Study Title:	An Open-Label Trial of Triheptanoin in Patients with Glucose Transporter Type-1 Deficiency Syndrome(GLUT1 DS)
Investigational Product:	Triheptanoin
Indication:	Glucose Transporter Type-1 Deficiency Syndrome (GLUT1DS)
IND Number:	120505
NCT Number:	02036853
Sponsor:	**Cook Children's Medical Center**
Primary Investigator:	Adrian Lacy, MD
Cook Children's Study Number:	2013-NEUR-001
Protocol Version Date:	Version 4.1, 23-Mar-2018
Company:	Ultragenyx Pharmaceutical, Inc.
Study Site:	Cook Children's Medical Center, 801 7th Ave, Fort Worth, TX 76104
Phase of Development:	Phase 2

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An Open-Label Trial of Triheptanoin in Patients with Glucose Transporter Type-1 Deficiency Syndrome (GLUT1 DS)

1.0 GOALS AND OBJECTIVES

1.1 The primary objective of the study is:
- To evaluate the safety of triheptanoin via adverse event rates and laboratory values.

1.2 The secondary objective of the study is:
- To evaluate the long-term efficacy of triheptanoin as measured by the change in seizure frequency from historical baseline.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Disease Background

Glucose Transporter Type-1 Deficiency Syndrome (GLUT1 DS) is a devastating disease characterized by seizures, developmental delay and movement disorder.[1] It is caused by a mutation in solute carrier family 2, member 1 gene (SLC2A1), which encodes for glucose transporter type-1. This protein transports glucose from blood into the brain. Because glucose is the primary source of energy for the brain, this disorder results in a chronic state of energy deficiency in the brain. Current treatment consists of ketogenic diet, which generates ketone bodies that provide an alternative energy source to glucose.[1,2] However, ketogenic diet is difficult to tolerate and some patients are not compliant with or are otherwise not on the diet. As such, in order to improve control of break-through seizures, patients may require one to two antiepileptic drugs (AEDs).

2.2 Supporting Previous Studies

2.2.1 *Nonclinical Studies*

Triheptanoin, which is the name of the substance to be provided by the Company and is under investigation in this trial, is synonymous with other names for the same substancewhich have been the subject of investigations published in the scientific and medical literature. A number of in vitro and rat studies have been conducted with triheptanoin by research investigators.[4-8] Triheptanoin is likely hydrolyzed in the intestine and the heptanoate and glycerol absorbed efficiently in the rat liver. The 7 carbon heptanoate is cleaved to two acetyl-CoA and one propionyl-CoA. These are metabolized to several possible compounds including C4 and C5 ketone bodies, which can distribute via the circulation and can be taken up by the brain and muscle. Some propionyl-CoA will be converted to succinyl-CoA to refill the TCA cycle, and some will be converted, via the TCA cycle, to oxaloacetate to generate glucose via gluconeogenesis.

In a study of the biochemical effects of triheptanoin in the brains of a mouse model of GLUT1 DS, gluconeogenesis in the brain was established based on the presence of radiolabeled glucose after intravenous infusion of radiolabeled heptanoate.[8] In addition, intravenous infusion of radiolabeled heptanoate led to higher levels of acetyl-CoA and glutamine in the brain of G1D mice relative to normal mice. Brain glutamine concentration and 13C enrichment were also greater when compared with glutamate in both animal groups, suggesting that heptanoate and/or C5 ketones were primarily metabolized by glia. The effects of triheptanoin on the seizure activity in this mouse model have not yet been reported.

Triheptanoin has been found to be effective in 4 of 7 animal models of epilepsy. In the corneal kindling chronic model, triheptanoin delayed development of kindled seizures in a dose-dependent manner, but did not protect against fully kindled seizures.[9] In the chronic model of PTZ (pentylenetetrazole) in pilocarpine-status epilepticus, triheptanoin partially reversed the lowered PTZ threshold for tonic seizures but not clonic seizures in the chronic stage.[9] In the maximal electroshock threshold model, triheptanoin increased the seizure threshold.[10] In the genetic mouse model of generalized epilepsy due to the GABA-A-gamma2(R43Q) mutation, triheptanoin halved the time spent in seizures and reduced the frequency of seizures caused by insulin-induced hypoglycemia.[11] However, triheptanoin was not effective in the fluorothyl, pentylenetetrazole nor 6Hz models.[10] The efficacy of triheptanoin in some but not all animal models of epilepsy is similar to that found with other AEDs.[8]

In toxicology studies, there were no toxic effects on animal growth, lipid digestibility, clinical chemistry parameters, or the histopathology of liver, kidney and small intestine in rats fed for 9 months with triheptanoin at levels that replaced up to 50% of the standard soybean oil in rodent chow. Hepatic steatosis and alterations in intestinal villi were the only findings observed in a single 9 month repeat dose oral rat toxicology study.[12] The findings may be due to the effect of extreme fat overload compared with the normally low fat intake in rats (~10-fold normal fat intake) and the efficient direct absorption, non-bile-dependent of triheptanoin and metabolites. This adverse effect has not been observed in previous human clinical trials in which FAOD patients have shown the opposite finding, a reduction in hepatomegaly/steatosis, with triheptanoin treatment.

