Health Technology Briefing
November 2021

Triheptanoin for long-chain fatty acid oxidation disorders

Company/Developer	Ultragenyx Pharmaceutical Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 16126	NICE ID: 10165	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase II clinical trials.

Summary

Triheptanoin is being developed for the treatment of long-chain fatty acid oxidation disorders (LC-FAOD). LC-FAOD is a group of six rare and ultra-rare life-threatening 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 hospitalisations 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 LC-FAOD.

Proposed Indication

Treatment of paediatric and adult patients with long chain fatty acid oxidation disorders (LC-FAOD).[1]

Technology

Description

Triheptanoin (UX007, Dojolvi) is a synthetic, medium-chain triglyceride consisting of three odd-chain 7-carbon (heptanoate) fatty acids on a glycerol backbone. Following oral administration, triheptanoin undergoes hydrolysis by pancreatic lipases in the intestines, releasing the heptanoate molecules. Heptanoate can traverse the double mitochondrial membrane independent of an active transport system or the carnitine carrier. Oxidation of heptanoate within the mitochondria yields two molecules of acetyl-CoA and one molecule of propionyl-CoA for each molecule of heptanoate. In LC-FAOD, triheptanoin is used as an anaplerotic compound, acting as a source of calories and fatty acids to bypass the LC-FAOD enzyme deficiencies.[2]

In the phase II clinical trial (NCT01886378), participants were followed to evaluate the effects of triheptanoin 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] Triheptanoin is a colourless to light yellow clear liquid for oral use or by gastronomy tube, at the target dose range of 25-35% of the patient's total prescribed daily caloric intake (DCI), converted to mL. Triheptanoin should be mixed thoroughly with food or drink, and the dose should be divided four times per day, including at mealtimes or with snacks.

Key Innovation

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).[4] Unlike current LC-FAOD management, including MCTs, the odd-chain triheptanoin restores the tricarboxylic acid (TCA) cycle intermediates and supports glucose reserves through gluconeogenesis and, potentially, increases 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, improved cardiac function in the face of acute cardiomyopathy and an improved quality of life.[3,5,6]

If licenced, triheptanoin could provide a source of calories and fatty acids for the treatment of paediatric and adult patients with molecularly confirmed LC-FAOD for whom there are no effective therapies available.

Regulatory & Development Status

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).[7]

EU orphan designation was granted to triheptanoin for several forms of LC-FAOD:[4,8-10]

- long-chain 3-hydroxyacyl-coA dehydrogenase deficiency (LCHAD) in June 2015
- very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) in July 2015
- carnitine palmitoyltransferase II (CPT II) deficiency in July 2015
- long-chain 3-hydroxyacyl-coA dehydrogenase deficiency (LCHAD) in July 2015 carnitine-acylcarnitine translocase (*CACT*) deficiency in June 2020.

Triheptanoin is also in phase II clinical development for Rett syndrome.[11]

Patient Group

Disease Area and Clinical Need

Long chain fatty acid oxidation disorders (LC-FAOD) are a group of rare, life-threatening, genetic disorders caused by inherited autosomal recessive defects in transport proteins or metabolic enzymes in the mitochondrial long-chain fatty acid β-oxidation pathway, preventing the conversion of 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).[12] Chronic symptoms of LC-FAOD may include fatigue, muscle pain, muscle cramps, muscle weakness, and foggy thinking. These 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.[13]

LC-FAODs are included in new-born screening panels across the U.S. and in certain European countries due to the risk for serious outcomes including death early in life.[14] The literature suggests a LC-FAOD incidence of ~0.002%. In June 2020, the company's model predicted 470 patients were living with LC-FAOD in the UK.[15] Hospital Episode Statistics for England in 2020-21 show there were 181 Finished Consultant Episodes (FCEs), 155 hospital admissions and 963 FCE bed days recorded with the diagnosis of disorders of fatty-acid metabolism (ICD 10 E71.3) which includes LC-FAOD.[16] In 2020 there was 1 death registered with the same diagnosis as the underlying cause of death.[17] 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.[18]

Recommended Treatment Options

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.[19] 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.[19]

