

HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Triheptanoin for long chain fatty acid oxidation disorders

NIHRIO ID	16126	NICE ID	10165
Developer/Company	Ultragenyx Pharmaceutical Inc	UKPS ID	Not available

Licensing and market availability plans	Currently in phase III trials.
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SUMMARY

Triheptanoin (UX007) is being developed for the treatment of long chain fatty acid oxidation disorders (LC-FAOD). LC-FAOD is a group of six rare genetic disorders in which the body is unable to convert dietary fatty acids into energy. This inability to produce energy from fat can lead to severe depletion of glucose in the body and serious, unpredictable complications, which can lead to hospitalizations or early death despite the best current care. LC-FAOD has no specifically approved treatments. The current disease management includes avoidance of fasting, maintenance of a low fat diet, and supplementation of diet with oils rich in essential fatty acids.

Triheptanoin is an orally administered synthetic (artificially produced) fat, which is broken down in the liver into substances that can be used to generate energy. Triheptanoin could provide a source of calories and fatty acids for patients with LC-FAOD, potentially improving their muscle function, exercise tolerance, and health-related quality of life. If licenced, triheptanoin could provide a treatment option for paediatric and adult patients with molecularly confirmed LC-FAOD who currently have no approved therapies.

PROPOSED INDICATION

The treatment of paediatric and adult patients with long chain fatty acid oxidation disorders (LC-FAOD).¹

TECHNOLOGY

DESCRIPTION

Triheptanoin (UX007, Dojolvi) is a highly purified synthetic seven carbon fatty acid triglyceride intended to provide patients with medium-length, odd-chain fatty acids that can bypass the genetic block in long-chain fatty acid metabolism. Due to its odd-chain properties, triheptanoin is metabolized into ketones that replace deficient intermediates in the Krebs cycle, a key energy-generating process. Triheptanoin can also support production of glucose (gluconeogenesis) and is glycogen sparing. Together, the substrates produced by triheptanoin during metabolism are intended to improve energy production in LC-FAOD patients.²

Triheptanoin is a colourless to light yellow clear liquid for oral use or by gastrostomy tube, at the target dose range of 25-35% of the patient's total prescribed daily caloric intake (DCI), converted to mL.^{1,3} In the phase III clinical trial (NCT01886378) participants were followed to evaluate the effects of UX007 over 24 weeks (treatment period), then continued treatment in the extension period for an additional 54 weeks for a total of 78 weeks of treatment.¹

INNOVATION AND/OR ADVANTAGES

No medicinal products have been approved for the specific treatment of LC-FAOD. Current methods of disease management include avoidance of fasting, maintenance of a low-fat diet, and ingestion of medium-chain triglycerides (MCTs) to bypass the degradation defect in long-chain fatty acids. In spite of these measures, many patients still experience major clinical events, and mortality rates remain high, revealing an unmet medical need for improved LC-FAOD therapies.³

Triheptanoin is a new synthetic fat, which is broken down in the liver into substances that can be used to generate energy without the need for long-chain 3-hydroxyacyl-coA dehydrogenase (LCHAD).² Unlike current LC-FAOD management, including MCTs, the odd-chain triheptanoin restores the Krebs cycle intermediates and supports glucose reserves through gluconeogenesis and, potentially, increased glycogen accumulation. Furthermore, due to its role in improving oxidative phosphorylation as well as gluconeogenesis, triheptanoin is believed to provide an efficient alternative source of energy for long-chain fatty acids in muscle, so that fasting and aerobic exercise can be better tolerated.³

Several retrospective and compassionate use studies of triheptanoin in patients with LC-FAOD have suggested benefit with reduced episodes of hypoglycemia or rhabdomyolysis and improved cardiac function in the face of acute cardiomyopathy.³

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Triheptanoin does not currently have Marketing Authorisation in the EU/UK for any indication. Triheptanoin is licenced in the US as a source of calories and fatty acids for the treatment of paediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD).⁴

The most common gastrointestinal (GI)-related adverse reactions reported in the pooled safety population of Studies 1 and 2 were abdominal pain (abdominal discomfort, abdominal pain, abdominal distension, abdominal pain upper, GI pain) [60%], diarrhea [44%], vomiting [44%], and nausea [14%].⁴