2.2.2 *Clinical Studies*

Approximately 130 subjects with various disorders, including fatty acid oxidation disorders (FAOD), Adult Polyglucosan Body Disease, pyruvate carboxylase deficiency, Pompe disease, Congestive Heart Failure, Huntington Disease, and GLUT1 DS, have been treated with triheptanoin for periods of up to 13 years.[13-15]Triheptanoin treatment has been well tolerated by subjects with these disorders.

Triheptanoin has been most extensively studied in long-chain FAOD (LC-FAOD) and has improved a wide range of LC-FAOD symptoms in the subjects studied. For example, three subjects with very long-chain acyl-CoA dehydrogenase (VLCAD) had numerous clinical problems, including cardiomyopathy, hepatomegaly with associated hypoglycemia, and muscle pain with Gowers' sign, despite receiving standard of care treatment.[13] These problems improved within hours to weeks of initiating triheptanoin treatment.

Similarly, 48 subjects with FAOD, including 43 with LC-FAOD, experienced a large number of important beneficial effects of triheptanoin treatment in different body systems, including improvement of problems in the heart (arrhythmia or cardiomyopathy), muscle (rhabdomyolysis and weakness), and liver (hypoglycemia and hepatomegaly).[14] During the study, 6 of the 59 FAOD subjects (10%) died (including 1 subject who had not been compliant with any therapy). The mortality rate of 6 deaths in 59 triheptanoin -treated LC-FAOD subjects is approximately 10% and is much less than the 50% mortality rate in patients treated with standard of care,[16] although cross-study comparisons need to be interpreted with caution.

None of the 21 subjects from this group who continued on long-term triheptanoin treatment for total periods of up to 13 years has died. Improvements have continued in these subjects. For example, cardiomyopathy fully resolved in six of nine subjects with cardiomyopathy; two others improved and one subject with advanced cardiomyopathy requiring heart transplant worsened.[17] Follow-up discussion with Dr. Gerard Vockley revealed that the heart transplant subject has continued on triheptanoin and is stable.

Triheptanoin has been generally well tolerated when administered to subjects with all subtypes of FAOD. Some subjects have had difficulties with gastrointestinal upset or have diarrhea when taking the oil. Small doses and mixing with foods or drinks is important in tolerability. Many of the serious adverse events (SAEs) reported for these subjects involved events consistent with FAOD (e.g., muscle weakness or pain, myoglobinuria, rhabdomyolysis, metabolic crisis or decompensation, cardiomyopathy, hypoglycemia, elevated CK), often in association with events known to precipitate metabolic crises in these patients, such as infections (e.g., upper respiratory infection, flu, cold, urinary tract infection, gastrointestinal illness) or exercise, or during periods of limited triheptanoin treatment. Other SAEs involved events such as infections without reported FAOD exacerbation, fever and/or vomiting from unspecified cause, respiratory distress/breathing problems, falling oxygen saturation rate, seizure, or medical procedures apparently unrelated to FAOD. Almost all of the reported SAEs were considered unrelated to triheptanoin treatment. Triheptanoin has been administered in 44 pediatric subjects with LC-FAOD. Of these, three subjects had treatment initiated between the ages of 0-1 month, eight between ages 1 month-2 years, 29 between ages 2-12 years, and four between ages 12-16 years. Twenty of these subjects had triheptanoin treatment for over five years. The safety profile in pediatric subjects is similar to that found in adults, with ADR consisting of GI disturbance and excess

weight gain (Section 5.4 of Investigator Brochure).

Triheptanoin is being studied in approximately 30 GLUT1 DS subjects in a clinical trial sponsored by Dr. Juan Pascual at the University of Texas, Southwestern. The study is ongoing and no results have been published, although public reports from patient families have suggested significant benefit in seizure reduction and development improvement.

2.3 Protocol Rationale

GLUT1 DS results in insufficient transport of glucose into the brain. The rationale for triheptanoin treatment in GLUT1 DS is that:

1) Triheptanoin is metabolized to heptanoate and C4 and C5 ketone bodies. These metabolites provide an alternative energy source to the brain

2) Triheptanoin has the ability to provide succinyl-CoA via propionyl-CoA in order to resupply intermediates of the citric acid cycle (i.e., anaplerosis). In contrast, ketogenic diet and medium chain triglyceride (MCT) oil provide only even-carbon chain ketone bodies and fatty acids, neither of which can be anaplerotic

3) Triheptanoin treatment has the additional potential advantage over ketogenic diet in that ketogenic diet requires severe restriction of carbohydrate intake, which leads to reduced serum glucose; this state of low normal serum glucose further exacerbates the glucose deficiency in the brain and partially offsets the benefits of ketone body generation. In contrast, triheptanoin treatment allows for greater carbohydrate intake and higher serum glucose levels relative to ketogenic diet and thus does not exacerbate the deficiency of glucose transport into the brain.

Because of the difficulties in maintaining a ketogenic diet, some patients are not able to comply with or tolerate the diet. These patients represent the subgroup of GLUT1 DS patients who are most in need of an alternative therapy to ketogenic diet.

3.0 STUDY DESIGN

This is an open-label study to assess the safety and efficacy of triheptanoin in patients with GLUT1 DS over a four (4)-year initial treatment period with a one (1)-year extension period.

3.1 Study Population

The study will enroll GLUT1 DS patients (between 1 and 50 years of age) who are currently not on ketogenic diet or medium chain triglycerides (MCT). Eligible patients may be those who (1) have participated in a prior clinical trial of triheptanoin, or (2) are naïve to

triheptanoin and not eligible for another trial.

