Effectiveness of ambroxol in children and adults with Gaucher disease 3: n-of-1 series

Published: 06-12-2022
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This study has been transitioned to CTIS with ID 2024-514012-28-00 check the CTIS register for the current data. Assess the neurological efficacy of ambroxol in adults and children with GD3.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON51936

Source
ToetsingOnline

Brief title
ATTACK-GD3

Condition

- Metabolic and nutritional disorders congenital

Synonym
Gaucher disease: a lysosomal storage disease, metabolic disorder

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: MetaKids;Vriendenloterij

Intervention

Keyword: Ambroxol, Gaucher disease, Lysosmal storage disease, N-of-1

Outcome measures

Primary outcome

Lyso-GL1 in CSF

Secondary outcome

• Lyso-GL1, GL-1, chitotriosidase and Lyso-GM3 in plasma

• GL-1 and Lyso-GM3 in CSF

• GCase activity in leukocytes

• Goal Attainment Scaling (GAS)

• Quality of Life (PedsQL)

• Assessment and rating of ataxia (SARA)

• Neuropsychological assessment (ANT/Wechsler scale)

• Behavioural assessment (SDQ/SWAN)

• If epilepsy: seizure control (UMRS, seizure log book)

Study description

Background summary

Gaucher disease (GD) is an autosomal recessive lysosomal storage disease (LSD), caused by bi-allelic mutations in GBA1 resulting in a deficiency of the lysosomal enzyme glucocerebrosidase (GCase). GD is biochemically characterized by lysosomal accumulation of glucosylceramide (GL-1) and its deacylated form, glucosylsphinogosine (Lyso-GL1). Clinically, GD is classified intro three subtypes (GD1-3). All present with multisystemic disease manifestations (i.e. enlarged liver and spleen, anaemia). GD2 and GD3 are less common and include involvement of the central nervous system (CNS). GD3 patients present with untreatable progressive neurodegenerative disease, i.e. progressive developmental delay, myoclonic epilepsy, supranuclear gaze palsy and ataxia.

The systemic manifestations of GD can be treated by enzyme replacement therapy (ERT). However, ERT is not able to cross the blood-brain barrier (BBB) and hence no treatment for the devastating neurological symptoms is available. Ambroxol is a small molecule chaperone that has been shown to increase GCase activity in vitro and is able to cross the BBB. Because classical randomized controlled trials (RCTs) are unfit to perform due to a low prevalence and heterogeneity of GD3, we will combine the results of several n-of-1 trials. The purpose of this study is to evaluate the neurological efficacy of ambroxol in patients with GD3, using an n-of-1 series.

Study objective

This study has been transitioned to CTIS with ID 2024-514012-28-00 check the CTIS register for the current data.

Assess the neurological efficacy of ambroxol in adults and children with GD3.

Study design

A series of prospective double-blind randomized and placebo-controlled multiple cross-over, single centre studies within a participant (multiple n-of-1 trials).

Intervention

Each patient receives multiple blocks consisting of three time daily ambroxol (25 mg/kg/day) alternated with placebo and washout periods.

Study burden and risks

No treatment is available for this severely affected patient group. There is an unmet medical need to treat this progressive neurodegenerative disease. High dose ambroxol has been used in several (pre)clinical case studies including children and adults without any serious adverse events. Because of the progressive nature of GD3, early innervation is necessary. Therefore paediatric patients with GD3 are necessary to include. Risks for subject participating in this trial consist of additional blood draw and lumbar punctures at baseline and during treatment. As this clinical trial enables a potential treatment for patients that lack treatment options, we will expect that the benefits substantially outweigh the burden of participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1) The patient or the parent(s) / legal guardian(s) must provide written informed consent before start of the study;
2) Male and female patients with documented deficiency of GCase activity and GBA genotype fitting GD3;
3) 3) Male and female patients > 2 years of age;
4) Able to travel to the study site;
5) Patients receive ERT with treatment ongoing at the time of enrollment;

Exclusion criteria

1) The patient is transfusion dependent;
2) The patient has received an investigational product within 30 days prior to

enrollment;
3) Known hypersensitivity reactions, intolerance or adverse reactions to ambroxol or to the inactive ingredients;
4) Pregnancy, because there are no sufficient data for the use of ambroxol in pregnant women (see Summary of Product Characteristics (SPC));
5) The patient is lactating. Ambroxol crosses into the breast milk. As there is no adequate experience in humans to date, ambroxol should not be used in lactation in a study setting (see SPC);
6) The patient is unwilling or, in the investigator*s opinion, unable to adhere to the requirements of the study;
7) The patient is unable to swallow powder and has no other enteral access (e.g. gastrostomy);
8) Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-09-2024
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mucoangin

Generic name:	Ambroxolhydrochloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-12-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-514012-28-00
EudraCT	EUCTR2021-002550-82-NL
CCMO	NL76160.018.21