EU orphan designation was granted to triheptanoin for several forms of LC-FAOD: long-chain 3-hydroxyacyl-coA dehydrogenase deficiency (LCHAD), very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) and carnitine palmitoyltransferase II (CPT II) deficiency in July 2015.^{2,5,6}

The EU orphan designation has recently been obtained for carnitine-acylcarnitine translocase (CACT) deficiency.⁷

PATIENT GROUP

DISEASE BACKGROUND

Fatty acid β -oxidation (FAO) is a key metabolic pathway for maintaining energy homeostasis in humans, and its importance is dependent on the organ and physiological state. It is particularly important for some high-energy-requiring organs, such as heart and skeletal muscle, and provides the main energy supply for organisms during prolonged fasting.⁸

Long chain fatty acid oxidation disorders (LC-FAOD) represent a group of six rare and ultra-rare inborn errors of metabolism. These autosomal recessive genetic disorders are caused by defects in nuclear genes encoding mitochondrial enzymes critically involved metabolic pathway that converts dietary long-chain fatty acids into energy.³ The forms of LC-FAOD include carnitine palmitoyltransferase (CPT I or CPT II) deficiency, carnitine-acylcarnitine translocase deficiency (CACT), very long chain Acyl-CoA dehydrogenase deficiency (VLCAD), long-chain 3-hydroxy-acyl-CoA dehydrogenase deficiency (LCHAD) and trifunctional protein deficiency (TFP).⁹

Chronic symptoms of LC-FAOD may include fatigue, muscle pain, muscle cramps, muscle weakness, and foggy thinking. Chronic symptoms can be brought on or made worse by fasting, illness, sustained exercise, and physiologic stress and can lead to hypotonia. Patients with LCHAD and TFP may also experience retinopathy and peripheral neuropathy. Acute episodes can be triggered by illness or fasting, but they may also occur spontaneously and unpredictably. These episodes can include serious conditions such as cardiomyopathy, rhabdomyolysis (which can cause myoglobinuria) and hypoglycaemia.¹⁰ This varies across types of LC-FAOD, VLCAD patients typically have severe cardiomypothpay.¹¹

CLINICAL NEED AND BURDEN OF DISEASE

LC-FAODs are included in newborn screening panels across the U.S. and in certain European countries due to the risk for serious outcomes including death early in life.¹² To the EMA the company provided an approximate prevalence of 0.071 per 10,000 using a flow incidence-to-prevalence- forecast model for all FAODs.⁷

Hospital Episode Statistics for England in 2018-19 show there were 277 Finished Consultant Episodes (FCEs), 250 hospital admissions and 801 FCE bed days recorded with the diagnosis of disorders of fatty-acid metabolism (ICD 10 E71.3) which includes LC-FAOD.¹³ In 2019 there were 5 deaths registered with the same diagnosis as the underlying cause of death.¹⁴

Mortality is usually associated with intercurrent illnesses or other stressors that drain the patient's energy reserves and lead to hospitalization. LC-FAOD patients as a group have an overall premature mortality rate of more than 50% when diagnosed symptomatically and treated, though rates are much higher for some LC-FAOD subtypes.⁸

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of LC-FAODs involves avoiding fasting, providing aggressive management during illness, and possible supplementation with carnitine, if deficient. LC-FAODs differ from other fatty-acid metabolism disorders by requiring a fat restricted diet, potentially a higher protein intake, and supplementation of MCT.¹⁵

Avoiding essential fatty acid deficiency is important, and the majority of long chain fat consumption should come from oils rich in essential fatty acids instead of saturated long chain fatty acids (i.e. butter, fatty meats, etc.). Supplementation with specific oils such as walnut or flaxseed oil may be necessary to meet essential fatty acid requirements.¹⁵

CURRENT TREATMENT OPTIONS

There are currently no approved pharmacological options for the treatment of LC-FAOD.

