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Triheptanoin (UX-007) for glucose transporter type 1 deficiency syndrome (de vivo disease) – first line

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LAY SUMMARY

Glucose transporter type 1 deficiency syndrome (Glut1 DS) is a rare genetic disorder that affects how the body moves glucose (used for energy) into the brain. The most common symptom of this condition is seizures (epilepsy), which usually begin within the first few months of life. However, the symptoms and severity of Glut1 deficiency syndrome can vary substantially from one person to another.

Triheptanoin is a novel drug being developed to reduce seizures and other symptoms in patients with Glut1 DS. The drug acts by producing a substitute compound that can produce glucose in the brain. The safety and efficacy of triheptanion is currently being evaluated. If marketed this will become the first licensed treatment in reduction of seizures in patients with Glut1 DS.

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TARGET GROUP

Glucose transporter type 1 deficiency syndrome – first line

TECHNOLOGY

DESCRIPTION

Triheptanoin (UX007) is a purified, pharmaceutical-grade, specially designed synthetic triglyceride compound created via a multi-step chemical process. Triheptanoin is metabolized and intended to provide patients with heptanoate, which can diffuse across the blood-brain barrier and be converted into glucose. Heptanoate can be further metabolized to four- and five-carbon ketone bodies in the liver. These also cross the blood-brain-barrier and provide an additional energy source to the brain. Heptanoate and five-carbon ketone bodies can regenerate new glucose in the brain, which is deficient in these patients.[1]

Triheptanoin is a substrate replacement therapy to restore deficient intermediates in the mitochondria and to enable energy metabolism in patients with Glut1 DS. The drug candidate provides two tricarboxylic acid cycle (TCA) substrates that are converted from fat to energy by the TCA cycle. The substrate replacement therapy may exhibit therapeutic intervention by checking the underlying cause of disease progression.[2]

The phase III clinical trial is planned to assess the efficacy, safety, pharmacokinetics and pharmacodynamics of UX-007 in the treatment of movement disorders associated with Glut1 DS. In the experimental arm, subjects receive UX-007 liquid orally for 10 weeks followed by placebo. After a washout period of 2 weeks, then receive placebo for 10 weeks. In the control arm, subjects receive placebo followed by UX-007 liquid orally. After a washout period of 2 weeks, they then receive UX-007 for 10 weeks.[2]

UX-007 is also under global development for the treatment of:[3]

- Metabolic disorders (phase III)
- Central nervous system, Huntington's disease, hemiplegia (phase II)
- Genetic disorders, fatty acid biosynthesis disorders (phase II)
- Genetic disorders, Acyl-CoA dehydrogenase deficiency, carnitine palmitoyltransferase II (CPT-II) deficiency (phase II)
- Metabolic disorders, mitochondrial diseases (phase II)

INNOVATION and/or ADVANTAGES

If approved, UX-007 will offer a novel treatment option in reduction of seizures in patients with Glut1 DS. There are currently no FDA approved treatments specific to Glut1 DS, though patients with the seizure phenotype are typically on the ketogenic diet. Patients are also typically treated with antiepileptic drugs (AEDs) for seizure control, although the seizures of Glut1 DS may not respond well to AEDs.[3]

DEVELOPER

Ultragenyx Pharmaceutical Inc

AVAILABILITY, LAUNCH or MARKETING

UX-007 is a designated orphan drug in the EU and USA for Glut1 DS.[4]

PATIENT GROUP

BACKGROUND

Glucose transporter type 1 deficiency syndrome (Glut1 DS) is a rare genetic metabolic disorder characterized by deficiency of a protein that is required for glucose to cross the blood-brain barrier. Glut1 DS affects the nervous system that can cause a variety of neurological signs and symptoms.[5]

The most common form of Glut1 DS, called the classic type, may be characterized by:[5,6,7]

- Recurrent seizures (epilepsy) beginning in the first months of life
- Microcephaly (unusually small head size) that develops after birth
- Developmental delay
- Intellectual disability
- Speech and language impairment
- Movement abnormalities (i.e. involuntary eye movements, spasticity, ataxia, dystonia)
- Behavioural problems

Other signs and symptoms may include headaches, confusion, loss of energy and/or myoclonus (muscle twitches).[5] Approximately 10% of affected people have the non-epileptic form of Glut1 deficiency syndrome. This form is associated with all the typical symptoms of the condition without seizures.[5,7]

Glut1 DS is caused by mutations of the SLC2A1 gene. This gene mutation is inherited as an autosomal dominant (or rarely recessive) trait or occurs as a spontaneous genetic change (i.e., new mutation) that is not inherited, but occurs sporadically for no apparent reason.[6]

Glut1 deficiency syndrome affects males and females in equal numbers. The incidence and prevalence of Glut1 deficiency syndrome in the general population is unknown. Because the disorder may go unrecognized or misdiagnosed, determining its true frequency in the general population is difficult.[6]

CLINICAL NEED and BURDEN OF DISEASE

The population likely to be eligible to receive UX-007 in the UK could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Newer drugs for epilepsy in children (TA79). April 2004.
- NICE technology appraisal. Newer drugs for epilepsy in adults (TA76). March 2004.
- NICE clinical guidance. Epilepsies: diagnosis and management (CG137). January 2012.

