12 December 2024
EMA/586378/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Emcitate

International non-proprietary name: Tiratricol

Procedure No. EMEA/H/C/005220/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AHDS	Allan-Herndon-Dudley syndrome
ALT	alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve (exposure)
BAP	Bone alkaline phosphatase
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BMD	Bone Mineral Density
BMI	Body Mass Index
Bpm	Beat Per Minutes
BSID-III	Bayley Scale of Infant and Toddler Development, Third Edition
BW	Body weight
CHMP	Committee for Evaluation of Human Medicinal Products
CI	Confidence Interval
CK	Creatine Kinase
CMAs	Critical Material Attributes
Cmax	Maximum serum concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CQA	Critical Quality Attribute
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CYP	Cytochrome P
DBP	Diastolic blood pressure
DDI	Drug Drug Interaction
DEV	Development product
DIAC	3,5-diiodothyroacetic acid
DKO	Double Knock-Out
DLP	Data Lock Point
DLT	Dose Limiting Toxicity
DRF	Dose Ranging Finding
EAS	Endocrine Active Substance
EBD	European Birth Date
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EMA	European Medicines Agency
EMC	Erasmus Medical Center
EoS	End of study
ERA	Environmental risk assessment

EU	European Union
FCP	Final Commercial Product
GABA	Gamma-aminobutyric acid
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practices
GMFM-88	Gross Motor Function Measure 88
h	Hours
HED	Human Equivalent Dose
hERG	Human ether-a-go-go-related gene
HINE	Hammersmith Infant Neurological Examination
HPLC	High performance liquid chromatography
HR	Heart rate
HS-GC	Headspace gas chromatography
IC50	Concentration of Drug Producing 50% Inhibition
IR	Infrared
ITT	Intention to Treat
KO	Knock out
LDPE	Low Density Polyethylene
LLDPE	Linear Low Density Polyethylene
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LT4	Levothyroxine
M/O dko	Mct8/Oatp1C1 double knock-out
MAA	Marketing Authorization Application
MATE	Multidrug and Toxin Extrusion Protein
MCR	Metabolic Clearance Rate
MCT8	Monocarboxylate Transporter 8
MedDRA	Medical Dictionary for Regulatory Activities
ML	Molecular Layer
MO	Major objection
MoA	Mechanism of Action
mRNA	Messenger Ribonucleic Acid
MS	Mass Spectrometry
MTD	Maximum Tolerated Dose
MYOD	Myoblast determination protein 1
NA	Not Available
NMR	Nuclear Magnetic Resonance
NOAEL	No Observed Adverse Effect Level
NPU	Named Patient Use
OAT	Organic Anion Transporter
P1NP	Procollagen 1 N-Terminal Propeptide
PAC	Premature Atrial Contraction
PAX7	Paired-box protein 7
PBT	Persistent, Bioaccumulative, Toxic

PC	Purkinje cell
PD	Pharmacodynamic
PEC surface water	Predicted Environmental Concentration in Surface Waters
PEG	Percutaneous Endoscopic Gastrostomy
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PI	Prediction Interval
PK	Pharmacokinetics
PND	Postnatal day
POP-PK	Population PK
PP	Per protocol
PSUR	Periodic Safety Update Report
PVC	Polyvinyl Chloride
QbD	Quality by design
QC	Quality Control
QTPP	Quality target product profile
RMP	Risk Management Plan
rT3	Reverse T3
SAE	Serious Adverse Events
SBP	Systolic Blood Pressure
SC	Satellite Cell (SC)
SD	Standard Deviation
SHBG	Sex Hormone Binding Globulin
SmPC	Summary of Product Characteristics
SOC	System Organ Class
T1/2	Elimination half-life
T3	3,3',5 triiodothyronine
T4	3,3',5,5' tetraiodothyronine (thyroxine)
TA3	3,3',5 triiodothyroacetic acid (tiratricol; Triac)
TEAE	treatment-emergent adverse event
TEP	Treatment Extension Period
TETRAC	3,3’,5,5’-tetraiodothyrocaetic acid
TH	Thyroid hormone
Tmax	Time to Maximum Concentration
TR	thyroid hormone receptor
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Stimulating Hormone
TTC	Threshold of toxicological concern
UGT	Uridine 5'-diphospho--glucuronosyltransferases
ULN	Upper Limit of Normal
UV	Ultraviolet
VABSII	Vineland Adaptive Behavior scale II
WHO	World Health Organisation
WT	Wild Type

XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Rare Thyroid Therapeutics International AB submitted on 6 October 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Emcitate, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2018.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant initially applied for the following indication:

Emcitate is indicated for the treatment of monocarboxylate transporter 8 (MCT8) deficiency in all age groups.

The final applied indication was as follows:

Emcitate is indicated for the treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth.

Emcitate, was designated as an orphan medicinal product EU/3/17/1945 on 8 November 2017, in the following condition:

Treatment of Allan-Herndon-Dudley Syndrome

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Téatrois 0.35 mg tablet
- Marketing authorisation holder: Rare Thyroid Therapeutics International AB
- Date of authorisation:25-06-1974
- Marketing authorisation granted by:
  - Member State (EEA): France
    - National procedure
- Marketing authorisation number: 34009 317 373 5 3

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Téatrois 0.35 mg tablet
- Marketing authorisation holder: Rare Thyroid Therapeutics International AB
- Date of authorisation: 25-06-1974
- Marketing authorisation granted by:
  - Member State (EEA): France
    - National procedure
- Marketing authorisation number: 34009 317 373 5 3

Medicinal product which is or has been authorised in accordance with Union provisions in force used in other studies:

- Product name, strength, pharmaceutical form: Téatrois 0.35 mg tablet
- Marketing authorisation holder: Rare Thyroid Therapeutics International AB
- Date of authorisation: 25-06-1974
- Marketing authorisation granted by:
  - Member State (EEA): France
    - National procedure
  - Marketing authorisation number(s): 34009 317 373 5 3
- Study reference number(s): 2014-000178-20

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Emcitate as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Emcitate

1.5. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication

subject to the present application:

Date	Reference	SAWP co-ordinators
26 July 2018	EMEA/H/SA/3841/1/2018/PA/SME/III	*Dr Kolbeinn Gudmundsson, Dr Mario Miguel Rosa*
13 October 2022	EMA/SA/0000099877	*Audrey Sultana, Fernando de Andrés Trelles*

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

Quality:

- Proposed registered starting materials and the related control strategy for manufacture of the drug substance
- Stability strategy and data availability at time of MAA submission for drug substance and drug product

Non-clinical:

- Overall non-clinical development to support a phase IIb study and MAA

Clinical:

- Primary, secondary and exploratory endpoints to evaluate the effect on neurological development in children and secondary endpoints to evaluate the effect on peripheral symptoms of MCT8 deficiency
- Open-label design, sample size and statistical methods of the Phase IIb study
- Overall adequacy of Triac I trial together with the proposed Phase IIb study to support a MAA in all age groups and the acceptability of a CMA based on one-year data

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Elita Poplavska

The application was received by the EMA on	6 October 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 January 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	29 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to	22 February 2024

the applicant during the meeting on	
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 August 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	25 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	11 November 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 November 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Emcitate on	12 December 2024

2. Scientific discussion

2.1. Problem statement

MCT8-deficiency (Allan-Herndon-Dudley syndrome) is an ultra-rare, chronic, severely debilitating disease caused by mutations in the gene coding for the thyroid hormone (TH) transporter MCT8 protein. Given that the functional mutation is located on the X-chromosome, the condition occurs almost exclusively in males.

Thyroid hormones regulate a multitude of fundamental developmental and physiological processes. The major hormone produced by the thyroid is Thyroxine (T4; 3,3',5,5'-tetraiodothyronine), which is essentially a prohormone. The most important active thyroid hormone is T3 (3,3',5-triiodothyronine), which is mostly derived by de-iodination of T4 and to a lesser extent directly produced by the thyroid gland. Most of thyroid hormone action is mediated via nuclear receptors, which upon binding elicit distinct transcriptional programs. As amino acid derivatives, thyroid hormones need plasma membrane transporters to reach their nuclear receptors. Several transporters from different gene families mediate thyroid hormone uptake into cells.

Monocarboxylate transporter 8 (MCT8) is a highly active and selective thyroid hormone transporter that facilitates the cellular uptake of thyroid hormones in different tissues. MCT8 is abundantly expressed in liver and brain, as well as in the placenta from the first trimester onwards, allowing the transport of thyroid hormone from mother to fetus.

All patients with MCT8 deficiency present with a broad spectrum of both neurological and peripheral symptoms, resulting from disrupted or dysfunctional MCT8-mediated TH transport in various tissues. Since both neural cells and endothelial cells forming the blood-brain-barrier are dependent on MCT8 for TH transport, MCT8 deficiency leads to impaired neurodevelopment resulting in severe intellectual and motor disability. Patients only rarely achieve independent sitting, and most will not be able to maintain head control.

Affected patients never gain even basic neurocognitive functions or early developmental milestones. Peripheral symptoms are dominated by signs of thyrotoxicosis (i.e. low body weight, tachycardia, insomnia, and muscle wasting) caused by elevated serum T3 levels. This may result in serious complications like heart failure and death. The combination of high serum T3, low or low-normal serum free T4 and normal to modestly elevated serum TSH levels is typical for MCT8 deficiency.

The applicant initially applied for the following indication:

Emcitate is indicated for the treatment of monocarboxylate transporter 8 (MCT8) deficiency in all age groups.

The final applied indication was as follows:

Emcitate is indicated for the treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth.

About the product

Tiratricol is a naturally circulating metabolite of active TH (T3), with a very high degree of structural similarity and following the same downward degradation pathway (deiodination and conjugation), eventually being eliminated via bile and urine. Tiratricol is biologically active and demonstrates a largely similar signalling pattern as T3, with similar affinity for the TH receptors TRα and TRβ. Unlike T3, tiratricol is able to pass across cellular membranes, including the blood-brain barrier, in the absence of a functional MCT8 transporter protein. It is this characteristic which provides the theoretical rationale for the use of tiratricol in MCT8 deficient patients.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as dispersible tablets containing 350 micrograms tiratricol as active substance.

Other ingredients are: lactose monohydrate, calcium hydrogen phosphate, maize starch, and magnesium stearate.

The product is available in PVC/Aluminum blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is 2-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid corresponding to the molecular formula $C_{14}H_9I_3O_4$. It has a relative molecular mass of 621.93 and the following structure:

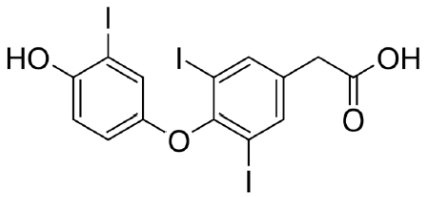

Figure 1: Active substance structure

The chemical structure of active substance was elucidated by a combination of mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy and infrared (IR) spectroscopy.

The active substance is a white to off-white non-hygroscopic solid sparingly soluble in pure water.

The active substance does not exhibit stereoisomerism as tiratricol has no chiral centre and is not an optically active compound.

In relation to polymorphism, the active substance can exist in different solid forms. Only one form is produced in the established manufacturing process .

Manufacture, characterisation and process controls

Satisfactory GMP documentation has been provided for the active substance manufacturers.

Particle size reduction of active substance is performed at a manufacturer different from the manufacturer performing the chemical steps. During evaluation an updated QP declaration including this site was requested as a Major Objection (MO) by the CHMP, the requested information was provided and the response was considered satisfactory.

The active substance is synthesised in eight main steps using well defined starting materials with acceptable specifications.

The manufacturing process has been described in detail including standard quantities of used raw materials along with allowed ranges, equipment, processing times, reaction conditions, yields ranges. The particle size reduction step is included in the manufacturing process.

The particle size of the active substance is reduced to achieve a standardised and homogenous powder. Test for particle size is included in the specification of the active substance The process parameters for the particle size reduction step are specified.

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Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

During evaluation, an MO was raised that any impurity with structural alert in its structure should be discussed and controlled according to ICH M7 which is applicable for this active substance. According to the applicant response, compounds identified as potentially mutagenic are found in early steps of the manufacturing process of tiratricol. There is a scientific rationale to expect a substantial purge in the downstream process and the purge factor analysis (PFA), performed according to the *ICH M7*-recommended methodology, shows that the theoretical carryover of the potentially mutagenic compounds is below the TTC of 357 ppm by a factor of >100. Spiking experiments have also been performed showing that the worst-case amounts (i.e. specification acceptance criteria or higher) of all specified impurities in the intermediates and starting materials are well purged in the process, and subsequent crystallisations have proven to be very effective in removing a range of impurities from the up-stream process.

All identified potentially mutagenic related compounds have been discussed and the specification acceptance criteria for alerting impurities are now equal to, or lower than, what were used in the spiking experiments.

The presented risk assessment, and the resulting control strategy is a combination of purging experiments, theoretical, scientifically based, justifications and analytical testing of those alerting compounds present in the largest amounts. Combined, this confirms that the applied control strategy will yield active substance with none of the identified alerting compounds above the acceptable level. The response was considered satisfactory.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The manufacturing process development has been discussed in detail. Significant optimisation of synthesis has been done during development. This includes change of reagents and solvents, variations in process conditions, such as temperature, change in isolation procedures of intermediates etc.

The manufacturing process of the active substance has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment, and NOR (Normal Operating Range). However, design spaces have not been proposed.

The active substance is packaged in double anti-static LDPE/LLDPE bag, each sealed with a tamper evident cable tie. The material complies with the Ph. Eur. monograph for Polyolefins 3.1.3 and with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for description (visual), identification (IR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (HS-GC), acetic acid (HPLC), water (Ph. Eur.), free iodine (HPLC), microbiology (Ph. Eur.), and particle size distribution (Laser diffraction).
The limits for the related substances were set according to the ICH guideline on impurities and justified by results.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set (refer also to the discussion above on the MO about the potential mutagenic impurities).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. A forced degradation study has been presented.

Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data for commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Considering that tiratricol is an existing active substance, this is sufficient in line with the requirements stated in Guideline on stability testing: stability testing of existing active substances and related finished products Rev 1 (CPMP/QWP/122/02, rev 1).

The following parameters were tested: description, assay, impurities, water content, microbiological tests, particle size distribution and polymorphic form. The analytical methods used were the same as for release and were stability indicating.

Results from the ongoing stability studies at 25 °C, including results of particle size distribution and polymorphic form results, are available until 12 months. The active substance is shown to be stable and within specification at long-term condition (25 °C/60 % RH). The finalized study at the accelerated condition (40 °C/75 % RH) shows a stable impurity profile with no trends of further decrease in assay or increase in related substances nor changing of particle size or polymorphic form.

Photostability testing following the ICH guideline Q1B was performed on one batch. Taking into account the results, the active substance is photostable and there is no need for extra precautions regarding photodegradation during normal handling of tiratricol.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months with no storage conditions in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as white, oblong tablet (size: 10 mm long, 5 mm wide) with score lines on both sides.

The finished product is a hybrid product with the reference medicinal product Teatrois. The finished product has been developed to be equivalent to Teatrois. Consequently, the objective was to prepare a dispersible tablet being essentially similar to the reference medicinal product.

The active substance is described including information about the pH depending solubility of the active substance, and the particle size. The finished product is dispersed in a small volume of water before administered to patients and the excipients in the product generate a pH in the small volume in the range of

approx. pH 6.2 to 6.5, therefore, it is considered unlikely that the solubility of the active substance would impact the product performance when the suspension is administered to the stomach that holds pH of about 1-2. The proposed particle size limit is adequately justified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The similarities and differences among the reference medicinal product Teatrois, Emcitate-DEV (a similar product used in clinical studies) and final commercial product Emcitate FCP has been discussed in detail and are stated below.

As the tablets must be dispersed in 30 mL of water before being administered to patients, the standard term of the finished product is "Dispersible tablet" according to Ph. Eur. monograph 0478 for tablets.

The Quality Target Product Profile (QTPP) forms the basis for the design of the development of the final commercial product.

The Critical Quality Attributes (CQAs) are derived from the QTPP. CQAs are defined as the aspects affecting product purity, strength, drug release and stability. The CQAs identified for the finished product are: assay, content uniformity, degradation products, dissolution, disintegration, and fineness of dispersion.

The targets and limits of the CQAs have been defined and, together with other quality attributes, form the basis for the proposed specification of the finished product. As part of the formulation and process development, the Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) were defined and the probability and degree of impact on the CQAs were assessed using risk assessment tools. Risk assessment has been updated as needed when additional information, data and manufacturing experience have been obtained. However, no design spaces were claimed.

The suitability of the finished product for use in children has been considered and the selection of excipients have been made in context of EMA's *Guideline on pharmaceutical development of medicines for pediatric use (EMA/CFMP/QWP/805880/2012 Rev. 2)*. Only minor composition changes were introduced as compared to the original composition of the reference medicinal product that was judged to be suitable also for children.

Initially Emcitate-DEV 350 µg tablet batches was developed and compared to available Teatrois batches with regards to dissolution to evaluate product performance. All batches had more than 85 % dissolved at 15 minutes. Hence, it was concluded that Teatrois and Emcitate-DEV could be considered equivalent.

The difference between the reference medicinal product and Emcitate-DEV includes minor changes in the manufacturing process, and the shape of the tablet (from a 8 mm biconvex round tablet to a 7 mm flat tablet).

The tablet shape was further changed to an oblong sub-dividable 350 µg dispersible tablet with score lines to facilitate handling and dosing to the paediatric patient group. The divisibility of the tablets has been shown according to the requirements in Ph. Eur. Tablets 0478. Also, to improve compressibility, the tablet filler calcium hydrogen phosphate dihydrate was changed to calcium hydrogen phosphate. The optimised final commercial product is denoted Emcitate FCP in this dossier.

Dosing is individualised based on a patient's response. A large portion of the children have difficulties in swallowing, and many also have percutaneous endoscopic gastrostomy (PEG), the tablets are therefore developed to be easily dispersed in a small volume of water for dosing of a suspension. Studies were performed on tube sizes appropriate for the intended use to ensure acceptable recovery and ease of

administration, as well as confirming that tube blocking was not an issue.. The amount of water used for dispersing the tablets needed to be kept at a minimum to not interfere with volumes needed for providing daily volumes of liquids and food given to the patients to cover the necessary calory intake. This study demonstrated compatibility.

No BE/BA study is performed with Teatrois tablets since the reference medicinal product was withdrawn from the market in 2020. The differences between Teatrois and Emcitate-DEV are changes in the tablet shape and size. The presented dissolution results showed differences in all tested media (pH 1.2; 4.5; 6.8) in both products. In addition, it was concluded that the QC method could detect differences in dissolution profiles between the tablet formulations. These differences are explained by the disintegration behaviour in the dissolution vessels, where Teatrois and Emcitate-DEV take longer time to disintegrate. Both Emcitate-DEV and Teatrois have been used in clinical studies and the established PK-PD relationship between Teatrois and Emcitate-DEV confirms the scientific bridge between these products. For more information of this issue please refer to Clinical part.

Moreover, a bioequivalence (BE) study of Emcitate-DEV vs Emcitate FCP was performed but no information on this could be found in Module 3 of the dossier. During evaluation, the CHMP requested as MO that a summary of the BE study Emcitate-DEV vs Emcitate FCP should be provided in Module 3. As a response to the MO a summary of the BE study Emcitate-DEV vs Emcitate FCP has been included in Module 3.

During evaluation, due to differences in dissolution behaviour, the equivalent in-vitro dissolution between Teatrois, Emcitate DEV and Emcitate FCP was not demonstrated. Consequently, the pharmaceutical equivalence could not be concluded based on the provided data. Therefore, the CHMP requested as MO that the comparative dissolution testing in line with Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev .1/Corr needed to be performed. Considering that in vivo bioequivalence has been shown between Emcitate-DEV and Emcitate FCP, the lack of in vitro dissolution similarity suggests that the in vitro dissolution method is over-discriminating. Indeed, the BE study demonstrated Emcitate-DEV and Emcitate FCP are bioequivalent; this was considered satisfactory. (For assessment of these issues please refer also to the clinical part of the report). Satisfactory information has been provided with respect to Emcitate-DEV and Emcitate FCP batches used in the BE study, and it can be concluded that the BE study batches complied with the requirements as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev .1/Corr). Together with the established PK-PD relationship between Teatrois and Emcitate-DEV mentioned above, the scientific bridge between all three products – Teatrois, Emcitate-DEV and Emcitate FCP has been confirmed from a quality point of view.

The development of dissolution method has been described in detail and the discriminating power of the chosen method has been investigated. The dissolution method can discriminate between formulations used during development that visually show different disintegration behaviour in the dissolution vessels. The development to set the dissolution method parameter has included all relevant aspects and based on that, the proposed QC dissolution method is regarded as suitable The dissolution parameters are justified but not the specified limits. Therefore, the CHMP requested as MO that the dissolution specification should be set based of the results of bio-batches according the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action. The dissolution specifications were revised accordingly, therefore the response was considered satisfactory.

Based on the prior knowledge from the manufacturing of the commercial product Teatrois and the initial risk assessment of the process parameters with regards to the impact on the CQAs, investigations were performed to reduce risk of the CPPs and to optimize the process. The main part of process development studies has been performed on the formulation Emcitate-DEV. The only difference from the final commercial

product, Emcitate FCP, is the grade of the filler calcium hydrogen phosphate and the tablet shape. For Emcitate FCP, studies to investigate impact of selected CPPs on relevant CQAs have been performed, as well as manufacturing of batches to verify set points, targets and ranges for the intended commercial manufacturing process. The process is scaled up to the intended commercial batch size.

The primary packaging is in PVC/Aluminum blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory GMP documentation has been provided.

The manufacturing process consists of 9 main steps: blanketing, sieving, pre-mixing, sieving pre-mix, mixing, sieving, lubrication, tablet compression, and packagingThe process is considered to be a non-standard as the amount of the active substance is ≤ 2% of the composition.

Critical steps were discussed in detail and the critical process parameters (CPPs) are clearly stated. The justification and supportive data for the CPPs and control strategy are described in sufficient detail.

During evaluation, as the manufacturing process is considered non-standard, the CHMP requested as MO that process validation data for three consecutive production scale batches should be submitted. As a response, process validation data of three consecutive batches have been conducted according to an approved validation protocol with predefined acceptance criteria, which included testing according to final product specification and extended and additional testing for validation purposes . The validation results provided in the response confirm that the finished product can be successfully and reproducibly produced by the manufacturer, when using the batch formula and intended commercial manufacturing process. In addition, the process validation confirmed that the established control strategy is appropriate, resulting in the desired product quality. The response was considered satisfactory. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual examination), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), disintegration, dissolution (Ph. Eur.), fineness of dispersion (Ph. Eur.), and microbiological tests (Ph. Eur.).

The release and shelf life specifications presented cover relevant parameters for this dosage form and are suitable to control the quality of the finished product.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the

"Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). During the evaluation, the CHMP requested as MO to perform confirmatory testing for available batches of finished product or final active substance if adequately justified to confirm that there is no need to control levels of nitrosamines in routine. Considering that trace levels of amines and nitrites may form nitrosamines during storage of the finished product, the actual batch results instead of theoretical calculations were requested. Additionally, to exclude the risk caused by nitrocellulose in the primary packaging, the applicant was advised to use primary packaging materials which do not contain nitrocellulose. Based on the results from the confirmatory testing of the active substance showing results consistently below 10% of the acceptable limit, the updated information for potential contamination during the manufacturing and the statements from excipient and packaging suppliers, the conclusion is that there is no risk of nitrosamine presence in the finished product. Therefore, the CHMP considered that no specific control measures are deemed necessary

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 18 months under long term conditions at 5°C/amb, and 12 months at accelerated condition 25 ºC / 60% RH according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

During evaluation, the CHMP requested as a MO that stability data should be updated with further data from the ongoing stability studies. Updated stability data, evaluated against the shelf-life specification was provided and considered satisfactory.

Samples were tested for description, assay, degradation products, disintegration, dissolution, fineness of dispersion, and microbial limit. The analytical procedures used are stability indicating.

All results meet the proposed specification criteria at all three tested conditions for all three batches up to the tested time points. However, based on available data at 12 months 25 °C/60 %RH and 6 months 40°C /75% RH, it can be concluded that degradation occurs in these conditions to a larger extent than initially expected. Therefore, it is recommended that the finished product is stored in refrigerator (2 °C – 8 °C).

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results showed an impact on stability after direct light exposure of tablets and tablets in blisters. However, the finished product is protected when kept in the cardboard box.

Based on available stability data, the proposed shelf-life of 18 months when stored in a refrigerator (2 °C to 8 °C) and in the original package in order to protect from light as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During evaluation, seven MOs were raised by the CHMP in relation to update QP declaration, impurities of the active substance, BE study of the finished product, dissolution data of the finished product, process validation of the finished product, risk assessment of nitrosamines, and stability of the finished product. The responses from the applicant to the MOs were considered satisfactory and all the issues were considered to be resolved, as explained above.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design space was claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Emcitate (Tiratricol; Triac) is a structural analogue of T3 and an endogenous, naturally occurring metabolite of T3 present at low titers in the human body. Tiratricol is primarily formed in the liver through side chain modification of T3. It binds with high affinity to thyroid receptors, and thus exerts similar biologic effects as T3.

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. Nevertheless, a new pharmacology study of tiratricol on brain development was conducted in mouse model. In addition, toxicity information from the dossier of the reference product were submitted, which further support the absence of full non-clinical development. Except for an in vitro hERG assay, information from dedicated safety pharmacology studies were not available. The applicant performed a 3-month toxicity study in rat and a 14-day oral dose ranging finding (DRF) study in dog. Moreover, in vitro DDI studies have been completed as well as in vitro and in vivo genotoxicity assays. The additional non-clinical data are presented below.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamics

In vitro data on primary pharmacodynamics such as receptor binding or cellular uptake of tiratricol were derived from published literature.

The study of Everts and colleagues (Everts et al., 1994) shows that Triac uptake into anterior pituitary cells isolated from adult WT rats is higher compared to uptake of T3. Moreover, Triac was shown to be more potent to suppress TSH secretion compared to T3.

The Mct8-ko mouse model is not a suitable model for the neurocognitive phenotype of MCT8 deficiency in humans since these mice lack any evident neurological deficit. The discrepancy between Mct8-ko mice and MCT8 deficiency patients is probably explained by the compensatory role of the specific T4 transporter Oatp1c1 that is present in rodent blood-brain-barrier (BBB) but absent in primate BBB (Mayerl et al., 2012). Therefore, the applicant studied Triac treatment in mice deficient for Mct8 and Oatp1c1.

PCs in M/O dko mouse displayed stunted dendritic arborisation reminiscent of the situation under hypothyroidism, with a reduction in thickness of the ML to almost 60% of the respective wt control levels. Treatment with Triac dose-dependently improved the dendritogenesis of PCs. At the lower dose, Triac (50 ng/g bw) increased the thickness of the ML by around 10%. Upon treatment with Triac at 400 ng/g bw M/O dko mice showed a ML thickness at around 90% of the wt controls.

Figure 2 shows effect of Triac treatment on cerebellar development (Staining of cerebellar sagittal sections from P12 animals with an anti-calbindin antibody; Bar graph shows group means ± SD; ** P < 0.05; *** < 0.001; N=3/4 per group; scale bar 50 µM). The effect of dKO on ML thickness was rather low. Tiratricol dose-dependently increased ML thickness.

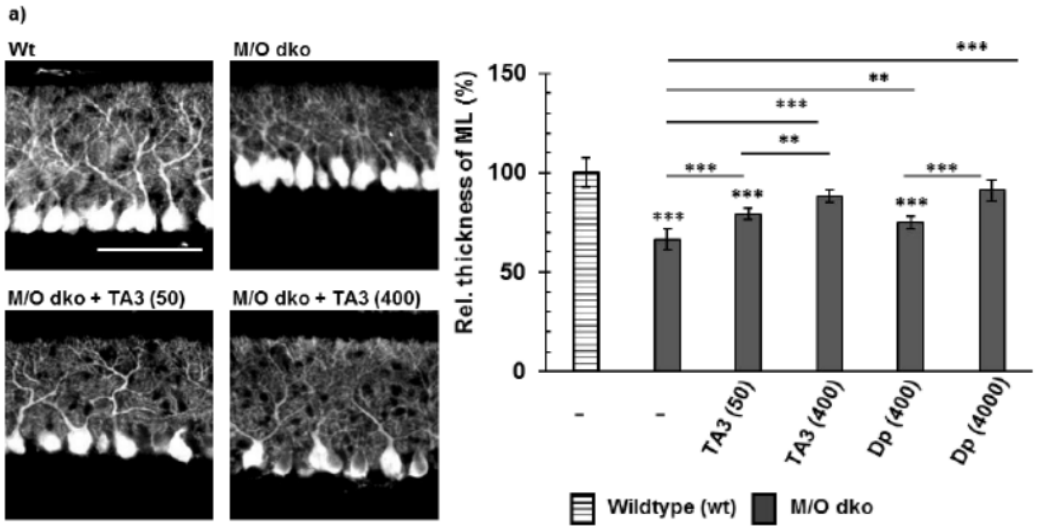


Figure 2. Effect of Triac treatment on cerebellar development

Overall, the study showed that tiratricol had an ameliorating effect on parameters of brain development, as evidenced by improvements in cerebellar PC dendritogenesis, status of myelination, and development of the GABAergic system. Furthermore, tiratricol showed an upregulating effect on Hr gene expression in the brain and a suppressive effect on Trh and Tsh transcription, indicating improved feedback control on the HPT axis. These ameliorating effects were more pronounced at high doses of tiratricol. Moreover, these data suggest that administration of tiratricol within the first three postnatal weeks in mice is critical.

In a study by Mayerl et al. 2018 on thyroid hormone transporters MCT8 and OATP1C1 controlling skeletal muscle regeneration, the authors elucidate satellite cells (SC) function and regenerative capacity in Mct8/Oatp1c1-deficient mice. The authors demonstrate that both TH transporters become upregulated in activated SCs and that a combined Mct8/Oatp1c1 deficiency results in impairments in SC differentiation, thereby leading to a delayed skeletal muscle regeneration.

THs are known to orchestrate the differentiation process within the myogenic program. For further elucidation whether the absence of MCT8 and/or OATP1C1 might interfere with the activation and differentiation of SCs, EDL myofibers were isolated from WT and TH transporter-deficient, 4-month-old female mice and analysed directly or after 72 hr in culture. Staining for the SC marker PAX7 and the differentiation marker MYOD demonstrated no aberrant activation of SCs under resting conditions in TH transporter-deficient mice.

The overall percentage of PAX7-positive cells per cluster was comparable between the genotypes after 72 hr in culture. However, differences in their differentiation state became apparent: the percentage of non-differentiated SCs expressing only PAX7, but not MYOD, per cluster was almost doubled in EDL cultures of Mct8/Oatp1c1 DKO mice, whereas the percentage of committed SCs (PAX7/MYOD double-positive) was reduced by 47% , suggesting a delay in differentiation of SCs.

SC Activation and Differentiation is delayed in myofiber cultures of M/O DKO Mice Marker-positive cell nuclei were quantified and revealed a higher percentage of PAX7 only immunopositive nuclei in M/O deficiency at 72 hr. Group means + SEM are shown. *p < 0.05; **p < 0.01; ***p < 0.001. Two-way ANOVA and Bonferroni-Holm post hoc testing. Scale bar: 10 mm.

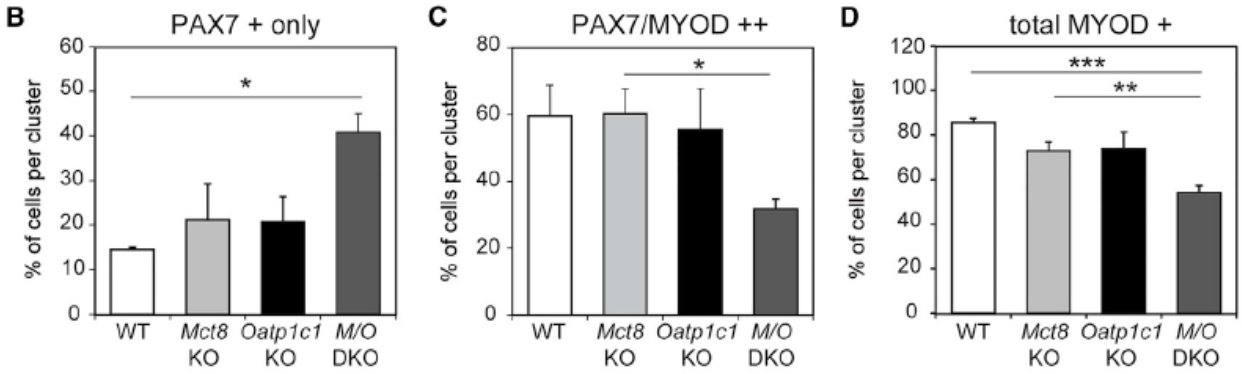


Figure 3. SC Activation and Differentiation

According to this publication, the lack of intracellular thyroid hormones (THs) affects differentiation of muscle stem cells (satellite cell) to mature myofibers. This could be an alternative explanation for the observed muscle weakness in AHDS. Usually, it is assumed that the muscle weakness is a consequence of peripheral hyperthyroidism, i.e. a secondary effect TH deficiency in the brain. However, it is noted that muscular hypotension and hypoplasia is a very typical finding of AHDS that is – in contrast to clearly secondary signs like spasms – already present at birth.

