Long-term safety study of personalized cholic acid treatment in patients with bile acid synthesis defects

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This study has been transitioned to CTIS with ID 2024-518652-23-00 check the CTIS register for the current data. Investigating the long-term safety of personalized cholic acid treatment in patients with defects in bile acid synthesis based on...

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

Summary

ID

NL-OMON56230

Source
ToetsingOnline

Brief title
Cholic Acid

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism

Synonym
Metabolic disease, Zellweger spectrum disorder

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: VriendenLoterij

Intervention

Keyword: Bile acid synthesis defect, Cholic acid, Magistral preparation, Safety study

Outcome measures

Primary outcome

1. Degree of suppression of endogenous bile acid synthesis (decrease in urine and/or serum DHCA and THCA bile acid intermediates and increase in FGF-19)

2. Type and number of adverse events

3. Type and number of side effects (change in plasma transaminases (aspartate transaminase [AST], alanine transaminase [ALT]) and conjugated bilirubin)

Secondary outcome

- Increase in normal primary bile acids (increase in urine CA)

- Change in serum ALT, AST, transminases, γ-glutamyltrans- peptidase, conjugated bilirubin, total bilirubin levels, gamma-GT, alkaline phosphatase, alpha-1-phetoprotein

- Change in liver protein synthesis (determined by prothrombin time [PT])

- Change in degree of coagulopathy (measured by PT, aPTT, Factor V and Factor VII)

- Change in weight gain (weight-for-height percentile)

- Change total body length growth rate (cm/year; only in those with remaining growth potential).

- Change in fat soluble vitamins (A,D,E) level and total cholesterol

- Development of fibrosis (determined by fibroscan and ELF-test)

- Development of cirrhosis

- Neurological development

Study description

Background summary

Bile acid synthesis defects such as single enzyme disorders in bile acid synthesis (known as SED) and Zellweger spectrum disorder (ZSD) are severe disabling disorders. At least some of the clinical abnormalities including severe liver dysfunction and growth retardation are caused by the accumulation of toxic bile acid intermediates. Bile acid supplementation by cholic acid (CA) has been hypothesized to decrease endogenous bile acid production, stimulate bile secretion and to improve bile flow and micellar solubilization in these patients. CA treatment is an authorized therapy for SED patients in the Netherlands. For ZSD, however, CA is only authorized in the United States. CA is registered as an orphan drug and CA treatment is very expensive, however research into CA treatment of bile acid synthesis defects is limited. Personalized treatment with pharmacy prepared CA capsules could make costs of CA treatment lower and more sustainable.

The primary objective is to investigate the long-term safety of personalized CA treatment of patients with bile acid synthesis defects. Our secondary objectives are to investigate the long-term effect (treatment of 5 years) of cholic acid treatment on clinical and biochemical parameters and the pharmacokinetics of CA in this patient population. Another secondary objective is to determine the feasibility and sustainability of personalized treatment for patients with a rare disease.

Study objective

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Investigating the long-term safety of personalized cholic acid treatment in patients with defects in bile acid synthesis based on clinical and biochemical parameters.

Study design

Open label, single centre and non-randomized intervention study. This design is most suitable since patient numbers are small due to the rarity of the disease and heterogeneous phenotype of the disorder. A single centre design was chosen because of the expertise in ZSD and SED within the Academic Medical Center (AMC). Moreover, almost all ZSD patients in the Netherlands visit the

outpatient clinic of the AMC. The duration of the study will be 5 years.

Intervention

Cholic acid treatment

Study burden and risks

The burden on patients is limited as most examinations take place at the time of regular outpatient visits and blood tests are a standard part of these visits (650 uL extra blood is collected per visit).
The extra investigations during these outpatient visits consist of: collecting urine portion through a urine collection bag, scoring neurological milestones, fibroscan measurement. The scoring of neurological milestones is a small time burden. Fibroscan is a 1-minute examination in the consultation room that is not burdensome and free of rays. An additional visit to the hospital is necessary in week 2 and 6 after start of treatment, or 4 weeks after a dose change. During this visit, weight and height are measured, blood is collected (550 µL) and urine is collected (minimum volume 5 ml).

Cholic acid is a body's own substance of which long-term safety data are known when treating Zellweger Spectrum and other bile salt synthesis disorders.

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)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Bile acid synthesis defect due to single enzyme deficiency OR Zellweger spectrum disorder with at least one of the following hallmarks: steatorrhea (confirmed per local protocol), elevated transaminases (ALAT and/or ASAT), developmental delay, neurological symptoms

Exclusion criteria

• Short life expectancy of < 12 months (severe multiple organ dysfunction)
• Decompensated liver cirrhosis
• High bilirubin serum levels (conjugated bilirubin > 20 µmol/L)
• Prolonged prothrombin time (PT > 15s not due to vitamin K deficiency)
• Pregnancy and high total bile acid serum level (> 40µmol/L)
• Allergy to one of the components of CA capsules.

Additional exclusion criteria are set for Zellweger spectrum disorder:
• Increased liver enzymes during previous CA treatment
• Normal biochemical parameters (THCA and/or DHCA <=1.0 µmol/L)

Study design

Design

Study phase: 4

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-05-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cholic acid
Generic name:	Cholic acid

Ethics review

Approved WMO Date:	27-03-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	01-05-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	19-09-2023
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	CTIS2024-518652-23-00
EudraCT	EUCTR2019-001528-37-NL
CCMO	NL69597.018.19