3.2 Number of Subjects Planned

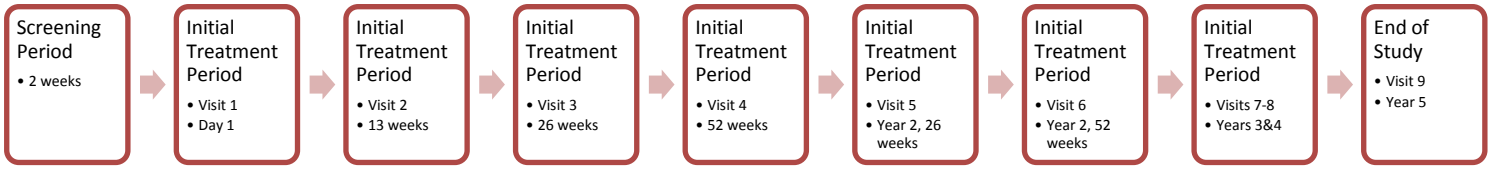
The study will enroll up to 50 subjects in total.

3.3 Study Timeline

The total duration for individual subjects is five (5) years, including four(4) years with eight (8) visits to the clinical site during the initial treatment period and one (1) additional year in the extension period. After a two-week Screening period, subjects will enter the initial treatment period on one of two schedules. Study Visit window will be +/- 2 weeks from the scheduled date.

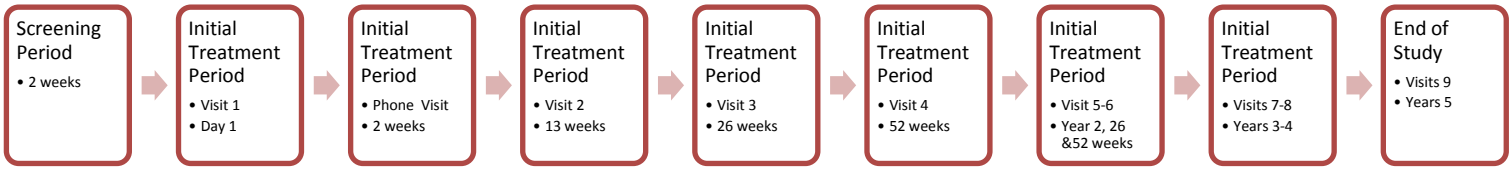
3.3.1 Schedule A:

For subjects previously treated with triheptanoin the visit schedule will be as follows, with telephone follow-up between visits as needed: (Table 1)



3.3.2 Schedule B:

For subjects who are naïve to triheptanoin, the visit schedule will be as follows with telephone follow-up between visits as needed:(Table 2)



4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1) Patients with GLUT1 DS by physician diagnosis
2) Males and females, aged 1 to 50 years
3) Allowed to be on concomitant AEDs
4) Patients are able to tolerate triheptanoin if they have been (or are currently being) treated with this medication
5) Must, in the opinion of the investigator, be willing and able to comply with study procedures and schedule
6) Provide written assent (if appropriate) and written informed consent by a Legally Authorized Representative (LAR) after the nature of the study has been explained, and prior to any research-related procedures
7) Sexually active subjects must be willing to use an acceptable method of contraception while participating in the study
8) Females of childbearing potential must have a negative pregnancy test at Screening and be willing to have additional pregnancy tests during the study

4.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1) Patients and their Legally Authorized Representatives (as appropriate) not willing or able to give writtenor verbal assent or written informed consent.
2) Concomitant administration of a ketogenic diet for the treatment of GLUT1 deficiency at time of study drug initiation
3) Concomitant administration of valproic acid
4) In the Investigator's opinion, the patient may not be compliant
5) Pregnant or breastfeeding an infant at screening
6) Has a concurrent disease or condition, or laboratory abnormality that, in the view of the Investigator, places the subject at high risk for adverse events, or introduces additional safety concerns
7) History of or current suicidal ideation, behavior and attempts
8) Patient qualifies for any other clinical trial designed to progressively evaluate the safety and efficacy of triheptanoin as approved by the FDA under a separate IND which is open at Cook Children's

4.3 Consent Procedures

Informed consent and assent will be obtained following an informed consent conference wherein the principal investigator or their IRB-approved designee will discuss with the LAR the purpose of the study, procedures to be followed, the duration of participation, alternate modes of treatment, and the risks and benefits of participation, as described in the consent form.

A signed consent form will be obtained from the LAR for each enrolled subject. As per the Cook Children's IRB guidelines, written assent from a minor aged 13-18 and verbal assent from a minor aged 8-12 will be obtained. The patient and LAR will be provided written copies of both the informed consent and assent documents. The signed original consent and assent documents will become a part of the permanent medical record and copies will be provided to the patient and LAR. A consent note will be completed and placed in the subject's research chart to document properly-obtained consent.

This study will be conducted in compliance with all United States Federal and local laws, regulations, and guidelines for the conduct of research in a vulnerable population.

5.0 METHODS

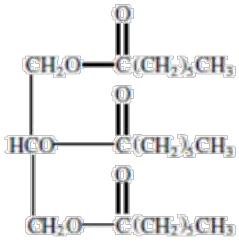
5.1 Recruitment of Subjects

Eligible patients will be identified either from the outpatient neurology clinic or inpatient neurology population at Cook Children's Medical Center; or patients who are referred for treatment for their GLUT 1 DS. Recruitment of subjects will be performed by the principal investigator or their IRB-approved designee.

