STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Dietary treatment of Glucose Transporter Type 1 Deficiency (G1D).

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PROTOCOL TITLE: **Dietary treatment of Glucose Transporter Type 1 Deficiency (G1D)**

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SYNOPSIS

Study Title
Dietary treatment of Glucose Transporter Type 1 Deficiency (G1D)

Objectives

Primary Objectives: To evaluate the impact of triheptanoin (C7 oil; C7) supplementation on measures of neuropsychological function primarily indicative of attention in G1D subjects receiving normal diet.

Secondary Objectives: 1. To evaluate the effect of C7 supplementation of a regular diet on a EEG activity in addition to IQ, language, working memory, processing speed, emotional and behavioral functioning, ataxia, and other neuropsychological and neurological performance indices in children and adults genetically diagnosed with G1D receiving a regular diet at enrolment. 2. To evaluate the safety of C7 supplementation in pediatric and adult subjects diagnosed with G1D on normal diet over a 6 month treatment period.

Design and Outcomes

This is a single-site, open-label, phase II trial of C7 in subjects diagnosed with the most common (epileptic) form of G1D, on no dietary therapy (i.e., consuming a normal diet, unchanged for this study other than for the replacement of some of the diet fat with C7), to explore the feasibility and impact of anaplerotic therapy (C7 dietary supplementation) in G1D using outcome measures that closely trace the disease process. The primary outcome measure will be attention, as measured by performance on a computerized neuropsychological measure as described in section 6.3.9. Attention is a core cognitive function that permits access to other areas of cognition and is commonly impaired in association with seizure disorders. Existing research has indicated that dietary interventions have the potential to promote attention functioning in children with G1D (26, 27). The secondary outcome measures are: 1. Changes in other aspects of neuropsychological (IQ, language, working memory, processing speed, emotional and behavioral functioning) and neurological performance, including ataxia and global impression scales. 2. EEG changes (as precisely defined below) during C7 treatment. 3. Safety of 6 month supplementation with C7 as measured by the absence of clinically significant changes in standard laboratory measures (blood cell count, blood electrolytes, AST, ALT, blood urea nitrogen, creatinine, lipid panel, plasma glucose and Beta-hydroxybutyric acid).

Interventions and Duration

This is an open-label, single arm trial of orally-administered C7 in G1D. Subjects will replace a fixed percentage of their daily caloric intake (based on the results of Protocol 1) with C7 for 6 months, undergo full evaluation and discontinuation of treatment at a 6 month visit, and return for an off-treatment follow up visit 3 months after C7 oil discontinuation, for total duration of participation of 9 months. Subjects will undergo

treatment initiation on a 24-hour inpatient basis. During that 24-hr inpatient treatment initiation, subjects will have continuous EEG both to monitor for real-time seizure activity (for safety) and to determine EEG changes (secondary outcome) before, during, and after treatment initiation. Subjects will undergo clinical evaluation, comprehensive blood work, ataxia scale rating, EEG, and neuropsychological testing at baseline, 6 months, and 9 months.

Important: As described in the Proposal and in (1), C7 is always administered as a **replacement** (nor as a source of extra calories for an otherwise unchanged regular diet) to a fraction of the daily calories that are normally consumed by each subject via other nutrients. As such, there is **no caloric impact** of C7 (i.e., the calories that a subject will consume remain unchanged by the addition of C7 to the diet to replace other nutrients – predominantly fat).

Sample Size and Population

Forty-five subjects receiving no dietary therapy (i.e., consuming a normal diet) with a proven (genetically determined) G1D diagnosis will be enrolled. Subjects may be male or female, between the ages of 2 and 35 years old (N=15 per age group: 2 to 6, 7-11, and 12-35 years old), and must be willing to provide assent if they are of age 10-17. Subjects may be English or Spanish speaking. Subjects may be currently taking anticonvulsants or other medications. Subjects must agree not to change their dietary therapy during the trial without consulting with the study team. Subjects must have evidence of abnormal EEG in the last 36 months.

