STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: Compatibility of triheptanoin (C7) with the Ketogenic Diet in Patients Diagnosed with Glucose Transporter Type 1 Deficiency (G1D)

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PROTOCOL TITLE: **Compatibility of triheptanoin (C7) with the Ketogenic Diet in Patients Diagnosed with Glucose Transporter Type 1 Deficiency (G1D)**

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SYNOPSIS

Study Title
Compatibility of triheptanoin (C7) with the Ketogenic Diet in Patients Diagnosed with Glucose Transporter Type 1 Deficiency (G1D)

Objectives

Primary Objectives: To explore triheptanoin (C7 oil; C7) compatibility with the ketogenic diet by evaluating EEG (for the determination of outcome EEG as defined below), and seizure rate, glycemia and ketosis in proven G1D patients receiving (both prior to enrolment and for the duration of this study) a ketogenic diet.

Secondary Objectives: N/A

Design and Outcomes

This is a single-site, open-label proof of principle exploratory trial to investigate the compatibility of C7 oil with the ketogenic diet in subjects genetically diagnosed with G1D. The primary outcome measure is change in EEG during C7 supplementation. The secondary outcome measures are: changes in seizure rate, glycemia (blood glucose lev- els), and ketosis (beta-hydroxybutyrate levels).

Interventions and Duration

This is an open-label, single arm proof of principle trial of orally-administered C7 in subjects diagnosed with G1D and currently receiving (i.e., prior to enrolment) a ketogenic diet. The ketogenic diet will have been previously prescribed by the patient's treating physician independently of this study and for clinical reasons (i.e., the treatment of G1D epilepsy). **Because the ketogenic diet supplies well over 50% of calories from fat, subjects, who are already tolerating over this much fat as part of their previously-prescribed ketogenic diet, will replace 45% of their daily caloric intake with C7** for 24 hours, during a 48 hour inpatient stay. During observation, subjects will have continuous EEG to monitor for any potential C7-related changes in seizure activity before, during, and after C7 ingestion. Subjects will undergo clinical evaluation and comprehensive blood work at baseline and discharge, and continuous EEG and evaluation of glucose and beta-hydroxybutyrate levels while inpatient and receiving C7. Total time of participation is 4 days.

Sample Size and Population

Fifteen subjects receiving ketogenic diet and with a known (genetically determined) G1D diagnosis will be enrolled. Subjects may be male or female, between the ages of 2.5 and 35 years 11 months old (N=5 per age group: 2.5 to 6, 7-11, and 12-35 years 11 months), and must be willing to provide assent if they are of age (age 10-17). Subjects may be English or Spanish speaking. Subjects may be currently taking anticonvulsants or other medications. Because of potential C7- supplemental dietary medium chain triglyceride interference, subjects may not have had medium chain triglyceride dietary

supplements in the past 24 hours and must agree not to consume additional supplemental medium chain triglyceride while on this trial. In practice, subjects will replace any supplemental medium chain triglyceride with any other fat that they are currently consuming.

1. STUDY OBJECTIVES

1.1. The main hypotheses tested are:

- C7 metabolism will not interfere with previously-acquired ketosis in G1D, as measured by no change in EEG from pre-C7 baseline.
- C7 metabolism will not interfere with previously-acquired ketosis in G1D, as measured by no increase in observable seizure rate and no clinically relevant changes glycemia and ketosis, as measured by random glucose levels and beta-hydroxybutyrate levels.

2. BACKGROUND

2.1. Rationale

Glucose transporter deficiency type 1 (G1D), a prototypic glycolytic defect that impairs the first step of glucose metabolism, was first described in 1991 and is caused by haploinsufficiency of the blood brain barrier and astrocyte glucose transporter (1-3). In its most common form, G1D leads to epilepsy and intellectual discapacity. Associated features include microcephaly (signifying limited brain growth) and movement incoordination (ataxia). There is no alteration of systemic carbohydrate metabolism.

Some manifestations of G1D are treatable in a significant fraction of patients: In ~2/3 of over 100 subjects that we have cared for over the years, a ketogenic diet has been efficacious for seizure control but without significantly impacting intellectual discapacity or ataxia ((4) and PI observations). Therefore, G1D is at least partially responsive to the alternative fuels generated by the diet in a fraction of patients, namely even-carbon-number fatty acids and ketone bodies (2). We currently care for over 100 G1D genetically-confirmed subjects, representing ~40% of all North American and ~10% of European subjects either reported or genotyped (often by us (5) under our NIH CETT Program for G1D) and we have elucidated the principal brain metabolic pathways in G1D (6). Although much work remains to be carried out to fully understand the biochemistry of the disorder, significant progress has been made in G1D, such that we believe that the finding of enhanced anaplerosis after administration of the C7 constituent heptanoate and related indicators of tricarboxylic acid (TCA) cycle stimulation (7) warrants the trial of anaplerotic therapy at this time in this disease. An additional sense of urgency is imposed by the potential window of opportunity that closes once the child brain matures.

Because heptanoate metabolism generates acetyl-CoA, C7 can potentially stimu-

late hepatic neoglucogenesis and this can decrease ketosis via insulin release (113). Neoglucogenesis stemming from heptanoate was observed by us after infusion of heptanoate in G1D mice (28). However, the relative amount of heptanoate infused was far greater than that used for G1D subjects. This was expected because a large quantity of labeled substrate is necessary to achieve labeling of brain intermediary metabolites in human and mouse ^{13}C NMR experiments as developed by us (27, 32, 114, 115). Thus, no significant neoglucogenesis (i.e., an increase in glycemia >10 mg/dl) is obligatorily anticipated after C7 ingestion.

Preliminary studies. One G1D subject has received C7 at 45% while on a 3.5:1 ketogenic diet without clinical or analytical consequence. Our 14 G1D subjects on a regular diet studied in the fasting state (8) exhibited a mean blood glucose of 88.5±1.9 mg/dl (mean ± SEM), which did not significantly change 30-60 min after ingestion of the base dose (35%) of C7 (87.8±2.4 mg/dl). Beta- hydroxybutyrate levels were also unchanged (0.25±0.10 mM in the fasting state relative to 0.23±0.1 mM in the post-C7 state; mean±SEM). The same conclusion was reached after 10 of these subjects were tested after 3 months on C7. Thus, C7 metabolism does not appreciably interfere with glucose metabolism and related ketosis (beta-hydroxybutyrate) under a regular diet.