2.3.2.2. Secondary pharmacodynamics

No secondary pharmacodynamics studies were conducted with tiratricol. Instead, published data on pharmacologic effects of tiratricol on the cardiovascular system, the liver and adipose tissue, as well as on basal metabolism and bone metabolism was presented and discussed. This was considered acceptable by the CHMP. See section 2.3.7.

2.3.2.3. Safety pharmacology

Tiratricol produced a concentration-dependent inhibition of hERG tail current amplitude by 5.0 ± 1.4%, 12.2 ± 2.1%, 16.8 ± 1.3% and 23.0 ± 2.0% in the presence of TIRATRICOL at 0.1, 1, 10 and 30 µmol/L, respectively. This inhibition was statistically significant ($p<0.01$).

2.3.3. Pharmacokinetics

TK data generated in association with the small (n=1/sex/dose) 14-day oral DRF study in dogs showed overall an increase in exposure with dose. Tmax occurred in most animals at the 1-hour time point. After 14 days of repeat dosing, a decrease trend in the exposure was noted in all groups with the exception in the male given 0.15 mg/kg/day. Although the blood sampling was not sufficiently frequent to assess the elimination half-life with any degree of certainty, data suggest a figure in the range of 1.5-10.5 hours. No obvious gender difference was noted.

2.3.3.1. Pharmacokinetic drug interactions

Around 99.9% of tiratricol is bound to plasma proteins. For estimating the likelihood of PK drug-drug interactions, an unbound fraction of 1% was assumed in line with ICH Guideline M12.

In line with the Protocol Assistance, in vitro DDI studies were performed to evaluate the potential for interaction of tiratricol with CYP450 metabolizing enzymes and transporters, and to assess the potential for clinically relevant DDI. Direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (midazolam and testosterone used as the substrates) was observed for tiratricol with IC50 values of 52.8, 18.6, 1.68, 3.38, 82.2, 23.3, 34.3, and 47.6 µM, respectively. Moreover, the IC50 shift ratios of tiratricol without pre incubation and with 30 min pre-incubation (with and without NADPH) were all less than 1.5-fold, indicating no time-dependent inhibition potential in the tested concentration range 1 to 300 µmol/L.

The potential for tiratricol to induce CYP450 metabolizing enzymes was assessed. The results indicated potential for in vivo induction of CYP3A4 at 10 µM in 3/3 donors, of 1A2 in 1/3 donors, and 2B6 in 2/3 donors.

Evaluation of tiratricol inhibitory potential on UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15 and UGT2B17 enzymes was performed and IC50 values of 5.93, 6.99, 4.81, 11.2, 2.86, 7.66, 14.7 and 1.28 µM, respectively, were determined.

Tiratricol is not a substrate of P-gp or BCRP efflux transporters, nor of solute carrier transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2-K.

2.3.4. Toxicology

2.3.4.1. Repeat dose toxicity

In a 4-week dose ranging study of tiratricol (0, 50, 150 or 450 µg/kg/day from postnatal Day 7 to Day 34), administration of tiratricol to juvenile rats by oral gavage was associated with low incidences of minor clinical signs at 450 µg/kg/day (fur staining, abnormal faecal output or abnormal gait). At doses of 450 µg/kg/day food consumption was generally higher than control with the greatest effect at the time of weaning but did persist to the end of the study.

Tiratricol induced a dose-related reduction in TSH, T3, and T4 in both male and female animals. At 450 µg/kg/day, the suppression was highly marked and T3 was below the limit of quantification in all animals. There were no gross findings at necropsy, however, organ weight analysis of the 450 µg/kg/day group showed a higher weight of the heart and spleen (both absolute and relative to body weight) in both genders. Higher kidney weights were also evident in female animals at 450 µg/kg/day but were not evident in males. Based on these observations, the dose levels in the main study were set to 0, 50, 100 and 300 µg/kg/day.

In a 14-day dose-range finding toxicity and toxicokinetic study of tiratricol in Beagle dogs; once daily oral intubation administration of tiratricol at doses up to 5 mg/kg/day for 14 consecutive days was tolerated in Beagle dogs. The most prominent findings were decreased cholesterol levels in animals given ≥0.15 mg/kg/day independent of sex and increased ALT in males at 5 mg/kg/day.

During the procedure, final results from a 13-week repeat dose toxicity GLP study in dogs were submitted. The dose levels (0, 0.15, 0.5 and 5 mg/kg day) used in this study were the same as those used in a previous 6-month non-GLP study submitted for the reference product. There were no mortalities or tiratricol-related changes in food consumption, body temperature, blood pressure, or macroscopic findings in the study animals. Significant tiratricol-related decreases in T3 and T4 levels were observed in animals receiving ≥0.15 mg/kg/day on days 52 and 91, which were completely recovered at the end of the recovery phase. TSH levels were only slightly reduced on Days 52 and 91 in animals given ≥ 0.15 mg/kg/day.

The main tiratricol-related clinical effects were a reduction in body weight in males at 5 mg/kg/day and lower body weight gains in males at 0.5 mg/kg/day and in females at 5 mg/kg/day. At terminal sacrifice, tiratricol-related differences in organ weight parameters were limited to differences in heart and thyroid gland weights. Heart weight parameters were increased in both sexes at 5 mg/kg/day. Thyroid gland weight parameters were decreased in animals received 5 mg/kg/day and correlated microscopically with decreased colloid.

At the recovery sacrifice, tiratricol-related microscopic changes were observed in the pituitary gland (increased incidence and severity of decreased eosinophilic granules (eosinophils)) and liver (centrilobular mixed cell infiltrates) at doses ≥0.15 mg/kg/day, in the lung (an increased incidence and/or severity of perivascular mononuclear cell infiltrates) at doses ≥0.50 mg/kg/day, and in the eye (lens fibre degeneration) at the 5 mg/kg/day dose level. Microscopic observations in the pituitary gland, liver, and eye noted at the recovery sacrifice were consistent with a partial reversal of the changes observed at the terminal sacrifice.

Tiratricol-related changes in ECG parameters included increased heart rate on days 52 and 87 in animals at 0.5 and 5 mg/kg, with significance achieved at 5 mg/kg. There was also a prolongation on the heart rate corrected QT interval (QTcV) in animals at 5 mg/kg/day at pre-dose and post-dose on Days 52 and 87. No increase in heart rate or prolongation of QTcV were observed at the end of the recovery phase.

2.3.4.2. Genotoxicity

Tiratricol was negative in GLP-compliant in vitro Ames tests and an in-vitro Micronucleus test in TK6 cells.

In a GLP-compliant in vivo micronucleus assay, it was also found not genotoxic in vivo up to the MTD yielding large exposure margins to the maximum clinical dose.

2.3.4.3. Carcinogenicity

No carcinogenicity studies were conducted with tiratricol. Due to the nature of tiratricol as non-genotoxic T3 metabolite, which is administered clinically to restore TH balance in MCT8 deficiency, the risk for carcinogenic effects in patients is considered low and no carcinogenicity studies are warranted.

This is further supported by the results of two dose-range finding studies in Tg RasH2 mice. These showed that triatricol at doses up to 3000 µg/kg/day for 28 consecutive days was clinically well tolerated; no unexpected toxicities were observed.

2.3.4.4. Reproduction toxicity and developmental toxicity

Emcitate has not been studied for adverse effects on fertility and early embryonic development, embryo-foetal toxicity, prenatal and postnatal development, including maternal function. Reference to Téatrois was made and considered acceptable by the CHMP.

2.3.4.5. Toxicokinetic data

Data are described in section 2.3.3.

2.3.4.6. Local tolerance

The Applicant has not undertaken local tolerance studies with tiratricol, nor were such studies described in the literature. This is in line with the current Guideline on non-clinical local tolerance testing of medicinal products (EMA/CHMP/SWP/2145/2000 Rev. 1, Corr.*) stating that for medicinal products administered by the oral route of administration, local tolerance investigations are considered unnecessary unless excipients are used that are likely to have an irritant potential.

2.3.4.7. Other toxicity studies

Potential mutagenic impurities were evaluated. Purge calculations indicated that from the identified potential mutagenic impurities none would be present in the final drug substance at levels above the TTC of 1.5 µg/day. Two main non-mutagenic impurities have been identified for the tiratricol drug substance, i.e. DIAC (3,5-diiodothyroacetic acid) and TETRAC (3,3',5,5'-tetraiodothyrocaetic acid) above the ICH Q3A qualification threshold of 0.15%. Both impurities can be considered qualified by use as they were consistently found at higher levels in the reference medicinal product Téatrois. Furthermore, DIAC and TETRAC were also present in 6-months repeat-dose toxicity study in dogs at sufficiently high levels so that they can also be considered as toxicologically qualified.

2.3.5. Ecotoxicity/environmental risk assessment

The Action Limit of 0.01 µg/L is not exceeded in Phase I of the ERA for tiratricol. Tiratricol is considered an endocrine active substance (EAS). A phase II ERA should be considered, however, tiratricol is a naturally occurring substance and is considered a metabolite of triiodthyronamine. Therefore, a deeper environmental risk assessment is not necessary. The partition coefficient at environmentally relevant pH values is below 4.5 (pH 7 log Dow= 2.4). Therefore, a PBT Assessment is not considered necessary.

Table 1. Summary of main study results

Substance (INN/Invented Name): Tiratricol			
CAS-number (if available): 51-24-1			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD107	log Dow (pH 7) = 2.4 log Dow (pH 9) = 1.24	Potential PBT N
PBT-assessment			
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined with prevalence	0.0000021	µg/L	> 0.01 threshold N

2.3.6. Discussion on the non-clinical aspects

Pharmacodynamics

The applicant has not conducted own primary in vitro pharmacodynamics studies. Instead, a wide number of published literature was provided and discussed. These publications applied cell and tissue models from different species such as rat, monkey, or a human neuroblastoma cell line. Altogether, the published data confirm that tiratricol is a potent thyromimetic agent, which shows the ability to penetrate CNS cells and improve impairments in early neurological development. Moreover, the data discussed were overall supportive for the beneficial role of tiratricol in regulating thyroid signalling in comparison to T3. Nevertheless, as expression patterns of TR are crucial for particular effects of tiratricol compared to T3, a more comprehensive expression analysis of thyroid receptors in human (primary) cells would have been desirable.

In vivo, the applicant provided a pivotal study of tiratricol treatment of Mct8/Oatp1c1 dKO mice, which is a better model for Mct8-deficiency in humans. Overall, the study showed that tiratricol had an ameliorating effect on parameters of brain development, as evidenced by improvements in cerebellar PC dendritogenesis, status of myelination, and development of the GABAergic system. Furthermore, tiratricol showed an upregulating effect on thyroid hormone target gene expression in the brain and a suppressive effect on Trh and Tsh transcription, indicating improved feedback control on the HPT axis. These ameliorating effects were more pronounced at high doses of tiratricol. Moreover, early tiratricol treatment at high dose (400 µg/kg/day) exerted long-term beneficial effects (improved locomotor function and muscle strength). Moreover, these data suggest that administration of tiratricol within the first three postnatal weeks in mice is critical. The presented data suggest that for suppression of TSH mRNA expression in the pituitary gland much lower tiratricol doses are needed than for correcting neurological deficits. This has implications for clinical dose selection, which is further discussed below (interspecies comparison).

With regard to secondary pharmacodynamics, the applicant provided literature indicating a profound effect of tiratricol on periphery organs, most prominently on cardiac hypertrophy and bones.

No preclinical studies have been conducted by the applicant or identified in the literature that describe adverse respiratory effects of tiratricol. No clinical signs affecting the respiratory system have been reported in the conducted 13-week toxicity study in dogs or the 13-week juvenile toxicity study in rats. This is considered acceptable by the CHMP.

Pharmacokinetics

Exposures over the range of dose levels used in toxicity studies are lacking. The average residence time of tiratricol in the exchangeable compartment after i.v. injection was 5.5 h compared with 10.9 h for T3 and the MCR was 144 mL/h/kg for tiratricol and 176 mL/h/kg for T3. The average distribution space was 40% lower for tiratricol compared to T3.

Literature data showed that tiratricol is metabolized in rats, dogs, and humans via similar pathways as T3, i.e. by stepwise deiodination, resulting in urinary iodide excretion, and by conjugation predominantly with glucuronic acid but also with sulfate. The excretion of tiratricol-related material in rats and dogs occurs mainly via the fecal route and to a lesser degree via the kidneys and into the urine. In contrast, elimination via urine seems to be the main route of excretion in humans. Distribution studies have shown that human plasma protein binding is 99.9% over a tiratricol concentration range of 5-50 µmol/L.

The applicant has performed DDI studies as recommended in the 2018 Protocol Assistance. *In vitro* studies suggest that tiratricol is not a perpetrator of metabolism mediated DDI due to direct or time dependent CYP450 inhibition or CYP450 induction at clinical doses. CYP inhibition study demonstrated a direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A with tiratricol IC50 values of 52.8, 18.6, 1.68, 3.38, 82.2, 23.3, 34.3 and 47.6 µM, respectively. There is an effect on expression of particular CYP subtypes at high doses; however, the clinical relevance is most likely low.

Evaluation of tiratricol inhibitory potential on UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15 and UGT2B17 enzymes was performed and IC50 values of 5.93, 6.99, 4.81, 11.2, 2.86, 7.66, 14.7 and 1.28 µM, respectively, were determined. Tiratricol showed a concentration dependent inhibition of BCRP-, P-gp-, OAT1-, OAT3-, OATP1B1-mediated transport with an IC50 values of 1.53 µM, >30 µM, 1,18 µM, 0.578 µM, 0.432 µM, respectively. Tiratricol inhibited OCT-1-, OCT-2-, OATP1B3- and MATE1-mediated transport with an IC50 value of >5 µM.

Tiratricol was not a substrate for efflux transporter BCRP, P-gp and was not a substrate of human solute carrier transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2-K.

Interspecies comparison

The therapeutic approach of treating MCT8 deficiency with tiratricol is based on animal PD studies.

These studies revealed that a tiratricol daily dose of 400 µg/kg was able to counteract the unfavourable neurological consequences of MCT8 knock-out (in mice also lacking OATP1C1, i.e. dKO mice).

A comparison of the dose effective in mice to a human dose was requested by the CHMP. However, this was not possible with the available mice and human PK data and the following PK based approach was thus made by CHMP:

In the two clinical trials, Triac I and Triac II, the participants received mean daily tiratricol doses of 37 µg/kg and 175 µg/kg, respectively. In the adult BE study, the tiratricol dose was approximately 13 µg/kg. The latter yielded an AUC (0-last) of 56.7 ng·h/mL. Linear extrapolation to the mean dose in Triac I, 37 µg/kg, yields an AUC of around 160 ng·h/mL.

In the mouse PK studies, two strains were used, RasH2 wt and KI.C57-RAS wt. The first strain received tiratricol doses of 0, 200, 1000 and 3000 µg/kg, the second 0, 50, 200 and 1000 µg/kg. In both strains, the 200 µg/kg dose yielded an AUC (0-last) of around 150 ng·h/mL. Thus, the dose used in Triac I approximately corresponded to a murine dose of 200 µg/kg. This is half of the dose shown to be effective in the pivotal mouse PD study, which was 400 µg/kg. Hence, it cannot be excluded that dosing in Triac I was not maximally effective.

Such PK considerations were aligned with another possible approach to dose comparison and PD based, considering the primary PD effect of tiratricol, which is lowering circulating T3 and T4. Based on this approach and using the available data, it could be derived that the maximal T3 and T4 suppression was reached with 1000 µg/kg tiratricol. A dose of 200 µg/kg caused a sub-maximal suppression. Since the aim of Triac I was to bring (the elevated) T3 into the normal range and not to suppress it maximally, it is reasonable to assume that the doses used in Triac I approximately correspond to 200 µg/kg in mice, based on the extent of T3 suppression.

Toxicology

Deaths of possible cardiovascular origin were observed in a rat repeat-dose study of 6-month duration already from the lowest dose investigated (150 µg/kg/day) for the reference product. This dose corresponds to a human equivalent dose (HED) of 24 µg/kg/day. It is well established that thyrotoxicosis is associated with sudden deaths (Chaker et al., 2016) and this is not uncommon in untreated MCT8-deficient patients (Groeneweg et al., 2020). QT prolongation and associated cardiac arrhythmias would not appear to be associated with the sudden deaths since tiratricol showed no relevant inhibition of the human ether-a-go-go related gene (hERG) potassium channel. However, tachycardia was previously reported in the 6-month study in dogs for the reference product, that subsided over time. It is also known that long-term TH overload results in cardiac hypertrophy (Barreto-Chaves et al., 2020), an effect that was seen in the new 28-day DRF study in juvenile rats. Since there is clinical experience with tiratricol at a dose level of up to 207 µg/kg/day and since there are documented clinical benefits on heart rate and blood pressure, it is not expected that these data can translate into clinical effects. Tiratricol is intended to reduce thyrotoxic T3 levels in MCT8-deficient patients. Therefore, toxicities seen in animal studies that are related to exaggerated pharmacology such as damaging effects on the heart, might have limited clinical relevance. Importantly, clinical experience in MCT8-deficient patients shows reduced heart rate and blood pressure, and a reduced incidence of premature atrial complexes (Groeneweg et al., 2019).

In addition to the well-documented effects of tiratricol (and T4 and T3) on the heart (considered an effect on TRα receptors), thyromimetics like tiratricol should have at sufficient exposures, pharmacological actions that affect tissues such as liver, adipose tissue, and bone. Again, the aforementioned exaggerated pharmacological activities might have limited clinical relevance as long as the TH monitoring is carried out appropriately.

Consistent findings were observed in the new 13-week GLP study in dogs as compared to data from the reference product. With the exception of the ocular changes observed at high doses (5 mg/kg/day), all treatment-related changes were consistent with exaggerated pharmacological effects, i.e. effects induced by TH receptor activation. The cataractogenic activity of tiratricol could be related to its effect on cholesterol synthesis and the subsequent significant decrease in plasma cholesterol in animals at this dose. Cholesterol is the major lipid component of the ocular lens, and the impaired cholesterol biosynthesis may contribute to cataract formation. The NOAEL of the ocular changes (lens deposits and opacification) observed in dogs was 500 µg/kg/day. This corresponds to a HED of 278 µg/kg/day which is 2.5-fold higher than the highest administered clinical dose in the Triac Trial I and the Erasmus Medical Center (EMC) cohort study.

Thyroid hormones are generally not regarded carcinogenic and with the presented data, carcinogenicity studies are not considered necessary.

Emcitate has not been studied for adverse effects on fertility and early embryonic development, embryo-foetal toxicity, prenatal and postnatal development, including maternal function. This is considered acceptable by the CHMP in accordance with the guideline on the non clinical documentation for mixed marketing authorisation (CPMP/SWP/799/98). It is not expected that this medicinal product is to be used in women of child-bearing potential or during pregnancy and lactation because of the severity of the neurocognitive condition and because MCT8 deficiency is a condition almost exclusively affecting males. A contraindication has been recommended during pregnancy due to reproductive toxicities of the reference product. Women of childbearing potential have to use effective contraception during treatment.

Assessment of paediatric data on non-clinical aspects

Tiratricol was not tolerated in the 3-month juvenile toxicity study at doses equal to or greater than 50 µg/kg/day for periods of 3 months due to excessive mortality, and a no-observed-adverse-effect level (NOAEL) was not established in this study.

There was pronounced suppression of the thyroid hormones (TSH, T3 and T4) at all dose levels.

Tiratricol administration was also associated with increases in organ weights.

Low dose males and mid dose males and females showed a slightly reduced bone mass and density. Mid dose males also showed reduced bone size and geometry parameters; high dose animals were not available for bone measurement.

Tiratricol was not associated with any memory or learning changes, changes in blood coagulation, ophthalmic assessment, sexual maturation in either male animals (as assessed by preputial separation) or female animals (as assessed by vaginal opening), testicular and epididymal sperm reserve, or sperm motility.

All of the above findings were considered to be primary or secondary to the well-characterised pharmacology of tiratricol. Furthermore, rats appear to be more sensitive to tiratricol than other species.

The hyperthyroidism and findings observed in the juvenile toxic study are generally consistent with data from the 6-month non-GLP study in adult rats with the reference product.

The findings in the embryo-foetal development studies as well as in the rat pre-/postnatal study are described in the SmPC and Package Leaflet in line with the reference product.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, tiratricol is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of tiratricol have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

To support the application, the applicant has submitted the MCT8-2023-5 bioequivalence study, and the MCT8-2014-1 (TRIAC I) study as main evidence to support the change in the therapeutic indication from the reference medicinal product. In addition, MCT8-2019-2 (TRIAC II) results have been submitted in the present

application, together with additional efficacy information from ongoing studies MCT8-2021-3 (ReTRIACt) and the extension study MCT8-2019-2 (TRIAC II, part II).

Table 2. Tabular overview of clinical studies

Study Population	Study number and abbreviated title
COMPLETED STUDIES	
Healthy volunteers	MCT8-2023-5: Bioequivalence of two tiratricol tablets and relative bioavailability of tiratricol in the fasted and fed state in healthy male subjects combined with an assessment of dose-proportionality: A randomized, five-period crossover study
MCT8 deficient patients	MCT8-2014-1: Thyroid hormone analog therapy of patients with severe psychomotor retardation caused by mutations in the MCT8 thyroid hormone transporter: The Triac trial I (MCT8-2014-1 CSR, Groeneweg et al 2019)
MCT8 deficient patients	MCT8-2019-2: Tiratricol treatment of children with Monocarboxylate Transporter 8 deficiency: Triac Trial II (Part I)
ONGOING STUDIES	
MCT8 deficient patients	MCT8-2021-3 (ReTRIACt): Withdrawal of tiratricol treatment in males with monocarboxylate transporter 8 deficiency (MCT8 Deficiency): A double-blind, randomised, placebo-controlled study
MCT8 deficient patients	MCT8-2019-2: Tiratricol treatment of children with Monocarboxylate Transporter 8 deficiency: Triac Trial II long-term extension with an additional 2years of treatment (Part II)

2.4.2. Pharmacokinetics

A Phase I study (MCT8-2023-5) was conducted to:

- establish bioequivalence between two different 350 µg tiratricol tablets (Emcitate-FCP [Tiratricol 350 µg, oblong tablets] vs Emcitate-DEV [Tiratricol 350 µg, round tablets]) administered in the fasted state;
- investigate the effect of food on tiratricol PK following administration of the Emcitate-FCP oblong tablet in doses of 175 and 1050 µg;

- assess the dose-proportionality of the Emcitate-FCP oblong tablets administered at three dose levels 175, 350 and 1050 µg (in a fasted state).

MCT8-2023-5 was a Phase 1, randomised, blinded, five-period cross-over study in healthy adult male subjects (N=30). The design was a hybrid combination of a two-period cross-over and a three-period balanced incomplete block design, with six different treatments administered via 20 fixed sequences to which subjects were assigned randomly to receive 5 of the 6 treatments. Tiratricol was administered in single oral doses of 175 µg [0.5 × 350 µg tablet], 350 µg [1 × 350 µg tablet] or 1050 µg [3 × 350 µg tablets] (all dispersed in water) with a washout of ≥3 days between periods. Subjects had a follow-up visit 5-7 days after the final dose.

A validated (LC/MS/MS) chromatographic procedure was used to analyse tiratricol, L 3,3',5 Triiodothyronine (T3) and L-Thyroxine (T4) in human serum samples. Internal standards were used. The analytical method employed solid phase extraction for sample preparation followed by liquid chromatography with tandem mass spectrometry detection using Electrospray ionisation in multiple reaction monitoring mode. Due to the high endogenous levels of Total T3 and Total T4 in human serum and a number of potential surrogate serums tested from alternative species, surrogate analytes were to be spiked into calibration standards and some QCs, depending on the endogenous concentrations established during serum screening.

Absorption

The absorption of tiratricol following oral dosing was rapid with a median T_{max} of 0.5 hours following doses between 175 and 1050 µg. Following Cmax, serum concentrations declined in a generally biphasic manner and remained quantifiable until 3 to 48 hours post dose. The geometric mean T1/2 was between 13.3 – 14.0 hours for the 350 µg and 1050 µg. See Figure 4.

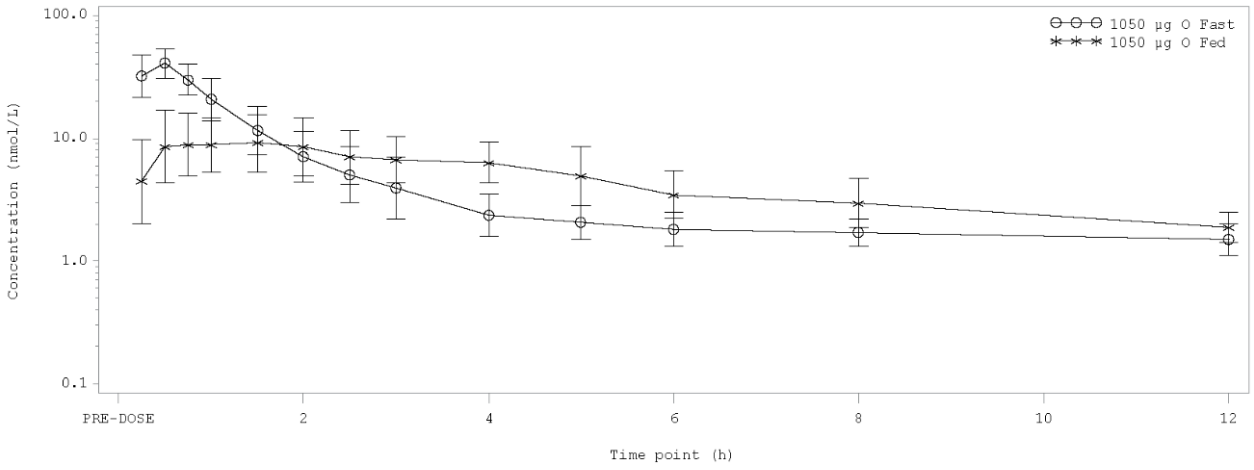


Figure 4. Geometric Mean (×/÷ Geometric SD) Serum Tiratricol (TA3) Concentrations Following Administration of Single Oral Doses of Emcitate (Tiratricol) Tablet(s) – 1050 µg Emcitate FCP Tablet, Fed vs 1050 µg Emcitate FCP, Fasted

The results from the bioequivalence study (MCT8-2023-5- see below) are similar to the results published by C. Menegay *et al.* (1989; Pharmacokinetics of 3,5,3'-triiodothyroacetic acid and its effects on serum TSH levels. Acta Endocrinol (Copenh), 121(5), 651-658).

The applicant analysed PK measurements from 10 patients from the ReTRIACt study with the Population PK modelling. The Population PK modelling of the ReTRIACt data supports that in patients tiratricol PK is similar to healthy volunteer PK. The applicant stated that the Population PK model can be used to estimate exposure for individual patients, based on dose and body weight, in Triac Trial I and Triac Trial II.

Bioequivalence

The main body of efficacy evidence is acquired in the TRIAC I in which the reference product "Téatrois, 0.350 mg IR tablet" approved in France during the period from 1974 to 2020 was used. This formulation is now discontinued. In the completed EMC cohort study, which provided additional efficacy evidence, Emcitate-DEV formulation (round tablet) has been used. The same formulation is used in the ongoing clinical study ReTRIAC and TRIAC II, whereas the to-be-marketed formulation is Emcitate FCP 350 µg. Emcitate FCP is a dispersible oblong tablet and should be dispersed in a small amount of water prior to administration. The applicant claims that previous formulations, Téatrois and Emcitate-DEV are very similar to the proposed commercial formulation. Reportedly, the only difference between Téatrois /Emcitate-DEV and Emcitate FCP with regards to excipients is the tablet filler, where calcium hydrogen phosphate dihydrate is replaced by calcium hydrogen phosphate to improve tablet properties. According to the applicant, in vitro dissolution testing of dispersed tablets demonstrated comparable in vitro dissolution profiles in 0.1 M HCl and pH 6.8 media between tablets used in the pivotal clinical studies and the proposed commercial tablets; however, no detailed description covering all media has been presented in the clinical part of the dossier.

The MCT8-2023-5 study established bioequivalence between the two formulations Emcitate-DEV and Emcitate FCP for both C_{max} and the various measures of AUC considered, with all 95% confidence intervals within the acceptance region of [0.80, 1.25]. See Table 7.

Table 3. Results of the Assessment of Bioequivalence for Serum Tiratricol Pharmacokinetic Analysis Set (MCT8-2023-5 study)

		Test (350 µg O Fast)		Reference (350 µg R Fast)				
Comparison	Parameter	n	GLSmean (1)	n	GLSmean (1)	Ratio (2)	90% CI (3)	CVw (%)
350 µg O Fast vs 350 µg R Fast	Cmax (nmol/L)	28	15.4	29	14.6	1.0537	(0.9380, 1.1837)	26.86
	AUC(0-72) (nmol.h/L)	28	30.4	29	29.3	1.0366	(0.9653, 1.1131)	16.26
	AUC(0-last) (nmol.h/L)	28	25.2	29	23.8	1.0604	(1.0017, 1.1227)	12.99
	AUC(0-inf) (nmol.h/L)	14	30.1	8	31.6	0.9520	(0.8573, 1.0572)	11.70

Overall exposure based on AUC was similar between the fed and fasted states for both the 175 and 1050 µg doses of Emcitate-FCP, but with a 67-70% reduction in tiratricol C_{max} in the fed state vs the fasted state. In the fed state, dosing of 175 and 1050 µg Emcitate-FCP oblong tablet following a high-fat breakfast resulted in a delay to median tiratricol T_{max} (1.500 and 1.250 h post dose, respectively), compared with the fasted state (0.500 h post-dose for both dose levels).

Dose proportionality and time dependencies

Dose proportionality could be concluded for C_{max} over the examined dose range. The overall tiratricol exposure (AUC) increased in a slightly greater than proportional manner with increasing dose. Over the dose range examined, estimates of 2β indicated that exposure increased by 1.983, 2.140, 2.272 and 2.227-fold following

a 2-fold increase in the dose for C_{max}, $AUC_{(0-72)}$, $AUC_{(0-last)}$ and $AUC_{(0-inf)}$, respectively. However, it should be noted that particularly at 175 µg dose tiratricol serum concentrations quite quickly dropped below the limit of quantification. After administration of 175 µg tiratricol concentrations remained quantifiable until between 2.5 and 24 h post-dose, with the majority of subjects (15 out of 25 subjects) having quantifiable concentrations up to at least 12 h post-dose. This factor may contribute to the apparent minor supra-proportionality observed for AUC.

The Population PK model predicts some accumulation of AUC and Cmax when comparing a single administration versus steady state. However, accumulation ratios based on the same dose frequency on day 1 to steady state are modest (≤1.5) regardless of dose frequency, dose and body weight, consistent with the relative short half-life of tiratricol.

Special populations

No formal clinical study to investigate the impact of special populations on tiratricol PK has been conducted. This is considered acceptable by the CHMP.

No PK data concerning age were submitted. For MCT8 deficiency the median age of reported onset of first symptom is 4 months. The median age of diagnosis is 24 months. In Triac Trial I at baseline the age ranged from 0.8 to 66.8 years and the median age of the patients was 7.1 years. In Triac Trial II at baseline the age ranged from 5 to 28 month and the median age of the patients was 16 months.

The available data indicate a weight dependence of PK.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. This is considered acceptable by the CHMP.

The applicant provided the relation between the normalised dosing and reduction in serum T3 level from TRIAC I and II. See Figure 5.

