Withdrawal of Tiratricol Treatment in Males with Monocarboxylate Transporter 8 Deficiency (MCT8 Deficiency): A Double-blind, Randomized, Placebo-controlled Study

Published: 25-10-2022
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This study has been transitioned to CTIS with ID 2024-516124-34-00 check the CTIS register for the current data. Primary Objective:• To evaluate the effects of withdrawal of tiratricol treatment (placebo group) on serum total triiodothyronine (T3)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Endocrine disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53686

Source
ToetsingOnline

Brief title
reTRIACt

Condition

- Endocrine disorders congenital
- Thyroid gland disorders
- Neuromuscular disorders

Synonym
Allan-Herndon-Dudley syndrome, MCT8 deficiency

Research involving

Human

Sponsors and support

Primary sponsor: Rare Thyroid Therapeutics
Source(s) of monetary or material Support: Rare Thyroid Therapeutics International

Intervention

Keyword: Allan-Herndon-Dudley Syndrome, MCT8, Thyroid hormone analogue, Triac

Outcome measures

Primary outcome

Proportion of participants who meet the rescue criterion (serum total

T3 > ULN) from samples obtained during the 30-day double-blind

Randomized Treatment Period

Secondary outcome

Secondary efficacy endpoints:

• Change in serum thyroid hormone variables (T3, T4, TSH, fT3, and fT4) from

baseline (start of the Randomized Treatment Period) to the end of

Randomized Treatment Period (completion or rescue)

• Change in serum thyroid hormone variables (T3, T4, TSH, fT3, and fT4) from

initiation of tiratricol administration at screening to the last

measurement prior to randomization (Cohort B only)

• Change in the cardiovascular variables from extended ECG assessments, 24-hour

ABPM, and heart rate assessments from the last measurement prior to the start

of the Randomized Treatment Period to the end of the Randomized Treatment

Period (completion or rescue)

• Serum concentrations of tiratricol

• Change in serum SHBG from baseline (start of the Randomized Treatment Period) to the end of the Randomized Treatment Period (completion or rescue)

• Time (days) from randomization to the time when the rescue criterion is met or the time of completion of the Randomized Treatment Period (whichever comes first)

Exploratory efficacy endpoints:

• Change in serum thyroid hormone variables (T3, T4, TSH, fT3, and fT4) from baseline (start of the Randomized Treatment Period) to the end of the Follow-up Period

• Change in serum thyroid hormone variables (T3, T4, TSH, fT3, and fT4) from the end of the Randomized Treatment Period (completion or rescue) to the end of the Follow-up Period

• Evaluation of sleep variables recorded in parent/caregiver diaries and questionnaires from enrollment to completion of the study

• Number and structure of tiratricol metabolites

• Individual metabolite concentrations and metabolite:tiratricol ratios

• Population PK outputs for tiratricol

• Relationship between serum total T3 concentrations and serum concentrations of tiratricol

• Relationship

Study description

Background summary

Thyroid hormone is important for the development of the brain and many other tissues. To perform its action, the hormone needs to enter the cells of these tissues via *gates/channels*. One of these gates is called MCT8. The brain depends on MCT8 to allow thyroid hormone to enter. If MCT8 is not working properly (as happens in MCT8 deficiency), less or no thyroid hormone will enter the brain, resulting in developmental abnormalities. This is the cause of the severe developmental delays and neurological problems which are seen in patients with MCT8 deficiency.
At the same time, other body tissues, such as the muscles and liver, do not depend on MCT8 to allow thyroid hormone to enter their cells. In patients with MCT8 deficiency, the blood level of active thyroid hormone in these organs is too high, which results in adverse effects such as muscle wasting, a low body weight and peripheral thyrotoxicosis.
Unfortunately, there is no approved effective treatment for patients with MCT8 deficiency available at the moment. In the past, the standard treatment for overactive thyroid, consisting of anti-thyroid medication in combination with the administration of the thyroid hormone levothyroxine has been used in patients with MCT8 deficiency. This (potentially) has a positive effect on the negative effects of the increased level of the active thyroid hormone in body tissues other than the brain. This treatment does not increase the level of active thyroid hormone in the brain and is therefore not expected to have a positive effect on the developmental disorder. This treatment is therefore not currently used in patients with MCT8 deficiency.
Tiratricol (also known as Triac) is a specific kind of thyroid hormone that does not need to use the MCT8 normal pathway for thyroid hormones to get into the brain. The purpose of this research study is to learn more about the use of the new study medicine tiratricol for the treatment of MCT8 deficiency. This research study will include 16 boys from 4 years of age who all have MCT8 deficiency

Study objective

This study has been transitioned to CTIS with ID 2024-516124-34-00 check the CTIS register for the current data.

