, 24, 36, 48 and 72 weeks follow-up motor assessments (UPDRS III) will take place at the UMCG or at the patient*s home. At 48 weeks an extra blood draw (40 mL) will be performed and the ECG and laboratory blood test will be repeated. The burden of research is related to the radiation burden of PET scans, i.e. F-DOPA PET, with a total radiation burden is 5,2mSv (with 200MBq injection) and an additional low-dose CT of 1,5 mSv. The overall radiation burden therefore will be 13.4mSv in 72 weeks. The expected risk associated with the investigational treatment is low. Ambroxol is available for adults and children in low doses in more than 50 countries for over 30 years. Studies in humans have examined higher doses in a longer period and have shown that ambroxol can be given safely. However, potential side effects of ambroxol will be recorded accurately.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Diagnosis of Parkinson*s disease, according to Movement Disorders Society (MDS) criteria <10 years
- PD patients carrying a GBA1 mutation
- Willingness to cooperate and sign written informed consent
- Willing and able to self-administer oral ambroxol medication

Exclusion criteria

- The refusal to be informed about an unforeseen clinical finding
- Pregnant or breast feeding women
- Use of an implanted Deep Brain Stimulation (DBS) system
- MRI imcompatible implants in the body

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2023
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ambroxol
Generic name:	Ambroxol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-03-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-04-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-09-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-01-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-001833-38-NL
CCMO	NL77347.042.22