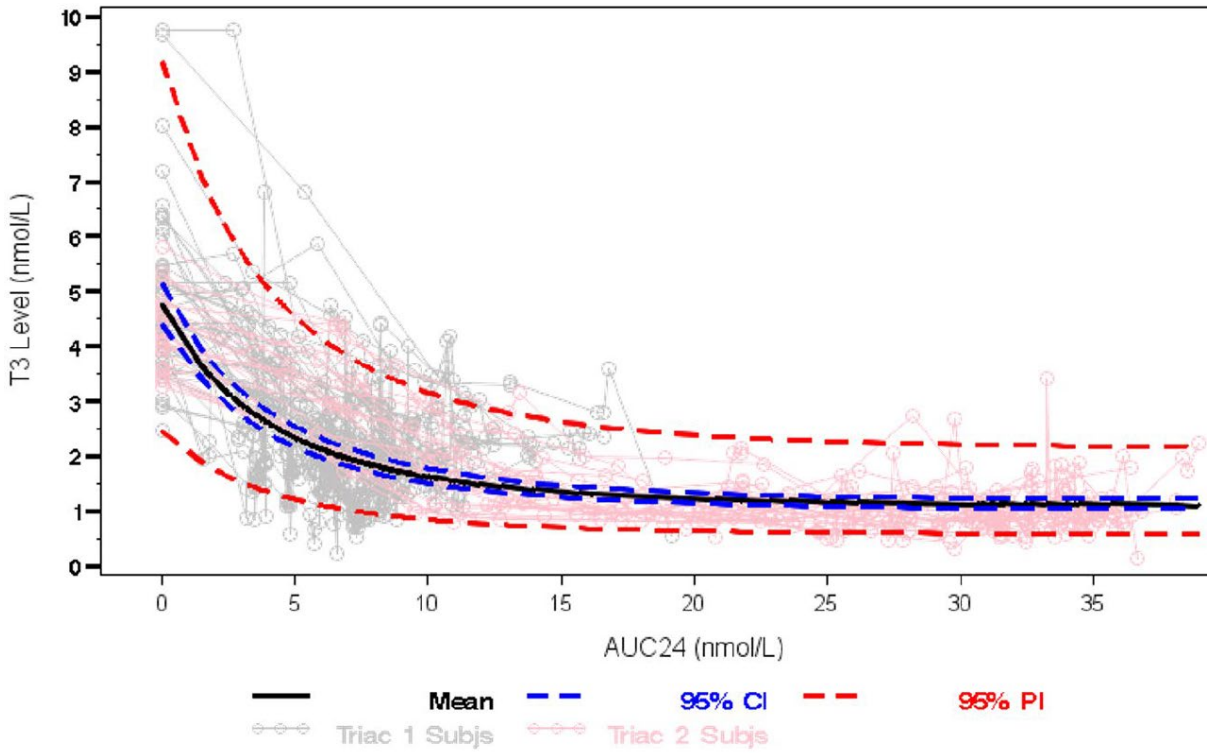


Figure 5. PK-PD relationship between average concentration of tiratricol (nmol/L) and serum T3 (nmol/L), including patient data from Triac Trial I and Triac Trial II (PI = Prediction Interval).

This suggests that dosing tiratricol higher than a mean concentration of 15 nmol/L (corresponding to an AUC of 360 nmol*24h/L and a daily dose of ~ 80 µg / kg) has a limited additional effect on serum T3.

Further treatment responses (e.g. heart rate) were submitted. From the changes in heart rate, the applicant calculated a lower potency ratio than Menegay et al. between T3 and tiratricol somewhere in the range of 6-12. Based on these data, a titration target of a serum T3 level was suggested within the lower half of the normal range for age. The rationale of the modification is optimising a total ”thyromimetic pressure” composed essentially from serum T3 and tiratricol plasma activity. For further details and assessment of the dosing recommendations please see section 2.4.4.

2.4.4. Clinical efficacy

The Emcitate tablet formulation is based on the formulation of the reference medicinal product Téatrois 350 µg. No distinct dose-finding was performed in the development program of tiratricol for use in MCT8-deficiency and the dose had been adopted from the reference medicinal product Téatrois. The starting dose for children with a body weight above 10 kg is 350 µg. The starting dose for children with a body weight below 10 mg is 175 µg (half a tablet). Dosing is uptitrated based on the patient`s clinical response. This is further discussed in section 2.4.6.

2.4.4.1. Main study

Study MCT8-2014-1: Thyroid hormone analog therapy of patients with severe psychomotor retardation caused by mutations in the MCT8 thyroid hormone transporter (TRIAC trial I)

The study is represented in Figure 6.

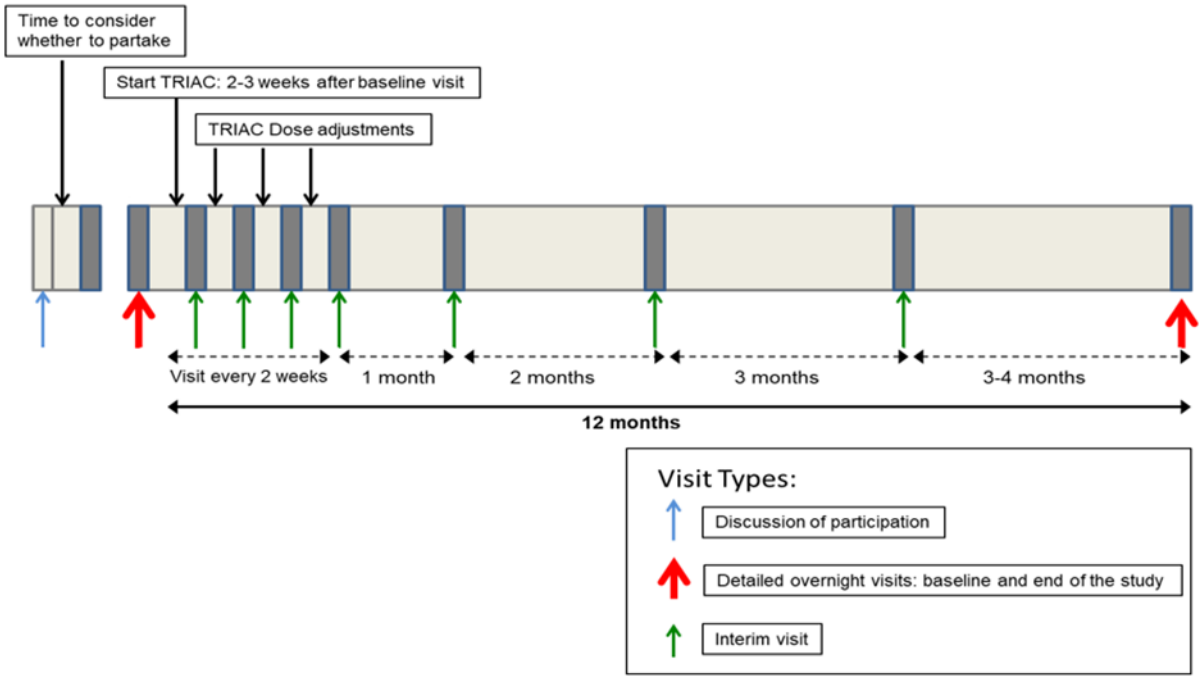


Figure 6. Study design of TRIAC I

Methods

- **Study Participants**

Inclusion criteria

• Patients with a clinically relevant pathogenic mutation in the MCT8 (SLC16A2) gene.

Main exclusion criteria

• Major illness or recent major surgery (within four weeks) unrelated to MCT8 deficiency.

• Patients who are participating in ongoing randomized controlled trials of therapeutic interventions (including clinical trials of investigational medicinal products).

- **Treatments**

The starting dose was 350 µg daily (175 µg in patients <10 kg). The daily tiratricol dose was increased in steps of 350 µg (175 µg for patients <10 kg) every 2 weeks on an individual basis until the patient's serum T3 levels were within the target range (1.4 to 2.5 nmol/L; equal to the normal range in adults), or until predefined dose-limiting toxicities occurred. After the titration period, patients were treated with their individual dose until Month 12. See Table 8.

Table 4. Six Dose escalation scheme

Dose level	Dose per administration (µg)	Number of administrations per day	Total daily dose (µg)
2	350	2	700
3	350	3	1050
4	350	4	1400
	700	2	
5	700	3	2100
6	1050	3	3150
7	1400	3	4200

Concomitant therapies: any medications, including over-the-counter medications or herbal supplements, were recorded as concomitant drug therapy in the electronic case report form (eCRF). All participants were expected to *discontinue treatment with anti-thyroid drugs and/or levothyroxine* (if applicable) before initiation of study treatment.

Co-administration of levothyroxine (LT4) was allowed during the trial if free T4 levels decreased more than 50% below the baseline value.

Treatment compliance was monitored through a study drug diary to record doses taken/missed and any adverse events. Compliance with study treatment was recorded at each visit to the clinic.

- **Objectives**

Primary objective

To evaluate the effect of tiratricol treatment on serum T3 concentrations.

As a complement to the primary objective, other laboratory markers were assessed. These were the change from baseline in serum thyroid stimulating hormone (TSH), free thyroxine (fT4), total thyroxine (T4), and reverse triiodothyronine (rT3) concentrations.

Secondary objectives

•To evaluate the effect of tiratricol on clinical outcomes affected in MCT8 deficiency (body weight, heart rate, and blood pressure).

• To evaluate the effect of tiratricol on well-established biochemical outcomes that reflect thyroid status in peripheral tissues affected in MCT8 deficiency (serum sex hormone binding globulin [SHBG], total cholesterol and creatine kinase [CK]).

Exploratory objectives

To describe the effects of tiratricol treatment on the neurocognitive phenotype measured by: change from baseline in gross motor function (Gross Motor Function Measure-88, change from baseline in cognition (Cognition scale of the Bayley Scales of Infant Development III), change from baseline in gross motor and fine motor skills (BSID III), and change from baseline in expressive and receptive language (BSID), change from baseline in adaptive behaviour (Vineland Adaptive Behavior scale II, VABSII), physical neurological examination.

- **Outcomes/endpoints**

Efficacy endpoints are presented in Table 9.

Table 5. Efficacy endpoints

Endpoint	Change from baseline to Month 12
Primary	Serum total T3
Complementary primary	Serum TSH, free T4, total T4, and rT3
Secondary	Body weight, heart rate and blood pressure, SHBG, cholesterol, and creatine kinase
Exploratory	Height, BMI, GMFM-88, BSID-III, VABS-II, and physical neurological examination

Abbreviations: BSID-III = Bayley Scales of Infant Development III; GMFM-88 = Gross Motor Function Measure-88; VABS-II = Vineland Adaptive Behavior Scales II.

The assessment of GMFM-88, BSID-III and VABS-II were only done at study sites with experience in the use of the rating scales. The VABS-II survey was completed in the presence of a trained neuropsychologist or physician. Twenty-six patients underwent GMFM-88 assessment, 16 patients were assessed by the BSID-III.

The GMFM-88 is an assessment tool originally validated to measure changes in gross motor function over time primarily in children with cerebral palsy. The GMFM-88 samples motor skills that are typical of normal developmental milestones and is therefore useful for other diagnostic populations as well. The rated items span the spectrum of gross motor activities in five dimensions of increasing difficulty: lying and rolling; sitting; crawling and kneeling; standing; walking, running, and jumping.

GMFM-88 is validated in children 5 months to 16 years of age. The items are appropriate for those with motor skills at or below those of a 5-year-old child without any motor disability. Currently, there are no published references of use of the GMFM in adult populations. GMFM-88 assesses the gross motor function in which scores range from 0 to 100%, with higher scores indicating better motor function and where a 100% score is achieved by a normal developing child of 4 years of age.

BSID-III is a multi-scale battery assessing various aspects of child development. BSID-III measures the developmental age ranging from 1 to 42 months. Scores on the subscales are presented as age equivalent scores representing the developmental age in months. Changes from baseline to Month 12 in the subscales of cognition, expressive language, receptive language, fine motor skills, and gross motor skills were assessed. The age-equivalent scores are provided in "months" and is regarded as a continuous variable.

VABS-II is a survey which assesses different aspects of development. In Triac Trial I, the following areas were assessed: communication with the subdomains of receptive, expressive and written language; daily living skills with the subdomains of personal, domestic, and community skills; socialization with the subdomains of interpersonal relationships, playing, and coping; motor skills with the subdomains of gross and fine motor skills. The VABS-II measures the developmental age ranging from birth to 90 years of age.

Caregiver reported outcomes were collected by asking study-specific questions to the parents at visits during the study. In essence, there were three principal types of questions. First, a general question asked at the end of study visit: "What are the most prominent changes that the parents have observed upon Triac treatment?" where the answer was entered as free text. To provide quantitative summaries of this data, the Applicant has categorized the information provided into areas of prominent changes noted (behavior, motor, weight, sleep, general, food intake, sweating, seizures, cardiac, gastrointestinal), where the free text for each patient could identify one or several of these areas. The free text in each area has also been classified as a positive or negative change.

Second, at control visits, there were questions related to the presence of putative effects of treatment at the specific time point of assessment, known to be common in thyrotoxicosis, concerning diarrhea, vomiting, sweating, shortness of breath, skin rash, anxiety, seizure, dry mouth, complains of constipation, urinary incontinence or poor bladder control. Regarding the amount of sweating, an additional question ascertained the amount of sweating on an ordinal scale (from very little to very much). The results are presented as comparisons of the presence of such effects at baseline and end of study.

Third, at control visits, there were questions related to the change in food intake, behavior, sleeping pattern and seizure frequency. To provide quantitative summaries of this data, the Applicant has classified the change throughout the study period as improvement, worsening and experiencing no change, respectively, for each patient. Also, for these assessments each patient's classification together with source data, including the free text comments at each timepoint, are provided in Appendix G to provide transparency of the data handling.

- **Sample size**

The power calculation was based on serum T3 concentrations. Anticipating a very efficient reduction of serum T3 levels following tiratricol treatment the power calculation indicated that a number of 10 patients is sufficient to demonstrate a clinically relevant change of 1.8 nmol/L (117 ng/dL) in serum T3 concentrations with a power of 80% ($\alpha = 0.05$).

Since the availability of detailed data on secondary outcome variables was limited at that time, it was deemed unfeasible to conduct meaningful power calculations for key secondary outcomes. The number of patients in centers willing to participate in the trial was the leading determinant of the final sample size.

- **Randomisation**

Not applicable

- **Blinding (masking)**

Not applicable

- **Statistical methods**

The statistical analyses are reported using summary tables, figures and data listings. All statistical tests are two-sided at the 0.05 level of significance and 2-sided 95% confidence intervals (CI) are used. All p-values are reported as nominal p-values and two-sided p-values of 0.05 or less were considered to denote statistical

significance. Continuous variables are summarized with means, standard deviation (standard error of the mean if appropriate), medians, interquartile range (IQR; defined as the interval between the first [Q1] and third [Q3] quartile), minimums and maximums. Categorical variables are summarized by counts and by percentages of subjects in the corresponding categories.

Continuous variables are reported quantitatively. Non-normally distributed variables are transformed to a logarithmic scale. Assuming a normal distribution, mean values at baseline and end-study were assessed with paired t-tests. For all serum thyroid function tests, p-values and 95% CI were calculated for the mean change from baseline to Month 12 with the use of paired Student`s t-tests. Serum TSH and CK concentrations were first log-transformed to improve the distribution. Body weight was expressed as body weight to age z scores, and p-values and 95% CIs were calculated for the mean change from baseline to Month 12 with the use of paired Student's t-tests. P-values and 95% CIs were calculated for the mean change in heart rate (in beats per minute) and blood pressure (in mm Hg and in age and height adjusted percentiles) from baseline to Month 12 with the use of paired Student's t-tests.

For all secondary/exploratory measures, 95% CIs were calculated for the mean change from baseline to 12 months of tiratricol treatment. Demographic and baseline data were summarized as appropriate depending on the data type.

These summaries were produced for the safety analysis set and the Intention to treat (ITT). Analysis of the primary endpoint was performed in the ITT population (considered to be the main analysis) and the Per-Protocol (PP) population. The primary analyses of the secondary and exploratory endpoints were carried out in the PP population as defined in the Final Statistical Analysis Plan. Safety analyses were performed on the Safety Population.

Due to the lack of a control group, the lack of a well-defined comparative estimand, the lack of multiplicity control and the number of missing data, all analyses are considered to be descriptive and assessed as such. Since no clear comparison can be made to the counterfactual outcome of what would have happened if tiratricol had not been applied, nominally significant results and the corresponding confidence intervals of the changes to baseline of all parameters are of limited value to derive the treatment effect tiratricol.

Missing data were replaced in the ITT analyses were replaced by using the last observed value. Given the non-comparative nature of the study and the approach is considered acceptable.

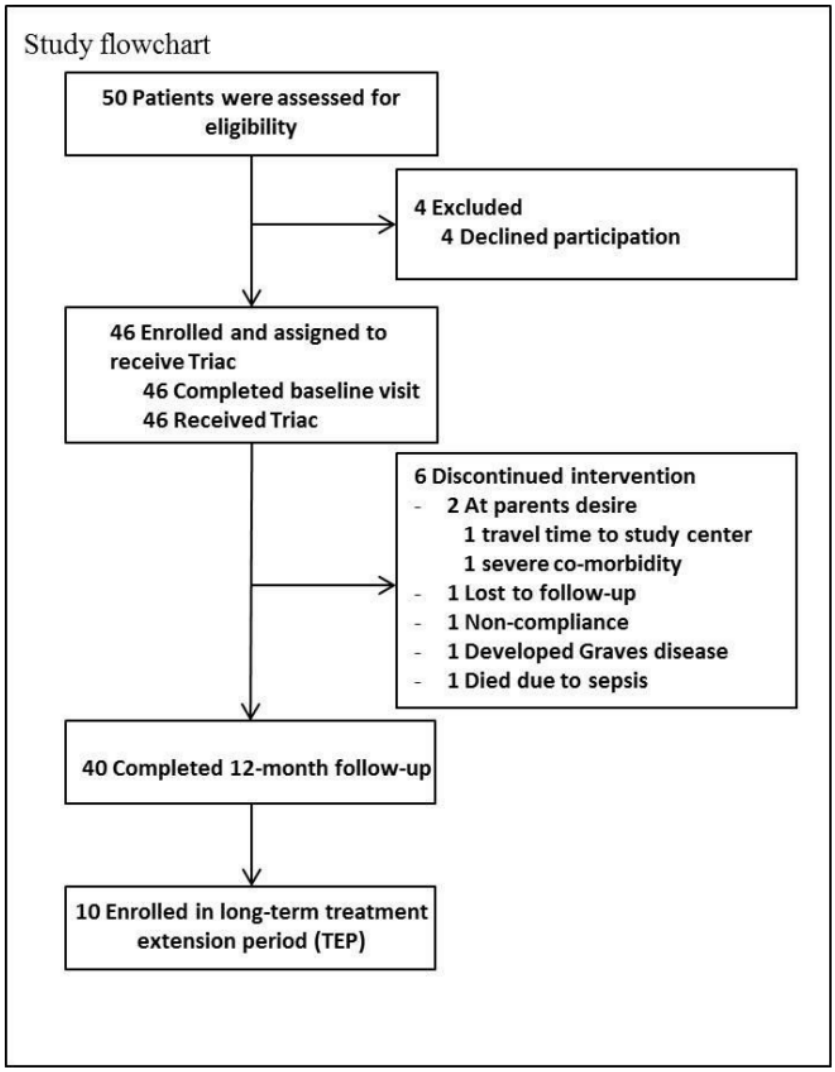
Results

- **Participant flow**

Forty-six subjects were enrolled in the study, two patients were discontinued at the wish of the caregiver (1 due to long travel time to study center, 1 due to severe co-morbidity). One patient was lost to follow-up, 1 patient was discontinued due to non-compliance, 1 patient was discontinued due to development of Graves' disease, 1 patient died due to sepsis.

Patients enrolled in The Netherlands (who started long before the patients from other countries were enrolled) who completed the first 12 months of treatment were offered to continue in the long-term extension protocol, which continued until the last patient last visit for the whole trial population. Ten patients were enrolled in the long-term extension. These patients were treated for 24-42 months.

Participant flow is represented in Figure 7.



Source: Figure S3, Groeneweg et al 2019 (24) (Appendix 16.1.11)

Figure 7. Study flow chart

- **Recruitment**

The study was conducted at 12 sites in: Netherlands, Germany, Italy, Belgium, France, Romania, Czech Republic, United Kingdom, South Africa. The first patient was enrolled on 15 October 2014 and the last patient last visit was on 28 May 2018.

- **Conduct of the study**

There were 3 amendments to the original protocol. These relate mainly to expanding the recruitment, change in the decision flowchart related addition of levothyroxine, prolongation of the treatment after the 12 months period until final analysis, clarifications on primary endpoint and complementary endpoints to the primary endpoint and exploratory endpoints.

- **Baseline data**

The median age of the 46 enrolled patients was 7.1 years at baseline (no age limit for inclusion). 30 out of 46 (65.2%) patients were underweight (defined as Z score of <-2, Groeneweg et al. 2019; WHO). The mean weight-for-age Z score was -2.84 (SD 1.88). Among patients with available data, 18 out of 44 (40.9%) patients were suffering from tachycardia and 12 out of 35 (34.3%) patients from systolic hypertension. Mean serum total T3 concentration was 4.91 (SD 1.57) nmol/L at baseline. All patients had severe intellectual and motor disability requiring daily care: 41 out of 46 (89.1%) patients were wheelchair bound, and 32 patients (69.6%) had poor or no head control. See Table 10.

Table 6. Patients characteristics at baseline (TRIAC Trial I)

Characteristic	Safety analysis set (N=46)
Age (years), median (range)	7.1 (0.8 to 66.8)
Sex (males), count (%)	46 (100%)
Race, count (%)	
White	44 (95.7%)
Asian	1 (2.2%)
Other	1 (2.2%)
Living situation, count (%)	
At home	34 (73.9%)
Institution	5 (10.9%)
Both	7 (15.2%)
Level of development, count (%)	
Wheelchair bound	41 (89.1%)
None or poor head control	32 (69.6%)
Able to sit independently	5 (10.9%)
Serum T3 (nmol/L),	
mean (SD)	4.91 (1.57)
Weight-for-age (Z score),	
mean (SD) [a]	-2.84 (1.88)
Underweight, count (%) [b]	30 (65.2%)
Feeding tube, count (%)	19 (41.3%)
Tachycardia, count (%) [n] [c]	18 (40.9%) [n=44]
Systolic hypertension, count (%) [n] [d]	12 (34.3%) [n=35]

Source: Table 14.1-1, MCT8-2014-1 CSR.
[a] Age adjusted Z score relative to healthy controls.
[b] Underweight defined per WHO criteria as a Z score <-2 (WHO).
[c] Tachycardia is defined as a resting heart rate above the 90th percentile for the corresponding age, using cut-offs described in Fleming et al. 2011. Denominator for the percentage is n=44, i.e. percentage is adjusted for missing values in 2 patients.
[d] Hypertension is defined based on systolic blood pressure per the American Academy of Pediatrics guidelines (Flynn et al. 2017) and American College of Cardiology/American Heart Association (Whelton et al. 2017). The denominator for the percentage is n=35, i.e. percentage is adjusted for missing values in 11 patients.

- **Numbers analysed**

46 patients received at least one dose of study drug. Safety analysis set included all patients (N=46). ITT set for primary endpoint included majority of patients (N=45), where one patient did not have any control visit after the baseline visit and therefore was excluded from the ITT analysis set. For analysis of secondary endpoints significantly fewer patients were included in ITT.

40 patients completed the 12-month study period and were included in the PP analysis set, from which 10 patients were enrolled in long-term extension period.

- **Outcomes and estimation**

Primary endpoint

Treatment with tiratricol reduced the mean serum T3 concentration from 4.97 nmol/L at baseline to 1.82 nmol/L at Month 12 (p<0.0001) (target range: 1.4 to 2.5 nmol/L). In the 10 patients included in the treatment extension period, the mean serum T3 concentration was reduced from 4.41 nmol/L at baseline to 1.81 nmol/L at last assessment (p<0.0001), after a median treatment duration of 3.4 years. See Table 11.

Table 7. Serum T3 (nmol/L) – Analysis of mean change from baseline to month 12 (Intention To Treat)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	45	4.97	1.55	2.87	4.55	9.76	[4.50 ; 5.43]	-
Month 12	45	1.82	0.69	0.53	1.77	3.91	[1.61 ; 2.02]	-
Difference	45	-3.15	1.56	-7.52	-2.88	-1.02	[-3.62 ; -2.68]	<.0001

Source: Table 14.2-2

Analysis based on a paired t-test according to SAP. Last observation carried forward approach applied for patients discontinued treatment prior to month 12 visit.

All 45 patients with post-baseline T3 values presented a decrease from baseline to Month 12 or last available assessment (5 patients with LOCF). At Month 12, or last available assessment, 38 out of 45 patients (84%) attained serum T3 levels within *or below* the target range. Of the seven remaining patients, two patients had values just above the target range (2.51 and 2.52 nmol/L, respectively).

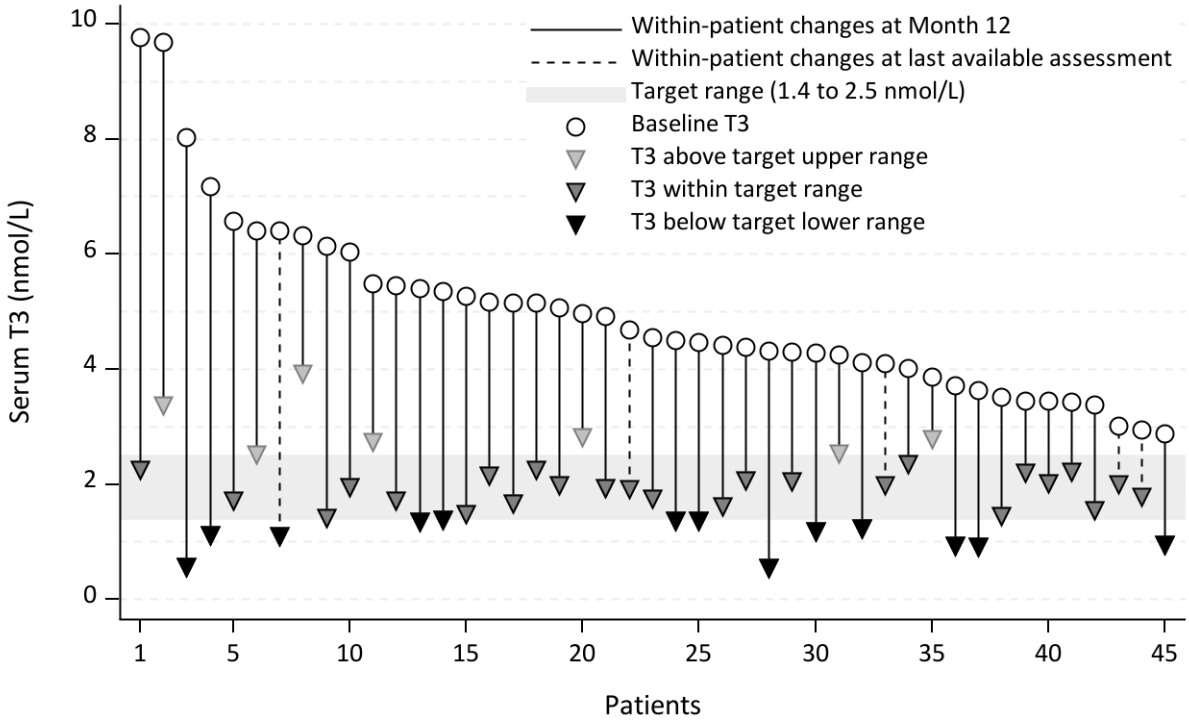
A sensitivity analysis using a per protocol analysis of the primary endpoint, including only the 40 patients who had serum T3 data collected at month 12, showed similar results; treatment with tiratricol reduced the mean serum T3 concentration from 5.06 nmol/L at baseline to 1.83 nmol/L at month 12.

A sensitivity analysis using more conservative approach for primary endpoint was used, where instead of using LOCF for 5 patients missing data at month 12, it was assumed that no treatment effect in patients with missing data was observed at the 12 months visit. Sensitivity analysis showed similar results; treatment with tiratricol reduced the mean serum T3 concentration from 4.97 nmol/L at baseline to 2.09 nmol/L at month 12.' See Table 12 and Figure 8.

Table 8. Serum T3 (nmol/L) – Sensitivity analysis of mean change from baseline to month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	45	4.97	1.55	2.87	4.55	9.76	[4.50 ; 5.43]	-
Month 12	45	2.09	1.11	0.53	1.94	6.40	[1.76 ; 2.42]	-
Difference	45	-2.88	1.78	-7.52	-2.82	0.00	[-3.41 ; -2.34]	<.0001

Analysis based on a paired t-test. Baseline T3 value imputed in case T3 is missing at month 12



Source: Figure C-1, Technical report Triac Trial I.

Note: ITT analysis set.

T3 at last available assessment was imputed as last observation carried forward for patients who discontinued treatment prior to Month 12.

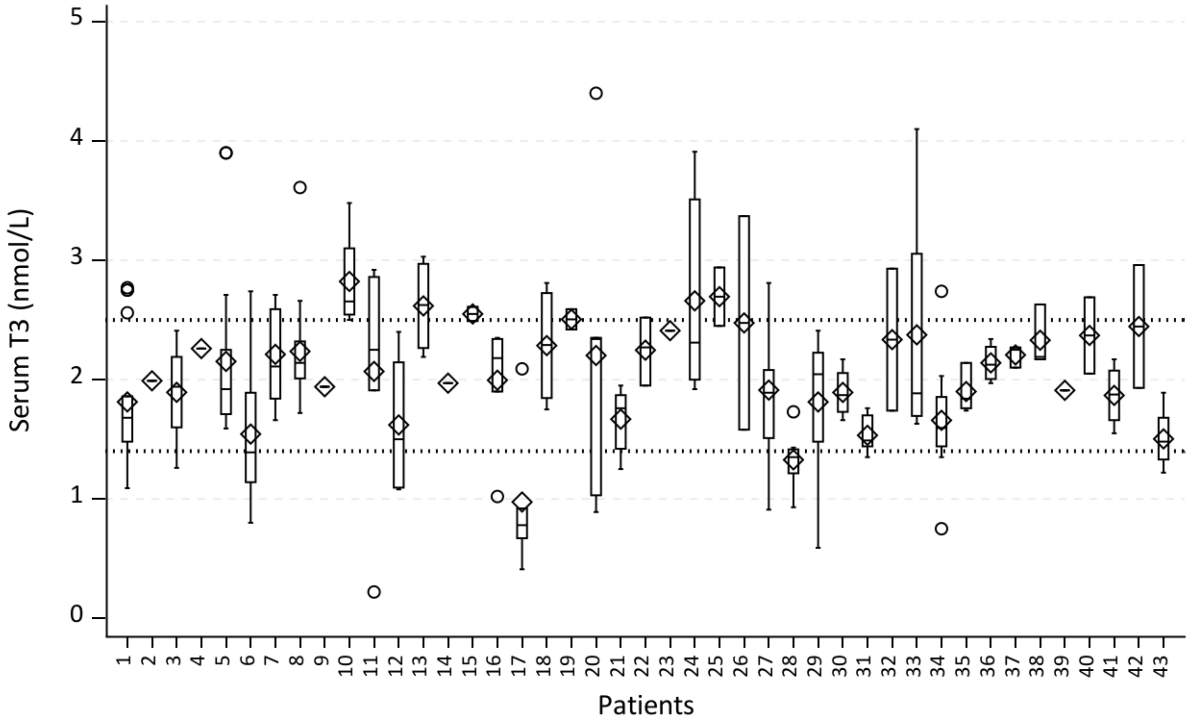
Within-patient changes per patient are ordered by Baseline Serum T3.

Figure 8. Serum T3 – changes from baseline to month 12 by patient (TRIAC Trial I)

The five patients with missing data at month 12 are displayed with a dashed line.

On average, serum T3 levels reached target range 80 days after initiation of treatment. The median maintenance dose was 38.9 µg/kg body weight.

Figure 9 provides a visualisation of the intraindividual change in T3 serum level.



Source: Figure Q088-1-A of Additional analyses for responses to Day 120 questions in Module 5.3.5.3.

This is a corrected version of Figure A-25 as initially provided within Technical Report for Triac Trial I.

Note: ITT analysis set.

Box top border: Q3 (75th percentile); Box lower border: Q1 (25th percentile); IQR: Q3-Q1 (Intra-quartile range); Box horizontal line: Median; Whiskers: 1.5×IQR; Circle: Outlier; Square: Mean.

Figure 9. Distribution of serum T3 (nmol/L) during maintenance dosing (ITT)

Complementary endpoints to the primary endpoint

Results are presented in Table 13.

Table 9. Other thyroid hormones – analysis of mean change from baseline to Month 12 (TRIAC Trial I)

Variable	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	P-value [a]
TSH (mU/L)[b]	45	2.91 (1.68)	1.02 (1.14)	-1.89 [-2.39; -1.39]	<0.0001
Free T4 (pmol/L)	45	9.68 (2.96)	3.39 (1.60)	-6.28 [-7.15; -5.41]	<0.0001
Total T4 (nmol/L)	45	55.96 (12.95)	24.38 (9.44)	-31.58 [-35.15; -28.01]	<0.0001
rT3 (nmol/L)	45	0.12 (0.10)	0.04 (0.04)	-0.08 [-0.10; -0.05]	<0.0001

Source: Table 14.2-5, Table 14.2-7, Table 14.2-9, and Table 14.2-11, MCT8-2014-1 CSR.
[a] Paired *t*-test.
[b] TSH concentrations were log-transformed for purposes of paired *t*-test which require normally distributed data. Non-transformed mean, SD and CI are presented.
Note: ITT analysis set.
Data at follow-up were imputed as LOCF for patients who discontinued treatment prior to Month 12 visit.

In the 10 patients included in the TEP, the TSH, free T4, total T4, and rT3 were reduced from baseline to the last assessment after a median treatment duration of 3.4 years.