Fifteen subjects with G1D (five per each of three age groups) and currently receiving a ketogenic diet will participate. After baseline measurements of common blood analytes, EEG, and blood ketone body levels, subjects will be given triheptanoin dosed by individual daily caloric intake, divided in 4 daily fractionated doses.

All subjects will take triheptanoin for 24 hours (4 doses) on an inpatient basis.

This study, if the hypothesis is correct, will enable future combined or comparative studies because, for 1/3 of G1D patients, the ketogenic diet is insufficient and may be supplemented with C7 or replaced by it depending on future work, whereas, conversely, C7 may prove insufficient as first line therapy in some patients and necessitate the addition of a ketogenic diet.

2.2 Supporting Data

There is evidence of beneficial effects of C7 metabolism on the TCA cycle G1D (7). This evidence stems from work in the G1D mouse model via ^{13}C nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry. Open-label treatment using triheptanoin has been pioneered by us in several disorders characterized by impaired anaplerosis (9-12), proving safe, tolerable and efficacious.

The dosing, tolerability, and safety profile of triheptanoin has been documented in other disorders (9-12). Therapeutic response is seen at approximately 35% of the daily caloric needs supplied by C7 oil, and 14 years of experience administering C7 has elicited no serious adverse events. However, side effects of mild stomach upset, nausea, and mild weight gain have been observed. Because C7 oil is a fat, it is possible that subjects will

experience changes in lipid levels, cholesterol, and triglycerides, but these changes have not been observed.

3. STUDY DESIGN

This is an open-label, proof of principle trial of C7 in subjects with G1D and currently on ketogenic diet.

Fifteen subjects with G1D receiving ketogenic diet will be enrolled. Subjects will undergo baseline and exit clinic procedures in the Neurology Outpatient Clinic located in the Children's Medical Center Ambulatory Care Pavilion. Inpatient procedures including blood draws will be completed in the Children's Medical Center Epilepsy Monitoring Unit (EMU). These facilities can accommodate both pediatric and adult patients.

Evaluation of EEG will be accomplished at the pre- and post-C7 assessments. Evaluation of random glucose and beta-hydroxybutyrate levels will be accomplished at the baseline, 4 on-treatment, and exit assessments.

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1. Inclusion Criteria

4.1.1. Diagnosis of glucose transporter type I deficiency (G1D), confirmed by clinical genotyping at a CLIA-certified laboratory.

4.1.2. Stable on ketogenic diet at 2.5:1 to 4:1 ratio (i.e., no changes in ratio will have taken place for 2 months). The initiation of a ketogenic diet is previous to -and thus is not part of- this study.

4.1.3. Males and females 30 months to 35 years 11 months old, inclusive.

4.2. Exclusion Criteria

4.2.1. Subjects with evidence of independent, unrelated metabolic and/or genetic disease.

4.2.2. Subjects with a chronic gastrointestinal disorder, such as irritable bowel syndrome, Crohn's disease, or colitis that could increase the subject's risk of developing diarrhea or stomach pain.

4.2.3. Subjects with a BMI (body mass index) greater than or equal to 30.

4.2.4. Subjects currently not on ketogenic diet.

4.2.5. Women who are pregnant or breast-feeding may not participate. Women who plan to become pregnant during the course of the study, or who are unwilling to use birth control to prevent pregnancy (including abstinence)

may not participate. Females age 10 and over will be asked to provide a serum or urine sample for a pregnancy test via dipstick. Subjects will be asked to
agree to abstinence or another form of birth control for the duration of the study.

4.2.6. Allergy/sensitivity to C7.

4.2.7. Previous use of triheptanoin less than 1 month prior to study initiation.

4.2.8. Treatment with medium chain triglycerides in the last 24 hours.

4.2.9. Subjects exhibiting signs of dementia, or diagnosed with any degenerative brain disorder (such as Alzheimer's disease) that would confound assessment of cognitive changes, in the opinion of the investigator.

4.2.10. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.

4.2.11. Inability or unwillingness of subject or legal guardian/representative to give written informed consent, or assent for children age 10-17.

4.2.12. Addition of a new antiseizure drug in the previous 3 months.

4.3. Study Enrollment Procedures

4.3.1. Recruitment

Dr. Pascual is the Director of the Rare Brain Disorders Clinic at UT Southwestern Medical Center and Children's Medical Center Dallas. This clinic currently provides care for approximately 100 confirmed G1D subjects from around the United States. Dr. Pascual's current subjects will be contacted by Dr. Pascual to determine interest in participating in this research. Our experience has been that, due to the childhood manifestations of this disease, the chronic nature of symptoms, and the difficulty in finding effective treatments, these families and subjects are particularly eager for clinical trial opportunities. Our pilot study of G1D (8), which was conducted to establish the feasibility of the EEG protocol as well as providing other preliminary data, recruited 14 subjects in 15 days and had to decline as many as twice that number of interested subjects who made contact just after recruitment was complete.

In addition, Dr. Pascual maintains a collaborative relationship with the Glut1 Deficiency Foundation, a community-based patient advocacy 501(c)(3) organization dedicated to supporting research in G1D. Dr. Pascual is an invited speaker to their annual meeting, and the G1D Foundation has expressed its willingness to support and promote our research efforts through their community boards and newsletters.

Information regarding the trial will also be posted on the ClinicalTrials.gov and UT Southwestern websites, the latter of which includes a searchable database for current trials ongoing at UT Southwestern.

An additional recruitment tool is the web-based, patient-generated G1D patient registry. The registry is an IRB-approved, HIPAA-compliant inclusive questionnaire that captures all relevant aspects of G1D natural history and therapies. The registry, which has been accessible for 1 year now, is housed in the UT Southwestern servers that contain the medical center medical records and currently has over 100 unique enrollees.