5.2 Sources of Research Material

5.2.1 Investigational Product

An investigational form of triheptanoin will be utilized as study drug. This form of triheptanoin is a highly purified form intended for oral administration. It is a medium chain triglyceride of three seven-carbon fatty acids whose formula is:[3]



This investigational form of triheptanoin is being developed by Ultragenyx PharmaceuticalInc. as a substrate replacement therapy for the treatment of long-chain fatty acid oxidation disorders (LC-FAOD) and GLUT1 DS.

5.2.2 Mechanism of Action

Triheptanoin is metabolized to heptanoate and C4 and C5 ketone bodies. These metabolites bypass the GLUT1 transporter to cross the blood-brain-barrier and provide an alternative energy source to the brain. These metabolites also have the ability to provide succinyl-CoA via propionyl-CoA in order to resupply intermediates of the citric acid cycle (i.e., anaplerosis) within the brain.

5.2.3 Dose and Mode of Administration

Triheptanoin is colorless to light yellow oil. Triheptanoin will be administered orally (PO) with food or by gastrostomy tube at least four times per day (breakfast, lunch, dinner, and before bed), comprising 35-40% of total calories titrated to a maximum tolerated dose level. The dose may be divided into smaller more frequent doses with food as needed. The dose may be mixed with small amounts of food or drink as indicated in the administration guideline provided by Ultragenyx.

The rationale for the chosen dose (1-4 g/kg of body weight per day divided into 4 doses) is based on the demonstrated safe and effective use of triheptanoin at the suggested dose in patients with Fatty Acid Oxidation Disorders.[14]

5.3 Duration of Treatment

Duration of the initial treatment is 4 years with an additional one-year extension period.

Triheptanoin will be provided to the patient by the CCMC Investigational Drug Service pharmacy (IDS pharmacy) during visit 1 and at all scheduled clinic visits. In lieu of dispensation at time of study visit, the IDS pharmacy may choose to ship either a 3-month or 6-month supply to patients, as prescribed by the PI.

5.4 Study Procedures

The dose will be ~35-40% of total caloric intake (~1-4 g/kg/day, depending on age), for up to 5years, including the extension period, with a visit to the clinical siteat day 1, Months 3, 6, 12, 18, 24, and annual thereafterfor both groups. Enrolled subjects are otherwise able to maintain standard of care treatment which may include anti-epileptic drugs (AEDs) throughout the duration of the study.

Up to 50 patients with a diagnosis of GLUT1DS who have or have not been previously on Triheptanoinwill be enrolledbased on their prior treatment status.

During a two-week screening period, subjects will record daily seizures and diet (last threedays) in a diary to serve as a baseline measurement. If a patient has recorded all screening criteria prior to consent, that data may be used in lieu of additional screening. If, in the opinion of the Investigator, a patient who is currently on the ketogenic dietwould be placed at potential risk for compromise of patient safety by stopping ketogenic diet for two weeks before initiation of treatment protocol, the two-week screeningperiod from consent to initiation may be waived by the Investigator. In the instance of waiving the screening period, seizure and diet information will be gathered retrospectively via parent/patient interview. After the Screening period, subjects will enter the treatment period on one of two protocol schedules. Study Visit window will be +/- 2 weeks from the scheduled date.

5.4.1 Schedule A

- Subjects previously treated with triheptanoin will continue to dose at approximately 35-40% of total daily calories (~1-4g/kg/day, depending on age).

- The visit schedule will be: Visit 1 (day 1), Visit 2 (13 weeks), Visit 3 (26 weeks), Visit 4 (52 weeks), Visit 5 (Year 2, week 26), Visit 6 (Year 2, Week 52), Visit 7 (end of Year 3), Visit 8 (end of Year 4), and Visit 9 (end of Year 5), with telephone follow-up between visits, as needed.(Table 1)

5.4.2 Schedule B

- Subjects who are naïve to triheptanoin will begin a 2-week fixed titration schedule up until they have reached 35-40% of total daily calories (~1-4 g/kg/day depending on age). If a subject has not reached the target of 35-40% of total daily calories, by the end of the 2-week fixed titration period, dose titration should continue until achieved or until the maximally tolerated dose has been established.

- The visit schedule will be Visit 1 (day 1), Phone Visit (2 weeks), Visit 2(13 weeks), Visit 3(26 weeks), Visit 4 (52 weeks), Visit 5 (Year 2, week 26), Visit 6 (Year 2, Week 52), Visit 7 (end of Year 3), Visit 8 (end of Year 4), and Visit 9 (end of Year 5), with telephone follow-up between visits, as needed. (Table 2)

5.4.3 Dose Titration Recommendations

The table below is a guide for dose titration of a subject to 35-40% of caloric intake or the maximum tolerated dose if the maximum dose is <35%. Some discretion and flexibility can be used by the Investigator for each subject.

Days of Dosing	Caloric Intake	If Tolerability Issues Arise:
Days 1-2	10%	N/A
Days 3-5	15%	N/A
Days 6-8	20%	N/A
Days 9-11	25%	Down-titrate to 20% for 3 more days, then continue to titrate up if possible.
Days 12-14	30%	Down-titrate to 20% for 3 more days, then continue to titrate up if possible.
Day 15 – study duration	35-40%	Down-titrate to 20% for 3 more days, then continue to titrate up if possible.