Secondary endpoints

Body weight-for-age (Z score) relates the body weight of an individual with the normal weight-for-age and is measured in SDs in healthy controls. A Z score equal to 0 equals the mean weight for the age population. Children with a Z score of <-2 (i.e. >2 SDs below the mean) were considered underweight (Groeneweg et al. 2019, WHO). For example, a 5-year old boy with a Z score of -2 SD would weight 14.1 kg, whereas the median weight-for-age would be 18.3 kg. A body weight increase over time which is larger than expected for age compared to healthy controls leads to an increase in the body weight-for-age Z score. Correspondingly, a body weight-for-age MCT8 Z score relates the body weight to untreated patients with MCT8 deficiency (Groeneweg et al. 2020a). A body weight-for-age equal to the mean weight-for-age in patients with MCT8 deficiency equates to an MCT8 Z score equal to 0. A body weight increase over time which is larger than expected for age, compared to the untreated MCT8 deficiency population, leads to an increase in the body weight-for-age MCT8 Z score. Low body weight-for-age Z score is a risk factor for premature death in patients with MCT8 deficiency and the body weight-for-age Z score in untreated patients with MCT8 deficiency shows a progressive deterioration over time compared to healthy controls (Groeneweg et al. 2020a).

Data on body weight for age are presented in Table 14.

Table 10. Body weight- for-age- analysis of mean change from baseline to Month 12 (TRIAC Trial I)

Variable	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	P-value [a]
Body weight (kg)	40	21.78 (12.20)	24.48 (12.60)	2.70 [1.90; 3.51]	<0.0001
Weight-for-age (Z score) [b]	40	-2.98 (1.93)	-2.71 (1.79)	0.27 [0.03; 0.50]	0.0253
Weight-for-age (MCT8 Z score) [c]	36	0.46 (1.79)	0.96 (1.70)	0.51 [0.25; 0.76]	0.0003
Underweight, count (%) [d]	40	26 (65%)	25 (62.5%)	Not calculated	Not calculated

Source: Table 14.2-12, Table 14.2-119, MCT8-2014-1 CSR and Table C-2 and Table C-24, Technical Report: Triac Trial I.
[a] Paired *t*-test.
[b] Age adjusted Z score relative to healthy controls.
[c] Age adjusted Z score relative to untreated patients with MCT8 deficiency (Groeneweg et al. 2020a). Z scores were not derived for patients older than 18 years.
[d] Underweight defined per WHO criteria as a Z score <-2 (WHO).
Note: PP analysis set.

When analyzed in the ITT population, the improvement in body weight for age z-score/BMI was not statistically significant. See Table 15.

Table 11. Body weight for age (z-score)- analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	45	-2.85	1.90	-8.76	-2.62	-0.12	[-3.42 ; -2.28]	-
Month 12	45	-2.63	1.74	-7.44	-2.26	0.02	[-3.15 ; -2.10]	-
Difference	45	0.22	0.77	-1.39	0.30	2.38	[-0.01 ; 0.45]	0.0580

Analysis based on a paired t-test according to SAP. Body weight is expressed relative to the healthy control population using a body weight for age z-score.

Data for height (as z-scores for age) are presented in Table 16.

Table. 12 Height for age (z score)- analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	45	-1.96	1.58	-6.81	-1.92	1.52	[-2.43 ; -1.48]	-
Month 12	45	-1.98	1.47	-6.33	-1.93	0.86	[-2.42 ; -1.53]	-
Difference	45	-0.02	0.53	-1.62	0.08	1.28	[-0.18 ; 0.14]	0.8127

Source: Table 14.2-35

Analysis based on a paired t-test according to SAP. Last observation carried forward approach applied for patients discontinued treatment prior to month 12 visit. Z-scores as retrieved from the TNO groeicalculator.

Data for heart rate and tachycardia are presented in Table 17.

Table 13. Heart rate and tachycardia – analysis of mean change from baseline to Month 12 (TRIAC Trial I)

Variable	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	P-value [a]
Resting heart rate (bpm)	34	112.4 (23.1)	103.5 (17.0)	-8.9 [-15.6; -2.3]	0.0100
Heart rate-for-age (Z score) [b]	21	1.72 (1.07)	1.38 (0.99)	-0.33 [-0.77; 0.10]	0.1235
Mean heart rate 24-hour (bpm) [c]	31	102.4 (13.6)	97.3 (9.2)	-5.1 [-9.0; -1.2]	0.0116
Tachycardia, count (%) [d]	34	16 (47%)	16 (47%)	Not calculated	Not calculated
Patients with Tachycardia [d]					
Resting heart rate (bpm)	16	131.4 (16.8)	109.6 (12.2)	-21.9 [-30.0; -13.8]	<0.0001
Heart rate-for-age (Z score) [b]	9	2.80 (0.37)	1.75 (0.65)	-1.05 [-1.55; -0.54]	0.0015
Mean heart rate 24-hour (bpm) [c]	12	103.8 (7.5)	102.1 (8.8)	-1.8 [-6.3; 2.8]	0.4161

Source: Table 14.2-13 and Table 14.2-14, MCT8-2014-1 CSR, and Table C-8, Table C-16, Table C-18, Table C-20, and Table C-22 in Technical Report Triac Trial I.
[a] Paired *t*-test was used for mean difference in blood pressure.
[b] Age adjusted Z score relative to healthy controls.
[c] Heart rate measured by 24-hour ambulatory cardiac monitoring.
[d] Tachycardia is defined as a resting heart rate above the 90th percentile for the corresponding age, using cut-offs described Fleming et al. 2011.
Note: PP analysis set.

Data for blood pressure are presented in Table 18.

Table 14. Blood pressure- analysis of mean change from baseline to Month 12 (TRIAC Trial I)

Variable	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	P-value [a, b]
Systolic BP (mmHg)	32	107.4 (7.6)	102.4 (10.2)	-4.9 [-8.8; -1.1]	0.0130
Systolic BP (percentile) [c]	32	77.5 (24.7)	60.7 (29.3)	-16.8 [- 28.4; -5.1]	0.0063
Diastolic BP (mmHg)	32	64.2 (8.6)	62.5 (9.4)	-1.8 [-5.7; 2.2]	0.3729
Diastolic BP (percentile) [c]	32	73.7 (21.7)	67.3 (21.5)	-6.4 [-17.3; 4.5]	0.2378
Hypertension, count (%)	32	14 (43.75%)	5 (15.63%)	Not calculated	0.0067
Patients with hypertension [d]					
Systolic BP (mmHg)	14	110.9 (5.2)	102.5 (5.7)	-8.4 [-11.7; -5.0]	0.0001
Diastolic BP (mmHg)	14	66.9 (9.4)	61.2 (10.5)	-5.7 [-12.8; -1.4]	0.1066

Source: Table 14.2-15. Table 14.2-16, Table 14.2-17, and Table 14.2-18, MCT8-2014-1 CSR, and Table C-10, Table C-12, and Table C-14 in Technical Report Triac Trial I.
[a] Paired *t*-test was used for mean difference in blood pressure.
[b] McNemar's test was used for difference in percentage of patients.
[c] Percentile scores relative to age and height for healthy controls (Fleming et al. 2011).
[d] Hypertension is defined based on systolic or diastolic blood pressure per the American Academy of Pediatrics guidelines (Flynn et al. 2017) and American College of Cardiology/American Heart Association (Whelton et al. 2017).
Note: PP analysis set.

Table 19, Table 20, Table 21, Table 22, Table 23 describe results in the ITT analysis set.

Table 15. Systolic Blood Pressure (mmHg) – analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	35	107.1	8.4	87.0	109.0	121.0	[104.2 ; 110.0]	-
Month 12	35	103.0	10.4	88.0	104.0	128.0	[99.5 ; 106.6]	-
Difference	35	-4.1	11.6	-24.0	-8.0	28.0	[-8.1 ; -0.1]	0.0451

Analysis based on a paired t-test according to SAP. Last observation carried forward approach applied for patients discontinued treatment prior to month 12 visit.

Table 16. Systolic Blood Pressure (percentile) analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	35	75.4	26.4	12.0	89.0	99.0	[66.4 ; 84.5]	-
Month 12	35	61.2	28.7	6.0	69.0	98.0	[51.4 ; 71.1]	-
Difference	35	-14.2	35.4	-82.0	-12.0	83.0	[-26.4 ; -2.0]	0.0234

Analysis based on a paired t-test according to SAP. Last observation carried forward approach applied for patients discontinued treatment prior to month 12 visit. Percentiles based on age and body height.

Table 17.Diastolic blood pressure (mmHg) – analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	35	63.7	8.9	50.0	64.0	85.0	[60.6 ; 66.7]	-
Month 12	35	62.9	9.8	48.0	63.0	87.0	[59.6 ; 66.3]	-
Difference	35	-0.7	11.7	-22.0	0.0	29.0	[-4.7 ; 3.3]	0.7198

Analysis based on a paired t-test according to SAP. Last observation carried forward approach applied for patients discontinued treatment prior to month 12 visit.

Table 18. Diastolic blood pressure (percentile) – analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	35	70.8	23.5	22.0	74.0	99.0	[62.7 ; 78.9]	-
Month 12	35	67.2	21.8	16.0	68.0	99.0	[59.7 ; 74.7]	-
Difference	35	-3.6	32.0	-70.0	-4.0	75.0	[-14.6 ; 7.4]	0.5141

Analysis based on a paired t-test according to SAP. Last observation carried forward approach applied for patients discontinued treatment prior to month 12 visit. Percentiles based on age and body height.

Table 19 Number (%) of hypertensive patients at baseline to Month 12 (ITT)

N	Baseline	Month 12	P-value
35	14 (40%)	6 (17.14%)	0.0209

P-value based on McNemars test.

Post-hoc analyses were performed by the Investigators assessing PACs, defined as an interval to the preceding QRS complex less than 80% of the mean RR interval before the event (Conen et al., 2012). The number of PACs is presented as the number of events per 24 hours, corrected for differences in registration times by dividing the number of registered PACs by the registration time, multiplied by 24. The number of PACs is regarded as a continuous variable.

The mean number of PACs decreased from 899.7/24-hours at baseline to 313.9/24-hours at Month 12 (p=0.0029). The occurrence of PACs was reduced to less than 100/24 hours in the 10 patients enrolled in the TEP, and completely subsided in 3 (43%) out of 7 patients.

Data on serum SHBG are presented in Table 24.

The mean concentration of SHBG decreased with a mean change of -34.7nmol/L at month 12 (95% CI [-54.8, -14.5], P=0.0013).

Table 20. Serum sex hormone binding globulin (nmol/L)- analysis of mean change from baseline to Month 12 (Per Protocol)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	39	212.4	90.8	62.2	222.0	377.0	[183.0 ; 241.9]	-
Month 12	39	177.8	76.1	43.2	170.0	344.0	[153.1 ; 202.4]	-
Difference	39	-34.7	62.2	-228.0	-35.0	111.0	[-54.8 ; -14.5]	0.0013

Source: Table 14.2-19
Analysis based on a paired t-test according to SAP.

Data on serum lipid levels are presented in Table 25 and Table 26.

Table 21. Serum total cholesterol (mmol/L) – analysis of mean change from baseline to Month 12 (Per Protocol)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	40	3.23	0.74	1.80	3.10	4.60	[2.99 ; 3.46]	-
Month 12	40	3.39	0.71	2.10	3.30	5.40	[3.16 ; 3.61]	-
Difference	40	0.16	0.51	-0.70	0.10	1.60	[-0.00 ; 0.32]	0.0558

Source: Table 14.2-20
Analysis based on a paired t-test according to SAP.

Table 22. Serum total cholesterol (mmol/L) – analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	45	3.27	0.76	1.80	3.10	4.70	[3.04 ; 3.50]	-
Month 12	45	3.41	0.73	2.10	3.30	5.40	[3.19 ; 3.63]	-
Difference	45	0.14	0.52	-0.70	0.10	1.60	[-0.02 ; 0.29]	0.0825

Analysis based on a paired t-test according to SAP. Last observation carried forward approach applied for patients discontinued treatment prior to month 12 visit.

Data on serum creatine kinase are presented in Table 27 and Table 28.

Table 23. Serum creatine kinase (U/L) -– analysis of mean change from baseline to Month 12 (Per Protocol)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	40	108.0	90.0	25.0	93.0	602.0	[79.2 ; 136.8]	-
Month 12	40	160.7	117.2	27.0	130.0	562.0	[123.2 ; 198.2]	-
Difference	40	52.7	79.3	-52.0	27.0	297.0	[27.3 ; 78.1]	0.0001

Source: Table 14.2-24

Analysis based on a paired t-test according to SAP.

The following table describes results in the ITT analysis set:

Table 24. Serum creatine kinase (U/L) -– analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	45	111.8	97.5	25.0	93.0	602.0	[82.5 ; 141.1]	-
Month 12	45	168.1	140.6	27.0	131.0	717.0	[125.9 ; 210.3]	-
Difference	45	56.3	84.8	-52.0	26.0	299.0	[30.9 ; 81.8]	<.0001

Analysis based on a paired t-test according to SAP. Last observation carried forward approach applied for patients discontinued treatment prior to month 12 visit.

The serum creatinine concentration was increased from 32.8 µmol/L at baseline to 37.5 µmol/L (p<0.0001) at Month 12.

Efficacy in the treatment extension period (n=10 patients)

Data are presented in Table 29.

Table 25. Efficacy results from baseline to end of treatment extension period (ITT)

Assessment	N	Baseline Mean (SD)[1]	TEP Mean (SD)	Mean change from baseline [95% CI]	P value[2]
T3 (nmol/L)[3]	10	4.41 (0.92)	1.81 (0.65)	-2.59 [-3.35, -1.84]	<.0001
TSH (mU/L)	10	3.25 (1.89)	1.32 (1.04)	-1.93 [-3.13, -0.73]	0.0054
Free T4 (pmol/L)[3]	10	8.48 (3.09)	4.01 (1.71)	-4.47 [-6.04, -2.90]	0.0001
Total T4 (nmol/L)[3]	10	54.00 (11.29)	24.80 (8.08)	-29.20 [-37.06, -21.34]	<.0001
Reverse T3 (nmol/L)[3]	10	0.13 (0.06)	0.05 (0.03)	-0.08 [-0.12, -0.04]	0.0007
Weight to age (z-score)	10	-2.18 (1.54)	-1.52 (1.39)	0.66 [0.08, 1.24]	0.0292
Mean heart rate 24 h (bpm)[4]	10	98.20 (14.94)	90.80 (8.12)	-7.40 [-15.63, 0.83]	0.0724
SHBG (nmol/L)	9	176.2 (86.4)	121.0 (52.1)	-55.1 [-98.2, -12.0]	0.0184
Total cholesterol (mmol/L)	10	2.93 (0.92)	3.44 (0.69)	0.51 [0.08, 0.94]	0.0244
LDL cholesterol (mmol/L)	10	1.62 (0.58)	1.74 (0.39)	0.12 [-0.14, 0.38]	0.3238
HDL cholesterol (mmol/L)	10	1.13 (0.36)	1.33 (0.40)	0.20 [0.04, 0.36]	0.0190
Triglycerides (mmol/L)	10	0.68 (0.44)	0.75 (0.35)	0.08 [-0.22, 0.37]	0.5746
CK (U/L)	10	164.7 (157.1)	193.6 (116.0)	28.9 [-36.0, 93.8]	0.3399

Source: Tables 14.2-60, 14.2-61, 14.2-65 – 14.2-69, 14.2-109 – 14.2-111, 14.2-115 – 14.2-117

[1] Provided data at baseline is restricted to subjects (n=10) enrolled in the long-term treatment extension period (TEP).

[2] Paired T-tests were used to detect significant changes from baseline to the end of the TEP.

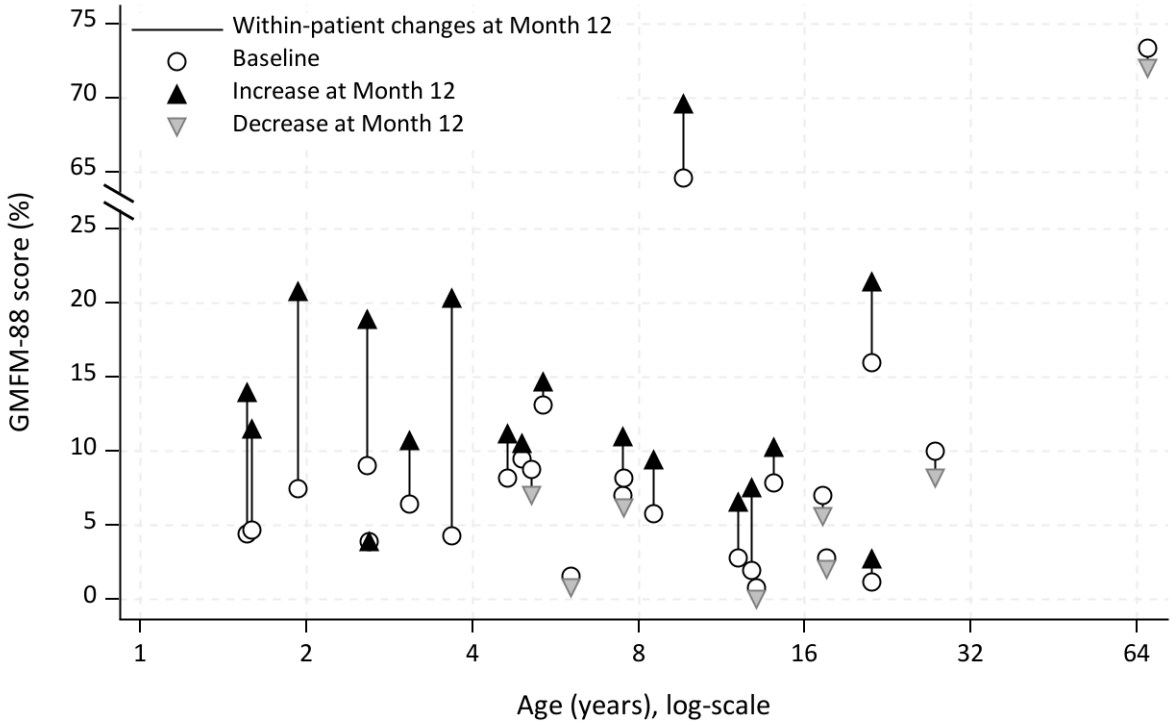
[3] Data in ng/dL are given in Tables 14.2-62, 14.2-63, 14.2-64, and 14.2-108.

[4] Measured by 24h ambulatory cardiac monitoring.

CK=Creatine kinase; HDL=High density lipoprotein; LDL=Low density lipoprotein; SHBG=Sex hormone binding globulin; TSH=Thyroid stimulating hormone; T3=Triiodothyronine; T4=Thyroxine

Exploratory endpoints

Data on GMFM-88 are presented in Figure 10, Table 30 and Table 31.



Source: Figure D-1, Technical report Triac Trial I.

Note: ITT analysis set.

Y-axis is broken for GMFM-88 scores between 25% and 65% (slanted lines).

Figure 10. GMFM-88 total score- change from baseline to Month 12 by patient (TRIAC Trial I)

Table 26. GMFM-88 total score- analysis of mean change from baseline to Month 12- by age (TRIAC Trial I)

Patients	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	P-value [a]
All ages	26	11.18 (17.45)	14.50 (17.61)	3.31 [1.39; 5.24]	0.0016
<4 Years	7	5.75 (1.94)	14.31 (6.16)	8.56 [3.56; 13.56]	Not calculated
4-10 Years	9	14.08 (19.19)	15.60 (20.63)	1.52 [-0.48; 3.51]	Not calculated
11+ Years	10	12.38 (21.97)	13.64 (21.34)	1.27 [-0.81; 3.34]	Not calculated

Source: Table 14.2-42 and Table 14.2-73, MCT8-2014-1 CSR.
[a] Paired *t*-test.
Note: ITT analysis set.

Table 27. GMFM-88 dimension score - analysis of mean change from baseline to Month 12- by age (TRIAC Trial I)

Age groups	Dimension	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]
<4 Years	A: Lying and rolling	7	26.4 (7.0)	57.4 (23.0)	31.0 [12.2; 49.9]
	B: Sitting	7	2.4 (4.2)	13.1 (8.7)	10.7 [2.2; 19.2]
	C: Crawling and kneeling	7	0.0 (0.0)	1.0 (1.9)	1.0 [-0.7; 2.8]
	D: Standing	7	0.0 (0.0)	0.0 (0.0)	0.0 [Not applicable]
	E: Walking, running, and jumping	7	0.0 (0.0)	0.0 (0.0)	0.0 [Not applicable]
4-10 Years	A: Lying and rolling	9	40.4 (24.6)	44.6 (25.5)	4.2 [-3.6; 12.0]
	B: Sitting	9	13.7 (32.6)	14.3 (32.6)	0.6 [-1.9; 3.1]
	C: Crawling and kneeling	9	13.5 (33.0)	13.5 (33.0)	0.0 [Not applicable]
	D: Standing	9	2.8 (7.6)	3.7 (10.3)	0.9 [-1.2; 2.9]
	E: Walking, running, and jumping	9	0.0 (0.0)	1.9 (5.7)	1.9 [-2.5; 6.2]
11+ Years	A: Lying and rolling	10	33.5 (31.1)	38.3 (33.2)	4.8 [-3.3; 12.9]
	B: Sitting	10	11.6 (31.3)	13.9 (30.7	2.2 [-0.7; 5.2]
	C: Crawling and kneeling	10	10.0 (31.6)	10.0 (31.6)	0.0 [Not applicable]
	D: Standing	10	4.6 (14.5)	3.9 (12.3)	-0.7 [-2.3; 0.9]
	E: Walking, running, and jumping	10	2.1 (6.6)	2.1 (6.6)	0.0 [Not applicable]

Source: Table D-1 to D-5, Technical Report Triac Trial I.
Note: ITT analysis set.

Data on the on the Bayley Scales of infant development are presented in Table 32, Table 33, Table 34, Table 35 and Table 36.

The mean age equivalent scores on the Bayley Scales of infant development in all age groups representing the developmental age in months were low both at baseline and after 12 months of treatment. However, the mean scores were numerically slightly higher at Month 12 in all subscales and all age groups in the total study population.

Table 28. Bayley scales on infant development (BSID III): Cognition subscale score- analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	16	3.30	1.31	0.60	3.30	6.00	[2.60 ; 4.00]	-
Month 12	16	4.23	1.69	1.00	3.80	7.00	[3.33 ; 5.13]	-
Difference	16	0.93	1.76	-1.70	0.85	3.70	[-0.01 ; 1.87]	0.0517

Source: Table 14.2-43
Scores on the BSID III subscales are presented as age equivalent scores representing the developmental age in months.

Table 29. Bayley scales on infant development (BSID III): Gross motor subscale score- analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	16	0.99	0.73	0.50	0.60	3.00	[0.60 ; 1.38]	-
Month 12	16	2.21	1.55	0.50	2.15	6.00	[1.39 ; 3.04]	-
Difference	16	1.22	1.05	0.00	1.25	3.00	[0.66 ; 1.78]	0.0003

Source: Table 14.2-44

Scores on the BSID III subscales are presented as age equivalent scores representing the developmental age in months.

Table 30. Bayley scales on infant development (BSID III): Fine motor subscale score- analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	16	2.51	1.60	0.50	3.00	6.00	[1.66 ; 3.37]	-
Month 12	16	3.46	2.03	0.50	3.30	9.00	[2.37 ; 4.54]	-
Difference	16	0.94	1.55	-1.50	0.65	3.10	[0.12 ; 1.77]	0.0282

Source: Table 14.2-45

Scores on the BSID III subscales are presented as age equivalent scores representing the developmental age in months.

Table 31. Bayley scales on infant development (BSID III): Expressive language score subscale score- analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	16	4.58	2.24	1.00	4.60	9.00	[3.38 ; 5.77]	-
Month 12	16	6.11	2.79	2.60	5.30	12.00	[4.63 ; 7.60]	-
Difference	16	1.54	2.48	-3.00	1.20	6.40	[0.22 ; 2.86]	0.0254

Source: Table 14.2-46

Scores on the BSID III subscales are presented as age equivalent scores representing the developmental age in months.

Table 32. Bayley scales on infant development (BSID III): Receptive language score subscale score- analysis of mean change from baseline to Month 12 (ITT)

Assessment	N	Mean	SD	Min	Median	Max	95% CI	P-value
Baseline	16	6.57	3.66	1.30	7.00	12.00	[4.62 ; 8.52]	-
Month 12	16	9.08	3.25	4.60	8.00	18.00	[7.34 ; 10.81]	-
Difference	16	2.51	3.67	-4.00	3.15	8.70	[0.55 ; 4.46]	0.0155

Source: Table 14.2-47

Scores on the BSID III subscales are presented as age equivalent scores representing the developmental age in months.

Results of a post-hoc sensitivity analysis by age groups are given in Table 37.

Table 33. Post-hoc sensitivity analyses on exploratory neurological and neuropsychological outcome measures stratified by age (ITT)

	<4 years			4-10 years			11+ years		
	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]
GMFM-88[1]									
N	7			9			10		
Total score (%)	5.75 (1.94)	14.31 (6.16)	8.56 [3.56, 13.56]	14.08 (19.19)	15.60 (20.63)	1.52 [-0.48, 3.51]	12.38 (21.97)	13.64 (21.34)	1.27 [-0.81, 3.34]
BSID III[2]									
N	2			8			6		
Cognition	2.95 (1.91)	5.00 (0.00)	2.05 (0.70-3.40)[4]	3.60 (0.66)	4.83 (1.92)	1.23 [-0.26, 2.71]	3.02 (1.88)	3.18 (1.13)	0.17 [-1.60, 1.93]
Expressive language	3.60 (1.41)	5.80 (1.70)	2.20 (2.00-2.40)[4]	4.88 (2.34)	7.23 (3.51)	2.35 [0.21, 4.49]	4.50 (2.54)	4.73 (1.08)	0.23 [-2.34, 2.81]
Receptive language	4.65 (1.91)	7.50 (0.71)	2.85 (2.00-3.70)[4]	7.20 (3.12)	10.08 (4.09)	2.88 [-0.06, 5.81]	6.37 (4.86)	8.27 (2.20)	1.90 [-3.05, 6.85]
Fine motor	2.40 (2.69)	3.65 (0.92)	1.25 (0.00-2.50)[4]	3.16 (1.46)	4.25 (2.38)	1.09 [-0.14, 2.32]	1.68 (1.34)	2.33 (1.31)	0.65 [-1.29, 2.59]
Gross motor	1.75 (1.77)	4.15 (2.62)	2.40 (1.80-3.00)[4]	1.00 (0.63)	2.54 (1.14)	1.54 [0.77, 2.31]	0.73 (0.34)	1.13 (0.97)	0.40 [-0.29, 1.09]

Data on VABS-II subscales are presented in Table 38.

The mean scores in the VABS-II subscales were low both at baseline and after 12 months of treatment. Except for gross and fine motor skills, there was little change in the subscales.

Table 34. Vineland Adaptive Behavior scale II (ITT)

Assessment	N	Baseline Median (min-max)	Month 12 Median (min-max)	Difference Median [95% CI]	P-value
Communication	26				
Receptive		11.50 (5.00-40.00)	12.00 (5.00-40.00)	0.00 [0.18, 2.05]	0.0207
Expressive		11.50 (0.00-74.00)	12.00 (4.00-62.00)	0.50 [-1.5, 1.7]	0.8846
Written		0.00 (0.00-17.00)	0.00 (0.00-20.00)	0.00 [-0.34, 0.34]	1.0000
Daily living skills	26				
Personal		6.00 (0.00-53.00)	7.50 (0.00-59.00)	1.00 [-0.40, 2.17]	0.1683
Domestic		0.00 (0.00-24.00)	0.00 (0.00-12.00)	0.00 [-1.54, 1.23]	0.8213
Community		0.00 (0.00-23.00)	0.00 (0.00-12.00)	0.00 [-0.90, 1.13]	0.8172
Socialization	26				
Interpersonal relationships		18.00 (12.00-39.00)	19.50 (15.00-42.00)	1.00 [-0.39, 2.93]	0.1274
Play and leisure time		5.00 (0.00-42.00)	7.00 (0.00-40.00)	0.50 [-0.50, -3.12]	0.1491
Coping skills		0.00 (0.00-12.00)	0.00 (0.00-8.00)	0.00 [-1.44-0.29]	0.1812
Motor skills	26				
Gross motor		2.50 (0.00-55.00)	4.00 (0.00-55.00)	0.00 [-0.12, 1.05]	0.1168
Fine motor		1.00 (0.00-53.00)	2.50 (0.00-47.00)	1.0 [-0.64, 2.17]	0.2703

Source: Table 14.2-48 – 14.2-58
Analyses based on paired t-tests.

Post-hoc analysis data on neurological examination by a certified neurologist are presented in Table 39.

Table 35. Hyperreflexia, Hypertonia and Primitive reflexes at baseline and Month 12 (ITT)

	<4 years		4-10 years		11+ years	
	Baseline N (%)	Month 12 N (%)	Baseline N (%)	Month 12 N (%)	Baseline N (%)	Month 12 N (%)
Hyperreflexia	6 (75.0)	8 (100.0)	15 (93.8)	13 (81.3)	10 (90.9)	10 (90.9)
Hypertonia	8 (100.0)	7 (87.5)	12 (75.0)	14 (87.5)	7 (63.6)	8 (72.7)
Primitive reflexes	8 (100.0)	8 (100.0)	12 (75.0)	11 (68.8)	12 (100.0)	12 (100.0)

Source: Tables 14.2-70 – 14.2-72

In total, the caregivers of 39 patients (86.7%) reported an improvement as most prominent change, whereas one caregiver (2.2%) reported a worsening. The most prominent improvements of tiratricol treatment are in terms of behavioural, motor and weight aspects of MCT8 deficiency. Improvements are also seen in food intake, sleeping pattern, sweating, anxiety, dry mouth and constipation. Data are presented in Table 40.

Table 36. Caregiver reported outcomes

Effect	Description	Unit	Worsening	Improvement	Uncertainties/ Strength of evidence	References
Most prominent change	Most prominent change observed upon treatment as reported in the end of 12 months tiratricol treatment	n (%)	Total number (%) of patients reporting worsening: 1 (2%) *By category:* Gastrointestinal: 1 (2%)	Total number (%) of patients reporting improvement: 39 (87%) *By category:* Behaviour: 31 (69%) Motor: 15 (33%) Weight: 10 (22%) Sleep: 8 (18%) General: 6 (13%) Food intake: 4 (9%) Sweating: 3 (%) Seizures: 2 (4%) Cardiac: 1 (2%)	Uncertainties: - Single-arm uncontrolled study - Exploratory data - Data collected at "End of study talk" with parents - No validated questionnaires Strengths of evidence: - Structured collection of data - Pattern is consistent with improvements in thyrotoxicosis - Improvements seen in most common aspects of disease	Triac Trial I (n=46)

Effect	Description	Unit	Worsening	No change	Improvement	Uncertainties/ Strength of evidence	References
Change in pre-specified areas related to daily care of MCT8 deficiency patients	Change in food intake	n/N %	4/45 9%	3/45 7%	24/45 53%	Uncertainties: - Single-arm uncontrolled study - Exploratory data - No validated questionnaires Strengths of evidence: - Structured collection of data - Improvements seen in most common difficulties in daily care of patients	Triac Trial I (n=46)
	Change in behaviour		4/45 9%	3/45 7%	35/45 78%		
	Change in sleeping pattern		2/45 4%	28/45 62%	14/45 31%		
	Change in seizure frequency		4/45 9%	2/45 4%	3/45 7%		

Effect	Description	Unit	Baseline	Month 12	Uncertainties/ Strength of evidence	References
Presence of certain pre-specified symptoms common in patients with MCT8 deficiency	Urinary incontinence or poor bladder control	n/N (%)	35/44 (80%)	31/39 (80%)	Uncertainties: - Single-arm uncontrolled study - Exploratory data - No validated questionnaires Strengths of evidence: - Structured collection of data - Improvements seen in most common symptoms of MCT8 deficiency	Triac Trial I (n=46)
	Complaints of constipation		26/44 (59%)	16/39 (41%)		
	Sweating		23/44 (52%)	8/40 (20%)		
	Seizures		14/44 (32%)	7/37 (19%)		
	Frequent dry mouth		13/43 (30%)	8/37 (22%)		
	Anxiety		8/44 (18%)	4/40 (10%)		
	Shortness of breath		3/44 (7%)	2/40 (5%)		
	Skin rash		3/44 (7%)	0 (0%)		
	Vomiting		2/44 (5%)	6/40 (15%)		
	Diarrhea		0 (0%)	2/40 (5%)		

Source: Table B-1 and Table B-3, Technical Report Triac Trial I.
Note: ITT analysis set.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit

risk assessment (see later sections).