1. STUDY OBJECTIVES

1.1. The main hypotheses tested are:

- C7 positively affects neuropsychological indices (sustained attention, IQ, language, working memory, processing speed, emotional functioning, adaptive behavior functioning, and quality of life indicators) and neurological performance, such as ataxia, in G1D.

1.2. The secondary hypotheses tested are:

- C7 provides a spectrum of short-term (hours to days) and long-term (over 6 months) benefits in subjects with G1D, defined as a decrease in abnormal EEG activity both in the acute and long-term, as measured by the change in EEG from pre-C7 baseline. These changes in EEG activity are defined and measured as specified below.
- C7 supplementation is safe when used over a long term (6 months), as measured by the absence of clinically significant changes in standard laboratory measures (blood cell count, blood electrolytes, AST, ALT, blood urea nitrogen, creatinine, lipid panel, plasma glucose, and beta-hydroxybutyric acid).

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 (2-4). 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 known 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 ((5) 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 (3). We currently care for well over 100 G1D genetically-confirmed subjects, representing ~40% of all North American and ~10% of European subjects either reported or genotyped (often by us (6) under our NIH CETT Program for G1D) and we have elucidated the principal brain metabolic pathways in G1D (7). 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 (8) 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.

We have established the dosing, tolerability, and safety profile of triheptanoin in adults in a broad variety of inherited carbohydrate and lipid metabolic disorders (of which G1D is a part) (9-13) (FDA IND 59303: “Dietary therapy for inherited disorders of mitochondrial fat oxidation, glycogenoses and mitochondrial myopathies”, responsible investigator Dr. Charles Roe and subsequent expansion to “glycolytic defects” and cross-referencing with responsible investigator Dr. Pascual). The C7 triglyceride has no discernible effects on normal metabolism as assessed by comprehensive analytical methods. However, this has not been sufficiently replicated in G1D. The goal of the accompanying **Protocol 1** is thus to determine the maximum tolerable dose (MTD) and safety profile of triheptanoin in pediatric G1D patients. While there are no significant natural sources of triheptanoin or odd-carbon number fatty acids in nature, triheptanoin is available commercially for cosmetic and food industry applications. C7 is a colorless and tasteless oil.

Forty-five subjects with G1D and currently receiving no dietary therapy diet will participate. After baseline measurements of common blood work analytes, neuropsychological performance, EEG, blood ketone body levels, blood anaplerotic precursor levels and neurological performance, subjects will be given triheptanoin at the MTD (i.e., dosed by individual daily caloric intake), divided in 4 daily fractionated doses.

All subjects will take triheptanoin daily for 6 months. Subjects will return for clinical evaluations, repeat blood work, and neuropsychological testing at this time point, will be discontinued from the oil at this visit, and returned to their usual diet. Subjects will also repeat EEG at this visit. At 3 months after oil discontinuation, subjects will return for a final clinical evaluation, blood work, EEG, and neuropsychological testing.

Rationale for attention functioning as primary outcome: Attention is a core cognitive function that permits access to other areas of cognition and is commonly impaired in association with seizure disorders. Existing research has indicated that dietary interventions have the potential to promote attention functioning in children with G1D (26, 27). With regard to long-term outcomes, research in the field of childhood absence epilepsy has shown that even after attaining seizure freedom, attention deficits may remain (28). In other words, even normal EEG findings may not correspond to functional neuropsychological improvements. These findings in the field of childhood absence epilepsy are significant for the present study given that EEG seizures are more common than observable seizures in children with G1D. Again, attention is a core cognitive function that permits access to other areas of cognition (including language) and is commonly impaired in association with seizure disorders. For all of these reasons, attention functioning as measured by neuropsychological testing (described below in 6.3.9) may be a more relevant primary outcome for the present study than EEG findings. Precedent for neuropsychological ratings as a primary outcome in epilepsy exists. For example, see https://clinicaltrials.gov/ct2/show/NCT02127918

Rationale for EEG as secondary outcome: As explained below, EEG seizures in G1D (which are generally defined clinically in idiopathic absence epilepsy as a generalized spike-wave episode lasting over 3.0 s) are more frequent than observable seizures (see also (1) for details) and improvement in EEG outcome (as independently defined for that article) was correlated with 1) improved language functioning, 2) improved cerebral metabolic rate for some subjects, 3) improved quality of life as demonstrated by patient and caretaker reports (see the proposal for details). Thus, EEG is potentially a clinically meaningful outcome that may correlate with patient benefit and disease burden reduction (1).

