NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
September 2022

Tiratricol for treating monocarboxylate transporter 8 deficiency (Allan-Herndon-Dudley syndrome)

Company/Developer	Rare Thyroid Therapeutics International AB

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23808	NICE ID: 11794	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II clinical trials

Summary

Tiratricol is in clinical development for the treatment of monocarboxylate transporter 8 (MCT8) deficiency, also known as Allan-Herndon-Dudley syndrome (AHDS). MCT8 deficiency is a ultra-rare genetic disorder mainly seen in males although rare females' cases have been reported. It is caused by a genetic change that results in the abnormal function of a transporter protein called MCT8. MCT8 enables the transport of a thyroid hormone (T3) into the brain which is needed for cell development. Dysfunctional MCT8 protein means T3 hormone cannot enter the brain which leads to increased T3 levels in the blood and in organs. This results in severe developmental, intellectual, and motor disabilities, as well as weight issues, muscle waste, and heart problems. MCT8 deficiency is a lifelong debilitating and life-threatening disorder, associated with poor survival. There are currently no treatments for MCT8 deficiency, patients only receive supportive care for symptoms.

Tiratricol is a modified version of T3 hormone found in the body, which is administered orally. It has a similar structure and works in the same way as T3, but unlike T3, it is not dependent on MCT8 to enter cells and would therefore be beneficial for AHDS patients who have a dysfunctional MCT8 transporter protein. If licensed, tiratricol will be the first treatment option available for patients with AHDS.

Proposed Indication

Treatment of monocarboxylate transporter 8 (MCT8) deficiency, also known as Allan-Herndon-Dudley syndrome (AHDS).[1]

Technology

Description

Tiratricol (Emcitate) is an analogue of thyroid hormone T3. It is designed to restore dysfunctional thyroid hormone signalling to reduce the hypothyroid state in the brain, and the peripheral hyperthyroid state in organs and tissues in patients with MCT8 deficiency. Unlike T3, tiratricol can enter cells without MCT8 protein, which is dysfunctional in patients with AHDS. This means tiratricol could treat both the hypothyroid state in the brain as well as the peripheral thyrotoxicosis in AHDS patients.[1,2] Successful treatment could thus reduce neurological impairment and relieve symptoms of the disease.[2,3]

Tiratricol is currently being investigated in males aged 30 months or younger with MCT8 deficiency. In the phase II clinical trial (NCT02396459), tiratricol will be administered orally at an individually titrated dose for 24 months.[1,4]

Key Innovation

AHDS is a long-term debilitating and life-threatening condition that is associated with poor survival. There are currently no treatments for AHDS other than best supportive care for the symptoms.[2] Preclinical studies have demonstrated that tiratricol fully rescued the brain development in animal models of MCT8 deficiency when administered directly after birth.[5] If licensed, tiratricol will be the first targeted treatment option for patients with AHDS, with the objective to reduce the peripheral hyperthyroid state and the hypothyroid state in the brain, and all associated symptoms.[1,6]

Regulatory & Development Status

Tiratricol does not currently have marketing authorisation in the EU/UK for any indication.

Tiratricol is not in phase III/ II clinical development for any other indications.[7]

Tiratricol has the following regulatory designations:[2,8]

- Orphan drug designation by the EMA in October 2017 for AHDS.
- Fast Track status by the US FDA for the treatment of AHDS in October 2021.

Patient Group

Disease Area and Clinical Need

AHDS or MCT8 deficiency is a rare genetic X-linked disorder of thyroid hormone transport leading to cerebral hypothyroidism impacting brain development as well as peripheral hyperthyroidism (thyrotoxicosis). It causes severe neurodevelopmental disability as well as chronic thyrotoxic state.[4,9] It occurs mainly in males (with very rare females cases reported).[10,11] It is caused by mutations in the SLC16A2 gene which results in alterations to the structure and function of the MCT8 protein, making it unable to transport thyroid hormone T3 into the brain cells, which is the hormone required for normal nerve development.[2,12] Symptoms start early in childhood and manifests as congenital hypotonia later followed by symptoms of dystonia and spasticity. Patients also have distinctive facial features and rarer symptoms include ocular manifestations, seizures. The majority of the patients are severely underweight

with muscle waste and cardiac symptoms including high blood pressure, tachycardia and premature atrial contractions.[10,13]