Title: Thyroid hormone analog therapy of patients with severe psychomotor retardation caused by mutations in the MCT8 thyroid hormone transporter: The Triac Trial (TRIAC I)			
Study identifier	Triac Trial, NL47771.078.14 / MCT8-2014-1 EudraCT 2014-000178-20 NCT02060474 http://dx.doi.org/10.1016/S2213-8587(19)30155-X		
Design	Open-label, international, multi-center, single-arm study to evaluate the safety and efficacy of tiratricol treatment in monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome [AHDS]) patients. Tiratricol was given in individual daily doses based on dose escalation until individual serum triiodothyronine (T3) levels were normalized or dose limiting toxicities (DLTs) occurred.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months Not applicable 24 to 42 months
Hypothesis	Exploratory: Within-patient changes in serum triiodothyronine (T3) concentrations during treatment, under the null hypothesis of no changes.		
Treatments groups	Treated patients		Treatment with tiratricol, up to 12 months, in 46 patients.
	Control group comparisons are not applicable due to the single-arm design		
Endpoints and definitions	Primary endpoint	Serum T3 (nmol/L)	Change in serum T3 concentrations from baseline to Month 12.
	Co-primary endpoints	TSH (mU/L)	Change in serum thyroid stimulating hormone (TSH) concentrations from baseline to Month 12.
		Free T4 (pmol/L)	Change in serum free thyroxine (FT4) concentrations from baseline to Month 12.
		Total T4 (nmol/L)	Change in serum total thyroxine (T4) from baseline to Month 12.
		rT3 (nmol/L)	Change in serum reverse triiodothyronine (rT3) from baseline to Month 12.
	Secondary endpoints	Weight-for-age (Z score)	Change in body weight from baseline to Month 12, relative to healthy controls.
		Heart rate (bpm)	Change in resting heart rate from baseline to Month 12.

		Systolic BP (percentile)	Change in blood pressure (BP) from baseline to Month 12.
		SHBG (nmol/L)	Change from baseline in serum sex hormone binding globulin (SHBG) from baseline to Month 12.
		Total cholesterol (mmol/L)	Change from baseline in total cholesterol levels from baseline to Month 12.
		Creatine kinase (U/L)	Change from baseline in serum creatine kinase (CK) from baseline to Month 12.
Database	Data was collected from October 2015 to May 2018.		
Results and Analysis			
Analysis description	Primary analysis		
Analysis population and time point description	The primary analysis was based on the Intent-to-treat (ITT) analysis set. 45 patients received tiratricol and had at least 1 follow-up assessment of thyroid function, fulfilling the criteria for the ITT analysis set. Differences from baseline to Month 12 visit, or last available assessment, were analysed as within-patient changes.		

Descriptive statistics, effect estimates and estimate variability per comparison

	Variable	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	Paired *t*-test p-value
Primary endpoint	Serum T3 (nmol/L)	45	4.97 (1.55)	1.82 (0.69)	-3.15 [-3.62; -2.68]	<0.0001
Co-primary endpoints	TSH (mU/L)	45	2.91 (1.68)	1.02 (1.14)	-1.89 [-2.39; -1.39]	<0.0001
	Free T4 (pmol/L)	45	9.68 (2.96)	3.39 (1.60)	-6.28 [-7.15; -5.41] The correct value: -6.1 [-6.8; -5.4]	<0.0001
	Total T4 (nmol/L)	45	55.96 (12.95)	24.38 (9.44)	-31.58 [-35.15; -28.01]	<0.0001
	rT3 (nmol/L)	45	0.12 (0.10)	0.04 (0.04)	-0.08 [-0.10; -0.05]	<0.0001

Notes	1 patient did not have at least 1 follow-up measurement of thyroid function because of study withdrawal before the first control visit due to noncompliance of study procedures. 5 of the 45 patients included in the ITT analysis set did not complete the planned visit at Month 12, and were analysed using the last available assessment: 1 patient developed Graves' disease after 8 months.

	1 patient was withdrawn after 2 months per parents' decision because of travel time to the study centre. 1 patient was withdrawn after 10 months per parents' decision because of severe comorbidity. 1 patient died from sepsis after 6 months. 1 patient was lost to follow up after 6 months. TSH concentrations were log-transformed for purposes of paired *t*-test which require normally distributed data. Non-transformed mean, SD and CI are presented.
Analysis description	Secondary analyses
Analysis population and time point description	The secondary analyses were pre-specified and based on Per-protocol (PP) analysis set. 40 patients in the ITT analysis set completed the Month 12 visit, fulfilling the criteria for the PP analysis set. Differences from baseline to Month 12 visit, or last available assessment, were analysed as within-patient changes.

Descriptive statistics, effect estimates and estimate variability per comparison

	Variable	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	Paired *t*-test p-value
Secondary endpoints	Weight-for-age (Z score)	40	-2.98 (1.93)	-2.71 (1.79)	0.27 [0.03; 0.50]	0.0253
	Heart rate (bpm)	34	112.4 (23.1)	103.5 (17.0)	-8.9 [-15.6; -2.3]	0.0100
	Systolic BP (percentile)	32	77.5 (24.7)	60.7 (29.3)	-16.8 [- 28.4; -5.1]	0.0063
	SHBG (nmol/L)	39	212.4 (90.8)	177.8 (76.1)	-34.7 [-54.8; -14.5]	0.0013
	Total cholest-erol (mmol/L)	40	3.23 (0.74)	3.39 (0.71)	0.16 [0.00; 0.32]	0.0558
	Creatine kinase (U/L)	40	108.0 (90.0)	160.7 (117.2)	52.7 [27.3; 78.1]	0.0001

Notes	5 of the 45 patients included in the ITT analysis set who did not complete the planned visit at Month 12 are excluded from PP analysis set. See notes for Primary analysis summarised above. At the Month 12 visit, resting heart rate was not assessed in 6 patients, systolic BP was not assessed in 8 patients, and SHBG was not assessed in 1 patient. Per statistical analysis plan, missing data at the nominal Month 12 visit was not imputed for the PP analysis set.

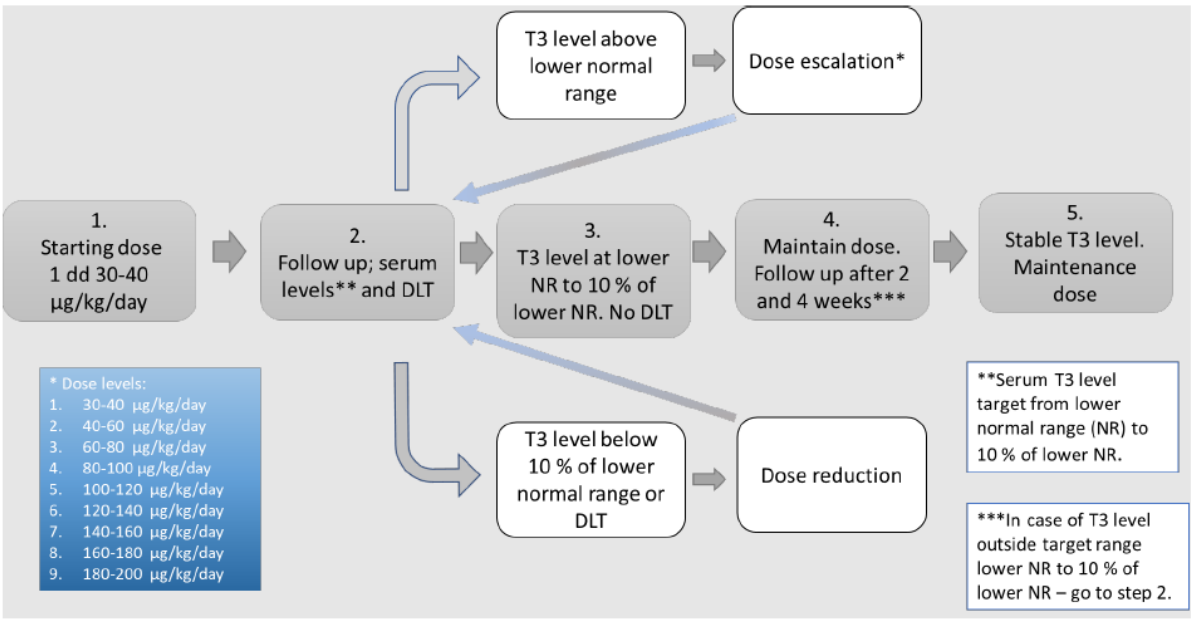
	Creatine kinase (U/L) was log-transformed for purposes of paired *t*-test which require normally distributed data. Non-transformed mean, standard deviation (SD) and confidence intervals (CI) are presented.

2.4.4.1. Supportive study

During the procedure, data from TRIAC II became available with the completion of part I.

Triac Trial II is a 96-week study (Part I) designed to evaluate the effects of tiratricol on neurodevelopment in young (≤30 months of age) patients with MCT8 deficiency. In addition, the study provides data on treatment effects on serum T3, clinical aspects of thyrotoxicosis and safety data in the youngest patients, dosed with considerably higher doses than in previous clinical studies. Part II of the study is a long-term extension with an additional 2 years of treatment and is currently on-going.

The initial starting dose of tiratricol was 30-40 µg/kg/day (dose level 1). Approximately 2 weeks after each dose-increase a blood sample was taken for serum T3 concentrations and other biochemical analyses, in order to determine the next step. Dose escalation targeted patients' T3 concentrations at the lower limit of the normal range (LLN) down to 10% of the LLN, without dose limiting toxicities (DLTs) or undesired side-effects. If a patient´s T3 value was below the LLN for age, the dose could be further increased as long as the T3 value did not drop below 10% of the lower normal range for age (e.g. with a LLN of 1.2 nmol/L for infants aged 6-12 months, the target range was 0.12 to 1.2 nmol/L). It was reasoned that tiratricol doses between 150 – 200 µg/kg/day would be a reasonable dose to administer in young children with MCT8 deficiency. In order to keep a constant dose/kg during maintenance and avoid an increase in T3 to above the LLN, the dose could be adjusted as needed during the study as patients grew older and gained weight. Tiratricol was administered orally or through a feeding tube, with the dose divided into 1-3 administrations per day. See Figure 11 for the dose titration scheme.



Tiratricol is available as 100 µg and 350 µg dispersible tablets for suspension for oral administration or through a percutaneous endoscopic gastrostomy (PEG)-tube. The dose was increased according to the dose-escalation scheme shown in the blue box, with the total daily dose adjusted within the interval to available 100 µg and 350 µg tablet strengths. These dose levels were to serve as a guideline; the dose escalation process was tailored to each patient.

Figure 11. Dose titration scheme

Of the 22 patients included in the ITT population, all were defined as having severe MCT8 deficiency, based on their genetic mutation. Median age at time of enrolment was 16 months, range: 5 to 28 months, with most patients (63.6%) aged >12 months at baseline. The median time since diagnosis was 3 months, range 0 to 21 months. Mean serum - T3 was above the upper limit of the reference range, irrespective of age.

A large proportion of patients (54.5%) was under-weight at baseline. Children with a body weight-for-age Z-score of <-2 (i.e. >2 SDs below the mean) were considered underweight (Groeneweg et al. 2020, WHO). Mean body weight-for-age MCT8 Z-score of -0.34 (i.e. close to zero) indicates mean body weight at baseline was consistent with that expected for untreated patients with MCT8 deficiency (Groeneweg et al.2020).

The majority of this young patient population had some difficulties with swallowing and choking, and there were 6 patients (27.3%) with a feeding tube at baseline.

Resting heart rate at baseline, estimated from pulse rate was generally within normal range for age at baseline, based on comparison with Fleming et al. 2011., mean Z-score -0.145. Two (9.5%) patients had resting heart rate (pulse rate) above the 90th percentile for the corresponding age, using cut-offs described in Fleming et al. 2011, and were defined as having tachycardia at baseline (compared with 40.9% of patients in TRIAC I).

Baseline systolic blood pressure was on average above that expected for age based on comparison with Flynn et al. 2017, mean Z-score 1.433. Thirteen (72.2%) patients had systolic hypertension at baseline based on definitions in Flynn et al. 2017 (compared with 34.3% in TRIAC I).

In accordance with the dose titration scheme and in order to increase the chances of a positive effect on the neurological phenotype of the disease, the dose escalation continued until patients were receiving approximately 150-200 µg/kg/day, provided T3 levels did not drop below 10% of the LLN, and while no DLTs were observed. The dose escalation was not stopped due to DLTs in any patient.

Reflecting that only 1 patient discontinued the study, overall median exposure to tiratricol during Part I of the study was 97.1 weeks, range 2 to 107 weeks. From approximately week 12, S-T3 levels had reached a maximum reduction and did not decrease further with increasing dose of tiratricol.

Data on GMFM-88 and BSID- III are presented in Table 41, Table 42 and Table 43.

Table 37. GMFM-88 total score (%) – analysis of effect of tiratricol after 96 weeks of tiratricol treatment compared to historical control estimate from the TRIAC Trial I study and compared to baseline (ITT)

Assessment	n/N	Mean	95% CI	P-value
Baseline	21/22	5.62	4.536 to 6.702	
Week 96	21/22	7.39	5.454 to 9.327	
Difference at week 96 versus historical control value (9.8%)	21/22	-2.41	-4.346 to -0.473	0.0173
Change from baseline to week 96	21/22	1.77	-0.054 to 3.597	0.0565

Source: Table 14.2.1.1.1 and 14.2.1.3.1

Primary analysis based on a one-sample t-test of mean at week 96 versus historical control value estimated from Triac I study. N is the number of patients in the ITT population and n is the number of patients with non-missing data at the respective timepoint.

Table 38. Bayley scales of infant development (BSID-III) Gross Motor Skills Domain (age equivalent score) – analysis of effect of tiratricol treatment compared to historical control estimate from the TRIAC Trial I study and compared to baseline (mITT)

Assessment	n/N	Mean	95% CI	P-value
Baseline	21/22	2.008	1.536 to 2.479	
Week 96	21/22	2.640	2.237 to 3.043	
Difference at week 96 versus historical control value (2.43 months)	21/22	0.210	-0.193 to 0.613	0.3791
Change from baseline to week 96	21/22	0.632	0.040 to 1.224	0.0804

Source: Table 14.2.1.8.1 and 14.2.1.10.1

Primary analysis based on a one-sample t-test of mean at week 96 versus historical control value estimated from Triac I study. N is the number of patients in the ITT population and n is the number of patients with non-missing data at the respective timepoint.

Table 39. GMFM-88 total score and BSID-III Gross Motor Skills Domain (age equivalent score) – analysis of change from baseline to week 96 (ITT)

Endpoint Baseline age group	n/N	Mean	95% CI	P-value
Change from baseline to week 96 in GMFM-88 total score				
0-12 months	8/8	2.30	-2.130 to 6.730	0.2592
>12 months	13/14	1.45	-0.476 to 3.369	0.1272
0-9 months	4/4	3.98	-2.348 to 10.298	0.1392
>9 months	17/18	1.25	-0.780 to 3.286	0.2099
Change from baseline to week 96 in BSID-III Gross Motor Skills Domain				
0-12 months	8/8	0.164	-0.444 to 0.773	0.6247
>12 months	13/14	0.920	0.008 to 1.833	0.0975

Source: Table 14.2.1.3.2 and 14.2.1.10.2.

Analysis based on a one-sample t-test of mean at week 96 versus historical control value estimated from Triac I study.
N is the number of patients in the subgroup of the ITT population and n is the number of patients with non-missing data at the respective timepoint in each subgroup.

Data on GMFM-88 Item 10 "lifts head upright" and GMFM-88 Item 24 "sit on mat" (maintain, arms free, 3 seconds), GMFM-88 Domain B (Sitting) are presented in Table 44, Table 45 and Table 46.

Table 40. Change from baseline to week 96 in GMFM-88 Item 10 "lifts head upright"- number (%) of patients at baseline and week 96 (mITT)

	Week 96					
	n/N	0	1	2	3	NT
Baseline	**0** 4/22	3 (75.0)	1 (25.0)	0	0	0
	1 5/22	0	2 (40.0)	1 (20.0)	2 (40.0)	0
	2 7/22	1 (14.3)	2 (28.6)	3 (42.9)	1 (14.3)	0
	3 5/22	1 (20.0)	0	3 (60.0)	1 (20.0)	0

Source: Table 14.2.2.1.1.

GMFM score: 0=does not initiate; 1=initiates; 2=partially completes; 3=completes; NT Not tested.

Table 41. Change from baseline to week 96 in GMFM-88 Item 24 "sit on mat"- number (%) of patients at baseline and week 96 (mITT)

		Week 96				
		0	1	2	3	NT
Baseline	0 19/22	19 (100.0)	0	0	0	0
	1 0	0	0	0	0	0
	2 0	0	0	0	0	0
	3 0	0	0	0	0	0
	NT 1/22	1 (100.0)				

Source: Table 14.2.2.2.1.
GMFM score: 0=does not initiate; 1=initiates; 2=partially completes; 3=completes; NT Not tested.

Table 42. GMFM-88 Domain B (Sitting) (%)- analysis of effect of tiratricol after 96 weeks of treatment compared to baseline (ITT)

Assessment	n/N	Mean	95% CI	P-value
Baseline	21/22	2.38	0.814 to 3.948	
Week 96	21/22	5.50	3.442 to 7.558	
Difference at week 96 versus baseline	21/22	3.12	1.007 to 5.231	0.0059

Source: Table 14.2.2.3.1.
Analysis based on a one-sample t-test of mean summary score of all Domain B items 18-37 of GMFM-88 at week 96 compared to baseline.N is the number of patients in the ITT population and n is the number of patients with non-missing data at the respective timepoint.

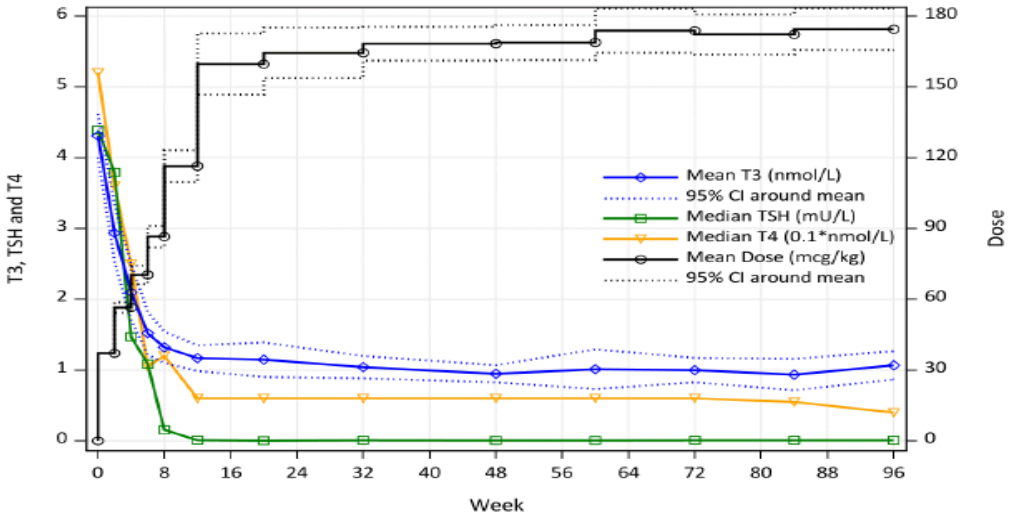
Data on section 2 of the Hammersmith Infant Neurological Examination (HINE) are presented in Table 47.

Table 43. Motor milestone responder analysis of Section 2 of the Hammersmith Infant Neurological Examination (HINE)- number (%) of patients with improvement, no change, or worsening at week 96 (mITT)

HINE Section 2 Motor Milestones	N	Improvement	No change	Worsening
Head control	21	6 (28.6)	12 (57.1)	3 (14.3)
Sitting	21	3 (14.3)	12 (57.1)	6 (28.6)
Voluntary grasp	21	8 (38.1)	9 (42.9)	4 (19.0)
Ability to kick in Supine	19	8 (42.1)	4 (21.1)	7 (36.8)
Rolling	20	5 (25.0)	13 (65.0)	2 (10.0)
Crawling	20	5 (25.0)	10 (50.0)	5 (25.0)
Standing	21	2 (9.5)	16 (76.2)	3 (14.3)
Walking	18	0 (0.0)	15 (83.3)	3 (16.7)

Source: Table 14.2.3.3.1.6

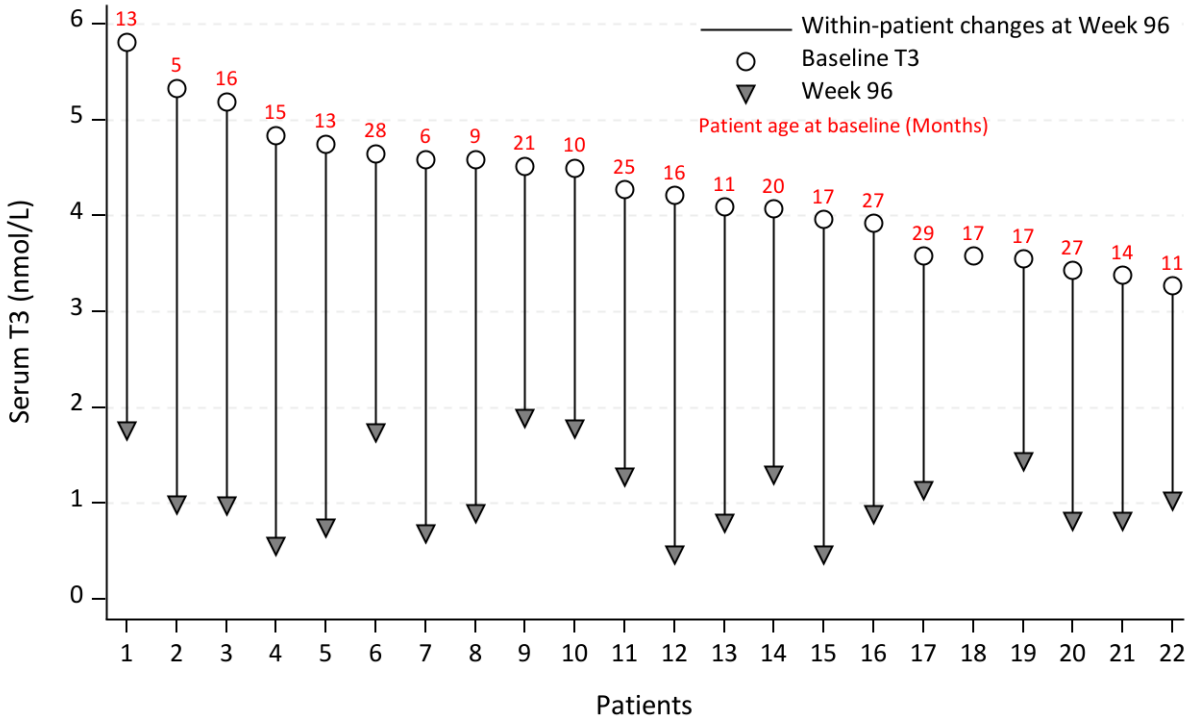
Data on tiratricol dose and corresponding T3, T4 and TSH level by week of dosing as well as change from baseline to week 96 in thyroid hormone levels are presented in Figure 12, Figure 13 and Table 48.



Source: Tables 14.1.14.1, 14.2.2.8.3, 14.2.2.9.1 and 14.2.2.11.1.

Medians are displayed instead of means for TSH and T4 due to flooring effect from values below limit of quantification.
95% CI (confidence intervals) around the mean were calculated for T3 and Dose (data-on-file).
T3: Baseline value is from immunoassay Lumipulse. T3 after baseline is derived using result from immunoassays Lumipulse and Immulite. TSH: Lower limit of quantification was 0.003 and 0.008 mU/L respectively, before and after change of assay 28OCT2022.
T4: Lower limit of quantification was 6 and 4 nmol/L respectively, before and after change of assay 02OCT2022.

Figure 12. Tiratricol dose and corresponding T3, T4, TSH by week of dosing (ITT)



Source: Adapted from figure 14.2.2.8.7, Clinical study report Triac Trial II.

Note: mITT analysis set.

Normal ranges for Serum T3: 3-6 months 0.8-3.9 nmol/L, 6-12 months 1.2-3.7 nmol/L, >=12 months 1.7-2.9 nmol/L.

Within-patient changes per patient are ordered by Baseline Serum T3.

Dataset: ADaM.ADLB. Program: \\MAA\prog\subprogs\tflpgm\273_fig2_tt2_epar.sas.

Figure 13. Change from baseline to week 96 in Serum-T3

Table 44. Analysis of mean change from baseline to week 96 in thyroid hormone levels (ITT)

Assessment	n/N	Baseline Mean (SD)	96 weeks Mean (SD)	Difference Mean [95% CI]	P-value
S-T3 (nmol/L)	21/22	4.310 (0.675)	1.067 (0.439)	-3.242 (-3.569, -2.916)	<0.0001
S-TSH (mU/L)	21/22	4.485 (1.523)	0.015 (0.023)	-4.470 (-5.166; -3.774)	<0.0001
Free T4 (pmol/L)	21/22	8.90 (1.51)	2.27 (0.74)	-6.629 (-7.456; -5.801)	<0.0001
Total T4 (nmol/L)	21/22	54.2 (13.4)	5.9 (2.7)	-48.38 (-54.32; -42.45)	<0.0001
Reverse T3 (nmol/L)	13/22	0.102 (0.020)	0.076 (0.033)	-0.026 (-0.050; -0.002)	0.0367

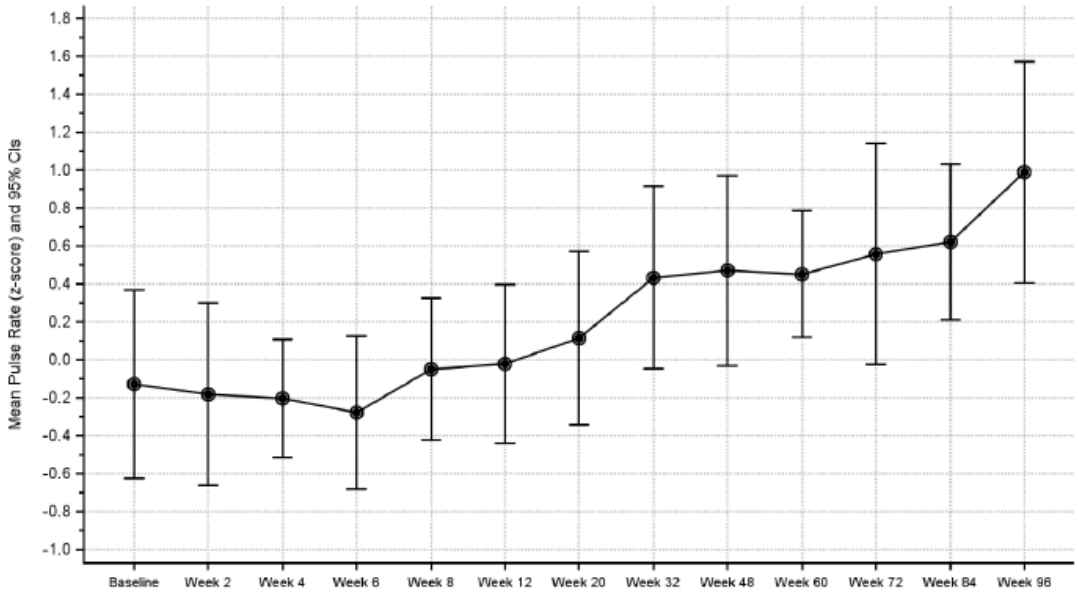
Source: Table Q087-D-1 of Additional analyses for responses to Day 120 questions in Module 5.3.5.3.
Reverse T3 at week 96 for subject 19-006 was set to missing here. This result was incorrectly included in the database. The reported value of 0.4 nmol/L pertained to reverse T3 using a LC/LC-MS assay, and was commented as being at the lower limit of quantification.
N is the number of patients in the ITT population; n is the number of patients with data at week 96.

Data on body weight, body weight SBP and resting heart rate are presented in Table 49 and Figure 14.

Table 45. Analysis of the secondary outcome measures of thyrotoxicosis – mean change from baseline to week 96 (ITT)

Assessment	n/N	Baseline Mean (SD)	96 weeks Mean (SD)	Change from baseline to week 96 Mean (95% CI)	P-value
Body weight (kg)	21/22	8.87 (1.69)	12.29 (2.19)	3.41 (2.7, 4.2)	<0.0001
Body weight-for-age z-score	21/22	-2.139 (1.152)	-1.986 (1.630)	0.154 (-0.452, 0.760)	0.6029
Body weight-for-MCT8 z-score	21/22	-0.421 (1.197)	0.708 (1.637)	1.129 (0.513, 1.745)	0.0011
Resting heart rate (pulse) (bpm)	19/22	114.5 (18.6)	118.1 (19.6)	3.6 (-9.8; 17.0)	0.5824
Resting heart rate (pulse)-for-age z-score	19/22	-0.222 (0.971)	1.007 (1.276)	1.229 (0.465; 1.992)	0.0033
24-hour Holter ECGs Heart Rate:					
Mean heart rate (bpm)	21/22	114.4 (9.9)	113.2 (10.5)	-1.2 (-6.5, 4.1)	0.6445
Minimum heart rate (bpm)	21/22	70.3 (13.1)	76.8 (13.0)	6.4 (-0.1, 13.0)	0.0535
Maximum heart rate (bpm)	21/22	178.9 (17.0)	174.3 (19.5)	-4.5 (-11.7, 2.6)	0.2030
Systolic blood pressure (mmHg)	16/22	103.9 (15.7)	110.1 (15.6)	6.2 (-5.0, 17.4)	0.2588
SBP Z-score	16/22	1.381 (1.201)	1.499 (1.054)	0.117 (-0.621, 0.856)	0.7393
SBP percentile	16/22	83.9 (27.7)	85.4 (25.1)	1.5 (-15.6, 18.6)	0.8539
Diastolic blood pressure (mmHg)	16/22	61.5 (12.3)	61.7 (12.2)	0.2 (-9.8, 10.2)	0.9686
DBP Z-score	16/22	1.651 (0.757)	1.176 (0.786)	-0.475 (-1.056, 0.106)	0.1019
DBP percentile	16/22	90.3 (13.5)	82.4 (18.0)	-7.9 (-20.0, 4.2)	0.1822
S-SHBG (nmol/L)	21/22	301.5 (117.5)	252.6 (70.1)	-48.9 (-99.7 to 1.9)	0.0583
S-CK (U/L)	20/22	125.1 (60.3)	101.1 (62.0)	-24.1 (-53.9 to 5.8)	0.1075
S-Creatinine (U/L)	21/22	23.8 (5.04)	25.2 (4.8)	1.4 (-0.5 to 3.3)	0.1339

Source: Table Q087-D-2 of Additional analyses for responses to Day 120 questions in Module 5.3.5.3
CK=Creatine kinase; DBP=Diastolic blood pressure; S=serum; SBP=Systolic blood pressure; SHBG=Sex hormone binding globulin.
N Number of patients with measurement at baseline; n number of patients with measurement at week 96.



Source: Table 14.3.6.6.1.
Error bars are 95% Confidence Intervals for the mean at each timepoint.

Figure 14 Change from baseline to week 96 in mean resting HR (pulse)-for-age Z scores

2.4.5. Clinical safety

2.4.5.1. Patient exposure

The safety of tiratricol in patients with MCT8 deficiency was evaluated based on data available at the DLP (30 June 2023) from the TRIAC I (systematic collection of safety data throughout the study), EMC cohort study (only AE data considered related to tiratricol treatment collected), TRIAC II (systematic collection of safety data throughout the study, SAEs until DLP available) and NPU/compassionate use (spontaneous reporting). Table 50 and Table 51 summarise the duration of exposure and exposure in patient-years.

Table 46. Summary of exposure to tiratricol (Triac Trial I and EMC cohort study)

Study	Exposure	n (%)
Triac Trial I including TEP N=46 n (%)	<2 years	36 (78%)
	2 to 5 years	10 (22%)
	>5 years	0 (0%)
	Median duration, years	1.1
	Range	0.0 to 3.6 years
EMC Triac Trial I Subset [a] N=27 n (%)	<2 years	3 (11%)
	2 to 5 years	13 (48%)
	>5 years	11 (41%)
	Median duration, years	4.3
	Range	1.5 to 6.2 years
EMC NPU Subset N=40 n (%)	<2 years	26 (65%)
	2 to 5 years	13 (33%)
	>5 years	1 (3%)
	Median duration, years	1.5
	Range	0.2 to 5.0 years

CSR=clinical study report; EMC=Erasmus Medical Center; NA=not available; N=number of patients analyzed; n=number of patients with the event; NPU=named patient use; TEP=treatment extension period.
a Patients participated in Triac Trial I prior to the EMC cohort study. Exposure includes treatment in both studies.

Table 47. Exposure in Patient Years

Age Group	All ages from birth		<2.5 years old		>2.5 years old	
Study	N	Exposure in patient years	N	Exposure in patient years	N	Exposure in patient years
Triac Trial I including TEP and EMC Triac Trial I Subset a	46	123	5	16	41	107
EMC NPU Subset	40	70	20	27	20	43
Triac Trial II b	22	36	22	36	0	NA
Total Exposure in Patient Years	108	229	47	79	61	150

CSR=clinical study report; EMC=Erasmus Medical Center; NA=not available; N=number of patients analyzed; n=number of patients with the event; NPU=named patient use; TEP=treatment extension period.

a 27 patients from Triac Trial I were subsequently enrolled in the EMC cohort study. Exposure includes treatment in both studies.

b Exposure until DLP.