This study will define meaningful outcome measures for G1D. Based on preliminary evidence, C7 oil therapy may improve important symptoms of G1D (seizures, ataxia, and neurocognitive deficits). Moreover, in contrast to the strict and often unsatisfactory ketogenic diet commonly used for G1D, addition of C7 to

a regular diet represents a simpler treatment that may facilitate compliance, and potentially lead to improved outcomes. Additionally, due to the differential metabolic effects of C7 relative to the ketogenic diet, there is potential for greater neurological and cognitive benefits to subjects than with the ketogenic diet alone.

Establishing long-term safety and tolerability of C7 in children is critical, as many epilepsies manifest in childhood and can negatively impact brain development. By providing a treatment in early childhood, it may be possible to avoid the deleterious effects of chronic, medication-refractory seizures in G1D patients.

2.2 Supporting Data

There is evidence of beneficial effects of C7 metabolism on the TCA cycle G1D (8). This evidence stems from our 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 and others in several disorders characterized by impaired anaplerosis (9, 11, 12, 14), proving safe, tolerable and efficacious.

C7 dosing will adhere to the MTD determined in Protocol 1. The dosing, tolerability, and safety profile of triheptanoin has been documented in other disorders (9, 11, 12, 14). Therapeutic response is seen at 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 stomach upset/ diarrhea, 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, phase II trial of C7 in subjects with G1D.

Forty-five subjects with G1D receiving a modified atkins diet or a normal diet will be enrolled. Subjects will undergo all baseline and follow-up 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 accept adults as well as children subjects.

Evaluation of outcome measures will be accomplished at the pre- and post-baseline assessments, 6 month post-treatment and 9 month off-treatment time points by comparing baseline, post-treatment, and endpoint measures. Analyses of changes in comprehensive blood work and side effects over time will help ensure further safety and tolerability of C7 oil at the specified dose; improvement in ataxia rating scale, EEG, clinical evaluation, and neuropsychological testing will confirm the use of the clinical measures to assess outcomes.

Neuropsychological testing at the 6-month time point is designed to capture changes in neuropsychological functioning secondary to oil treatment. Testing again at the 9-month time point is designed to assess whether those changes persist for at least the short term (3 months after discontinuation of C7 oil). Most of the measures have alternate forms that may be utilized to minimize practice effects between the 6-month and 9-month time points, or they have shown not to demonstrate practice effects over a 3-month timeframe. As the IQ measures do not have alternate forms and likely are more sensitive to practice effects over that 3-month timeframe, we will not be conducting a 6-month administration of those measures in order to obtain an optimally valid estimate of intellectual functioning at the 9-month time point.

To address the potential circumstance that C7 may be associated or coincide with an increase in clinical seizure frequency between visits, an additional optional procedure will include the performance of a routine outpatient clinical EEG. This procedure will be obtained and reported locally (i.e., in the area of patient residence) in an accredited clinical facility and the report forwarded to the M.D. investigators for decision and intervention as detailed below.

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 or by PET scan.

4.1.2. Stable diet on either a modified Atkins diet or on no dietary therapy (i.e., no dietary therapy for 1 month).

4.1.3. Males and females 24 months to 35 years 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 40.

4.2.4. Subjects currently on dietary therapy (i.e., ketogenic diet, medium chain triglyceride-supplemented diets, Atkins diet, and low glycemic index diet.).

4.2.5. Subjects with no evidence of abnormal EEG (spike-wave discharges).

4.2.6. 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.

4.2.7. Allergy/sensitivity to C7.

4.2.8. Previous use of triheptanoin in the past 1 month. Subjects who participate in Protocol 1 of this study are thus eligible.