4.3.2 Screening Log and Enrollment

We anticipate enrolling approximately 8 subjects in Year 1 and 7 subjects in Year 2. Because this study is resource intensive due to the inpatient stay, and because it will be enrolling concurrently with Protocol 1 (year 1) and Protocol 2 (year 2), enrollment at this rate will allow us to schedule around available resources of both personnel and facilities. This enrollment rate also allows for flexibility in scheduling the EMU with research patients, particularly in year 2.

A screening log will be maintained in an excel spreadsheet, documenting how subjects learned about the trial (Dr. Pascual, community group, clinicaltrials.gov, etc.), who referred them to the trial, the reasons for ineligibility (if applicable), and the reasons for nonparticipation of eligible subjects. The research coordinator will meet with Dr. Pascual at the end of each clinic day to confirm eligible and ineligible subjects seen during the day. The research coordinator will be responsible for screening the designated secure UT Southwestern email account, contacting interested subjects, and logging which subjects qualify and which subjects do not and why.

Enrollment will open in month 1, although screening will begin prior to this month. We anticipate reaching 25% enrollment for this study in month 6, 50% enrollment in month 12, 75% enrollment in month 18, and 100% enrollment in month 24.

Recruitment will be monitored monthly. If recruitment goals fail to be met within the first 6 months of opening enrollment, the recruitment log will be analyzed to clarify the reasons for lack of enrollment, and these reasons will be addressed if possible. In our experience, this population is eager for research studies and very willing to participate, even traveling from several states away to participate in research.

If we have not met recruitment goals, we have several steps in place to improve recruitment.

1. We will utilize our G1D Registry, which includes a clause to inform registered patients about clinical research, and reach out these patients if they have not been enrolled. This process will take approximately 1-2 weeks, and we will re- evaluate recruitment, based on scheduled visits, after 4 weeks.

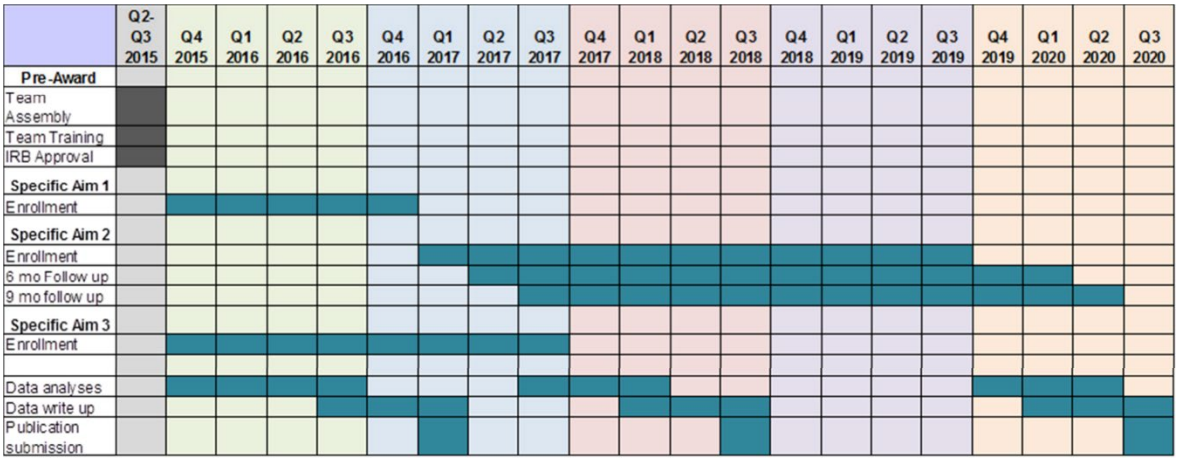
2. If recruitment is still lagging, or we have exhausted available patients in the registry, we will work with the Glut1 Deficiency Foundation. Per the FOA, researchers are encouraged to work with and engage patient groups. We have worked with the Glut1 Deficiency Foundation in various capacities over the past

several years and maintain an excellent working relationship with them , including making their broad patient base regularly aware of our research. The Glut1 Deficiency Foundation will send an email to members with information regarding the trial, and encourage interested families to contact us if desired. This process will take 1-2 weeks, and recruitment will be re-evaluated after 4 weeks, based on scheduled visits.

3. Finally, if we still experience a lack of patients, we will reach out to the G1D Research Consortium (G1DRC; which is not contributing support letters because the Consortium is not part of this proposal), which we have established for the broad purpose of clinical investigation and patient information. There are currently 10 U.S. institutions in the consortium, which cover virtually all densely populated areas of the U.S. The relationship with Consortium members is excellent, as, even before the Consortium was formed, members had previously referred to us a total of 36 G1D patients for specialized neurological consultation.

In addition, if enrollment is slower than anticipated, it is within the scope of this research to allow an additional 2 years to enroll (months 25-48). See Protocol Timeline below.

Protocol Timeline



4.3.3. Consent and Assent Procedures

Subjects will be asked to verify basic eligibility for the trial prior to enrollment (age, diagnosis, if they currently are on dietary therapy) and to provide a copy of their current medical record at the time of enrollment, if they choose to participate. Interested subjects will be securely emailed a copy of the consent prior to their enrollment appointment. The Rare Brain Disorders Clinic maintains a dedicated email address (Rare.Diseases@UTSouthwestern.edu) for correspondence with current and prospective subjects and research participants. Interested patients may ask any questions via this email, or arrange a phone conversation to answer questions prior to traveling to Dallas for enrollment. Dr. Pascual or M.D. co-investigator will consent the subjects in a private exam room. Each aspect of

the trial will be thoroughly explained to the legal guardian and subject. Time will be allowed for questions to be asked. The physician will explain that participation is voluntary, the decision not to participate does not affect the quality of their standard of care treatment with the physicians, and subjects may withdraw from the study at any time. Subjects ages 10 to 17 will be asked to provide their assent, and a legal guardian will be asked to sign the consent form. Subjects under the age of 10 are not required to sign assent. The subject's legal guardian will be asked to sign the consent form for these subjects.