2.4.5.2. Adverse events

TRIAC I

There was no comparator group so that relationship to Emcitate cannot be established based on an increased frequency compared to placebo. In total 43 participants (93.5%) had at least one AE. The most frequent SOC was "infections and infestations" (37 subjects, 80.4%), but these conditions most likely were related to the underlying disease.

All events of hyperhidrosis and psychiatric disorders (anxiety, nightmare and irritability) were considered probably related to study drug by the investigator; see table below. All seven adverse events considered probably related to study medication usually occurred at the start of treatment and/or when the dose was increased and were transient in nature.

The applicant considered nightmares, irritability and anxiety as predictable since they can be explained by pharmacological effects of a thyreomimetic drug, which is able to cross the blood-brain barrier. On the other hand, the applicant considers hyperhidrosis more difficult to explain when a general reduction in peripheral TH activity is expected by tiratricol therapy. See Table 52.

Table 48. Adverse events considered by the investigator to be at least possibly related to study medication (Safety Analysis Set)

System Organ Class	Preferred Term	Severity	Relationship to study medication	SAE
Skin and subcutaneous tissue disorders	Hyperhidrosis	MILD	Probable	N
Skin and subcutaneous tissue disorders	Hyperhidrosis	MILD	Probable	N
Skin and subcutaneous tissue disorders	Hyperhidrosis	MILD	Probable	N
Psychiatric disorders	Nightmare	MILD	Probable	N
Psychiatric disorders	Irritability	MILD	Probable	N
Psychiatric disorders	Anxiety	MILD	Probable	N
Skin and subcutaneous tissue disorders	Hyperhidrosis	MILD	Probable	N

EMC Cohort Study

Only AEs considered by the treating physician to be related to tiratricol (ADR) were reported retrospectively in the EMC cohort study. These AEs are listed in the following table. As in the Triac I trial, most possibly related AEs were anxiety, irritability and sweating. See Table 53.

Table 49. Adverse events considered by the Investigator to be at least possibly related to tiratricol (EMC cohort study)

Adverse event	Age at start of treatment (years)	Character	Dose (µg/day)	Action taken with tiratricol	Outcome
Increased irritability a	6.0	Transient	525	Dose decreased	Resolved without sequelae
Increased anxiety b	13.7	Transient	1050	None	Resolved without sequelae
Increased anxiety and sadness c	6.3	Transient	700	None	Resolved without sequelae
Increased irritability and reduced sleep d	1.2	Transient, after dose increase	350	Dose decreased	Resolved without sequelae
Increased sweating and irritability, tachycardia e	15.9	Transient	700	None	Returned later during treatment (irritability),

Adverse event	Age at start of treatment (years)	Character	Dose (µg/day)	Action taken with tiratricol	Outcome
					otherwise resolved without sequelae
Increased irritability and anxiety e	15.9	Transient	1400	None	Returned later during treatment (anxiety), otherwise resolved without sequelae
Increased blood pressure, tachycardia, and increased anxiety e	15.9	Transient, after dose increase f	1700	Dose decreased	Resolved without sequelae

Source: Table S4, van Geest et al. 2022 suppl.
EMC=Erasmus Medical Center.
a Patient in EMC Triac Trial I subset.
b Patient in EMC Triac Trial I subset.
c Patient in EMC NPU subset.
d Patient in EMC NPU subset.
e These 3 events occurred in the same patient in EMC NPU subset.
f For increased blood pressure and tachycardia.

TRIAC II

Overall, 21 (95.5%) patients in the Safety Analysis Set (ITT population) reported 208 TEAEs in Part I of the study. No TEAEs led to discontinuation of study treatment; one SAE led to treatment interruption. One patient withdrew from the study for other reasons prior to reporting any TEAEs. The majority of reported TEAEs were CTCAE Grade 1 (mild) or 2 (moderate) in severity. Thirteen patients (59.1%) reported 19 TEAEs graded CTCAE grade 3 or higher (all severe apart from 1 life-threatening), and 26 SAEs were reported in 10 (45.5%) patients. TEAEs considered at least possibly related to study treatment were reported in 13 (59.1%) patients. See Table 54.

Table 50. Overview of treatment-emergent adverse events (Triac trial II) (ITT)

MedDRA v22.0 System organ class Preferred term	Number of patients N=22 n (%)	Number of events
Any treatment-emergent adverse event (TEAE)	21 (95.5)	208
Any TEAE at least possibly related to study treatment	13 (59.1)	20
Any TEAE leading to discontinuation of study treatment	0	0
Any TEAE leading to treatment interruption	1 (4.5)	1
Any TEAE of CTC Grade 3 or higher	13 (59.1)	19
Any TEAE by CTCAE Grade		
CTCAE Grade 1 (mild)	21 (95.5)	141
CTCAE Grade 2 (moderate)	12 (54.5)	48
CTCAE Grade 3 (severe)	13 (59.1)	18
CTCAE Grade 4 (life threatening)	1 (4.5)	0
Any serious treatment-emergent adverse event (SAE)	10 (45.5)	26

MedDRA v22.0 System organ class Preferred term	Number of patients N=22 n (%)	Number of events
Any SAE leading to death	0	0
Any SAE at least possibly related to study treatment	1 (4.5)	2
Any SAE leading to treatment interruption	1 (4.5)	1

The most frequently reported TEAEs that were considered by the investigator to be at least possibly related to study treatment were in the gastrointestinal disorders MedDRA SOC, including diarrhoea reported by 3 (13.6%) patients. For 2 of the 3 TEAEs of diarrhoea considered treatment-related, the events were reported at a dose close to 200 µg/kg. Nervous system disorders of seizure/partial seizures/dyskinesia were reported in 3 (13.6%) patients.

Two treatment-related TEAEs of hypothyroidism were reported after tiratricol was abruptly withdrawn in 2 patients.

Other treatment-related TEAEs that had been observed in Triac Trial I such as hyperhidrosis, sleep disorder, and irritability, that were considered to potentially indicate signs of hyperthyroidism on initiation of treatment or dose increase were considered treatment-related in single patients only in Triac Trial II.

The only treatment-related TEAEs that started within approximately 1 week of last dose increase were nausea, diarrhoea, diarrhoea and weight decreased, dyskinesia, and vomiting.

Overall, these generally mild (CTCAE Grade 1) or moderate (CTCAE Grade 2) TEAEs resolved without any change in tiratricol dose.

Data on AEs considered by the investigator to be at least possibly related to tiratricol are presented in Table 55.

Table 51. Summary of Adverse events considered by the Investigator to be at least possibly related to tiratricol (Part I Triac trial II) (ITT)

MedDRA v22.0 System organ class Preferred term	Number of patients N=22 n (%)	Number of events
Endocrine disorders	2 (9.1)	2
Hypothyroidism	2 (9.1)	2
Psychiatric disorders	2 (9.1)	2
Irritability	1 (4.5)	1
Sleep disorder	1 (4.5)	1
Nervous system disorders	3 (13.6)	4
Dyskinesia	1 (4.5)	1
Partial seizures	1 (4.5)	1
Seizure	1 (4.5)	2
Gastrointestinal disorders	5 (22.7)	7
Diarrhoea	3 (13.6)	3
Constipation	1 (4.5)	2
Nausea	1 (4.5)	1
Vomiting	1 (4.5)	1
All other SOCs		
Weight decreased	2 (9.1)	2
Iron deficiency anaemia	1 (4.5)	1
Hyperhidrosis	1 (4.5)	1
Product administration error	1 (4.5)	1

2.4.5.3. Serious adverse event/deaths/other significant events

No AEs of special interest were defined.

TRIAC I

Data are presented in Table 56.

Table 52. Summary of serious adverse events by MedDRA system organ class and preferred term (Triac Trial I)

MedDRA v22.0 System organ class Preferred term	Number of patients with at least 1 event N=46 n (%)	Number of events
Overall SAEs a, b	18 (39)	26
Infections and infestations	13 (28)	13
Bronchiolitis	3 (7)	3
Bronchitis	2 (3)	2
Pneumonia	2 (3)	2
Gastroenteritis	2 (3)	3
Clostridium difficile infection	1 (2)	1
Upper respiratory tract infection	1 (2)	1
Urinary tract infection	1 (2)	1
Surgical and medical procedures	2 (3)	3
Hip surgery	1 (2)	1
Drug therapy	1 (2)	2
Nervous system disorders	2 (3)	2
Seizures (increase)	2 (3)	2
Product issues	2 (3)	2
Device malfunction	2 (3)	2
Respiratory, thoracic, and mediastinal disorders	1 (2)	2
Respiratory distress	1 (2)	2
Gastrointestinal disorders	1 (2)	1
Enterocolitis	1 (2)	1
General disorders and administration site conditions	1 (2)	1
Multiple organ dysfunction syndrome	1 (2)	1
Hepatobiliary disorders	1 (2)	1
Hepatic failure	1 (2)	1
Investigations	1 (2)	1
Endoscopy upper gastrointestinal tract d	1 (2)	1

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients analyzed; n=number of patients with the event; PSUR=periodic safety update report; SAE=serious adverse event.

a An SAE was defined as any untoward medical occurrence or effect that at any dose resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity other than may be expected by the effects of the disease-specific mutation, or was deemed to be serious for any other reason.

b A patient with multiple events within a category was counted only once in that category.

c Reported terms were ventriculoperitoneal shunt malfunction and ruptured percutaneous endoscopic gastrostomy tube.

d Reported term was planned hospital admission for diagnostic gastroscopy Indication recurrent vomiting (hypertrophic pyloric stenosis).

One patient died during this study due to shock and multiorgan failure. The event was not considered related to tiratricol by the Investigator nor the DSMB.

EMC Cohort Study

In the EMC cohort study, only SAEs considered related to tiratricol were actively monitored. No treatment related SAEs were reported.

Three of 67 patients (4.5%) death were reported: a 13-year-old patient suffered a sudden death (duration of tiratricol treatment >1.5 years); a 71 year-old patient died after aspiration (duration of tiratricol treatment >4 years) and a 14-year-old patient died of unknown causes (duration of tiratricol treatment >2.5 years).

TRIAC II

Data are presented in Table 57.

Table 53. Summary of serious adverse events by MedDRA system organ class and preferred term (Triac trial II) (ITT)

MedDRA v22.0 System organ class Preferred term	Number of patients N=22 n (%)	Number of events
Infections and infestations	6 (27.3)	10
Respiratory syncytial virus infection	3 (13.6)	3
Respiratory syncytial virus bronchiolitis	1 (4.5)	1
COVID-19	1 (4.5)	1
Hand-foot-and-mouth disease	1 (4.5)	1
Metapneumovirus infection	1 (4.5)	1
Pneumonia	1 (4.5)	1
Viral infection	1 (4.5)	1
Viral upper respiratory tract infection	1 (4.5)	1
Nervous system disorders	3 (13.6)	4
Seizures	2 (9.1)	3
Movement disorder	1 (4.5)	1
All other SOCs		
Cryptorchism	2 (9.1)	2
Vomiting	2 (9.1)	2
Feeding disorder	2 (9.1)	2
Gastrostomy	2 (9.1)	2
Magnetic resonance imaging brain	1 (4.5)	1
Gastroesophageal reflux disease	1 (4.5)	1
Acquired phimosis	1 (4.5)	1
Dyspnoea	1 (4.5)	1

Compassionate use program

As of 30 June 2024, 18 patients have received tiratricol treatment as part of the compassionate use program in Turkey, and adverse event notifications have been reported for 10 of these patients. Note that some notifications include more than 1 adverse event.

The adverse events that have been reported are generally in line with those expected in patients with MCT8 deficiency: Covid-19 infection*, sT3 increased×2, sT4 decreased, pneumonia*, sudden cardiac arrest*, seizures*, upper respiratory tract infection×2, lower respiratory tract infection*, loss of appetite, hip dislocation, dental abscess, and transaminases increased.

Only one non-serious report of a patient who experienced increased thyroid hormones (FT3) was considered expected and possibly related to tiratricol treatment based on a temporal relationship and the known product

safety profile. The natural course of the underlying disease was also considered likely to have contributed to the reported increased thyroid hormones and the reported infections and seizures.

The 5 adverse events highlighted with an asterisk* were serious, including one patient who died from sudden cardiac arrest.

One death (initially reported as sudden cardiac death, amended after data lock point to unspecified sudden death) has been reported. The sudden death was assessed as unrelated to treatment with tiratricol by the reporting paediatric endocrinologist and related to the underlying disease MCT8 deficiency.

2.4.5.4. Laboratory findings

In the Triac I trial, standard routine laboratory parameters were determined as well as markers of tissue-specific thyroid hormone action. In the EMC cohort study, a less extensive set of laboratory measurements was obtained, but the results were fairly in line with the findings in the Triac I trial. Laboratory values were also obtained in the natural history study (Groeneweg et al. 2020). These data are consistent with the baseline findings in the Triac I and EMC cohort study. The changes in thyroid hormones (TH) are described in the efficacy section since change in T3 was an important endpoint in the clinical trials of Emcitate.

The mean levels of ALT, AST and GGT did not increase during the TRIAC I. There were some cases of increased transaminases, but available data clearly indicate that these increases were due to accompanying anti-epileptic medication and not to Emcitate.

Natural history study data ((Groeneweg et al, 2020) show that serum levels of sex hormone binding globulin (SHBG) were increased in untreated AHDS patients. See Figure 16.

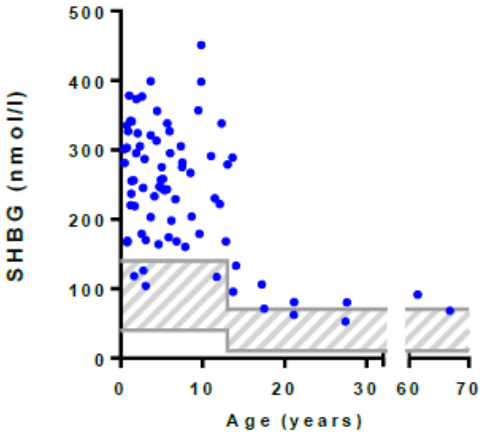


Figure 15. Groeneweg et al, 2020 (natural history study) – Serum sex hormone binding globulin (SHBG) (n=78)

In TRIAC I, during Emcitate treatment, SHBG decreased but was still above the normal range for most age groups. Accompanying changes were a slight increase in cholesterol (total, HDL and LDL) and triglycerides as well as a decrease in ferritin. All these changes are known to be related to decreased TH activity. See Table 58.

Table 54. TRIAC I: Efficacy results from baseline to end of treatment extension period (ITT)

Parameter	N	Baseline Mean (SD)	TEP Mean (SD)	Mean change from baseline [95% CI]	P value	Exemplary normal ranges from open source for orientation
SHBG (nmol/L)	9	176.2 (86.4) ↑	121.0 (52.1)	-55.1 [-98.2, -12.0]	0.0184	Males (nmol/L) 10.4y: 17-135 11.1y: 21-114 12.7y: 12-138 14.5y: 7.7-67 14.2y: 3.9-40
Total cholesterol (mmol/L)	10	2.93 (0.92)	3.44 (0.69)	0.5 [0.08, 0.94]	0.0244	<5.0 mmol/L
LDL cholesterol (mmol/L)	10	1.62 (0.58)	1.74 (0.39)	0.12 [-0.14, 0.38]	0.3238	<3.0 mmol/L
HDL cholesterol (mmol/L)	10	1.13 (0.36)	1.33 (0.40)	0.20 [0.04, 0.36]	0.0190	>1.0 mmol/L
Triglycerides (mmol/L)	10	0.68 (0.44)	0.75 (0.35)	0.08 [-0.22, 0.37]	0.5746	<2.3 mmol/L
Ferritin (µg/L)	40	44.95 (39.56)	29.15 (18.81)	-15.80 [-27.28, -4.32]	0.0082	Newborns: 25-200 ng/mL 1 mo: 200-600 ng/mL 2-5 mo: 50-200 ng/mL 6 mo to 15 y: 7-140 ng/mL

During the procedure, additional data on the relationship between SHGB and age-dependent normal range and its change over time were made available. These suggested that SHBG was far above ULN at treatment start and decreased with Emcitate but in most cases did not reach the normal range. See Figure 17.

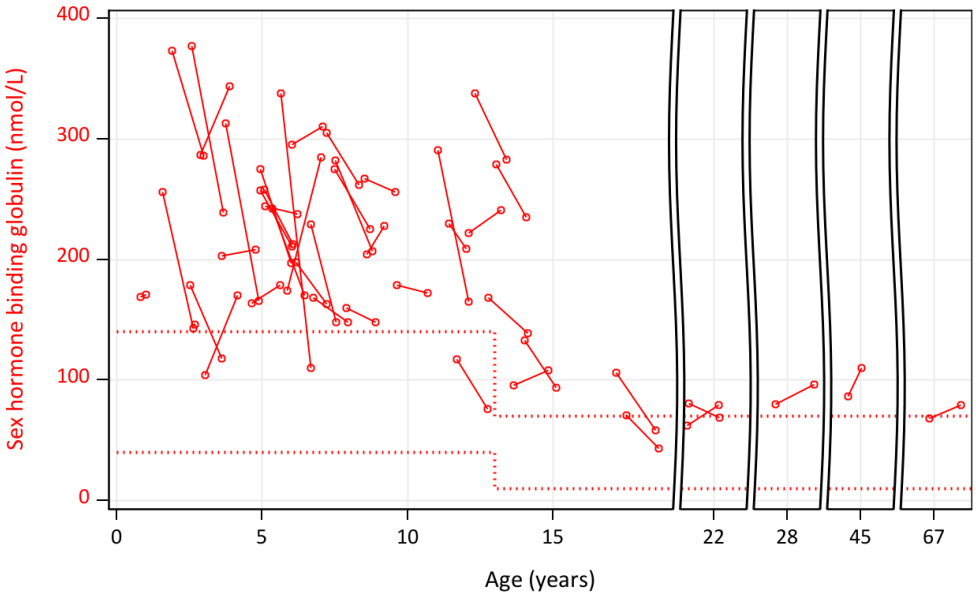


Figure 16. Sex Hormone Binding Globulin by age at Baseline and Month 12 Visit – TRIAC I

Based on the natural history study data, ADHS causes rather low bone mineral density (BMD), accompanied by low bone alkaline phosphatase (BAP), indication low bone formation. See Figure 18.

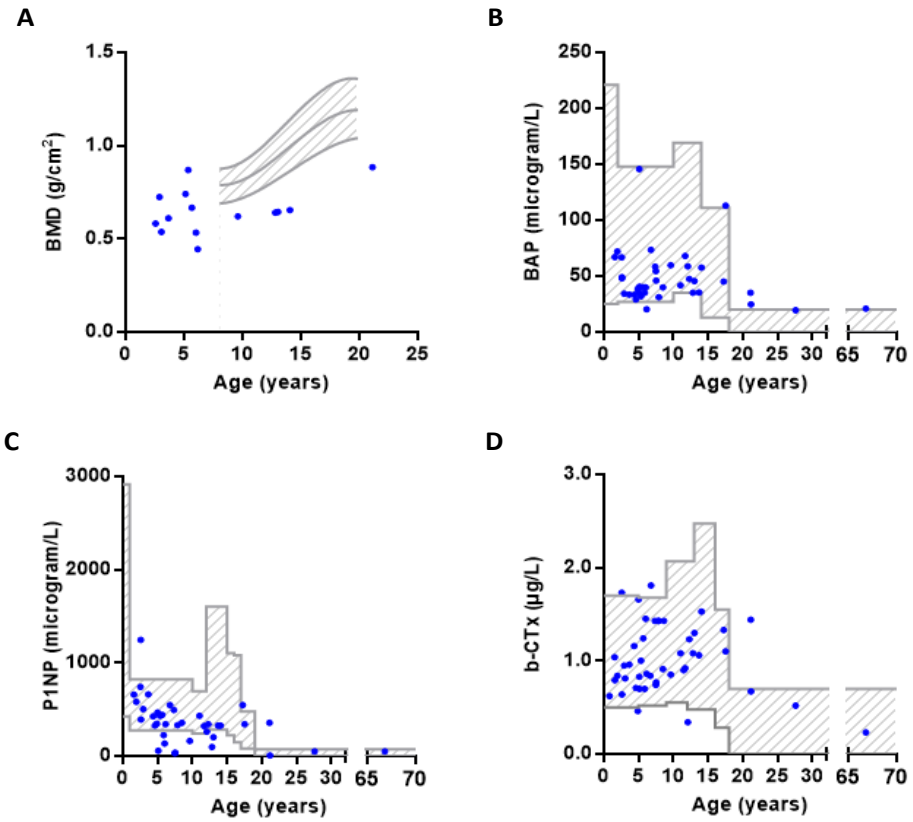


Figure 17. Groeneweg et al., 2020 suppl.: (A) Cross-sectional evaluation of total body bone mineral density. (B) Cross-sectional overview of serum bone alkaline phosphatase concentrations by age, (C) procollagen type I propeptides (PINP) concentrations by age, and (D) plasma C-terminal collagen crosslinks by age. Indicated are the measurements in individual patients (blue dots) and the age-specific normal ranges (grey shaded areas).

In TRIAC I, treatment with Emcitate led to an increase in the bone formation markers BAP and procollagen 1 N-terminal propeptide (P1NP). See Figure 18.

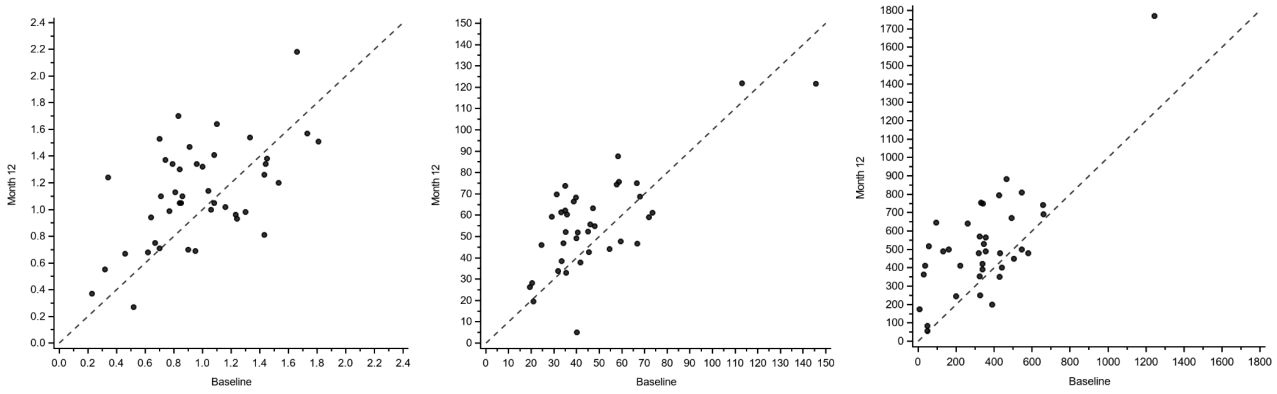


Figure 18. TRIAC I: Serum β-C-terminal telopeptide [µg/L](left), Bone-specific Alkaline phosphatase [µg/L] (mid) and Procollagen 1 N-Terminal Propeptide (P1NP) [µg/L] (right) at baseline and end of study (Safety Analysis Set)

In line with the increase in serum bone formation markers, BMD of the distal forearm increased by around 10% within 12 months as shown in the table below. Whole-body BMD increased by around 1% only, i.e. remained virtually unchanged. See Table 59.

Table 55. TRIAC I: Summary of BMD and laboratory data over time (Safety population)

Assessment	N	Baseline Mean (SD)	N out of range/ total N	12 months Mean (SD)	N out of range/ total N	Difference Mean [95% CI]	Exemplary normal ranges from open source for orientation
BMD forearm UDR (g/cm2)	6	0.263 (0.023)	n.a.	0.292 (0.041)	n.a.	0.029 [-0.010, 0.068]	Males around 0.58 g/cm2
BMD forearm UDU (g/cm2)		0.220 (0.039)	n.a.	0.241 (0.051)	n.a.	0.021 [-0.011, 0.054]	Males around 0.58 g/cm2
BMD total body (g/cm2)		0.654 (0.122)	n.a.	0.662 (0.117)	n.a.	0.008 [-0.034, 0.050]	

In TRIAC II, alkaline phosphatase remained unaffected by Emcitate whereas β-C-terminal telopeptide (also called beta-crossLaps increased from baseline to Week 48 (and remained stable up to Week 96). Thus, in TRIAC II, Emcitate tended to cause bone loss whereas in TRIAC I, there was a tendency to increased bone mass. The reason for this discrepancy most likely is the fact that in Triac II the peripheral hyperthyroidism

was not counteracted because of TH-like effects of the high tiratricol doses used in this study. Hence, the hyperthyroidism-driven bone loss remained. See Figure 20.

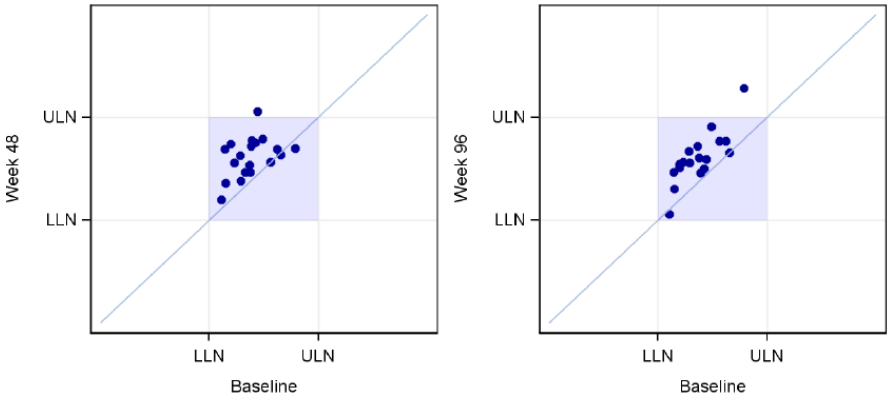


Figure 19. Triac II: Beta-Crosslaps (beta CTx) (normalised) - shift plot BL vs W48 and W96 (SAS)

In the natural history study, serum markers of muscle mass before treatment, creatine kinase (CK) was in the normal range whereas creatinine was remarkably low. The latter can be explained by the low muscle mass in patients with MCT8 deficiency and most likely was not related to kidney function since serum urea was in the normal range. See Figure 21.

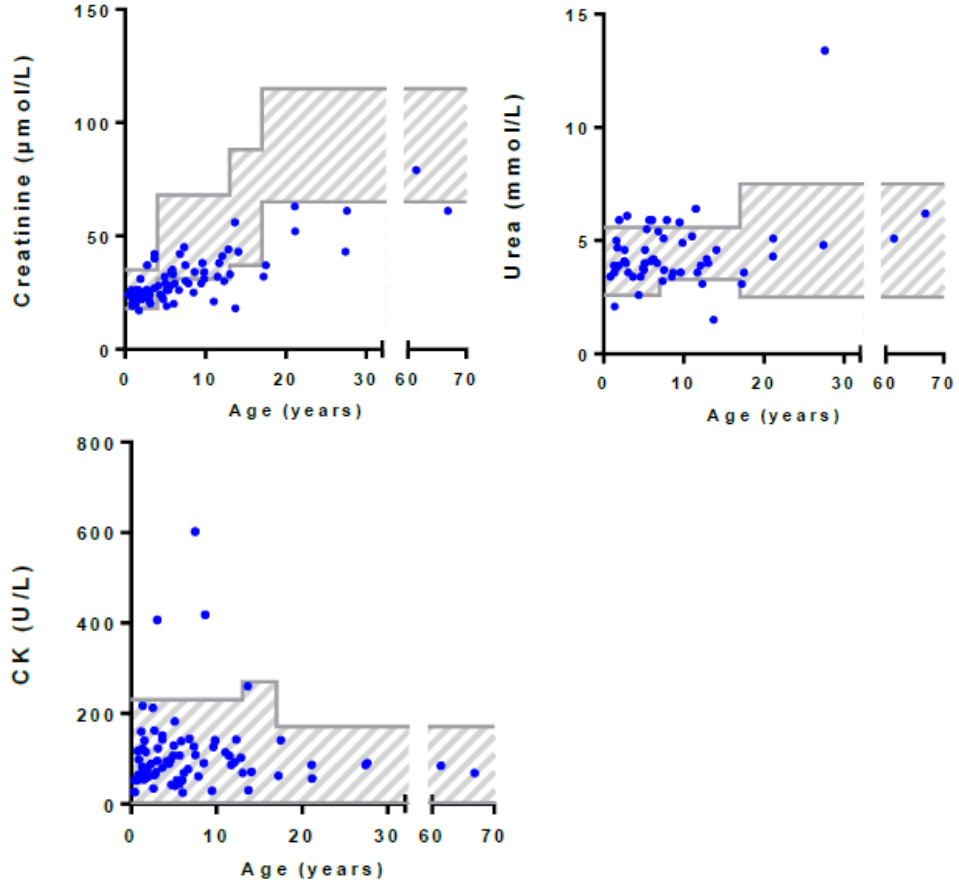


Figure 20. Groeneweg et al., 2020 (natural history study): Serum creatinine, urea and CK concentrations by age. Blue dots represent measurements in individual patients and grey areas mark the age-specific normal ranges.

Data from EMC cohort study are presented in Table 60.

Table 56. Van Geest et al., 2022 (EMC cohort study): Changes from baseline to last visit in secondary outcomes 155 on full analysis set

	Baseline mean (SD)	Last visit mean (SD)	Mean change (95% CI)	P value
Creatinine (µmol/L; n=46)	32 (11)	39 (13)	7 (6 to 9)	<0.0001
Creatine kinase (U/L; n=46)	110 (87)	128 (80)	18 (-8 to 45)	0.2166

In TRIAC I, treatment with Emcitate caused an increase in CK and creatinine by roughly 15% to 20%. Notably, the resulting CK values were rather high, i.e. in the upper normal range or above normal range. The applicant explained high CK with an increase in muscle mass. However, this explanation appears unlikely since creatinine and body weight still indicate a low muscle mass, even after treatment with Emcitate. Thus, the high CK level might indicate some kind of muscular damage. See Table 61, Figure 21 and

Figure 22.

Table 57. TRIAC I: Change from baseline in complementary biochemical laboratory measures (Intention to treat)

Assessment	N	Baseline Mean (SD)	Month 12 Mean (SD)	Difference Mean [95% CI]	P-value	Exemplary normal ranges from open source for orientation
Creatinine (µmol/L)	40	32.80 (11.52)	37.50 (13.71)	4.70 [2.76, 6.64]	<.0001	61.9 to 114.9 µmol/L
CK (U/L)	10	164.7 (157.1)	193.6 (116.0)	28.9 [-36.0, 93.8]	0.3399	Males 55 to 170 U/L

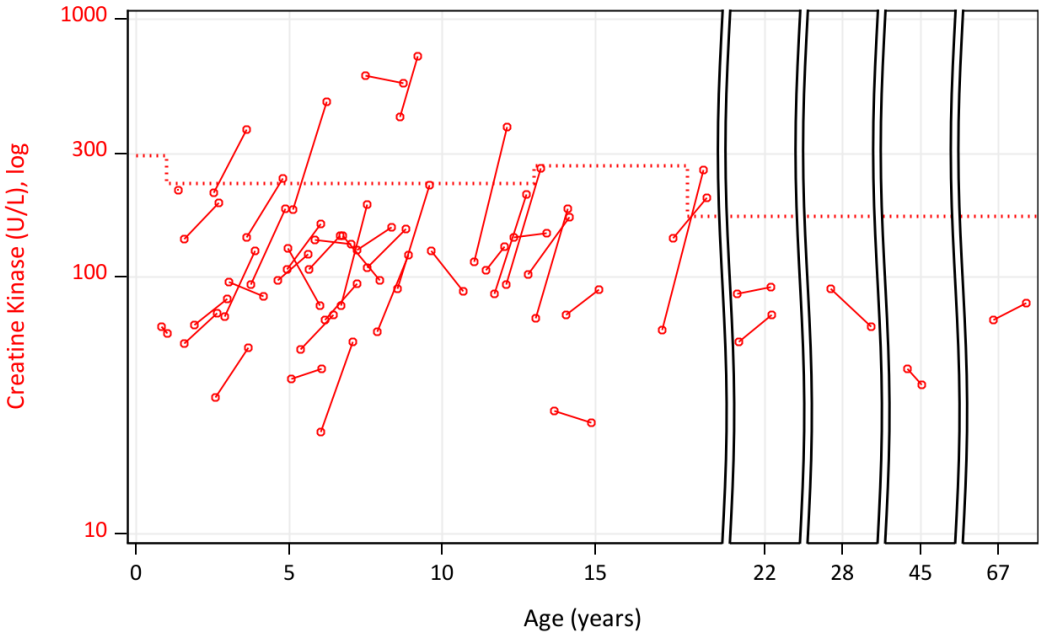


Figure 21. TRIAC I: Creatine Kinase by age at Baseline and Month 12 Visit

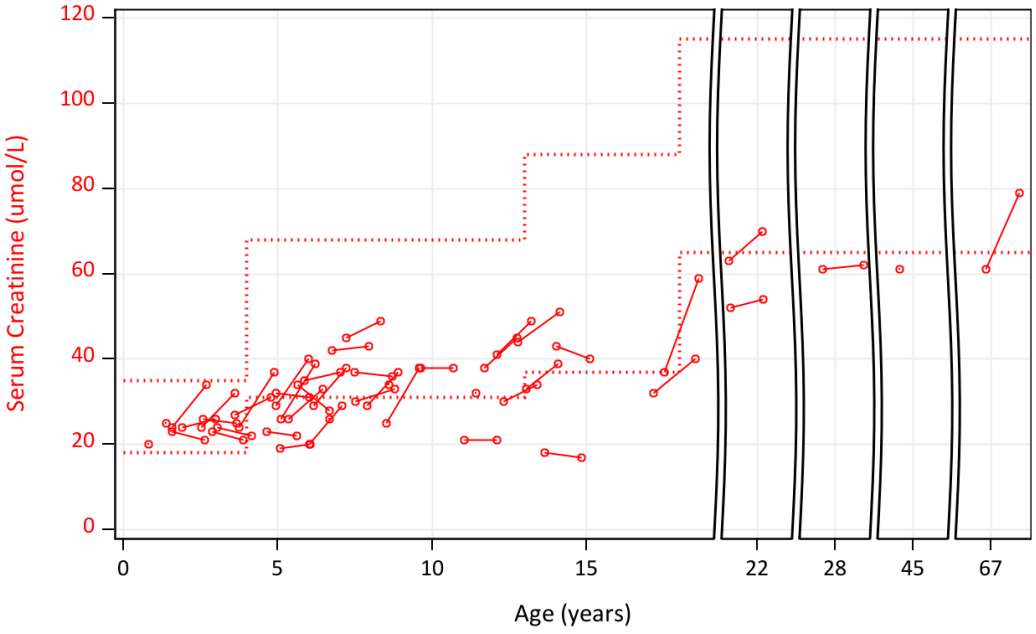


Figure 22. TRIAC I: Serum Creatinine by age at Baseline and Month 12 Visit

In TRIAC II, CK and creatinine were in the normal range for most subjects, and Emcitate did not cause meaningful changes of these parameters. Thus, at least according to serum creatinine, patients in TRIAC II had no extraordinary low muscle mass. It is questionable whether increase in muscle mass would affect the creatinine level when the latter is in the normal range.