PLACE OF TECHNOLOGY

If licenced, triheptanoin could provide a treatment option for paediatric and adult patients with long-chain fatty acid oxidation disorders (LC-FAOD) for whom there are no effective therapies available.¹

CLINICAL TRIAL INFORMATION

Trial	NCT01886378 , 2013-004830-14 ; An Open-label Phase 2 Study to Assess Safety and Clinical Effects of UX007 in Subjects With Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD) Phase II - Completed Location(s): United Kingdom and United States Primary completion date: August 2016	NCT02214160 ; An Open-label Long-Term Safety and Efficacy Extension Study in Subjects With Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD) Previously Enrolled in UX007 or Triheptanoin Studies Phase II - Enrolling by invitation Location(s): United Kingdom and United States Primary completion date: September 2021
Trial design	Open label, single group assignment	Open label, single group assignment
Population	N = 29, aged at least 6 months, diagnosis of CPT II, VLCAD, LCHAD, or TFP deficiency, and severe LC-FAOD.	N = 150 (planned), aged 6 months and older, prior participation in a clinical study assessing UX007/triheptanoin treatment for LC FAOD, diagnosis of LC-FAOD.
Intervention(s)	Triheptanoin dosing titrated to a target dose of 25-35% of total	Triheptanoin administered orally with food or by gastrostomy tube, at the

	caloric intake or maximum tolerated dose.	target dose range of 25-35% of total calories.
Comparator(s)	None	None
Outcome(s)	<p>Primary Outcome Measure(s):</p> <ul style="list-style-type: none"> • Change From Baseline in Total Area Under the Curve (AUC) for Workload During Cycle Ergometry at Week 24 [Time Frame: Baseline, Week 24] • Change From Baseline in Time-Adjusted AUC for Respiratory Exchange Ratio (RER) During Cycle Ergometry at Week 24 [Time Frame: Baseline, Week 24] • Change From Baseline in Actual Duration of Exercise During Cycle Ergometry at Week 24 [Time Frame: Baseline, Week 24] • Change From Baseline in Distance Travelled During the 12MWT at Week 18 [Time Frame: Baseline (last assessment during the 4-week run-in period), Week 18] <p>See trial protocol for full list.</p>	<p>Primary Outcome Measure(s):</p> <ul style="list-style-type: none"> • Annualized LC-FAOD Major Clinical Events (MCEs) [Time Frame: Post-triheptanoin treatment through the end of the study (up to 84 months)] • Number of Participants With Treatment-Emergent Adverse Events (TEAEs) or Serious TEAEs [Time Frame: Post-triheptanoin treatment through the end of the study (up to 84 months) plus 30-35 days] <p>See trial protocol for full list.</p>
Results (efficacy)³	<ul style="list-style-type: none"> • The mean annualized event rates decreased from 1.69 to 0.88 events/year following triheptanoin initiation (p=0.021; 48.1% reduction). • The mean annualized duration rate decreased from 5.96 to 2.96 days/year (p=0.028; 50.3% reduction). • Hospitalizations due to rhabdomyolysis, the most common event, decreased from 1.03 to 0.63 events/year (p=0.104; 38.7% reduction). • Initiation of triheptanoin eliminated hypoglycemia events leading to hospitalization (from 11 pre-triheptanoin hospitalizations, 0.30 events/year vs. 0; p=0.067) and ICU care (from 2 pre-triheptanoin ICU admissions, 0.05 events/year vs. 0; p=0.161) and reduced cardiomyopathy events (3 events vs. 1 event; 0.07 to 0.02 events/year, 69.7% decrease). 	-

Results (safety)³	<ul style="list-style-type: none"> The majority of treatment-related adverse events were mild to moderate gastrointestinal symptoms including diarrhea, vomiting, abdominal or gastrointestinal pain, which can be managed with smaller, frequent doses mixed with food. 	-
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ESTIMATED COST

The cost of triheptanoin is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England 2013/2014 Standard contract for metabolic disorders (Adult). E06/S/a.
- NHS England 2013/2014 Standard contract for metabolic disorders (Children). E06/S/b.
- NHS England 2013/2014 Standard contract for metabolic disorders (Laboratory Services). E06/S/c.

OTHER GUIDANCE

- European Federation of Neurological Societies. Task force guidelines handbook: EFNS guidelines on diagnosis and management of fatty acid mitochondrial disorders. 2006.¹⁶
- British Inherited Metabolic Disease Group. Management of new-born babies with a family history of a fatty acid oxidation disorder. 2017.¹⁷

ADDITIONAL INFORMATION

Ultragenyx Pharmaceutical Inc 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.

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