**Subjects who are unable to tolerate the 35% daily caloric intake will down titrate and re-titrate up to determine tolerability. If a subject is still unable to tolerate the 35% caloric intake, the maximum tolerated dose as determined by the Investigator will be administered for the duration of the study.*

5.4.4 Assessment Schedules

5.4.4.1 Diary

Beginning with the screening visit, subjects or caregivers will record daily seizure frequency and diet in the provided diary for 14 days and then during specified intervals. As such, subjects will record seizures and diet, as applicable, for 14 days post Visit 1 and for 14 days prior to each subsequent study visit.

5.4.4.2 Laboratory

Blood samples will be collected for CBC, Chem-7, ALT/AST, at Screening, Week 13, and every six months through the end of year 2, and annually thereafter for all subjects.

5.4.4.3 Functional Measures

Multiple assessments will be administered at Screening, Months 6 and 12, then once per year thereafter during the initial treatment period for all subjects. Those assessments are:

- The Vineland Adaptive Behavior Scales
- The Barry Albright Scales (BAS)*
- PedsQL
- Columbia Suicide Severity Rating Scale (C-SSRS)*

*The BAS and C-SSRS are the only functional measures that will be completed during the

extension period.

6.0 OBSERVATIONS AND MEASUREMENTS

6.1 Vineland Adaptive Behavior Scales, Second Edition (Vineland-II).[18]

Vineland-II is an assessment designed to evaluate personal and social skills in individuals from birth to age 90 with two forms, the survey interview form and the parent/caregiver rating form. The two forms are identical except for the mode of administration (either interview or rating scale). Eleven general subdomains are grouped into four domains: communication, daily living skills, socialization, and motor skills. The four domain composite scores then combine to form the adaptive behavior composite for those individuals aged birth to 6 years 11 months. Three domain composite scores (communication, daily living skills and socialization) combine to form the adaptive behavior composite for those aged 7 through 90. Total administration time for the parent/caregiver self-report rating scale is approximately 30-60 minutes.

The Vineland-II Parent/Caregiver rating scales were normed on a representative sample of 3,695 individuals from birth to 90 years. Data for norming and standardization were collected on eleven clinical groups: attention deficit/hyperactivity disorder, autism-nonverbal, autism-verbal, emotional or behavioral disturbance, deafness/hard of hearing, learning disability, cognitively delayed-mild (child and adult samples), cognitively delayed-moderate (child and adult samples), cognitively delayed severe/profound (adult sample) and visual impairment. Extensive analysis of the psychometric properties of the Vineland-II domain, subdomain, and adaptive behavior composite scores have been reported and generally reflect good to excellent reliability and validity (Sparrow et al., 2005). For instance, split half coefficients for the age groups under 3 ranged from .82 to .95 for the Domains and .96 to .98 for the Adaptive Behavior Composite; and from .78 to .92 for the Domains and .90 for the Adaptive Behavior Composite for children between the ages of 6 months and 2 years, 11 months.

6.2 Barry-Albright Dystonia Scale (BAS).[19]

The BAS is a 5-point, criterion-based, ordinal scale designed to assess dystonia in eight body regions: eyes, mouth, neck, trunk, upper extremities, and lower extremities. The scale ranges from none (0) to severe (4). The maximum total score is 32. Barry, VanSweringen, and Albright (1999) utilized 10 patients and 17 raters to assess the psychometric properties of the scale. They reported excellent intraclass correlation coefficients (ICC). The reported mean ICC scores were as follows: interrater reliability 0.866, intrarater reliability 0.967 and 0.978, and test-retest reliability 0.978 (before training) and 0.967 (after training).

6.3 The Pediatric Quality of Life Inventory Scale (PedsQL).[20]

The PedsQL is a modular approach used to measure the core dimensions of health as defined by the World health Organization (WHO) as well as role function. The inventory measures health-related quality of life in healthy as well as both acute and chronically ill children. For example, the 23-item Generic Core Scale measures across physical (8 items), social (5 items), school (5 items) and emotional functioning (5 items). It is developmentally age specific utilizing a self-report 5-point Likert scale for ages 8 to 18, and a 3-point scale for the young child. In addition there is a separate module for parents to report for ages 2 to 4 (toddler), 5 to 7 (young child), 8 to 12 (child), and 13 to 18 (adolescent) from the care-giver/parent perspective. It is validated in multi-language form including but not limited to English, Spanish and French.

Items are reverse-scored and linearly transformed to a scale of 0 to 100, such that higher scores indicate better health related quality of life. Internal consistency reliability alpha coefficients for the majority of the child self-report scales and parent proxy-report scales exceeded the minimum reliability standard of .70, with the exception of Self-Report School Functioning at 0.68. The Total Scale Score ($\alpha = 0.88$ child, 0.90 parent), Physical Health Summary Score ($\alpha = 0.80$ child, 0.88 parent), and Psychosocial Health Summary Score ($\alpha =$ 0.83 child, 0.86 parent) were acceptable as well.

One-way ANOVA's showing differences among chronically ill, acutely ill, and healthy children for all scales demonstrated construct validity. Multitrait-multimethod analyses revealing correlations with indicators of morbidity and illness burden in the medium to large effect size range demonstrated convergent and divergent validity. Factor analysis resulting in a five-factor solution for self-report and proxy-report supported the conceptualization of the PedsQL as a measurement of an integrated multidimensional construct.