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

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):** UK and USA **Study completion date:** August 2016	NCT02214160, 2016-000322-19; 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** - Completed **Location(s):** UK and USA **Study completion date:** October 2020
Trial Design	Open label, single group assignment.	Open label, single group assignment, extension study.
Population	N = 29, Subjects with a confirmed diagnosis of CPT II, VLCAD, LCHAD, or TFP deficiency; aged 6 months and older.	N = 94, Subjects with a diagnosis of LC-FAOD and prior participation in a clinical study assessing UX007/triheptanoin treatment for LC FAOD; aged 6 months and older.
Intervention(s)	Triheptanoin dosing titrated to a target dose of 25-35% of total caloric intake or maximum tolerated dose.	Triheptanoin administered orally with food or by gastrostomy tube, at the target dose range of 25-35% of total calories.
Comparator(s)	None	None
Outcome(s)	Primary Outcome Measure(s): • Change From Baseline in Total Area Under the Curve (AUC) for Workload During Cycle Ergometry at Week 24 [Time Frame: Baseline, Week 24] See trial record for full list of other outcomes.	Primary Outcome Measure(s): • Annualised LC-FAOD Major Clinical Events (MCEs) [Time Frame: Post-triheptanoin treatment through the end of the study (up to 84 months)] See trial record for full list of other outcomes.
Results (efficacy)	• The mean annualised 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).	• Seventy-five patients were enrolled (24 rollover, 20 naïve, 31 investigator-sponsored trials (IST/expanded access programs). Mean study duration was 23.0 months for rollover, 15.7 months for naïve, and 34.7 months for IST/other. • In the rollover group, mean annualized MCE rate decreased from

	• Hospitalisations 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).[3]	1.76 events/year pre-triheptanoin to 0.96 events/year with triheptanoin (P =.0319). Median MCE duration was reduced by 66%. • In the naïve group, median annualized MCE rate decreased from 2.33 events/year pre-triheptanoin to 0.71 events/year with triheptanoin (P =.1072). Median MCE duration was reduced by 80%.[20]
Results (safety)	The majority of treatment-related adverse events were mild to moderate gastrointestinal symptoms including diarrhoea, vomiting, abdominal or gastrointestinal pain, which can be managed with smaller, frequent doses mixed with food.[3]	The most common related adverse events (AEs) were diarrhoea, abdominal pain/discomfort, and vomiting, most mild to moderate. Three patients had serious AEs (diverticulitis, ileus, rhabdomyolysis) possibly related to drug; all resolved. Two patients had AEs leading to death; neither drug related.[20]

Estimated Cost

The cost of triheptanoin is not yet known.

Relevant Guidance

NICE Guidance

No relevant 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.[21]
- British Inherited Metabolic Disease Group. Management of new-born babies with a family history of a fatty acid oxidation disorder. 2017.[22]

Additional Information

References

1 Clinicaltrials.gov. An Open-label Phase 2 Study of UX007 (Triheptanoin) in Subjects With Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD). *Trial ID: NCT01886378*. 2013;Recruitment Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT01886378.

2 Shirley M. Triheptanoin: First Approval. *Drugs*. 2020 2020/10/01;80(15):1595-600. Available from: https://doi.org/10.1007/s40265-020-01399-5.

3 Vockley J, Burton B, Berry GT, Longo N, Phillips J, Sanchez-Valle A, et al. Results from a 78-week, single-arm, open-label phase 2 study to evaluate UX007 in pediatric and adult patients with severe long-chain fatty acid oxidation disorders (LC-FAOD). *Journal of inherited metabolic disease*. 2019 Jan;42(1):169-77. Available from: https://doi.org/10.1002/jimd.12038.

4 European Medicines Agency. *Public summary of opinion on orphan designation - Triheptanoin for the treatment of long-chain 3-hydroxyacyl-coA dehydrogenase deficiency.* 2015. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/15/1524-public-summary-opinion-orphan-designation-triheptanoin-treatment-long-chain-3-hydroxyacyl-coa_en.pdf [Accessed 1 October 2021].

5 Guffon N, Mochel F, Schiff M, De Lonlay P, Douillard C, Vianey-Saban C. Clinical outcomes in a series of 18 patients with long chain fatty acids oxidation disorders treated with triheptanoin for a median duration of 22 months. *Mol Genet Metab*. 2021 Apr;132(4):227-33. Available from: https://doi.org/10.1016/j.ymgme.2021.02.003.

