EFFECTS OF TIRATRICOL TREATMENT WITHDRAWAL IN MONOCARBOXYLATE TRANSPORTER 8 (MCT8) DEFICIENCY: ReTRIACt TRIAL

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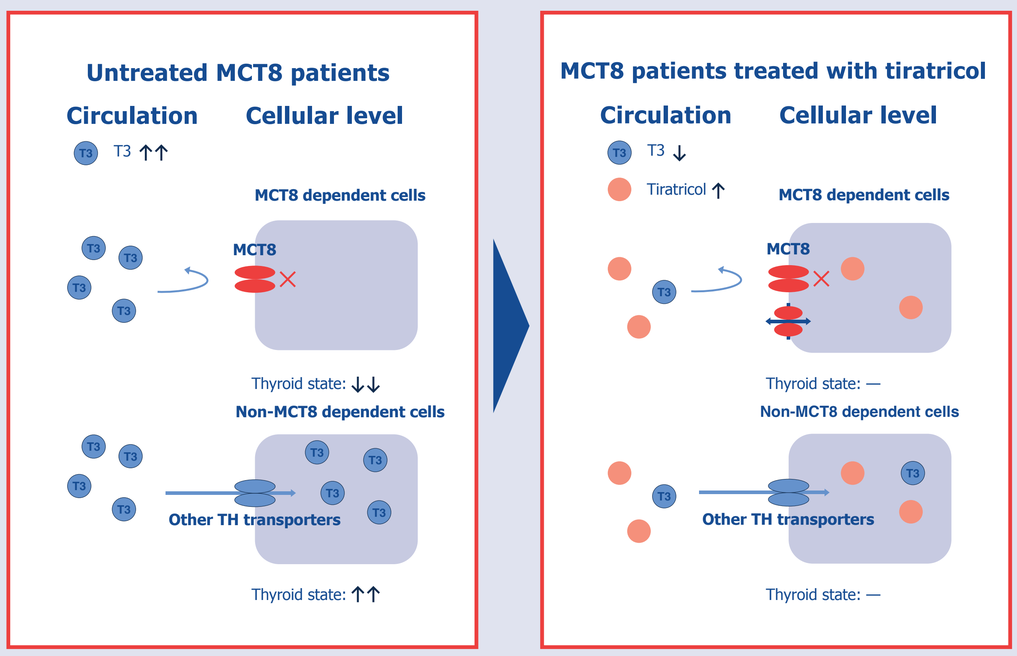
INTRODUCTION

- MCT8 deficiency is a rare, X-linked disorder caused by mutations in the thyroid hormone transporter MCT8.[1,2]
- Patients with MCT8 deficiency typically have profound early neurodevelopmental impairment and peripheral thyrotoxicosis.[1,3,4]
- With no approved medical treatments for MCT8 deficiency, management is primarily focused on supportive care including nutritional support, physical and occupational therapy for neuromuscular dysfunction and medication to manage complications (e.g. antiepileptic medication).[1]
- Tiratricol is an endogenous available metabolite of thyroid hormone, with similar bioactive properties as T3 **(Figure 1)**.[5-7]
  - Tiratricol enters the cell independently of MCT8, bypassing the pathophysiologic defect in MCT8 deficiency.[5-7]

Figure 1. Tiratricol reduces serum T3 concentration by suppressing TSH, leading to improved clinical and biochemical features of thyrotoxicosis.[5-9]



ReTRIACt TRIAL OVERVIEW

- Randomized, placebo controlled clinical trials are challenging to conduct especially within a vulnerable MCT8 deficient patient population[10] – the study uses a home-based nursing approach to minimize the impact on patients and care providers.
- Treatment withdrawal allows collection of randomized, blinded data using fewer participants than with standard parallel design, while minimizing the duration of time in which placebo-treated participants are off active treatment.
- Removal of tiratricol (placebo group) is expected to increase serum total T3 concentration above ULN and require more frequent rescue treatment with tiratricol, compared to those who continue with tiratricol.
- This trial was requested by the US FDA as pivotal for the New Drug Application submission for tiratricol.

METHODS

- This trial (NCT05579327) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study of 16 evaluable male patients, aged ≥4 years, with confirmed MCT8 deficiency, and maintained on a stable dose of tiratricol **(Figure 2; Table 1)**.[11]
- Participating sites are located in the Netherlands, US and UK. The trial is estimated to complete patient enrollment during 2023.

Figure 2. ReTRIACt trial design[11]