- NICE clinical guidance. The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care (CG20). October 2004.
- NICE quality standard. Epilepsy in children and young people (QS26). February 2013.
- NICE quality standard. Epilepsy in children and young people (QS27). February 2013.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: E06.Metabolic disorders.
- NHS England. 2013/14 NHS Standard contract metabolic disorders (children). E09/S/b.
- NHS England. 2013/14 NHS Standard contract metabolic disorders (adult). E09/S/a.
- NHS England. 2013/14 NHS Standard contract for paediatric neurosciences - neurodisability. E09/S/c.

OTHER GUIDANCE

- British inherited metabolic disease group (BIMDG). Emergency guidelines. GLUT1 Deficiency.[8]

CURRENT TREATMENT OPTIONS

There is no cure for Glut1 DS. The disorder is treated with the ketogenic diet, which may prevent seizure activity in many individuals with Glut1 DS. The response of seizure activity to the ketogenic diet is often prompt and dramatic. It is recommended that the ketogenic diet be started as early as possible and be continued to at least adolescence.[6]

The ketogenic diet is also effective in reducing the severity of movement disorders associated with the classical form of Glut1 DS in approximately half of cases. It is even more effective in treating movement disorders in individuals with non-classical forms of Glut1 deficiency syndrome.[6]

Thioctic acid, also known as alpha-lipoic acid, is a naturally occurring compound that is made in small amounts by the human body. Thioctic acid is believed to help glucose transport in the body and has been used as an adjunct therapy for some individuals with Glut1 DS.[6]

Drugs that are used to treat seizures (anti-convulsants) are generally ineffective in treating individuals with Glut1 deficiency syndrome. Other drugs including phenobarbital, narcotics and caffeine inhibit the function of Glut1 and can worsen Glut1 DS in some affected individuals. Other drugs such as valproate, topiramate, zonisamide and acetazolamide interact or interfere with a ketogenic diet. All such drugs should be avoided by individuals with Glut1 DS.[6]

Genetic counselling may be of benefit for affected individuals and their families. Other treatment is symptomatic and supportive.[6]

EFFICACY and SAFETY

Trial	NCT02960217; children aged 6 years and older; UX-007 followed by placebo vs placebo followed by UX-007; phase III
Sponsor	Ultragenyx Pharmaceutical Inc
Status	Ongoing, recruiting
Source of Information	Trial registry[9]
Location	10 of EU countries (incl UK), USA, Australia and Israel

Design	Randomized, Double-blind, Placebo-controlled, Crossover Study
Participants	N= 40 (planned); 6 years and older; Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)
Schedule	Randomised to UX-007 liquid orally for 10 weeks followed by placebo. After a washout period of 2 weeks, then receive placebo for 10 weeks or placebo followed by UX007 liquid orally. After a washout period of 2 weeks, then receive UX007 for 10 weeks.
Follow-up	Not reported
Primary Outcomes	Frequency of disabling paroxysmal movement disorders - 22 Weeks o Movement disorder events observed during the Maintenance Period of treatment, as recorded by the subject/caregiver in an event-based daily Glut1 DS symptom diary - Daily Glut1 Symptom Diary review: Weeks 0,2,4,6,10,12,14,16,18,22,26,30,34,46,58,70,82,94,106,118,130,142,154,178 Evaluate the efficacy and safety of UX007 in the treatment of disabling paroxysmal movement disorders associated with Glut1 DS.
Secondary Outcomes	Walking capacity and endurance - 22 Weeks o Determined by the distance walked in 12 minutes during the 12 Minute Walk Test (12MWT) Health-related quality of life assessing physical function - 22 Weeks o Mobility, upper extremity function, fatigue, pain and social health using a PROMIS-based questionnaire Patient/caregiver global impression of change in clinical status - 22 Weeks o Using the Clinical Global Impression - Improvement (CGI-I) Duration of disabling paroxysmal movement disorder events - 22 Weeks o Observed during the Maintenance Period of treatment, as recorded by the subject/caregiver in an event-based daily electronic Glut1 DS symptom diary Cognitive function -22 Weeks o Measured by the Cambridge Neuropsychological Test Automated Battery (CANTAB) (assessed at select sites)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	-

ESTIMATED COST and IMPACT

The cost of UX-007 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for carers, improved patient convenience*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☐ None identified

REFERENCES

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[9] ClinicalTrials.gov. *Crossover study to assess the efficacy and safety of UX-007 in the treatment of movement disorders associated with glucose transporter type 1 deficiency syndrome (Glut1 ds)*. Available from: https://clinicaltrials.gov/ct2/show/NCT02960217[Accessed 4th July 2017]