Subjects and legal guardians will also have the HIPAA Authorization for Research explained to them, and again any questions will be answered. The subject's legal guardian will be asked to sign the HIPAA form.

Subjects and their legal guardians will receive a signed copy of both the consent form and the HIPAA Authorization form. One copy will be placed in the research folder, and one copy will be placed in the subject's medical record.

Potential subjects who live out of state or outside the United States will have the option to consent to the study via telephone. Subjects will be provided a copy of the informed consent document, then a telephone call will be scheduled with Dr. Pascual. The process of obtaining informed consent will be conducted as outlined above. The subject will sign the consent form, then send the original copy of the informed consent to Dr. Pascual. A copy of the signed form from both parties will be emailed or mailed back to the family for their records.

4.3.4. Group Assignment

This is an open-label study; there is no group assignment.

5. STUDY INTERVENTIONS

5.1. Interventions, Administration, and Duration

5.1.1. Triheptanoin: A triglyceride oil containing three odd-carbon chain-length fatty acids (i.e., a triglyceride of 7-carbon heptanoic acid). Triheptanoin will be taken 4 times (approximately every 6 hours) by mouth for one day. It is dosed 4 times per day, added to ketogenic diet meals (replacing some of the fat in each meal). Subjects will receive supplementation at 45% of daily caloric intake. The oil should be taken with meals, and will be mixed with the rest of the ketogenic diet nutrients for administration.

5.1.2. Fifteen subjects will be enrolled in a 4 day proof of principle trial of triheptanoin. Administration of triheptanoin will be done in the Children's Medical Center Dallas Epilepsy Monitoring Unit.

5.1.3. Subjects will not be required to stop other medications. Subjects will be directed to maintain their usual medications, including rescue seizure medications, as necessary for the course of the study. Subjects may have any clinical medical records transferred back to their referring physician at completion of the study.

5.1.4. Side Effects: 14 years of experience with C7 diet therapy in children and adults (including 14 G1D subjects, and a larger group of patients with fatty acid oxidation defects) has failed to reveal any significant adverse effects (9-12). However, subjects may experience mild gastrointestinal upset or stomach pain, and mild diarrhea. Both of these side effects are usually resolved by lowering the initial dose of oil by one-half and gradually titrating up to the required dose. In addition, subjects who do not follow the recommendations to reduce other fat intake in their diet may experience weight gain. Once oil is discontinued, careful monitoring of fat and calorie intake usually effectively reverses the weight gain. The data indicate no adverse effects on normal metabolism. A side effects questionnaire will be used to track any self-reported side effects. Patient safety information will be updated, if necessary, after completion of this trial.

5.2. Handling of Study Interventions

5.1.1. 5.2.1. Triheptanoin will be purchased from 1) Stepan Lipid Nutrition headquartered in Maywood, New Jersey, where the company has also a production facility. The oil is supplied in 25 kg containers under a current Material Transfer Agreement, and/or 2) CKM Corporation headquartered in Racine, Wisconsin with the production facilitiy in Racine, Wisconsin.

5.2.2. Stepan Lipid Nutrition and/or CKM Corporation will distribute the oil to the Investigational Pharmacy Services (IPS) at Children's Medical Center. The pharmacists at the IPS will dispense the oil 4 times for each subject, during their inpatient stay.

5.3. Concomitant Interventions

5.3.1. Required Interventions: There are no additional required interventions.

5.3.2. Prohibited Interventions: Subjects are prohibited from starting or changing dietary therapy or other oil-based dietary modifications (including ketogenic diet ratio or medium chain triglyceride therapy) while on study protocol. Subjects who feel this change is necessary will be withdrawn from the study for their own protection. Because of potential C7- supplemental dietary medium chain triglyceride interference, subjects may not have had medium chain triglyceride dietary supplements in the 24 hours before study initiation and must agree not to consume additional supplemental medium chain triglyceride while on this trial. In practice, subjects will simply replace any supplemental medium chain triglyceride with any other fat that they are currently consuming.

5.3.3. Precautionary interventions: Subjects will be monitored by continuous EEG for the duration of C7 administration, and for approximately 18 hours after their last dose. If subjects experience breakthrough clinical seizures, Epilepsy Monitoring Unit physicians and nurses are trained to identify and treat these seizures. Study physicians will be contacted as soon as possible for treatment directives or, if after the event, subject status update, but in the event of an

acute epileptic crisis, staff on hand are qualified and capable of handling the event.

5.4. Adherence Assessment: All C7 is administered on an inpatient basis. There are no adherence assessments.

6. CLINICAL AND LABORATORY EVALUATIONS

6.1. Schedule of Evaluations

Evaluation	Screen	Day 1 Pre-Entry and Entry	Day 2	Day 3	Day 4
Informed Consent		X			
Documentation of Disease/Disorder	X	X			
Medical/Treatment History	X				X[1]
Clinical Assessment		X	X	X	X[1]
Targeted Physical Exam		X			X[1]
Side Effect Assessment		X	X	X	X[2]
Pregnancy Testing		X			
Nutritional Assessment		X			
Seizure Count		X		X	X
Inpatient		Admit: Noon		D/C: Noon	
Continuous EEG		X	X	½ day	
Laboratory Evaluations: Hematology, Chemistry		X	X	X	X
Laboratory Evaluations: Random glucose, Beta-hydroxybutyrate			X AM & PM	X AM & at D/C	
Blood collection to measure C7 ketones[1]		X	X	X	X
Triheptanoin Supplementation			X		

[1]Optional: completed only at discretion of PI or sub-Is

[2]VA Toxicity Scale optional & completed only at discretion of PI or Sub-Is

6.2. Timing of Evaluations

6.2.1. Pre-Entry Evaluations

6.2.1.1. Screening

In order to evaluate subjects' eligibility to participate prior to traveling to Dallas, a waiver of HIPAA Authorization will be obtained only for the purposes of obtaining information regarding age, diagnosis, height, weight, current dietary therapy, and medical history. Once the subject's basic eligibility has been confirmed, the subject will be scheduled for a screening visit in order to be consented and to continue the screening process.