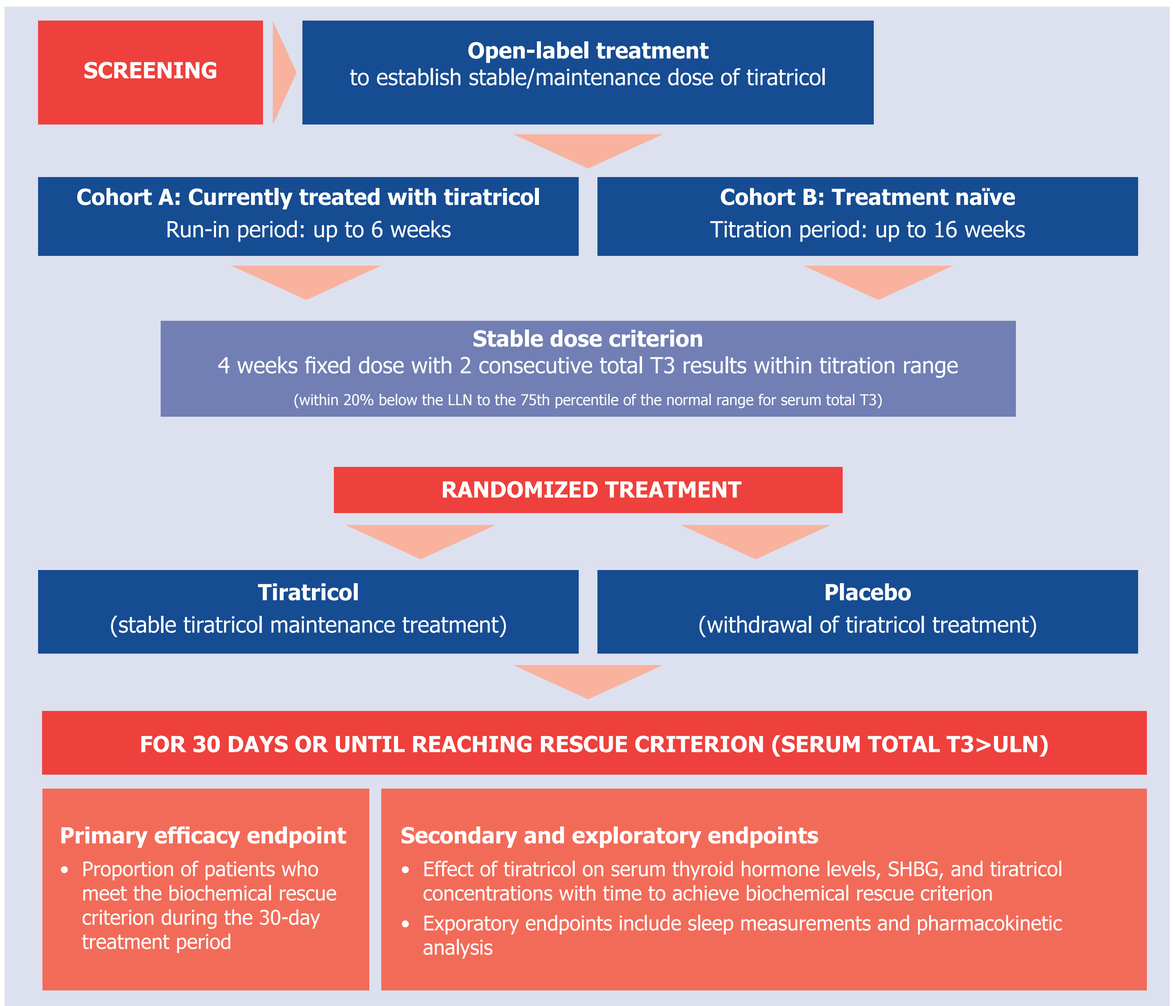


Table 1: Eligibility criteria[11]

INCLUSION	EXCLUSION
Male participants diagnosed with a pathogenic mutation in the MCT8 gene	Major illness or recent major surgery unrelated to MCT8 deficiency
Serum total T3 concentration above the ULN of the age specific normal range	Body weight <10 kg at the Screening Visit
Participants will be aged 4 years or older at the time of randomization	Patients who are participating, or intend to participate, in other therapeutic and/or interventional clinical studies during the study period
Signed and dated informed consent form from the parents or legal guardian	History of allergic reactions to components of tiratricol or any excipients
	Participants with any contraindication for treatment with tiratricol or any excipients
	Participants using other T3 analogues, levothyroxine, or propylthiouracil

HOME NURSING APPROACH

- As trials enrolling patients with severe disabilities who cannot travel or mobilize independently or easily are challenging to manage, a home nursing approach is used to help protect patient and carer quality of life.
- Only three visits to the hospital are required over the course of the trial.
- All remaining assessments are undertaken at home with the assistance of specialist domiciliary nurses and the use of home-based clinical monitoring devices.

POTENTIAL BENEFITS

- Reduced hospital visits
- Increases patient enrollment, promotes patient retention
- Limits exposure to infection
- Can utilize continued blood pressure monitoring and frequent blood sampling at home
- Continuity of care: the same nursing team visits the patient each time
- No need to travel frequently to expert centers that may be distant
- Supports day-to-day quality of life of patient/carers
- Increases patient diversity by including high-risk populations and those living in underserved areas at great distance from clinical sites

POTENTIAL CHALLENGES AND LIMITATIONS

- Increased initial costs, but potential cost saving later due to shorter study duration via increased patient recruitment and retention
- Institutional review board approval for home nursing to be incorporated into the protocol

SUMMARY

- The ReTRIACt Trial aims to verify the effects of tiratricol on thyroid hormone levels in patients with MCT8 deficiency, observed in previous studies.
- Developed with the patient and carer in mind, the ReTRIACt Trial is being conducted primarily in the domiciliary (patients' home) setting.
- The ReTRIACt Trial is part of ongoing research to develop treatment options which target the underlying pathology of MCT8 deficiency.

TRIAL INFORMATION

ClinicalTrials.gov ID: NCT05579327. This trial was developed in collaboration with a patient association and sponsored by Rare Thyroid Therapeutics International AB (now Egetis Therapeutics AB).

FDA, Food and Drug Administration; fT4, free thyroxine; LLN, lower limit of normal; MCT8, monocarboxylate transporter 8; SHBG, sex hormone binding globulin; T3, triiodothyronine; TH, thyroid hormone; TSH, thyroid stimulating hormone; ULN, upper limit of normal.

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