The exact prevalence of MCT8 deficiency is not known. Between 25-132 families have been reported to have individuals affected by the condition worldwide.[4,13] In the European Union it is estimated that ADHS affects less than 0.01 in 10,000 which equates to fewer than 500 individuals within the European Union.[2] Although several patients have survived into their 60s, overall life expectancy is compromised and quality of life is severely affected as most patients suffer from a chronic thyrotoxic state and are unable to hold their head up, sit, stand or walk independently.[13] Early death has occurred in some individuals, usually caused by recurrent infections and/or aspiration pneumonia as well as sudden death (cardiac arrythmia as the underlying basis).[9,14]

Recommended Treatment Options

There are no NICE recommended treatments for AHDS.[15] Treatment of AHDS is directed towards the specific symptoms each patient has, giving the best supportive care.[6,12,13]

Clinical Trial Information

Trial	**Triac Trial I;** NCT02060474, 2014-000178-20; Thyroid Hormone Analog Therapy of Patients With Severe Psychomotor Retardation Caused by Mutations in the MCT8 Thyroid Hormone Transporter: The Triac Trial **Phase II** – Completed **Location(s):** 6 EU countries, the UK and Romania **Study completion date:** June 2018
Trial Design	Single group assignment, open label
Population	N= 46; Male subjects with monocarboxylate transporter 8 deficiency
Intervention(s)	Tiratricol, individually titrated dose (oral administration)[4]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Serum T3 concentrations • Serum free T4 concentrations • Serum TSH concentrations • Serum total T4 concentrations • Serum reverse T3 concentrations [Time Frame: Participants will be evaluated with an expected average of 2 weeks during months 1-3 of the trial. During months 4-12 participants will be evaluated with an expected average of 6 weeks. For statistical analysis baseline and month 12 will be compared] See trial record for full list of other outcomes
Results (efficacy)	Patients required a mean dose of 38.3 µg/kg of bodyweight (range 6·4–84·3) to attain T3 concentrations within the target range. Serum T3 concentration decreased from 4·97 nmol/L (SD 1·55) at baseline to 1·82 nmol/L (0·69) at month 12 (mean decrease 3·15 nmol/L, 95% CI 2·68–3·62; p<0·0001), while serum TSH

	concentrations decreased from 2·91 mU/L (SD 1·68) to 1·02 mU/L (1·14; mean decrease 1·89 mU/L, 1·39–2·39; p<0·0001) and serum free T4 concentrations decreased from 9·5 pmol/L (SD 2·5) to 3·4 (1·6; mean decrease 6·1 pmol/L (5·4–6·8; p<0·0001). Additionally, serum total T4 concentrations decreased by 31·6 nmol/L (28·0–35·2; p<0·0001) and reverse T3 by 0·08 nmol/L (0·05–0·10; p<0·0001).[3]
Results (safety)	Seven treatment-related adverse events (transiently increased perspiration or irritability) occurred in six (13%) patients. 26 serious adverse events that were considered unrelated to treatment occurred in 18 (39%) patients (mostly hospital admissions because of infections). One patient died from pulmonary sepsis leading to multi-organ failure, which was unrelated to Triac treatment.[3]

Trial	**Triac II Trial;** NCT02396459, 2019-003370-35; Tiratricol Treatment of Children With Monocarboxylate Transporter 8 Deficiency **Phase II** – Active, not recruiting[a] **Location(s):** 3 EU countries and the USA[a] **Primary completion date:** November 2024[a]
Trial Design	Single group assignment, open label
Population	N= 21[a]; Male subjects with monocarboxylate transporter 8 deficiency; aged up to 30 months.
Intervention(s)	Tiratricol, individually titrated dose (oral administration)[4]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Gross motor function measure 88 (GMF88) total score [time frame: 24 months] • Bayley scales of infant development III gross motor skill domain score [time frame: 24 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of tiratricol is not yet known.

[a] Information provided by Egetis Pharmaceuticals

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Endocrinology and Diabetes. E03/S/e.

Other Guidance

- Genetic and rare diseases centre (GARD). Allan-Herndon-Dudley Syndrome. 2021.[10]
- Catherine Sarret et al. Allan-Herndon-Dudley Syndrome. 2020.[14]

Additional Information

Egetis Therapeutics AB did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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