After signing the informed consent, subjects will finish the screening for study eligibility. All screening evaluations to determine eligibility must be completed within one day prior to study entry. Screening and Pre-Entry evaluations may occur concurrently. All screening activities are consistent with standard of care. Screening includes documentation of diagnosis and medical history.

6.2.1.2. Pre-Entry Day 1

The first day of the subject's visit is Pre-Entry Day 1. Pre-Entry assessments consist of clinical assessment, targeted physical exam, side effect assessment, pregnancy testing if appropriate, and a seizure count.

6.2.2. On-Study/On-Intervention Evaluations

6.2.2.1. Entry Day 1

Subjects will be admitted for a 48 hour inpatient stay for oil administration and monitoring. Entry evaluations will be done within a day of pre-entry and consist of a nutritional assessment, and a blood draw to evaluate hematology and blood chemistry, including a random glucose. We will also obtain blood that is left over from the samples above (if available) or draw an additional 3 mL of blood, if needed, to measure C7 ketones. The collection of this blood for measurement of ketones is optional. A continuous EEG will be completed on subjects over the 48 hour inpatient stay. A peripheral IV will be placed to allow for immediate treatment of breakthrough seizures, should they occur.

6.2.2.2. Day 2

Subjects will be administered C7 starting on the morning of Day 2. Subjects will be given oil at a rate of 45% of their daily caloric intake, divided into 4 doses (breakfast, lunch, dinner, and before bed). A clinical assessment and a side effect assessment will be done. Subjects will be maintained on continuous EEG for the duration of C7 administration. Subjects will receive their final dose in the evening on Day 2. Subjects will have a blood draw to evaluate hematology and blood chemistry. Subjects will undergo a random glucose and beta-hydroxybutyrate level in the morning with their first dose of C7 and at bedtime with their last dose of oil. We will also obtain blood that is left over from the samples above (if available) or draw an additional 3 mL of blood, if needed, to measure C7 ketones. The collection of this blood for measurement of ketones is optional.

6.2.2.3. Day 3 (Intervention Discontinuation Evaluations)

Subjects will remain inpatient until approximately noon on Day 3 to ensure no untoward withdrawal effects from C7. A clinical assessment, a side effect assessment, and a seizure count will be done. Subjects will have a blood draw to evaluate hematology and blood chemistry. Subjects will undergo a random glucose and beta- hydroxybutyrate level in the morning and just prior to discharge. We will also obtain blood that is left over from the samples above (if available) or draw an additional 3 mL of blood, if needed, to measure C7 ketones. The collection of this blood for measurement of ketones is optional. EEG will be stopped just prior to discharge.

6.2.3. Final On-Study Evaluations

Subjects will return for a discontinuation visit on Day 4. Subjects will complete a seizure count, limited side effect assessment (Hague Side Effect Scale), and have non-fasting blood drawn to evaluate hematology and chemistry. We will also obtain blood that is left over from the samples above (if available) or draw an additional 3 mL of blood, if needed, to measure C7 ketones. The collection of this blood for measurement of ketones is optional. Medical history, clinical assessment, targeted physical exam, and VA Toxicity Scale are optional and will be completed

only at PI or sub-Investigator discretion.

This visit will complete their participation, and subjects will be discontinued from the study.

6.2.4. Pregnancy
Subjects will be inpatient for the duration of C7 administration. Subjects receive a pregnancy test prior to study entry, and no pregnancy is anticipated during the 4 day participation.

6.3. Special Instructions and Definitions of Evaluations

6.3.1. Informed Consent
Patients will be brought into a private exam room for the consent process. The coordinator will introduce the study, explain the procedures, the patient rights and responsibilities, and the risks and benefits of the study. Dr. Pascual or M.D. co-investigator will then discuss any additional questions regarding the study, ensure the patient and family understand the protocol, their responsibilities, and their commitment to the research. Once the Dr. Pascual or co-investigator is satisfied with the patient and family's understanding and intent to participate in the research, the patient and family will sign the consent form. If the subject is age 10-17 years, the subject must assent to the research study in order to participate. Dr. Pascual or co-investigator will then sign the consent form documenting that consent was obtained.

The institutional research HIPAA form will also be reviewed with the family and any questions answered. Once the research team feels the subject and family understand the HIPAA form, parent or subject signatures will be obtained.

Once the consent and HIPAA forms have been signed by the subject, parents, and PI or M.D. co-investigator, study procedures may be initiated. The research coordinator will create copies of the consent and HIPAA forms: one copy of each form will be returned to the subject and family, and the original of each document will be filed in the subject's research file for the duration of the subject's participation.

6.3.2. Documentation of Glucose Transporter Type I Deficiency (G1D)
Subjects must provide results of genotyping obtained in a CLIA-certified laboratory identifying the GID mutation.

6.3.3. Medical/Treatment History
Procedure location: Children's Medical Center Rare Brain Disorders Clinic. Facilitators: Principal Investigator or physician co-investigators. All subjects' symptoms, past medical history, and current and past treatments will be obtained using a standardized questionnaire that we have used extensively in metabolic encephalopathies to ensure that symptoms anticipated in G1D are sufficiently characterized (13, 14). For example, seizure frequency (the main indicator of neural dysfunction) is captured by this tool. However, in order to avoid ascertainment bias, a wide range of general questions related to all systems is included. This assessment takes approximately 30 minutes.

6.3.4. Clinical Assessments/Targeted Physical Exam
Procedure location: Children's Medical Center Rare Brain Disorders Clinic and Epilepsy Monitoring Unit. Facilitators: Dr. Pascual or physician co-investigators. We will utilize a

standardized scoring system previously used by us to assess the clinical findings on examination (13, 14). The tool focuses on the following domains: (a) height, weight, and head circumference; (b) general medical exam; (c) general neurological exam; (d) cranial nerves; (e) stance and gait; (f) involuntary movements; (g) sensation; (h) cerebellar function; (i) muscle bulk, tone and strength; (j) myotatic reflexes, (k) presence of Babinski signs; and (l) other findings. Results of these domains are scored as normal or abnormal and summarized as a total score with 76 being normal. This assessment takes approximately 30 minutes.