6 Sklirou E, Alodaib AN, Dobrowolski SF, Mohsen A-WA, Vockley J. Physiological Perspectives on the Use of Triheptanoin as Anaplerotic Therapy for Long Chain Fatty Acid Oxidation Disorders. *Frontiers in Genetics*. 2021 2021-January-15;11(1651). Available from: https://doi.org/10.3389/fgene.2020.598760.

7 Ultragenyx pharmaceutical. *Dojolvi™ (triheptanoin) oral liquid.* 2020. Available from: https://www.ultragenyx.com/medicines/dojolvi/ [Accessed 1 October 2021].

8 European Medicines Agency. *EU/3/15/1526* 2015. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151526 [Accessed 1 October 2021].

9 European Medicines Agency. *EU/3/15/1508.* 2015. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151508 [Accessed 1 October 2021].

10 European Medicines Agency. *Committee for Orphan Medicinal Products (COMP) Final minutes for the meeting on 16-18 June 2020.* 2020. Available from: https://www.ema.europa.eu/en/documents/minutes/minutes-comp-meeting-16-18-june-2020_en.pdf [Accessed 1 October 2021].

11 Clinicaltrials.gov. *Search for: UX007 | Recruiting, Not yet recruiting, Active, not recruiting Studies.* 2021. Available from: https://clinicaltrials.gov/ct2/results?term=UX007&Search=Apply&recrs=b&recrs=a&recrs=d&age_v=&gndr=&type=&rslt= [Accessed 13 October 2021].

12 FAOD in Focus. *Making Sense of LC-FAOD.* 2020. Available from: https://www.faodinfocus.com/ [Accessed 1 October 2021].

13 FAOD in Focus. *Understand What Causes LC-FAOD and How It Impacts the Body.* 2020. Available from: https://www.faodinfocus.com/learn-about-lc-faod/ [Accessed 1 October 2021].

14 Ultragenyx pharmaceutical. *Ultragenyx Announces U.S. FDA Approval of Dojolvi™ (UX007/triheptanoin), the First FDA-Approved Therapy for the Treatment of Long-chain Fatty Acid Oxidation Disorders.* 2020. Available from: https://ir.ultragenyx.com/news-releases/news-release-details/ultragenyx-announces-us-fda-approval-dojolvitm-ux007triheptanoin [Accessed 13 October 2021].

15 Kruger E, Marsden D, Thomas NA, McNiven P. PRO108 Method for Estimating Disease Frequency in Long Chain Fatty Acid Oxidation Disorders and Forecasting Future Trends in Europe. *Value in Health*. 2020;23:S708-S9. Available from: https://doi.org/10.1016/j.jval.2020.08.1844.

16 NHS Digital. *Hospital Admitted Patient Care Activity, 2020-21*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21

17 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality: 2019*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset

18 Pannier A. Long-Chain Fatty Acid Oxidation Disorders: Managed Care and Specialty Pharmacy Implications. *The American Journal of Managed Care,*. 2020;26:S155-S161. Available from: https://doi.org/10.37765/ajmc.2020.88479.

19 Merritt JL, Norris M, Kanungo S. Fatty acid oxidation disorders. *Annals of translational medicine*. 2018;6(24):473-. Available from: https://doi.org/10.21037/atm.2018.10.57.

20 Vockley J, Burton B, Berry G, Longo N, Phillips J, Sanchez-Valle A, et al. Effects of triheptanoin (UX007) in patients with long-chain fatty acid oxidation disorders: Results from an open-label, long-term extension study. *Journal of inherited metabolic disease*. 2021;44(1):253-63. Available from: https://doi.org/10.1002/jimd.12313.

21 Angelini C, Federico A, Reichmann H, Lombes A, Chinnery P, Turnbull D. Task force guidelines handbook: EFNS guidelines on diagnosis and management of fatty acid mitochondrial disorders. *Eur J Neurol*. 2006 Sep;13(9):923-9. Available from: https://doi.org/10.1111/j.1468-1331.2006.01482.x.

22 British Inherited Metabolic Disease Group. *Management of newborn babies with a family history of a fatty acid oxidation disorder.* 2020. Available from: http://www.bimdg.org.uk/store/guidelines/FAOneonatev12-522311-22-05-2013.pdf [Accessed 1 October 2021].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.