A possible explanation for this discrepancy to TRIAC II, is the younger age of the participants in TRIAC II. Loss of muscle mass may occur over years in case of untreated AHDS. This assumption is supported by the observation that low serum creatinine was most pronounced in the older participants (around 5 years onward) of TRIAC I. See Figure 23.

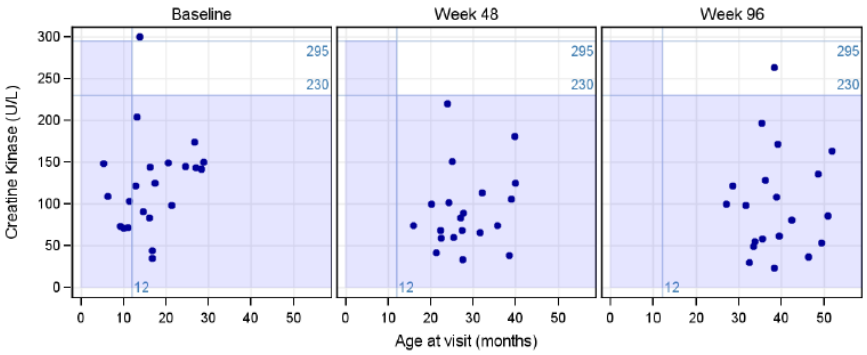


Figure 23. TRIAC II: Creatine Kinase (U/L) - scatter plot over age for BL W48 and W96 (SAS)

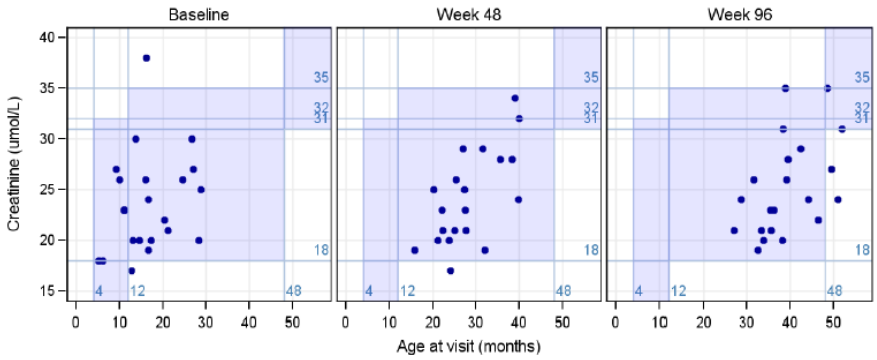


Figure 24. Triac II: Creatinine (µmol/L) - scatter plot over age for BL W48 and W96 (SAS)

In TRIAC II, a trend to a decrease in serum albumin was observed, most pronounced from baseline to Week 48, see scatterplot below. See Figure 26.

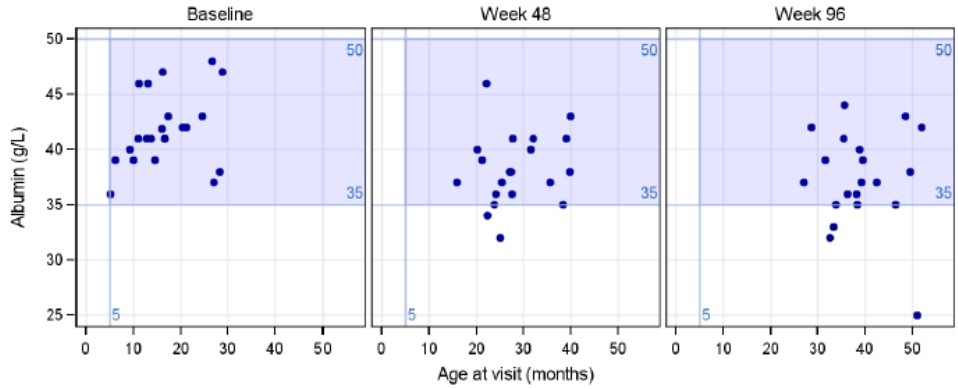


Figure 25. Triac II: Albumin (g/L) - scatter plot over age for BL W48 and W96 (SAS)

Vital signs

The vital signs (heart rate, blood pressure ECG and body weight) are mainly discussed in the efficacy section since these parameters were important endpoints for assessing treatment success of Emcitate.

In respect to safety, the effect of Emcitate on heart rate (HR) and premature atrial contractions (PACs) will be discussed based on data from TRIAC I and II. An important difference between these trials is beside the age of the participants, the Emcitate dosing. In TRIAC I (mean emcitate dose of 37 µg/kg), a reduction in mean HR was observed, from 98.2 bpm to 90.8 bpm. However, with the high Emcitate mean dose in TRIAC II (175 µg/kg), the TH-like effects of Emcitate came into play so that a relevant reduction in mean HR was not observed (baseline 115 bpm, Week 96, 113.2 bpm).

In TRIAC I, a decrease in the frequency of PACs accompanied the decrease in HR. PAC frequency fell from 900 events/24 hours (mean) to 314 events. In TRIAC II, the mean number of PACs per day was 19.2 at baseline. PAC frequency hardly changed from baseline to Week 48 (mean PAC rate of 18.5 per day at Week 48). However, PAC rate was markedly reduced at Week 96 of TRIAC II, with a mean of 2.2 events per day. It is unclear why the PAC-reducing effect of Emcitate in TRIAC II was most obvious from Week 48 onward and not from the beginning of treatment, but due to the low number of study participants, firm conclusions are not possible. Overall, Emcitate appeared to have a beneficial effect in respect to PAC reduction in TRIAC I as well as in TRIAC II.

In TRIAC I and II, weight for age was markedly below normal at baseline with a z-score of -2.85 and -2.14, respectively. At study end, the z-score was slightly improved in both studies but still negative (TRIAC I: -2.63; TRIAC II -1.99). In TRIAC II, the absolute body weight significantly increased by over 3 kg, and the z-score for MCT8-deficient patients turned positive (0.708). This means that TRIAC II participants gained more weight than expected for AHDS patients but compared to healthy children the z-score remained low.

2.4.5.5. Safety in special populations

Based on AE frequency by age group (<2.5 years vs. >2.5 years), no relevant differences between these age groups were observed.

As MCT8 deficiency is an ultra-rare disorder, specific studies in patients with concurrent hepatic or renal impairment were not performed.

Based on data available, there is currently no indication that specific genotypes vary significantly in phenotypes, in response to treatment with tiratricol treatment, or carry specific safety risks with tiratricol treatment.

2.4.5.6. Discontinuation due to adverse events

One patient was withdrawn from the Triac I trial because of the development of Graves' disease.

2.4.5.7. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.6. Discussion on clinical aspects

Based on the reference product (Téatrois) and scientific literature (C. Menegay,1989), the pharmacokinetic profile of tiratricol (distribution, metabolism and elimination) has been adequately characterised and the proposed SmPC information is considered in line with the state of scientific knowledge.

Téatrois /Emcitate-DEV and Emcitate FCP differs with regard to the tablet filler (excipient), where calcium hydrogen phosphate dihydrate is replaced by calcium hydrogen phosphate to improve tablet properties. in vitro dissolution testing of dispersed tablets demonstrated comparable in vitro dissolution profiles in 0.1 M HCl and pH 6.8 media between tablets used in the pivotal clinical studies and the proposed commercial tablets.

Bioequivalence has been established between the two formulations Emcitate-DEV and Emcitate FCP for both C_{max} and the various measures of AUC considered, with all 95% confidence intervals within the acceptance region of [0.80, 1.25].

2.4.6.1. Efficacy

Design and conduct of clinical studies

Efficacy of tiratricol in the treatment of patients with MCT8-deficiency was investigated in TRIAC-I and was supported by real-world data collected retrospectively in the EMC cohort study (van Geest et al. 2022). In addition, preliminary results of TRIAC-II were submitted during the procedure.

TRIAC-I was not designed to investigate tiratricol`s action at the site of the brain. The study included five patients below the age of two years. The small window of opportunity to target neurodevelopment most likely had passed in most (or all) patients. In addition, most likely, higher doses would have been necessary to target neurodevelopment.

Neurodevelopment had been investigated through application of validated tools (GMFM-88, Bayley scores). The overall improvements were very small and interpretation in the absence of a control group is difficult. In addition, the open-label design might have introduced bias through the investigator`s awareness of intervention. Many missing data, especially in the very young may impair the robustness of results (e.g., the two youngest participants (0.82 years and 1.38 years) had no end-of-study measurements for neurodevelopmental scales; only one patient >2.5 years had baseline and EOS assessment for both scales GMFM-88 and BSID III).

Efficacy data and additional analyses

In TRIAC-I, treatment with tiratricol reduced the mean serum T3 concentration from 4.97 nmol/L at baseline to 1.82 nmol/L at Month 12 ($p<0.0001$) (target range: 1.4 to 2.5 nmol/L). In the 10 patients included in the treatment extension period, the mean serum T3 concentration was reduced from 4.41 nmol/L at baseline to 1.81 nmol/L at last assessment, after a median treatment duration of 3.4 years. The effect size of T3 reduction is large. Theoretically, lowering of T3 is clearly beneficial in terms of cardiovascular protection and increased quality of life (e.g. less anxiety, better sleep). However, no consistent translation of T3 drop into clinical benefit became evident. Correlations between T3 lowering and improvements in clinical parameters are further discussed below.

Other markers of thyreoid function (TSH, T4, fT4, rT3) also dropped with tiratricol treatment.

The dose of tiratricol was titrated with the aim to reach the target range for adults of 1.4 to 2.5 nmol/L. When applying age-adjusted reference ranges, it was noticeable that in a considerable proportion of patients (75% of patients below 2.5 years, 42% of patients above 2.5 years) T3 levels fell below the reference range. On the other hand, seven patients remained above the T3 target range and in some patients large fluctuations in T3 levels were observed. Despite this finding, the goal of treatment is to alleviate symptoms of peripheral hyperthyreosis, and it appeared that achieving/not achieving a specific T3 target range was not predictive of clinical improvement as observed and discussed below for example, in terms of reduction in heart rate.

The potential impact of a decline in T4 and fT4 is not clear. The mean baseline value for T4 was 56nmol/L and for fT4 9.7pmol/L. The mean values at Week 12 were 24.4 nmol/L for T4 and 3.4pmol/L for fT4. This means that at baseline the fT4/T4 values were slightly below the normal range available in the public domain. and this is in line with the hormone profile typical for ADHS. During the study, T4/fT4 levels declined profoundly. Non-clinical findings pointed to a worsening of the hypothyreotic state in the brain in the presence of low T4 (Barez-Lopez S et al, 2016). The clinical implications of the drop in T4 were discussed during the procedure. References were made to the pivotal animal PD study in dKO mice, which showed that tiratricol could rescue neural development. It follows that the need for T4 appears to be low. Thereby it is assumed that tiratricol can fully

substitute for T3 and T4 and that not even small amounts of endogenous T4 can penetrate into the brain of AHDS patients.

Clinical implications of the drop in rT3 were also not fully elucidated. During the procedure it was clarified that it is unlikely that the drop in rT3 led to promotion of the conversion of T4 to T3; rather the reduction in rT3 occurred in the wake of lowering T4 levels (rT3 is built in the liver from excess T4).

The decline in TSH (2.91 mU/L at baseline to 1.02 mU/ L at Week 12) is difficult to interpret, as the negative feedback is disturbed in AHDS. No age-adjusted normal ranges were available. Baseline values were approximately within the normal range at baseline and fell to values just below the lower limit of the normal, noting that there is considerable variation in published data with wider reference ranges in children compared to adults (e.g. Onsesveren I et al., 2017).

Mean body weight (absolute values and Z-scores) slightly increased over the 12-month study duration; the increase in absolute weight (+2.7 kg) may partly be explained by physiological weight gain over the 12-month duration in children; the change in age-adapted Z score was small (-2.98, SD 1.93 at baseline; -2.71, SD 1.79 at Week 12). The percentage of underweight patients remained almost unchanged (26 underweight patients at baseline, 25 underweight patients at Month 12). In a post-hoc analysis, a more pronounced increase in body weight for age Z-score and body weight-for-age MCT8 Z-score was observed in those underweight at baseline, where tiratricol treatment increased the mean body weight-for-age Z score from -4.04 at baseline to -3.61 at Month 12 (p=0.0096), and a mean body weight-for-age MCT8 Z-score increased from -0.53 at baseline to 0.14 at Month 12 (p=0.0007), which is slightly above than expected for patients with MCT8 deficiency.

As the natural course of the disorder is characterised by a progressive deterioration in body weight, often requiring enteral tube feeding, the small positive trend in patients >2.5 years may reflect beneficial peripheral tiratricol action. Body height did not change over the 12-month treatment period (Z score at baseline -1.96, Z score at month 12 -1.98).

Mean Heart rate decreased (112 bpm at baseline, 104 bpm at Week 12); results for Z-scores showed comparably smaller effect sizes suggesting that physiological heart rate decrease in children over the 12-Month study duration had contributed to the effect. The observed effect size (mean decrease by -8.9 bpm) may indicate some amelioration of thyreotoxicosis. However, patients remained tachycardic at Month 12, indicating that peripheral euthyreosis had not been reached.

Results on heart rate were variable and did not correlate with the degree of T3 lowering, as exemplified by two patients who showed HR *increases* despite marked T3 lowering. In addition, HR depended on the measurement technique used, and there were heterogeneous results between HR captured by different methods (12-lead ECG, 24-hour Holter monitoring, HR as part of the vital signs measurement). For all three methods used, a decrease was reported in both the mean heart rate and the median heart rate between baseline and Month 12. This may not explain the vast variability in individual patients. However, the consistent findings for the mean/median decrease in these parameters is of relevance to support the beneficial effect of Emcitate on the HR.

Mean systolic BP was reduced from 107.4 mmHg at baseline to 102.4 mmHg at Month 12. The mean systolic percentile score based on age and height was reduced from percentile 77.5 at baseline to percentile 60.7 at Month 12. In hypertensive patients, the mean systolic BP was reduced by 8.4 mmHg, from 110.9 mmHg at baseline to 102.5 mmHg at Month 12. The percentage of patients with hypertension was reduced from 44% at baseline to 16% at Month 12. Smaller numerical reductions in diastolic BP were observed. Blood pressure lowering is considered a benefit as it might decrease cardiovascular risk.

The mean number of premature atrial contractions (PACs) decreased from 899.7/24-hours at baseline to 313.9/24-hours at Month 12. PACs were observed in 77.5% of patients at baseline. For 10 out of 24 patients with PACs at baseline, these were not present at Month 12. Studies have shown that PACs occur in around 13% of healthy children, in a frequency rarely above 4/24-hours (Scott et al, 1980). Although a threshold value for PAC frequency to predict the risk of adverse outcomes is not established, the published evidence is suggestive of a positive relation between frequency of PACs and risk of incident atrial fibrillation, stroke, and all-cause mortality (Farinha et al, 2023). In TRIAC-I a marked decline in PACs was observed which might reflect amelioration of hyperthyreosis. However, the mean number of PACs after 12 months of treatment was still high (314/ 24-hours), indicating that peripheral euthyreosis had not been reached.

Overall, effect sizes observed for body weight increase were small. As weight deteriorates during the natural course of the disease, the small weight gain observed in patients >2.5 years might be beneficial.

The drops in heart rate and systolic blood pressure likely reflect some improvement MCT8-related cardiovascular abnormalities. Of note, heart rate and blood pressure remained high (heart rate bpm at Month 12: 103.5 bpm, systolic BP percentile: 60.7 at Month 12). This indicates that tiratricol reduced values, but they were still increased above normal so that a peripheral euthyreoid state still was not reached. Correlations between T3 lowering and improvements in clinical parameters are further discussed below.

Premature atrial contractions, which are more prevalent in patients with hyperthyroidism (Flynn JT et al., 2017), subsided in 10/24 patients. Uncertainties remain, as the number of PAC remained very high in about half of the studied patients.

The decrease in SHBG, which did not lead to normalisation of SHBG, might indicate an incomplete reversal of a thyreotoxic state of the liver. This is in line with the HR findings, which also indicate incomplete reversal of peripheral hyperthyroidism.

During the procedure, the clinical relevance of the observed drop in T3 in the vast majority of TRIAC-I patients (84%) was questioned. Additional investigation was conducted by the applicant to support the correlation between T3 lowering and clinical improvement. The relationships between the degree of T3 lowering and changes in HR, BP and body weight were investigated. No relationship was found between baseline T3 level, degree of T3 lowering, target of T3 lowering (to a target above, within or below the pre-defined range) and change in any clinical parameters indicative of a peripheral hyperthyreoid state. Of note, there was also no correlation between clinical markers of HR, blood pressure and body weight at baseline. Overall, this was suggestive of a vast intra- and inter-individual heterogeneity in the disease`s phenotype and its response to tiratricol.

Rather than T3 lowering to a certain range, the goal of treatment should be to alleviate symptoms of peripheral hyperthyreosis. It appeared that achieving/not achieving a specific T3 target range was not predictive for clinical improvement. This is also supported by newly submitted PK and PopPK data, where the target range for an optimal effect on thyrotoxicosis (i.e. achieving the lowest combined thyromimetic activity of T3 and tiratricol) was quite wide and not sensitive to an exact dose of tiratricol or exact target T3 value. As already outlined, correcting undesired disease effects in different tissues appear to require different tiratricol doses, e.g. higher doses appeared to be required to increase body weight in younger children (based on TRIAC-II). Thus the CHMP recommended to add in section 4.2 of the SmPC more detailed guidance on the dosing of tiratricol and in particular that this should primarily be guided by clinical response in the individual patient. The general recommendation is to titrate the dose until the serum T3 level is below the midpoint of the normal range for age. Smaller dose escalation steps (half tablets) may be used when a patient is approaching target

serum T3 levels, as appropriate. The dose may be further adjusted based on the patient's response to treatment on clinical features of MCT8 deficiency.

Results of neurodevelopmental investigations performed in TRIAC-I showed very small improvements. The impact on intellectual abilities (Bayley scores) was low. For instance, a child with a speaking ability (subscore "expressive language") of 5.58 month is not much different compared to 6.11 months when it comes to interaction with family and society. In the GMFM-88 score, in the subgroup of patients below the age of four (n=5) a numerical improvement in the domains "lying and rolling" and "sitting" became discernible. It is unlikely that these changes were caused by tiratricol action at the site of the brain (they may reflect better coordination/ less agitation due to amelioration of peripheral hyperthyreosis). However, independent from tiratricol`s site of action, even small improvements may be relevant. During the Protocol Assistance discussion, a patient representative highlighted that acquisition of the ability to sit is a major improvement for parents which facilitates caring for the baby.

The neurological examinations detected no change in hyperreflexia, hypertonia and primitive reflexes. This is supportive of the notion, that tiratricol at doses administered in TRIAC I was without action on the CNS. Muscle hypertonia was present at baseline in almost all patients and numbers remained unchanged.

In total, the caregivers of 39 patients (86.7%) reported global improvement as most prominent change, whereas one caregiver (2.2%) reported a worsening. The most prominent changes were reported in "food intake", "behaviour" and "motor". Decreases in the frequencies of "sweating", "seizures", "dry mouth", anxiety" are compatible with decreases in THs through tiratricol action.

The reported changes were likely influenced by the caregiver`s awareness of tiratricol administration, which may have led to larger changes in more subjective items (e.g. change in behaviour) and less or no changes in more objective items (e.g. urinary incontinence). However, any improvement in coping with the disease and/or the patient`s well-being perceived by the caregiver is beneficial.

In the EMC cohort study, consistent decreases in T3 serum concentrations were observed in all patients, with a similar mean effect size as in TRIAC-I. In the 67 patients assessed for the primary endpoint, tiratricol reduced the mean serum T3 concentration from 4.58 nmol/L at baseline to 1.66 nmol/L at last assessment over a median treatment period of 2.2 years (range: 0.2 to 6.2 years). Mean change from baseline to last visit in serum T3 appeared not to depend on treatment duration. Sustainability of effect in this chronic condition is desirable.

As regards TSH, fT4 and T4, changes went in the same direction and were of the same order of magnitude as in TRIAC-I.

As the EMC cohort results covered a longer observational period (0.2 to 6.2 years, median duration 2.2 years) as compared to the TRIAC-I results, the results on weight and height better reflected how tiratricol affected the ability to thrive. Treatment with tiratricol resulted in a small numerical increase in the body weight-for-age Z score from -2.81 at baseline to -2.64 at the last visit, representing a mean increase of 5.7 kg. The mean height-for-age Z score *decreased* from -1.84 at baseline to -1.92 at last visit indicating no beneficial effect on growth by tiratricol.

Heart rate decreased in a clinically meaningful way (baseline mean 113 bpm; last visit mean 97 bpm). Tachycardia resolved in seven patients (11 patients still had tachycardia at last visit).

Additional analyses were performed using both the main study, TRIAC I and the EMC cohort study.

In the subset of the EMC cohort which took not part in TRIAC-I (n=40), effects on THs and other laboratory and clinical markers showed very similar effect sizes as shown in TRIAC-I. This independent repetition of the T3 lowering mode of action was supportive of the claimed benefit of Emcitate in MCT8 deficiency.

Furthermore, the analysis separating by age 2.5 years in a combined TRIAC-I and EMC cohort dataset, showed large effects on T3 lowering in both age groups. An important finding was, that the improved body weight development compared to a MCT8-deficiency population seen in the *total* population was driven by an improvement in patients ≥2.5 years, while the body weight development in patients <2.5 years old remained *on par* with the expected development in an MCT8-deficiency population. Tiratricol did not affect the ability to thrive in the under 2.5-year-old children.

Another important analysis compared patients below the age of 2.5 years and above the age of 2.5 years with respect to their T3 level at month 12; T3 levels were categorised as above, within or below the target range of 1.4 to 2.5 nmol/L or the age-adjusted target range. This analysis showed that almost all patients who were above the T3 target range at baseline had normal or hypothyreotic values at Month 12, independent of age group. A considerable proportion of patients fell below the T3 target range with tiratricol. This was more pronounced in children <2.5 years compared to older patients. Furthermore, when age adjusted target ranges for T3 were applied, higher proportions of children with month 12 values below the target range were reported : 75% of patients below the age of 2.5 years and 42% of patients above the age of 2.5 years fell below the T3 target range.

Overall, these additional findings further support the final dosing recommendation as outlined above.

In TRIAC II, very small numerical increases were observed at week 96 versus baseline on the primary endpoints reflecting neurodevelopment assessed by GMFM-88 total score (baseline mean 5.62%, week 96 mean 7.39%) and BSID-III Gross Motor Skills Domain (age equivalent score; baseline mean 2.0, week 96 mean 2.6). Improvements versus the pre-specified historical control thresholds (GMFM-88: 9.8%= upper limit of the 95% CI from 0-9 years aged TRIAC-I patients; threshold in the BSID-III Gross Motor Skills Domain: 2.34 years) were clearly not shown. There was no pattern of more pronounced improvement of neurological symptoms (with a focus on motor function) in the very young patients; on the contrary, results were mixed in the patients below 12 months of age.

Overall, the observed small changes in the GMFM-88 total score and the BSID-III Gross Motor Skills Domain and other BSID-III domains (cognitive, receptive communication, expressive communication, and fine motor skills) may reflect the change in development that would have been observed without treatment.

Additional analyses of selected items out of the GMFM domains were conducted. However, these evaluations did not show any impact of tiratricol on motor development; evaluation of the GMFM-88 Item "lifts head upright" showed no significant change from baseline to week 96 (five patients improved, six patients worsened, eight patients had no change); evaluation of the Item "sit on mat" showed that no patients at BL was able to initiate this movement and none improved by week 96; analysis of GMFM-88 Domain B (Sitting) summary score showed a small improvement by week 96 compared to baseline (p=0.0059; from 2.38 to 5.50%). However, since the assessment of "sitting"using the Hammersmith Infant Neurological Examination (HINE), showed no improvement in sitting, with 3 patients rated as "improved", 12 as "unchanged", and 6 as "worsened", the robustness of the result on sitting in the GMFM-88 is questionable. Mixed results were obtained as regards improvement in other motor milestones assessed by the HINE (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, or walking; worsening was reported for the motor milestones sitting, standing and walking). Overall, no improvement in clinically relevant motor milestones could be shown with these

additional analyses.

Overall, the CHMP concluded that the results of TRIAC-II did not support that tiratricol may beneficially influence the severe neurological phenotype of AHDS. It may be, that the window of opportunity had been closed in the majority of TRIAC-II patients; only two patients were below six months at baseline.

As regards the impact of tiratricol on peripheral thyreotoxicosis**,** the TRIAC II study confirmed the effect of tiratricol on reducing T3 concentrations found in TRIAC I. Mean serum T3 decreased by 3.24 nmol/L from 4.31 nmol/L at baseline to 1.07 nmol/L at week 96 ($p<0.0001$). From around week 12, serum T3 levels had reached a maximum reduction and did not decrease further with increasing dose of tiratricol.

Following 96 weeks of treatment there was a 3.4 kg improvement in mean body weight ($p<0.0001$) that corresponded to a significant improvement in body weight for age MCT8 Z scores (1.129; $p=0.0011$), thus showing a somewhat larger than expected body weight increase from baseline compared to an untreated MCT8 deficiency population. The change in body weight for age z-score was very low (0.154), which suggests that physiological body weight gain contributed to the effect on body weight.

Importantly, results on heart rate and systolic blood pressure in TRIAC II suggested higher-than-optimal dosing from a peripheral thyrotoxicosis perspective: there was an increase in SBP from 103.9 at baseline to 110.1 at week 96; DBP remained largely unchanged. There was also an increase in resting heart rate (pulse)-for-age Z-score over time (increase from 114.5 bpm to 118.1bpm).

This suggests that the trade-off between the further lowering of T3 by increasing the dose of tiratricol was no longer beneficial, and that tiratricol, as a thyreomimetic, starts to add to the total thyromimetic activity. In contrast, in TRIAC I, during which T3 within the normal range was targeted, improvements (decreases) in heart rate and blood pressure were shown after 12 months of tiratricol treatment.

With the TRIAC II findings, the proposed indication "Emcitate is indicated for the treatment of monocarboxylate transporter 8 (MCT8) deficiency in all age groups" was considered not acceptable by the CHMP.

The CHMP recommended to specifically formulate in the indication the fact that benefit had only been shown for amelioration symptoms of peripheral thyreotoxicosis.

Severe neurocognitive impairment prevails in the disease`s phenotype, the broad term "MCT8 deficiency" is suggestive of a benefit of tiratricol in terms of improvement of neurocognitive function. This had not been demonstrated in the main trial, TRIAC I. Furthermore, preliminary results for TRIAC-II in younger children did not show that tiratricol influenced the neurocognitive phenotype in a clinically relevant way despite administration of considerably higher doses of tiratricol.

The applicant followed the CHMP final recommendation and amended the wording of the indication as follows:

"Emcitate is indicated for the treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth."

2.4.6.2. Safety

Since no studies with comparator were submitted, any observed AEs were assumed by the investigator to be related to tiratricol when they occurred at start of dosing or during dose up-titration. Thereby, hyperhidrosis and a cluster of psychiatric conditions, consisting of nightmares, irritability and anxiety, were identified as probably related to tiratricol.

Furthermore, the TH-like activity of Emcitate – although relatively low compared to T3 - could be the reason for the observation that markers of peripheral hyperthyroidism such as increased heart rate or increased serum SHBG did not return to normal after treatment despite serum T3 was in the normal range or even below.

The transient fluctuations in serum creatinine, SHBG and CK observed in TRIAC I do not appear to be related to any of the AEs defined as possible, probable or related to tiratricol treatment.
In addition, no statistically significant correlation was observed between the occurrence of AEs, including vomiting and diarrhoea, and dose escalation of tiratricol in TRIAC I.
A few AEs reported during the TRIAC II were defined as possibly related to the dose escalation of tiratricol. However, limited information was provided to support this assumption.

Despite the higher doses of tiratricol being administered over 96 weeks in the TRIAC II in comparison to the TRIAC I, no adverse events have been observed that have resulted in the complete discontinuation of tiratricol. The available data did not suggest that the higher doses administered in the TRIAC II had an unfavourable effect on the incidence of seizures. The population analysis revealed no statistically significant differences in the incidence, frequency, or intensity of seizures in patients treated with a higher dose of Tiratricol compared to those in TRIAC II. The profile of serious adverse events was consistent with that observed in previous TRIAC I and EMC cohort studies, as well as with the natural history of MCT8 deficiency. The TEAEs documented in Part I of TRIAC II are comparable to those observed in TRIAC I.

The serious adverse event profile was consistent with previous tiratricol data and the diagnosis of MCT8 deficiency. As previously observed in TRIAC trial I, the most frequently reported SAEs were in the MedDRA SOCs of infections and infestations (10 SAEs in 6 (27.3%)) patients, and nervous system disorders (4 SAEs in 3 (13.6%)) patients.

Other SAEs included events requiring hospitalisation such as GI tube insertions for optimisation of feeding, surgical corrections of phimosis and cryptorchism, and hospitalisation to perform cerebral MRI. Many of these events were semi-elective or pre-planned to manage the complications of morbidity associated with MCT8 deficiency. The onset of SAEs was not dose-related. Tiratricol treatment was interrupted (then re-started on the same dose) due to one CTCAE Grade 2 (moderate) SAE of vomiting, considered unlikely to be related to treatment (one subject). In all cases, the SAE resolved with no change to the tiratricol dose.

A total of 18 patients have received tiratricol treatment as part of the compassionate use programme in Turkey up to 30 June 2024. Of these patients, 10 have reported adverse events, with some individuals experiencing multiple events. The majority of adverse events were considered unrelated to tiratricol treatment. A single non-serious event of increased thyroid hormones (FT3) was acknowledged as an expected consequence of the tiratricol treatment and was considered possibly related to tiratricol treatment. Five adverse events were classified as serious, including one report of a patient who died from sudden cardiac arrest. The reporter’s initial classification of the event as "sudden cardiac death" and unrelated to the drug was subsequently revised by the company to "unlikely related."

Treatment with tiratricol caused a decrease in the serum levels of TSH, T3, T4 and rT3. The T3:T4 ratio remained essentially unchanged. Tiratricol was generally titrated to achieve T3 values in the normal range, in some patients also in the sub-normal range (see efficacy section for details).

Transaminases were increased already at baseline (i.e. before tiratricol treatment) in the TRIAC I. As explained by the applicant, this may be related with the use of antiepileptic drugs or other compounds known to increase liver enzymes. S Mean transaminase levels decreased during treatment with tiratricol, indicating that the latter most likely is not hepatotoxic.

Regarding thyroid hormone-dependent liver changes, the respective markers clearly indicate a decrease in hyperthyroid state during tiratricol treatment. At baseline, the liver obviously was in a hyperthyroid state, identified by an increased mean plasma level of SHBG. The latter decreased during treatment, but did not reach the normal range. Hence, the liver hyperthyroidism was not completely counteracted. Other liver-related serum markers reacting to thyroid hormones include LDL-cholesterol and ferritin. Both were up-regulated by tiratricol, also indicating less thyroid hormone action on the liver. However, these two markers were within the normal range at baseline (due to their wide normal range) and cannot be used to identify hepatic hyperthyroidism.