6.3.5. Side Effect Assessment

Side effects will be assessed using the Hague Side Effect Scale (15) and the VA Toxicity Scale (16), which are part of the Common Data Elements for NINDS. These scales, between them, measure side effects of anti-epileptic medications, including some gastrointestinal symptoms and systemic effects measured by our safety blood work. Side effects reported by the family but not found on the scales will be noted. These scales take approximately 20 minutes to complete.

6.3.6. Pregnancy testing

Serum or urine pregnancy testing will be done to test for pregnancy. As the majority of our subjects are minors, we do not anticipate the timing will interfere with C7 initiation; however, C7 will not be initiated until the pregnancy results are returned and are confirmed negative.

6.3.7. Nutritional Assessment

The registered dietician will do a complete review of the subject's caloric intake, and work with PI to determine the optimal amount of oil based on the current caloric intake and ketogenic diet ratio. The consult will take approximately 45 minutes.

6.3.8. Seizure count

Subjects and caregivers will be asked to count any seizures they note during the inpatient stay, from prior to oil administration to discharge on Day 3. They will be given a log to record time and description of any visible seizures.

6.3.9. Electroencephalogram

The subjects will undergo continuous EEG recording of brain wave activity for approximately 48 hours during each inpatient stay. The EEG will involve placement of an electrode cap. The subject will be fitted with a cap containing up to 32 electrodes which rest against their scalp, and which allow their brain electrical activity (EEG) to be recorded. An additional electrode will also be placed directly to the skin in the chest. All skin preparation equipment coming into contact with skin is discarded after a single use, and electrodes and caps are cleaned and disinfected immediately after use in accordance with published guidelines. The EEG recording is harmless and painless. Only the application of the electrode cap may involve mild, temporary discomfort. At the end of the session we will remove the cap and electrodes, and help clean the skin if necessary.

6.3.10. Laboratory Evaluations

Hematological and chemical profiles (Comprehensive metabolic panel, lipid panel, , Lactate Whole Blood, Triglycerides, HDL Cholesterol, LDL Cholesterol, Cholesterol , Complete Blood Count, random plasma glucose, and beta-hydroxybutyric acid (a ketone body generated by ketogenic diets) will be measured by standard clinical laboratory methods and compared to normal values established in each laboratory. In addition, subjects will have

blood drawn via IV for random plasma glucose and beta-hydroxybutyric acid levels in the morning and evening on Day 2 and in the morning and before discharge on Day 3. Measurement of C7 ketones will be conducted by a collaborating research laboratory.

6.3.11. Triheptanoin Administration

Triheptanoin administration will be accomplished in the Epilepsy Monitoring Unit located in the Children's Medical Center. Initiation will be completed under the supervision of Dr. Pascual or one of the physician investigators.

6.3.12. Adherence Assessments

All C7 administration will be done on an inpatient basis, over one day. No adherence assessments are completed.

7. MANAGEMENT OF ADVERSE EXPERIENCES

Previous experience with C7 oil in different populations has yielded no serious adverse effects. Due to the limited nature of the use of C7 oil, there is no data available on how frequent the following side effects occur, nor if there are differences between normal diet or ketogenic diet.

Breakthrough Seizures: There is the possibility that the administration of C7 oil may result in the subject dropping out of ketosis very quickly, which may lead to breakthrough seizures. Management of these breakthrough seizures will follow standard of care protocol, which could include IV or rectally administered anti-convulsant medications.

Diarrhea: Subjects who experience diarrhea may be instructed to increase the amount of fiber consumed with each meal. In addition, C7 will be administered in a fat free, sugar free food item, such as yogurt or pudding, and subjects are instructed to consume this food over 30 minutes in order to minimize diarrhea. Subjects who cannot tolerate the maximum tolerable dose will be discontinued from the study.

Stomach pain: Subjects who experience stomach pain at any time during the treatment will, under the direct supervision of Dr. Pascual or M.D. co-investigator, be assessed for severity. If subjects cannot tolerate the recommended dose due to severe stomach pain, they will be discontinued from the study.

Weight gain: Although weight gain is a possible side effect of C7 ingestion, it is a long-term effect, and we do not anticipate significant weight gain over the course of one day.

8. CRITERIA FOR INTERVENTION DISCONTINUATION

Triheptanoin supplementation will be discontinued if any of the following occur:

- Any of the cited or other adverse experiences become intolerable to the subject
- Metabolic syndrome develops as assessed by glucose and lipid profiles
- Any elevation above laboratory normal range in hepatic transaminases or creatinine is noted
- Any blood cell count abnormality outside laboratory normal range develops
- Non-compliance occurs

- Severe intercurrent illnesses take place
- Severe seizures that are unusual for the subject take place

Subjects who discontinue due to the above reasons will be asked to return for a final research visit to complete exit procedures and receive referrals for ongoing care if necessary. Subjects who are discontinued due to adverse events will be followed via daily, alternate-day or weekly phone calls to assess resolution of the adverse event.

9. STATISTICAL CONSIDERATIONS

9.1. General Design Issues

The main aim of this proof of principle trial is to evaluate the compatibility of C7 with ketogenic diet in subjects diagnosed with G1D. This protocol will yield data that allow a go/no-go decision regarding whether C7 should proceed to an efficacy trial:

If EEG, clinical seizure activity, glycemia and ketosis (blood beta-hydroxybutyrate level) under the ketogenic diet remain unaltered (i.e., unchanged from normal laboratory value ranges) in at least 3 out of 5 G1D subjects in each age group after the partial substitution of ketogenic diet fat with C7, we will confirm compatibility of C7 with ketogenic diet and recommend proceeding to an efficacy trial for C7.

The sample size estimation for this optimal two-stage design is given in Section 9.3.

9.2. Outcomes

9.2.1. Primary outcome

9.2.1.1. EEG

C7 metabolism will not interfere with previously-acquired ketosis in G1D, as measured by no change in EEG from pre-C7 baseline.