6.4 Columbia Suicide Severity Rating Scale (C-SSRS)[21]

The US FDA has recommended the use of the C-CASA as a standardized suicidal rating system for anticonvulsant trials and other centrally acting agents and nonpsychotropic drugs.

The C-SSRS is a suicidality rating scale that is used extensively across primary care, clinical practice, surveillance, research and institutional settings. It is available in 103 languages and maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The C-SSRS was designed todistinguish the domains of suicidal ideation and suicidalbehavior using four constructs: severity of ideation, intensity of ideation, behavior, and lethality. Severity of ideation is rated on a 5-point scale with 1 being "wish to be dead", 2 "nonspecific active suicidal thoughts", 3 "suicidal thoughts with methods", 4 "suicidal intent", and 5 "suicidal intent with plan". The intensity of ideation subscale comprises 5 items, each rated on a 5-point scale: frequency, duration, controllability, deterrents, and reason for ideation. The behavior subscaleis rated as actual, aborted, and interrupted attempts; preparatory behavior; and nonsuicidal self-injurious behavior. The lethality subscale assesses actual attempts and is

rated on a 6-point scale. If actual lethality is zero, potential lethality of attempts is rated on a 3-point scale.The C-SSRS has demonstrated good convergent and divergent validity with other multi-informant suicidal ideation and behavior scales. It ishighly sensitive and specific for suicidal behavior classifications. Both the ideation and behavior subscales were sensitive to change over time. The intensity of ideation subscale demonstrated moderate to strong internal consistency

The C-SSRS uses different assessment periods, dependingon research or clinical need; the lifetime period assessesthe worst-point ideation, which research has suggestedmay be a stronger predictor of subsequent suicide thancurrent ideation. The following versions will be used in this study: (1) baseline, (2) since last visit, (3) pediatric baseline, (4) pediatric since last visit.

Assessments will be administered for subjects ten years of age and older.

6.5 Tracking Diary

6.5.1 Seizures

A seizure diary will be used to track date, type, number, and unusual presentation of seizures. Subjects will be given a seizure diary at screening to record daily seizure activity for incremental periods of time. They will be instructed to record date and answer the question "Did you/your child experience any seizures today?" An affirmative answer requires completion of the form; a negative answer does not. Regardless of whether a subject experienced a seizure, additional medications administered and not previously recorded will be reported on this daily form. Subjects will describe activity during and post seizure. They will also record the type or description and number of other seizures that occurred that day.

Subjects will complete this form daily during the screening period. They will return the completed diary to the research team at Visit 1. Subjects will then receive a new seizure diary. Subjects will track daily seizures for two weeks following Visit one and then for two weeks prior to each subsequent study visit. Subjects will return the completed diary and receive a new diary at each visit.

6.5.2 Diet

A diet diary will be used to track daily food consumption. Subjects will record the time of consumption, type of food or beverage, amount eaten, place eaten, and individuals present at time of consumption. This should be completed for each of the three days prior to a study visit. The form is incorporated into the seizure diary. Thus, a grid entitled Diet Diary is located below the seizure diary for each of the final days before a study visit.

7.0 CRITERIA FOR EVALUATION

7.1 Safety

Safety events and tolerability will be recorded as adverse events (AE) or serious adverse events (SAE) except for those events that are related to GLUT1 deficiency such as epileptic seizures or abnormal movements.

Physical examination, weight, vital signs, and laboratory tests will be conducted periodically

7.2 Safety Monitoring

Triheptanoin adverse drug reactions include GI disturbance and weight gain. Monitoring of these and other potential AEs will occur during study visits and telephone calls throughout the study, as needed. Consultation with a dietician will be utilized as needed.

7.3 Efficacy

Seizure frequency: The number of observable seizures will be recorded once per day, via diary by patient or caregiver

8.0 CRITERIA FOR REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

Subjects may be removed from the study for the following reasons:

1. Occurrence of an adverse event (AE), a collection of unassociated AE, or a pattern of AE which in the judgment of the Medical Monitor, make further participation in the trial an unacceptable risk of harm to the subject
2. An illness that, in the judgment of the Medical Monitor, might place the subject at risk
3. At the request of the subject or PI
4. In the judgment of the PI, an unacceptable number or seriousness of protocol deviations or unreliable behavior on the part of the subject

9.0 POTENTIAL RISKS AND POTENTIAL BENEFITS

Triheptanoin has been used clinically for over a decade in human studies and is currently being developed in a number of different diseases. Approximately 130 subjects with various disorders, including 65 FAOD subjects (ranging from neonates to adults), have been treated

with triheptanoin for periods up to 13 years with evidence of clinical benefit and no significant safety issues reported.

Data from nonclinical and clinical studies to date suggest triheptanoin does not pose any significant safety risks that can be identified at this time. Triheptanoin has been well tolerated in humans with no significant safety issues and toxicology or adverse pharmacology findings were not observed in triheptanoin -treated animals. Studies in animals and humans suggest triheptanoin consumed orally has side effects that are similar to those of orally consumed medium chain triglycerides. The most commonly reported adverse effects are gastrointestinal distress and excessive weight gain at high doses. Both of these issues appear to resolve when subjects consume triheptanoin in small doses mixed with foods throughout the day and when total caloric intake is appropriately managed.

Overall, the risk-benefit ratio of triheptanoin for GLUT1 DS appears to be favorable based on the safety record to date, the efficacy of triheptanoin in animal models of seizure, the mechanism of action of triheptanoin in providing energy and anaplerotic substrates to the brain, and the significant unmet medical need of GLUT1 DS.