Tiratricol was able to increase the mean levels of B-ALP and P1NP in TRIAC I; however, in several patients the levels of these markers remained below normal range. Mean BMD markedly increased in the distal forearm, but total body BMD hardly changed. Hence, tiratricol was able to improve BMD at least in part. Accordingly, in TRIAC II, where the peripheral hyperthyroidism remained due to the TH-like activity of the high tiratricol doses, serum markers of bone loss increased with Emcitate treatment.

Low serum creatinine was reported (with normal serum urea, indicating that the abnormal creatinine value was not related to altered kidney function). This may be reflecting the low muscle mass in AHDS patients following hypoplasia of the skeletal muscle.

Mean CK was in the normal range of the AHDS patients at baseline despite of low muscle mass. It is unclear whether hyperthyroidism itself causes CK increase, e.g. because of muscle wasting. With tiratricol, CK increased to high-normal to above-normal levels. CK should decrease with tiratricol since the decreasing T3 leads to decreased energy use in the muscle cells. Thus, the observed increase in CK to high-normal or above-normal levels could reflect muscular damage. Only limited information is available to conclude on this aspect.

In TRIAC II, high doses of Emcitate caused an increase in body weight (probably mainly due to increase in muscle mass), more than expected for AHDS patients when untreated, despite the presence of peripheral hyperthyroidism (as identified e.g. by increased HR). This indicates that the low muscle mass in AHDS is not (exclusively) due to hyperthyroidism, noting that in TRIAC II the peripheral hyperthyroidism was not induced by endogenous T3 but by the TH-like activity of Emcitate itself).

AHDS patients display increased heart rate (HR) and blood pressure (BP) as well as an increased frequency of premature contractions, mainly atrial (PAC). Furthermore, prolongation of the QTc interval was reported in some patients. All these are known sequels of hyperthyroidism, and they were reduced by treatment with tiratricol.

However, in the natural history study (Groeneweg et al., 2020), also symptoms were reported that usually are not associated with hyperthyroidism such as AV block, bundle block and small left ventricular wall. Particularly the latter sign could indicate that the myocardium is not fully developed in AHDS, similarly to the situation in skeletal muscle.

Sudden death or death of unknown cause was more often reported in AHDS patients than death of known cause (mostly infections). At least part of the cases of sudden death or death of unknown cause could be related to cardiac events. Hyperthyroidism is known to increase risk of cardiac death, probably by increasing the risk of CV disease, e.g. atrial fibrillation or heart failure. However, these conditions were not reported in the AHDS patients. Thus, it is unclear whether hyperthyroidism or heart defects mainly contributed to sudden cardiac death. This distinction has implications on whether correction of hyperthyroidism by tiratricol could relevantly reduce death rate or not. However, the applicant could not provide further insight since AV block or structural heart defects were not observed in TRIAC I and II.

Overall, Emcitate appeared to have a beneficial effect in respect to PAC reduction. Furthermore, during the Triac I trial, a few cases of transient systolic blood pressure (SBP) elevation were reported. From the applicant's perspective, association between SBP increase and dose up-titration has not been established, nevertheless the CHMP recommendation in this regard was followed. Transient elevations in SBP as an additional example of possible hypermetabolic symptoms in sections 4.2 and 4.4 of the SmPC. In addition, a further warning was added about the significant increase in blood pressure for some patients <6 years of age.

2.4.7. Conclusions on clinical aspects

The results from TRIAC-I in 46 patients with MCT8 deficiency, showed a rapid and sustained reduction in T3 levels in 84% of participants; this finding was confirmed within the independent EMC cohort subset and in younger patients (below 30 month of age) in the TRIAC-II study. Attenuation of hyperthyreosis would be clearly beneficial for MCT8 deficient patients who suffer from tachycardia, cardiac arrhythmias, muscle wasting and failure to thrive/difficulties gaining weight. The demonstrated small reductions in heart rate, blood pressure and premature atrial contractions in TRIAC-I may improve well-being and life expectancy. This likewise applies to the small gain in body weight. Results of neurodevelopmental investigations (scores) and neurological examinations showed no major improvements in the TRIAC-I population; data quality was impaired by many missing data.

The preliminary TRIAC II data did not show an effect of tiratricol on neurodevelopment, despite the inclusion of a younger patient population and the application of considerably higher tiratricol doses. Of note, the use of higher doses led to increases in heart rate and blood pressure; tiratricol, as a thyreomimetic, started to add to the thyreomimetic activity in a clinically relevant way.

The CHMP concluded that the efficacy of tiratricol was demonstrated in the treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth.

In addition, no unexpected adverse events have been identified with Emcitate. Overall, the safety of Emcitate is comparable to the well-known safety profile of tiratricol.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	• Use in infants (≤1 year of age) • Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)

2.5.2. Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
Study: Tiratricol treatment of children with MCT8 deficiency, Triac Trial II. An Open-Label Multicenter Phase 2 Trial. Ongoing	Part I Primary objective: Evaluate the effects of tiratricol on neurodevelopment in young MCT8-deficient patients, as measured by the GMFM-88 and BSID-III Gross Motor Skill Domain. Secondary objectives: 1. Evaluate the effect of tiratricol treatment at Week 96 on specific motor development milestones. 2. Evaluate the effect of tiratricol treatment on neurodevelopment in young MCT8-deficient patients as measured by the BSID-III. 3. Evaluate the effect of tiratricol at Week 96 on clinical and biochemical thyrotoxic features (serum T3 concentrations, tissue-specific markers of thyroid hormone action). Exploratory objectives:	• Use in infants (≤1 year of age) • Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)	*Part I* First patient first visit Database lock Final Clinical Study Report *Part II* Interim Report (4-year) Final Clinical Study Report (5-year)	 Dec 2020 Jun 2024 Oct 2024 Q4 2026 Q4 2027

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	1. Evaluate the effects of tiratricol treatment on quality of life for patients and parents. 2. Evaluate the effect of tiratricol treatment on neurological status. 3. Evaluate the effect of tiratricol treatment on brain function/brain imaging (EEG, BERA, VEP and MRI/MRS) (optional). 4. Study the pharmacokinetic profile of tiratricol in young children (optional and provided a medical reason prevails). 5. Evaluate the effect of tiratricol on cardiovascular features of the thyrotoxicosis. Safety objective: 1. Evaluate the safety of tiratricol treatment in patients 0-30 months of age. Part II Primary Objective: Evaluate the effects of long-term treatment (up to 5 years of total treatment) with tiratricol on neurodevelopment in young boys (≤30 months at time of enrolment) with MCT8 deficiency, as measured by the GMFM-88 and BSID-III Gross Motor Skill Domain. Secondary Objectives: 1. Evaluate the effect of long-term treatment (up to 5 years of total			

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	treatment) with tiratricol on specific motor development milestones. 2. Evaluate the effect of long-term treatment (up to 5 years of total treatment) with tiratricol as measured by the BSID-III. 3. Evaluate the long-term treatment effect (up to 5 years of total treatment) of tiratricol on clinical and biochemical thyrotoxic features (serum T3 concentrations, tissue-specific markers of thyroid hormone action). Exploratory objectives: 1. Evaluate the effect of tiratricol treatment on neurological status.			

BERA = Brainstem evoked response audiogram; BSID-III = Bayley Scales of Infant Development III; EEG = Electroencephalogram; GMFM-88 = Gross Motor Function Measure-88; MRI = Magnetic resonance imaging; MRS = Magnetic resonance spectroscopy; VEP = Visual evoked potentials.

2.5.3. Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in infants (≤1 year of age)	**Routine risk minimization measures**: Information in SmPC section 4.8 Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

	Additional risk minimization measures: None	• Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** Ongoing long-term Triac Trial II, including part II extension.
Long-term safety (including, but not limited to, long-term effects on skeletal muscles and heart)	**Routine risk minimization measures**: Information in SmPC sections 4.4 and 5.1 Prescription only medicine **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** Ongoing long-term Triac Trial II including part II extension.

PBRER = Periodic Benefit-Risk Evaluation Report; PIL = package information leaflet; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list, the PRAC is of the opinion that a new entry in the EURD list for Emcitate is needed. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the European Birth Date (EBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.7.2. Labelling exemptions

A request to omit certain particulars from the labelling (EN only outer and immediate labelling and package leaflet) as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group.

The QRD Group accepted the request for translation exemption only for the outer carton and the blister. However, for the package leaflet, the printed package leaflet in the national language should be distributed alongside the packs at the expense of the marketing authorization holder.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication applied for Emcitate (tiratricol) is *treatment of Monocarboxylate Transporter 8 (MCT8) deficiency in all age groups*. MCT8-deficiency (Allan-Herndon-Dudley syndrome) is an ultra-rare, chronic, severely debilitating disease caused by mutations in the gene coding for the thyroid hormone (TH) transporter MCT8 protein. Given that the functional mutation is located on the X-chromosome, the condition occurs almost exclusively in males.

Thyroid hormones require transporter proteins to facilitate their transport across cell membranes. Among the up to 16 different thyroid hormone transporters belonging to 5 distinct protein families, MCT8 is the most specific thyroid hormone transporter identified to date and is essential to the TH trafficking into and within the CNS (Groeneweg S et al. Endocr Rev 2020). A loss of function of MCT8 causes concomitant hypothyreodism in the central nervous system and thyreotoxicosis in peripheral tissues.

3.1.2. Available therapies and unmet medical need

There are currently no pharmacological treatments approved or routinely used in clinical practice for the treatment of MCT8-deficiency. Given the complex clinical picture with both over- and underexposure to THs simultaneously in various tissues, depending on their TH transporter profile, pharmaceutical approaches normally used for management of thyroid disturbances, including hormone substitution and thyreostatic therapies do not specifically address the underlying pathophysiology in MCT8 deficiency. THs or thyreostatic

agents are used in individual cases for symptomatic treatment. The most commonly used thyreostatic agent, propylthiouracil, holds significant safety concerns, particularly hepatotoxicity. It is not recommended as long-term therapy, especially not in children (Rivkees 2010). There is an unmet medical need for the treatment of MCT8 deficiency, for which no medicinal product is approved in the EU.

3.1.3. Main clinical studies

The main evidence comes from the pivotal study TRIAC I. Additional supportive data have been submitted and included the results of TRIAC II.

TRIAC I was a prospective, single-arm study in 46 children and adults conducted in 12 centers in nine countries. The study duration was 12 months. Patients with a clinically relevant pathogenic mutation in the MCT8-gene were included. Five patients <2.5 years were included. The tiratricol dose was titrated with the aim to reach a T3 target range of 1.4 to 2.5 nmol/L. Patients from the center in the Netherlands had the option to enter an extension period (up to 3.4 years). The primary endpoint was reduction of serum T3 from baseline.

The EMC cohort study was a retrospective data collection from 2014 to end of 2020 (published by van Geest et al., 2022). The population comprised patients who had previously been treated in TRIAC I (n=27) and patients who had started tiratricol treatment in a named patient use (NPU) setting (n=40, "independent dataset", age range 0.2 to 5 years).

TRIAC II was a 96-week open-label study designed to evaluate the effects of tiratricol on neurodevelopment in 22 young (≤30 months of age) patients with MCT8 deficiency. In addition, the study provides data on treatment effects on serum T3 and clinical signs reflective of thyrotoxicosis. The long-term extension with an additional 2 years of treatment and is currently ongoing.

Male patients with a pathogenic mutation of the MCT8 gene were included. Median age of the 22 patients included at time of enrolment was 16 months, range 5 to 28 months, with most patients (63.6%) aged >12 months at baseline. Two patients were younger than 6 months.

The dose of tiratricol was escalated to target T3 *at the lower limit of the normal range (LLN) down to 10% of the LLN*, without dose limiting toxicities or side-effects. Patients were treated with a mean daily dose of 175 mcg/kg (compared to a mean dose in TRIAC trial I of 37 mcg/kg). A higher dose was applied with the aim to improve the severe neurocognitive phenotype of MCT8-deficiency.

The co-primary endpoints were GMFM-88 total score and BSID-III Gross Motor Skill Domain (age equivalent score) at week 96 compared to baseline and natural history scores from the TRIAC I study. T3 change from baseline was a secondary endpoint.

3.2. Favourable effects

In TRIAC I, treatment with tiratricol:

- reduced the mean serum T3 concentration from 4.97 nmol/L (SD 1.55) at baseline to 1.82 nmol/L (SD 0.69) at Month 12 (p<0.0001; difference -3.15, CI -3.62; -2.68). In the 10 patients included in the treatment extension period, the mean serum T3 concentration was reduced from 4.41 nmol/L at baseline to 1.81 nmol/L at last assessment (p<0.0001), after a median treatment duration of 3.4 years.
- reduced the mean resting heart rate from 112.4 bpm (SD23.1) at baseline to 103.5 bpm (SD 17.0) at Month 12 (p=0.01; difference mean -8.9; CI -15.6; -2.3). In a subset of 16 patients with tachycardia

at baseline, treatment with tiratricol reduced the mean resting heart rate by 21.9 bpm (CI -30.0; -13.8), from 131.4 bpm (SD 16.8) at baseline to 109.6 bpm (SD 12.2) at Month 12. At the end of the treatment extension period (n=10) mean 24-hour heart rate was 90.8 bpm (SD 8.12).

- reduced the mean systolic BP from 107.4 mmHg (SD 7.6) at baseline to 102.4 mmHg (SD 10.2) at Month 12 (p=0.013; difference -4.9; CI -8.8; -1.1). In hypertensive patients, the mean systolic BP was reduced by 8.4 mmHg (CI -11.7; -5.0), from 110.9 mmHg (SD 5.2) at baseline to 102.5 mmHg (SD 5.7) at Month 12 (p=0.0001). The percentage of patients with hypertension was reduced from 44% at baseline to 16% at Month 12. Smaller numerical reductions in diastolic BP were observed.
- decreased the mean number of premature atrial contractions (PACs) from 899.7/24 hours at baseline (SD 1984) to 313.9/24 hours at Month 12 (SD 1576; p=0.0029). The occurrence of PACs was reduced to less than 100/24 hours in the 10 patients enrolled in the treatment extension period, and completely subsided in 3 out of 7 patients.
- increased body weight from a baseline mean of 21.78kg (SD 12.20) to 24.48kg (SD 12.60) at Month 12 (p<0.0001, difference 2.70; CI 1.90; 3.51). The mean body weight-for-age Z score increased slightly from -2.98 (SD 1.93) at baseline to -2.71 (SD 1.79) at Month 12 (p=0.0253, difference 0.27, CI 0.03; 0.50). The weight-for-age MCT8 Z score increased from 0.46 (SD 1.79) at baseline to 0.96 (SD 1.70) at Month 12 (p=0.0003; difference 0.51, CI 0.25; 0.76).
- in total, the caregivers of 39 patients (86.7%) reported an improvement as most prominent change, whereas one caregiver (2.2%) reported a worsening. The most prominent improvements were in terms of behavioural- (reported by 69% of caregivers), motor- (reported by 33% of caregivers), and weight- (reported by 22% of caregivers) aspects of MCT8 deficiency. Improvements were also seen in food intake (improvement reported by 53% of caregivers) and sleeping pattern (improvement reported by 31% of caregivers). Sweating was reported in 52% of patients at baseline and in 20% of patients at Month 12. Anxiety was reported in 18% of patients at baseline and 10% of patients at Month 12.

In the independent subset of patients of the EMC cohort not participating in TRIAC-I (EMC NPU subset), similar effects of tiratricol on thyroid hormones and heart rate were observed. From baseline to month 12, the mean serum T3 concentration was reduced from 4.52 nmol/L (SD 1.04) to 1.63 nmol/L (SD 0.69), (difference -2.89, 95% CI -3.27; -2.51; p<0.0001), the mean heart rate from 112 (SD 21) to 103 (SD14) (difference -10, 95% CI 122; 3).

In TRIAC II, treatment with tiratricol reduced the mean serum T3 concentration by 3.24 nmol/L from 4.31 nmol/L at baseline to 1.07 nmol/L at week 96 (p<0.0001).

3.3. Uncertainties and limitations about favourable effects

TRIAC I was not designed to investigate tiratricol`s action at the site of the brain. The study included five patients below the age of two years. The small window of opportunity to target neurodevelopment most likely had passed in most (or all) patients. In addition, most likely, higher doses would have been necessary to target neurodevelopment.

Neurodevelopment had been investigated through application of validated tools (GMFM-88, Bayley scores). The overall improvements were very small and interpretation in the absence of a control group is difficult. In addition, the open-label design might have introduced bias through the investigator`s awareness of intervention. Many missing data, especially in the very young impaired the robustness of results e.g. the two

youngest participants had no end-of-study measurements for neurodevelopmental scales; only one patient >2.5 years had baseline and EOS assessment for both scales GMFM-88 and BSID III.

Some improvement was found in the GMFM-88 score in the subgroup of patients below the age of four (n=7; total score at baseline 5.75%, SD 1.94, total score at Month 12 14.31%, SD 6.16), driven by improvements in the domains "lying and rolling" and "sitting". Even small improvements, e.g. achieving sitting, may be of relevance in daily care. The lack of improvement in other domains and inconsistent findings in TRIAC II as regards the ability to sit and to control the head render mediation of these effects by central tiratricol action unlikely.

The impact on intellectual abilities (Bayley scores) was low. For instance, a child with a speaking ability (subscore "expressive language") of 5.58 month is not much different compared to 6.11 months when it comes to interaction with family and society.

The neurological examination by a certified neurologist detected no change in the investigations of hyperreflexia, hypertonia and primitive reflexes. Muscle hypertonia was present at baseline in almost all patients and numbers remained unchanged. As increased muscle tone leading to spasticity and muscle contractions is a key feature of MCT8 deficiency carrying a high burden (Sarret C et al, 2010).

Due to the caregiver`s awareness of tiratricol intervention, perception and reporting may have been biased to some extent. More objective symptoms (seizure frequency, urinary incontinence, or poor bladder control) were reported to a similar extent at baseline and at Month 12. Tiratricol-induced T3 lowering may have contributed to facilitated feeding and better sleep. Concomitantly applied symptomatic therapy, e.g. muscle relaxants, anti-epileptics and/or analgetics, cannot be separated from the tiratricol effect in an uncontrolled study.

Results on heart rate were variable and did not correlate with the degree of T3 lowering, as exemplified by two patients who showed HR increases despite marked T3 lowering. With the response the Applicant explained this finding by distinct measurement techniques: heart rate by 12-lead ECG, heart rate by 24-hour Holter monitoring, and heart rate as a part of the vital signs examination. The vast variability between results obtained by different measurement techniques could not be entirely clarified. However, mean and median HR values obtained by the three methods declined to a similar degree.

No relationship was found between baseline T3 level, degree of T3 lowering, target of T3 lowering (to a target above, within or below the pre-defined range) and change in any clinical parameters indicative of a peripheral hyperthyreoid state. Of note, there was also no correlation between clinical markers of HR, blood pressure and body weight at baseline. Overall, this was suggestive of a vast intra- and inter-individual heterogeneity in the disease`s phenotype and its response to tiratricol.

In TRIAC II very small numerical increases were observed at week 96 versus baseline on the primary endpoints reflecting neurodevelopment assessed by GMFM-88 total score (baseline mean 5.62%, week 96 mean 7.39%) and BSID-III Gross Motor Skills Domain (age equivalent score; baseline mean 2.0, week 96 mean 2.6). Improvements versus the pre-specified historical control thresholds (GMFM-88: 9.8%= upper limit of the 95% CI from 0-9 years aged TRIAC-I patients; threshold in the BSID-III Gross Motor Skills Domain: 2.34 years) were clearly not shown. There was no pattern of more pronounced improvement of neurological symptoms (with a focus on motor function) in the very young patients; on the contrary, results were mixed in the patients below 12 months of age.

Some findings, e.g. the improvement in the subscore "receptive communication" in the patients below 12 months of age might have been clinically relevant. However, in an uncontrolled study, normal developmental

progress is not distinguishable from a potential tiratricol effect. In addition, high doses of tiratricol were used in this study which can lead to thyreotoxicity.

During the procedure, the clinical relevance of the observed drop in T3 in the vast majority of TRIAC I patients (84%) was questioned. Additional investigation was conducted by the applicant to support the correlation between T3 lowering and clinical improvement. The relationship between the degree of T3 lowering and changes in HR, BP and body weight were investigated. No relationship was found between baseline T3 level, degree of T3 lowering, target of T3 lowering (to a target above, within or below the pre-defined range) and change in any clinical parameters indicative of a peripheral hyperthyreoid state. Of note, there was also no correlation between clinical markers of HR, blood pressure and body weight at baseline. Overall, this was suggestive of a vast intra- and inter-individual heterogeneity in the disease`s phenotype and its response to tiratricol.

Rather than T3 lowering to a certain range, the goal of treatment should be to alleviate symptoms of peripheral hyperthyreosis. It appeared that achieving/not achieving a specific T3 target range was not predictive for clinical improvement. This is also supported by newly submitted PK and PopPK data, where the target range for an optimal effect on thyrotoxicosis (i.e. achieving the lowest combined thyromimetic activity of T3 and tiratricol) was quite wide and not sensitive to an exact dose of tiratricol or exact target T3 value. As already outlined, correcting undesired disease effects in different tissues appear to require different tiratricol doses, e.g. higher doses appeared to be required to increase body weight in younger children (based on TRIAC II).

3.4. Unfavourable effects

Overall, the safety profile of Emcitate appears acceptable. Adverse events and changes in laboratory values from baseline as far as considered related to tiratricol are generally manageable with adequate monitoring and dose adjustment or discontinuation. The most important safety concern could potentially be transient signs of increased thyrotoxicosis due to the thyroid hormone-like action of tiratricol. This is related to the mechanism of action and well known for the active substance tiratricol.

Adverse events (AEs) considered related to treatment with Emcitate were sweating, irritability, anxiety and nightmares. Relationship to Emcitate was assumed because these events occurred shortly after onset of treatment or during dose escalation. These AEs usually resolved later during treatment. In some cases, dose reduction was necessary. It is likely that these events were caused by the thyroid hormone (TH)-like action of tiratricol.

Tiratricol was marketed as Téatrois in France for TSH suppression. The adverse events listed in the product information of Téatrois are also reflecting the TH-like action of tiratricol.

Laboratory parameters and vital signs at baseline reflected the peripheral hyperthyroidism found in AHDS, e.g. increased SHBG, which reflects hyperthyroidism of the liver. The changes from baseline for markers for thyroid, liver, bone, and muscle function were in line with what would be expected when serum T3 is reduced; i.e. in most cases the laboratory values tended to normalise with treatment although the normal range was not always reached. In contrast, high doses of tiratricol can lead to hyperthyroidism as identified in TRIAC II with report of increased heart rate and increased markers of bone loss.

An unexpected finding was the observed serum creatine kinase (CK). The levels of this enzyme were in the normal range at baseline and increased with Emcitate treatment. CK should decrease with tiratricol since the decreasing T3 leads to decreased energy use in the muscle cells. Thus, the observed increase in CK to high-normal or above-normal levels could reflect muscular damage. Only limited information is available to conclude on this aspect.

3.5. Uncertainties and limitations about unfavourable effects

Since all clinical trials with Emcitate were uncontrolled, it is difficult to establish a relationship between observed AEs and Emcitate treatment. The most frequent AEs were infections and infestations; around 80% of study participants in TRIAC I had an event of this kind. These events were not regarded to be related to Emcitate by the investigator since the underlying disease, AHDS, itself is known to increase the risk for infections.

Long-term safety of Emcitate is also uncertain. Further data are expected in due time from ongoing studies and from a compassionate use programme.

3.6. Effects Table

Effects Table for tiratricol in the treatment of MCT-8 deficiency (TRIAC-I).

Effect	Short Description	Unit	Baseline to 12 month	Difference (95%CI)	Uncertainties/ Strength of evidence	References
(Potentially) favourable Effects						
Serum T3	Mean change from baseline to Month 12 in serum T3 (n=45)	nmol/L	4.97 (1.55) to 1.82 (0.69)	-3.15 (-3.62; -2.68) P<0.0001	Uncertainties: -clinical relevance of T3 decline low: no correlation to clinical parameters Strength of evidence: -large, consistent, and durable effect; supports tiratricol MoA to reverse peripheral hyperthyreosis. Elevated T3 is the endocrine hallmark of MCT8-deficiency.	TRIAC I
Serum T3	Mean change from baseline to Month 12 (N=40)	nmol/L	4.52 (1.04) to 1.63 (0.69)	-2.89 (-3.27; -2.51) P<0.0001	-results showed consistency to TRIAC I and strengthen the robustness of the uncontrolled TRIAC I results	Supportive EMC cohort subset (n=40).

Effect	Short Description	Unit	Baseline to 12 month	Difference (95%CI)	Uncertainties/ Strength of evidence	References
Heart rate	Mean change from baseline in resting heart rate	bpm	112.4 (23.1) to 103.5 (17.0) n=34	-8.9 (-15.6; -2.3 P=0.0100	-validity of measurement techniques is questioned.	TRIAC I
PAC frequency	Mean change from baseline in PAC frequency[a]	Events/24-hours	899.7 (1984) N=31 to 313.9 (1576) N=31	-586 (955; -217) P=0.013	-reduction in PACs most likely clinically relevant -no threshold below which PACs have to be lowered to confer clinical benefit -PAC frequency remained high	TRIAC I
Blood pressure	Mean change from baseline in systolic blood pressure	mmHg	107.4 (7.6) N=32 to 102.4 (10.2) N=32	-4.9 (-8.8; -1.1) p=0.013	-clinically relevant effect size; blood pressure remained above normal at Month 12.	TRIAC I
Blood pressure	% of patients with hypertension	%	43.8% (14/32) to 15.6% (5/32)	Not calculated	-reduction in the number of hypertensive patients	TRIAC I

Effect	Short Description	Unit	Baseline to 12 month	Difference (95%CI)	Uncertainties/ Strength of evidence	References
Body weight	mean change from baseline in weight-for-age Z-score[b]	SD	-2.98 (1.93) to -2.71 (SD1.79)	0.27 (0.03;0.50) P=0.0253	-very small effect size; 25 out of 26 patients remained underweight. -no weight gain at all in patients below the age of 2.5 years -in case of high muscle tone (spasticity, contractions) muscle mass gain is of questionable benefit -not accompanied by a gain in height	TRIAC I
Body weight in patients <2.5 years	Mean change in weight-for-age Z-score	SD	-1.93 (SD 1.31) to -2.39 (SD 1.15)	difference -0.46 (-0.78; -0.15)		TRIAC I
Body weight	Mean change from baseline in weight-for-age MCT8 Z-score[c]	SD	0.46 (1.79) N=36 to 0.96 (1.70) N=36	0.51 (0.25; 0.76) P=0.0003		TRIAC I
SHBG	Mean change from baseline to Month 12	Nmol/L	212.4 (SD 90.8) to 177.8 (SD 76.1) N=39	-34.7 (-54.8; -14.5)	-may reflect amelioration of hyperthyreotic state at the side of the liver; no normalisation of the hyperthyreoid state at the side of the liver	TRIAC I

Effect	Short Description	Unit	Baseline to 12 month	Difference (95%CI)	Uncertainties/ Strength of evidence	References
Caregiver reported outcomes	% of caregiver who reported most prominent change at the end of 12 month treatment	N/A	-improvement was reported by 87% of caregivers; N=39 -worsening was reported by 2% of caregivers; N=1 Improvement by category: Behaviour: 31 (69%) Motor: 15 (33%) Weight: 10 (22%) Sleep: 8 (18%) General: 6 (13%) Food intake: 4 (9%) Sweating: 3 (%) Seizures: 2 (4%) Cardiac: 1 (2%) Worsening by category: Gastrointestinal: 1 (2%)		-explorative data; no validated questionaires, bias in perception and reporting of symptoms in the open-label setting. Strength of evidence: -overall positive feedback from caregiver. Any improvement in tackling with daily difficulties of the disease is of benefit.	TRIAC I
Unfavourable Effects						
Possibly related AEs	Sweating, irritability, anxiety, nightmares					TRIAC I, EMC cohort

Effect	Short Description	Unit	Baseline to 12 month	Difference (95%CI)	Uncertainties/ Strength of evidence	References
Increase in serum CK		U/L	164.7 to 193.6 110 to 128	28.9 [-36.0, 93.8] 18 (-8 to 45)	Normal range is age-dependent; adult males: 55-170 U/L; High CK values cannot be explained by high muscle mass and could therefore reflect muscular damage	TRIAC I EMC cohort
Peripheral hyperthyroidism	Increased SHBG, increased HR despite normal serum T3				Remaining signs of peripheral hyperthyroidism related to the intrinsic TH-like activity of tiratricol	TRIAC I, TRIAC II

Abbreviations:
Notes:
a) Measured by 24-hour cardiac monitoring
b) Age-adjusted Z-score relative to healthy controls
c) age-adjusted Z-score relative to untreated patients with MCT-8 deficiency (Groeneweg et al. 2020a); no Z scores from patients >18 years

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the pivotal study (TRIAC I), the consistent, large and sustained decline in T3 indicates tiratricol`s potential to counteract peripheral hyperthyreosis. Elevated T3 levels are the endocrine hallmark of MCT8-deficiency. Still, T3 lowering cannot be seen as a benefit on its own and translation into clinical improvement is key. T3 lowering by tiratricol led to small improvements in clinical signs of peripheral hyperthyreosis like heart rate, blood pressure, and PACs; they reflect improvements of MCT8-related cardiovascular abnormalities and may improve both, life expectancy and well-being. The clinical phenotype of MCT8 deficiency is mainly driven by the "central component" with impaired psychomotor development including severe intellectual disability. In theory, tiratricol has the potential to bypass MCT8 and to activate TH receptors in CNS target cells. However, the pivotal trial, TRIAC I was not designed to investigate tiratricol`s action at the site of the brain. The study included five patients below the age of two years. In TRIAC II (supportive study), the observed small changes in the GMFM-88 total score and the BSID-III Gross Motor Skills Domain may overall reflect the change in development that would have been observed without treatment. The preliminary results of TRIAC II do not support that tiratricol may beneficially influence the severe neurological phenotype of AHDS. The window of opportunity might had been closed in the majority of TRIAC II patients as only two patients were below six months at baseline.

Mostly positive feedback on tiratricol treatment was received from the caregivers in the pivotal study. Any facilitation in tackling with the daily difficulties (feeding problems, sleep problems, agitation) is clearly an important benefit for the patient and for the caregiver. The importance of the results of caregiver reported outcomes is difficult to determine as these had been prone to bias in the open-label setting.

Unfavourable effects of tiratricol were mostly related to its thyroid hormone (TH)-like activity. The resulting AEs, e.g. sweating, irritability and anxiety were transient. In some cases, dose reduction was needed. The TH-like effect of tiratricol could have affected the therapeutic success since peripheral hyperthyroidism was not fully corrected despite serum T3 in the normal range or below.

A vast intra- and inter-individual heterogeneity in the disease`s phenotype and its response to tiratricol is expected in the absence of relationship between baseline T3 level, degree of T3 lowering, target of T3 lowering (to a target above, within or below the pre-defined range) and change in any clinical parameters indicative of a peripheral hyperthyreoid state. Subsequently, more detailed guidance on the dosing of tiratricol was considered necessary in the SmPC and is primarily guided by clinical response in the individual patient. The new T3 range ("serum T3 level within the lower half the normal range") is considered adequate. The newly proposed wording "generally recommends" this target T3 range, as such allowing for some flexibility.

3.7.2. Balance of benefits and risks

Tiratricol treatment at the doses administered was shown to mitigate but not to fully correct peripheral thyrotoxicosis in patients with MCT-8 deficiency. Reduction of signs and symptoms of peripheral thyreotoxicosis could benefit the individual patient; an individualised dosing strategy appears most appropriate as response to therapy cannot be predicted.

The CHMP concluded that the efficacy of tiratricol was thus demonstrated in the treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth.

Tiratricol only had effects of a thyroid hormone; no unexpected adverse events have been identified with Emcitate. Overall, the safety of Emcitate is comparable to the well-known safety profile of tiratricol and acceptable, provided appropriate dosing and monitoring are in place.

3.7.3. Additional consideration on the benefit-risk balance

Being engaged in the EMA pilot "CHMP early contact with healthcare professionals", the following feedback was received from the European Reference Network for Rare Endocrine Conditions (Endo-ERN):

- The Endo-ERN pointed to the lack of therapeutic alternatives for the treatment of MCT8-deficiency. Especially, treatment with PTU has to be prescribed with utmost caution due to its hepatotoxicity which is of special relevance in MCT8 deficiency where 40% of patients have elevated liver function tests.

- The Endo-ERN further outlined some promising findings with tiratricol, e. g. restoration of brain development in animals. In case that this finding cannot be replicated in humans (ongoing TRIAC II study), alleviation of symptoms of peripheral thyreotoxicosis (decrease in heart rate, increase in body weight) are considered of high clinical relevance on its own by the Endo-ERN.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Emcitate is favourable in the following indication:

Emcitate is indicated for the treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.