Subjects receiving C7 supplementation will experience no interference with ketosis, as measured by no change in EEG.

9.2.1.2. Laboratory Assessments

C7 metabolism will not interfere with previously-acquired ketosis in G1D, as measured by no increase in observable seizure rate and no clinically relevant changes glycemia and ketosis, as measured by random glucose levels and beta-hydroxybutyrate levels, which will remain within the pre-enrollment clinically acceptable ranges (i.e., the new values will typically be within 2SD of previous values, using as SD the SD of the normal values as determined by the laboratory).

Subjects will experience no clinically relevant changes in observable seizures, random plasma glucose, or beta-hydroxybutyrate levels, as compared to the baseline values defined above.

9.3. Sample Size and Accrual

In this exploratory pilot study, we will recruit 5 subjects in each of three age groups for a total of 15 subjects. The sample size is not justified because this is an exploratory pilot study that will yield data aimed to enable important future combined or comparative studies. We expect to complete the enrollment of study within 24 months.

9.4. Data and Safety Monitoring

A Monitoring Committee (MC) consisting of 5 external pediatric neurologists and a patient advocate has been assembled. The committee will be chaired by Dr. Marc Patterson of the Mayo Clinic in Rochester, MN. Dr. Patterson and the committee will review the side effect and adverse event data at each enrollment milestone (25%, 50%, 75%, and 100%), and additionally as recommended by the committee. The committee will meet via Skype or web conference at these milestones, and Dr. Patterson will communicate the results to PI, along with any recommendations the committee had regarding safety. The current committee is composed of the members listed in the following table.

Monitoring committee at a glance

Member	Affiliation	Credentials
Patterson, chair	Director of Pediatric and Adolescent Neurology, Mayo Clinic	Neurometabolic disorders, clinical trials (Niemann-Pick type C disease, lysosomal storage diseases)
DiMauro	Director emeritus, H. Houston Merritt Clinical Research Center Columbia University	Neurometabolic disorders, clinical trials (mitochondrial and neuromuscular diseases). Member, Institute of Medicine
Kossoff	Medical director, Ketogenic Diet Program, Johns Hopkins University	Ketogenic diet and alternative therapies. Coauthor of Treatment of Pediatric Neurologic Disorders and the 5th edition of The Ketogenic Diet
Rapaport	Patient advocacy representative: Glut1 Deficiency Foundation member (Education Committee)	Ph.D. (Environmental Engineering and Chemistry). Past Associate Director, Product Safety and Regulatory Affairs, Procter & Gamble. Led Department consisting of > 100 toxicologists in U.S., Europe and Asia.
Ronen	Professor of Pediatrics, McMaster University	Identified index case of G1D in 1989 (De Vivo el al., NEJM 325:703-9, 1991). Master's degree in clinical research methodology. Director of internationally-acclaimed research program in quality of life in children with epilepsy

Roach	Section Chief of Pediatric Neurosciences at Dell Children's Medical Center of Central Texas; Professor, Department of Neurology, University of Texas at Austin	Authored or edited 9 medical text books and more than 200 journal articles, many focusing on genetic neurological disorders or stroke in children and adults. Editor-in-chief of Pediatric Neurology and former president of the Child Neurology Society

If a physician committee member determines that they are no longer able to serve on the MC, the other committee members will be asked for recommendations for a replacement member, in consultation with PI. A replacement member will be identified, and the approval of NINDS will be sought prior to confirming the replacement.

In the event that the patient advocate representative makes the decision to step down, the board of the Glut1 Deficiency Foundation will be consulted, and a request for a replacement member will be made. The approval of NINDS will be sough prior to confirming the replacement of this committee member.

9.5. Data Analyses

Descriptive statistics will be computed for each group and combined age group in this pilot exploratory study. For normally distributed, continuous data, means and standard deviations will be used to describe the demographic and clinical characteristics of the patient population participating in the study. Medians, quartiles, and ranges will be used to describe characteristics of the patient population when the data are continuous, non-normally distributed. For categorical or dichotomous variables, the frequency or the proportion will be reported. The proportion of patients who do not alter EEG in subjects currently receiving the ketogenic diet will be computed along with the corresponding 95% confidence interval using the exact binomial method. The proportion of patients who have stable blood glucose and beta hydroxybutyrate levels during acute and long-term C7 supplementation will be computed using exact binomial method.

Paired t-tests or nonparametric one-sample signed tests will be conducted to test if there were significant changes in EEG and neurological performance indices such as ataxia in G1D patients receiving a normal diet between pre-C7 and post-C7. The objective of this study is to enable future combined or comparative studies to evaluate C7 comparability with the ketogenic diet by evaluating EEG and preservation of glycemia and ketosis. Descriptive statistics will be computed to inform (but not to determine; per the FOA) the sample size needed for a future larger study.

10. DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

10.1. Records to Be Kept

All signed informed consent forms will be maintained in a locked filing cabinet accessible only to the Dr. Pascual, Clinical Director, and research coordinator.

This cabinet is located in a limited-access room which requires an authorized badge to enter.

All records collected for research-only purposes (research EEG, metabolic assays) will be maintained in a secure fashion. Paper records will be maintained in a locked filing cabinet in a limited-access room. Electronic records will be maintained on an internal, secure UTSW server accessible only by authorized username and password. These servers are backed up nightly, are HIPAA and HiTECH compliant, and are behind the same level of security as UT Southwestern and Children's Medical Center Dallas' medical records.

Subject's will be assigned a study ID, and all materials collected for research purposes will be de-identified using this study ID, including data and case report forms. A file containing the link will be maintained for the duration of active study procedures and during data cleaning. Once the data has been cleaned, the file containing the link to patient ID will be deleted and destroyed.

Records collected for clinical and research purposes (e.g., blood tests and EEGs completed at Children's Medical Center) will become part of the subject's medical record at Children's Medical Center and may be copied and transferred to the subject's primary referring physician at the patient request.