10.0 DATA COLLECTION AND ADVERSE EXPERIENCE REPORTING

10.1 Clinical Data Collection

Data to be collected will include demographic features (gender, age, ethnicity and race), GLUT1 DS medical history, prior and concomitant medications and therapies, details of the 3-day diet record and seizure count from the daily patient diary, and results obtained at each office visit (weight, height, vitals, physical examination, and labs). In addition, data will be collected on adverse events. The entire list of variables and explanations can be found in the Data Dictionary.

10.2 Data Management

Data Management will be provided by Cook Children's Health Care System Research Administration Office (CCHCS RAO) and includes forms design, development of an electronic case report form (eCRF), collecting, managing, editing, storing, and reporting on data; as well as, training and access to the data for the study statistician.
The eCRF's will be maintained and updated by CCHCS RAO to reflect the changes within the protocol. This database will be converted to a REDCap database at such time as that platform is fully implemented within the CCHCS RAO.

10.3 Data Storage

Data will be stored in an electronic database created by CCHS RAO. The database will be password protected and identifiable information will be kept in the database. The database will be maintained on CCHCS servers. Only individuals listed as key study personnel approved by the IRB will have direct access to the database. Any written study-related records will be maintained for at least 3 years following the completion of the study; then destroyed using a cross-cut shredder. Electronic study-related records and results will only be kept in aggregate form following completion of the study.

10.4 Procedures to Maintain Confidentiality

To minimize the chance of harm associated with PHI and identifiable study data collection, all information abstracted from the electronic medical record will be stored in a password-protected database maintained on CCHCS servers by study staff. To maintain confidentiality, all patient identifiers will be removed prior to disclosure; any disclosed data will be for scientific abstract and publication to the medical community. Consent and assent forms will locked in the research administration office.

10.5 Quality Assurance

10.5.1 Edit checks and query resolution

Data entered into the eCRF will subjected to auto-validation (ranges, data checks) and edits on a "real time" basis as well as batch edits. The batch edits will query inconsistent responses, missing forms, missing data, and data anomalies. The Data Manager will review each discrepancy report. Resolved queries will then be incorporated into the database.

10.5.2 Audit trail

An electronic audit trail of all changes is maintained by the system (i.e., by recording the change, name of user making the change, date/time).

10.5.3 Site monitoring

Site monitoring will be completed by a Cook Children's Health Care System representative on an internal basis.The functions of internal monitoring include the review of timeliness of provision of data, the collection of initial and updated regulatory documents, and frequency of identified and resolved issues.

10.6 Adverse Event Reporting

10.6.1 Safety monitoring

Safety monitoring includes the systematic review of clinical laboratory results and measurement data for trends that may impact patient safety. The processing, reviewing, and reporting of adverse experiences and serious AE are also captured.

- A serious adverse event (SAE) is defined as: Death, or immediately life-threatening, or permanently [or significantly] disabling, or requiring hospitalization, or prolongation of hospitalization, or a congenital anomaly. Elective planned hospitalizations, unrelated to either the disease being studied or the study (e.g., for tonsillectomy), will not be considered serious adverse events.

- An unexpected adverse event is one that is not identified in nature, severity or frequency as described in for these AEDs.

10.6.2 Medical Safety Monitor

All SAEs will be reported per local IRB policy. This study will utilize a medical safety monitor named in the Independent Medical Monitoring Charter. The Medical Safety Monitor will provide the medical coverage needed when serious or unexpected AEs occur.

10.6.3 Stopping Rules

The Medical Safety Monitor will act in an advisory capacity to monitor the safety of subjects on a routine basis throughout the trial. The drug safety and pharmacovigilance group at Ultragenyx will review SAEs and may provide advice in any determination of whether study enrollment should be paused or if the study should be halted.

Individual subjects who experience any unexpected and possibly, probably, or definitely drug-related SAEs that represent a change in the nature or an increase in frequency of the serious event from their prior medical history will be assessed as to whether the subject will continue on the study.

Should unexpected and possibly, probably, or definitely drug-related SAEs occur, a full clinical evaluation will be performed by the medical safety monitor, the principal investigator, and drug safety and pharmacovigilance group in order to make a decision regarding what actions to take, including whether to recommend stopping the study and informing the IRB.

10.6.4 Safety Report

Copies of all reports will be stored in the Study File. All SAEs will be reported to the FDA, the CCHCS IRB, and the supporting institution, Ultragenyx, Inc.

10.6.4 Protocol Violations

Protocol violations are events that are inconsistent with the protocol to the extent of impacting the study outcome and / or GCP guidelines. Protocol violations include but are not limited to violations regarding consent and IRB issues, administration of wrong treatment and incorrect laboratory testing. Protocol violations should be reported per the CCHCS RAO policy.

11.0 STATISTICAL CONSIDERATIONS

11.1 Safety Analysis

Safety data will be reviewed annually or more frequently, as needed, by another physician investigator familiar with the disorder and treatment. For the safety analysis, the numbers (frequency) and incidence rates of AEs and SAEs will be summarized during exposure to triheptanoin throughout the study. The analyses of safety will include all subjects who receive any triheptanoin during the study and provide any post-treatment safety information. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class (SOC), Preferred Term (PT), relationship to study drug, and severity. A by-subject listing will be provided for those subjects who experience a SAE, including death, or experience an AE associated with early withdrawal from the study or study drug treatment.