Primary Objective:
• To evaluate the effects of withdrawal of tiratricol treatment (placebo group) on serum total triiodothyronine (T3) concentrations, measured by liquid chromatography with tandem mass spectrometry (LC/MS/MS), and the requirement for rescue treatment with tiratricol as compared to continuing tiratricol treatment (tiratricol group), in males diagnosed with MCT8 deficiency and on a stable maintenance dose of tiratricol

Secondary Objectives:
• To evaluate the safety and tolerability of tiratricol treatment
• To evaluate the effect of tiratricol treatment upon serum thyroid hormone measurements, sex hormone binding globulin (SHBG), and cardiovascular measurements
• To evaluate the serum concentrations of tiratricol

Exploratory Objectives:
• To evaluate the effect of tiratricol treatment upon serum thyroid hormone measurements (from baseline to the end of the Follow-up Period)
• To evaluate the effect of tiratricol treatment upon basic sleep measurements as
recorded in parent/caregiver diaries and questionnaires
• To investigate the presence and identity of metabolites of tiratricol
• To explore the relationship between pharmacokinetics (PK) and safety and efficacy endpoints, and the impact of participant characteristics on PK

Study design

This is a randomized phase 3 multicenter placebo-controlled study in at least 16 evaluable male participants diagnosed with MCT8 deficiency. Male participants, from 4 years of age (at randomization) and on stable maintenance treatment with tiratricol, will be randomized to receive placebo or tiratricol for 30 days.

Intervention

Participants from study Cohorts A and B who meet the Stable Dose Criterion and all randomization criteria will enter the Randomized Treatment Period. These participants will be randomized 1:1 in a double-blind manner to receive treatment for 30 days or until the rescue criterion is met (whichever comes first) in one of the following arms:
Tiratricol group: Continue the participant*s stable maintenance dose of tiratricol treatment as administered in the Run-in/Dose Titration Period (when Stable Dose Criterion confirmed).
Placebo group: Same frequency of dosing, and number of tablets per dose, as the stable maintenance dose prior to randomization using matched placebo tablets.

Study burden and risks

Given the low quality of life, the absence of an effective therapy, the expected beneficial effects on chronic thyrotoxicosis in patients with MCT8 deficiency, the risks to and the burden for the participants will be at least in proportion to the potential value of the research and the beneficial effects for the participating MCT8 deficiency patients. In addition, participants will be invited to participate in a compassionate-use program after they finish the

present study, which offers the benefit of continued access to a potentially effective treatment, when there are no alternatives available.

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. Male participants diagnosed with a pathogenic mutation in the MCT8 gene, confirmed with a genetic test.
2. Serum total T3 concentration above the ULN of the age-specific normal range:
a) at the time of diagnosis (or the closest sample taken prior to first ever treatment with tiratricol) for participants who are currently treated with

tiratricol
b) in the Screening Visit sample, or most recent standard of care sample prior to screening, for participants who have never received and/or currently not receiving tiratricol.
3. Participants will be aged 4 years or older at the time of randomization. Participants entering screening who are <4 years of age but expected to be aged 4 years at randomization should be discussed with the medical monitor.
4. Signed and dated informed consent form from the parents or legal guardian.

Exclusion criteria

1. Major illness or recent major surgery unrelated to MCT8 deficiency (in the principal investigator*s judgement), defined as:
• Conditions requiring repeated hospitalizations that are likely to confound ability to participate in the trial.
• Major illness in the 3 months prior to the Screening Visit that is likely to confound the ability of the participant to participate fully within the trial and/or confound the assessment of serum total T3 and/or safety.
• Major surgery within the 3 months prior to the Screening Visit or planned to take place during the study, including but not limited to major abdominal/thoracic/neurosurgical procedures.
• Major/minor abdominal and/or maxillofacial surgery that may inhibit the administration and/or absorption of study drug.
2. Body weight <10 kg at the Screening Visit.
3. Patients who are participating, or intend to participate, in other therapeutic
and/or interventional clinical studies during the study period.
4. History of allergic reactions to components of tiratricol or any excipients in
the investigational product (IP).
5. Participants with any contra-indication for treatment with tiratricol or any excipients in the IP.
6. Participants using other T3 analogues, levothyroxine, or propylthiouracil.

In addition to these eligibility criteria, participants must meet further criteria at the time
of randomization to enter the Randomized Treatment Period.
Randomization criteria:
1. Confirmation that the *Stable Dose Criterion* has been met.
2. Absence of any new or exacerbated medical or surgical condition that fulfils Exclusion criterion #1.
3. Confirmation that participant is at least 4 years of age at the time of randomization.

Study design

Design

Study phase:	3
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):	21-07-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Emcitate
Generic name:	tiratricol

Ethics review

Approved WMO Date:	25-10-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-03-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	11-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2024

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-08-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2024-516124-34-00
EudraCT	EUCTR2022-001478-78-NL
ClinicalTrials.gov	NCT05579327
CCMO	NL81812.078.22