The investigator-sponsor will maintain records in accordance with Good Clinical Practice guidelines; to include:

- FDA correspondence related to the IND application and Investigational Plan; including copies of submitted Form FDA 3500 A, supplemental IND applications, current investigator lists, progress reports, and failure to obtain informed consent reports;
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements.
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;
- Curriculum vitae (investigator-sponsor and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for investigator-sponsor and listed sub-investigators;
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol;
- Laboratory certification information;
- Instructions for on-site preparation and handling of the investigational study treatment (i.e., if not addressed in the clinical protocol);
- Signed informed consent forms;

- Completed Case Report Forms; signed and dated by investigator-sponsor;
- Source Documents or certified copies of Source Documents;
- Monitoring visit reports;
- Copies of investigator-sponsor correspondence to sub-investigators, including notifications of adverse effect information;
- Subject screening and enrollment logs;
- Subject identification code list;
- Investigational drug accountability records, including documentation of disposal;
- Final clinical study report.

The investigator-sponsor will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational product; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

10.2. Role of Data Management

This is a single site study; there are no other clinical sites or statistical center. The CTSA division at UT Southwestern Medical Center will create and maintain our database for this study.

10.3. Quality Assurance

Study personnel and physicians will be trained prior to protocol initiation. Dr. Pascual will participate in several subject intake and evaluations with the physician investigators throughout the study period to ensure quality of clinical exams. In addition, Dr. Pascual will review records collected during these clinical exams to ensure completeness and accuracy.

The Clinical Director will supervise training of all support personnel, including the research coordinator. She will provide monitoring of regulatory compliance on all aspects of the study, including review of research records and consent forms. The research coordinator will be responsible for submitting all IRB documentation, but will work with the Clinical Director when necessary to ensure compliance.

Dr. Pascual and Clinical Director will work together to ensure all personnel are properly trained on their role in the project, and will work together on all federal submissions to remain compliant with reporting requirements.

In the event that monitoring authorities request records, Dr. Pascual and the Clinical Director will work together with the authorities to provide all requested and required documentation.

10.4. Adverse Experience Reporting

Adverse experiences will be collected from subjects at each daily visit. Adverse experiences will be recorded using Adverse Event forms from the NINDS common data elements for epilepsy website (VA toxicity scale). Adverse events will be reported following all requirements set forth by the FDA, OHRP, and local IRB.

10.4.1. Adverse event definitions

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational product, regardless of the causal relationship of the problem with the product.

Associated with the investigational product. There is a reasonable possibility that the adverse effect may have been caused by the investigational product.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Hospitalization shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s) or elsewhere in the current IND application, as amended.

Unanticipated adverse effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, an investigational product, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IND application (including a supplementary plan or application), or any other unanticipated seri-

ous problem associated with an investigational product that relates to the rights, safety, or welfare of subjects.

10.4.2. Recording and assessment of adverse effects.

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational product will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and; 2) an assessment of the casual relationship between the adverse effect and the investigational product.

Adverse effects or abnormal test findings felt to be associated with the investigational product will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

10.4.3 Abnormal test findings:

An abnormal test finding will be classified as an adverse effect if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy. (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study.
- The test finding is considered an adverse effect by the investigator-sponsor.

10.4.4. Causality and severity assessment:

The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational product; and 3) if the adverse effect meets the criteria for a serious adverse effect.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the investigational product", the adverse effect will be

classified as associated with the use of the investigational product for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the investigational product", this determination and the rationale for the determination will be documented in the respective subject's case history.

10.4.5. Reporting of adverse effects to the FDA

The investigator-sponsor will submit a completed Form FDA 3500 A to the FDA for any observed or volunteered adverse effect that is determined to be an unanticipated adverse effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed Form FDA 3500 A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the investigator-sponsor first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse effect does, in fact, meet the requirements for reporting; the investigator-sponsor will submit a completed Form FDA 3500 A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted Form FDA 3500 A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed Form FDA 3500 A, the investigator-sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

10.4.6. Reporting of adverse effects to the responsible IRB.

In accordance with applicable policies of the University of Texas Southwestern Medical Center Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) associated with the investigational product; 2) a serious adverse effect; and 3) an unexpected adverse effect. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects which are 1) associated with the investigational drug or, if applicable, other study treatment or diagnostic prod-

uct(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

11. HUMAN SUBJECTS

11.1. Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB committee responsible for oversight of the study. A signed consent form will be obtained from the subject. For subjects who cannot consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

11.2. Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

11.3. Study Modification/Discontinuation

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

12. ETHICAL CONSIDERATIONS

12.1. Risk/benefit assessment

Prior experience with triheptanoin has seen no adverse events in approximately 100 patients (adults and pediatric). Side effects risks (weight gain and gastrointestinal distress, diarrhea, and nausea) do not persist after discontinuation or appropriate modification of diet. Extensive laboratory tests will be completed in order to monitor for any changes in patient health status, as well as continuous EEG in a specialized epilepsy unit.

There are no direct benefits anticipated for participants. However, benefits to other patients on ketogenic diet in the future potentially include improvement in movement symptoms (e.g., ataxia) and improvement in neuropsychological functioning. For these reasons, we find the risk/benefit assessment to be positive.

12.2 Pediatric Populations

Although this medical food is not yet approved for use in adults, the need for early intervention in many neurological disorders has led us to propose this trial. As mentioned previously, there is no history, in our experience, of adverse events related to triheptanoin use in either adult populations or in our small pilot sample. Additionally, subjects with G1D typically manifest symptoms very young, and it is still unclear as to whether impairment in adulthood is the result of the disorder or of chronic, unmanageable seizures throughout childhood and adolescence. Finally, this rare disorder has no treatment options that address all facets of the disorder: seizures, movement disorders, and neuropsychological impairment ([4] and personal observations). Very few children with G1D grow into adults who are capable of holding a job and living independently (personal observations of PI), which describes a critical need for improvement in treatment for this population.

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the NINDS prior to submission. All publications will meet ethical requirements for reporting patient data and institutional requirements for reporting conflict of interest.

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