Clinical laboratory data will be summarized by the type of laboratory test. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities after study drug administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for Baseline and all subsequent scheduled visits during which laboratory measurements were obtained. Changes from Baseline to the treatment visits will also be provided. Descriptive statistics of vital signs and concomitant medications will be provided in a similar manner.

11.2 Efficacy Analysis

For efficacy analysis, seizure frequency expressed as the number per month will be calculated during treatment and compared to the historical seizure rate prior to treatment with triheptanoin. Change from baseline will be expressed as median percent reduction in baseline seizure frequency.

12.0 HUMAN SUBJECTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent/assent documents and any subsequent modifications will be reviewed and approved by the CCHCS IRB. A signed consent form will be obtained from the LARfor each enrolled subject as described in detail in section 5.3.

12.2 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the Cook Children's IRB, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

TABLE 1: SCHEDULE OF EVENTS– SUBJECTS PREVIOUSLY ON AND CONTINUING ON TRIHEPTANOIN

	Screening	Initial Treatment				Extension	End of Study or Termination
Name of Visit	**Screening Visit**	**Visit 1**	**Visit 2, 3**	**Visits 4-6**	**Visits 7-8**	**Visit 9**	
Timepoint	**-14 days**	**Day 1**	**Week 13, 26**	**Every 6 mos**	**Annually**	**Annually**	
Informed Consent a) LAR b) Assent	X						
Demographics	X						
GLUT1 DS Medical History	X[1]						
Prior and Concomitant Medications & Therapies	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Dietician Consult[2] (including 3-day diet record review)		X	X	X	X	X	X
Daily Patient Diary Review: Seizure Count	X	X	X	X	X	X	X
Weight and vitals[3]	X	X	X	X	X	X	X
Physical Examination[4]	X	X	X	X	X	X	X
Labs a) CBC[5] b) Chemistry[6]	X		X	X	X	X	X
Vineland Adaptive Behavior Scales (Vineland-II)	X		X	X	X		X
Barry Albright Scale	X		X	X	X	X	X
PedsQL	X		X	X	X		X
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X
Urinalysis: dipstick To test for pregnancy in females of child-bearing potential	X	X	X				

TABLE 2: SCHEDULE OF EVENTS – SUBJECTS NAÏVE TO TRIHEPTANOIN

	Screening	Initial Treatment					Extension	End of Study or Termination
Name of Visit	**Screening Visit**	**Visit 1**	**Phone Visit**	**Visit 2, 3**	**Visits 4-6**	**Visits 7-8**	**Visit 9**	
Timepoint	**-14 days**	**Day 1**	**Day 14**	**Week 13, 26**	**Every 6 mos**	**Annually**	**Annually**	
Informed Consent c) LAR d) Assent	X							
Demographics	X							
GLUT1 DS Medical History	X[7]							
Prior and Concomitant Medications & Therapies	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Dietician Consult[8] (including 3-day diet record review)		X		X	X	X	X	X
Daily Patient Diary Review: Seizure Count	X	X	X[9]	X	X	X	X	X
Weight and vitals[10]	X	X		X	X	X	X	X
Physical Examination[11]	X	X		X	X	X	X	X
Labs c) CBC[12] d) Chemistry[13]	X			X	X	X	X	X
Vineland Adaptive Behavior Scales (Vineland-II)	X			X	X	X		X
Barry Albright Scale	X			X	X	X	X	X
PedsQL	X			X	X	X		X
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X
Urinalysis: dipstick To test for pregnancy in females of child-bearing potential	X	X		X				

Subjects currently or previously treated with triheptanoin

1 GLUT1-DS History, patients must have been confirmed via historical test or by physician diagnosis
2 Three-day diet diaries are to be reviewed with the dietician or study staff upon each indicated visit.
3 Weight (kg). Vitals includes blood pressure (mm Hg), heart rate in beats per minute, respiration rate in breaths per minute and temperature in degrees Celsius (°C), and should be performed at the beginning of each visit before additional assessments are completed.
4 Physical Examination: HEENT, neck, respiratory-auscultation of lungs.
5 CBC panel: Hematocrit, hemoglobin, platelet, RBC, WBC.
6 Chemistry panel:sodium, potassium, chloride, bicarbonate or CO_2, blood urea nitrogen (BUN), creatinine, glucose, ALP, ALT (or SGPT), AST (or SGOT), total bilirubin, GGT, albumin, total protein, calcium.

Subjects currently or previously treated with triheptanoin

7 GLUT1-DS History, patients must have been confirmed via historical test or by physician diagnosis
2 Three-day diet diaries are to be reviewed with the dietician or study staff upon each indicated visit.
9Discuss continued completion of seizure diary.
10 Weight (kg). Vitals includes blood pressure (mm Hg), heart rate in beats per minute, respiration rate in breaths per minute and temperature in degrees Celsius (°C), and should be performed at the beginning of each visit before additional assessments are completed.
11 Physical Examination: HEENT, neck, respiratory-auscultation of lungs.
12 CBC panel: Hematocrit, hemoglobin, platelet, RBC, WBC.
13 Chemistry panel:sodium, potassium, chloride, bicarbonate or CO_2, blood urea nitrogen (BUN), creatinine, glucose, ALP, ALT (or SGPT), AST (or SGOT), total bilirubin, GGT, albumin, total protein, calcium.

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