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 Program 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 (1), which was conducted to establish the feasibility of a similar 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 strong collaborative relationship (Medical Advisory Board chair) with the Glut1 Deficiency Foundation, the leading community-based patient advocacy 501(c)(3) organization dedicated to supporting research in G1D (see Letter of Support). 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 our web-based, patient-generated G1D patient registry (www.G1DRegistry.org). The registry is an IRB-approved, HIPAA-compliant comprehensive, inclusive questionnaire that captures all relevant aspects of G1D natural history and therapies. The registry, which has been accessible for 1 ½ years now, is housed in the UT Southwestern servers that contain the medical center medical records and currently has over 200 unique enrollees.

4.3.2 Screening Log and Enrollment

We anticipate enrolling approximately 1-2 subject(s) every month for 44 months (months 14-44). Because this study is resource intensive due to the inpatient stay, enrollment at a rate greater than 1-2 per month is not feasible for personnel and resource availability. This enrollment rate allows for flexibility in scheduling the Epilepsy Monitoring Unit (EMU) with these research patients.

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. All of these procedures are in place and have been successfully used by us for (1).

Enrollment will open in month 14, although screening will begin prior to this month in order to schedule appointments immediately. We anticipate reaching 25% enrollment for this study in month 20, 50% enrollment in month 27, 75% enrollment in month 35, and 100% enrollment in month 44.

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 and Canada to participate in research.

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

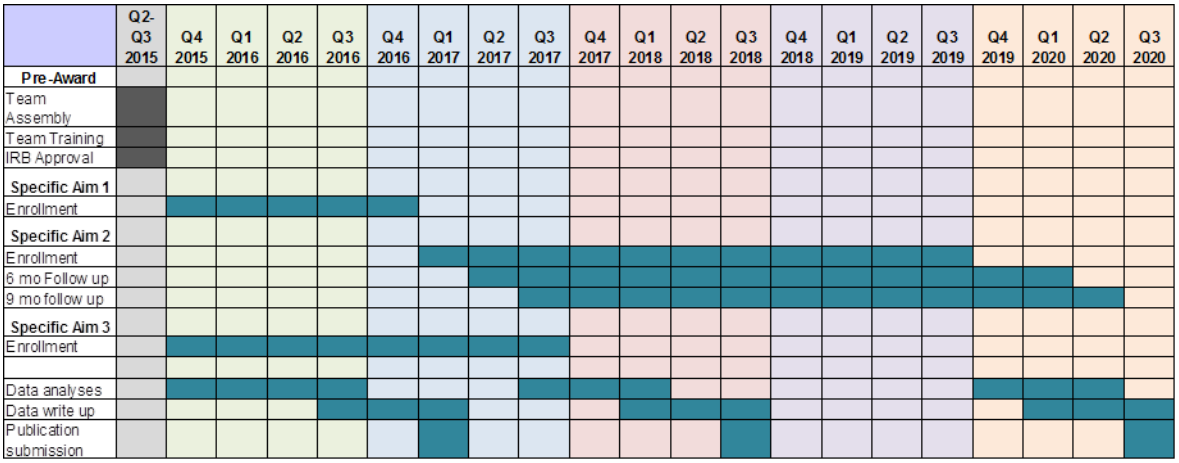
1. We will utilize our G1D Registry, which includes a patient-agreed clause to inform registered patients about clinical research, and reach out these patients if they have not been enrolled. This process will take approximately 1-2 weeks, and we will re-evaluate recruitment, based on scheduled visits, 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 (See Letter of Support), 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 6 months to enroll (months 45-50). 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 Program maintains a dedicated secure 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 age 10 to 17, inclusive, will be asked to sign the assent form, 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.

Subjects and their legal guardians will also be able to consent to the study via Redcap or by email.

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) manufactured for food applications. Triheptanoin will be taken 4 times per day (approximately every 6 hours: prior to breakfast, lunch and dinner and a mid-afternoon snack) by mouth. It is dosed 4 times per day, divided evenly. Subjects will receive supplementation at the maximum tolerable dose (MTD) determined in Protocol 1 (either 35%, 40%, or 45% of daily caloric intake). Subjects who experience acute gastrointestinal distress (nausea, mild stomach upset, mild diarrhea) may decrease the dose to 50% for two days, then increase the dose over the course of less than a week (in a manner similar to what is described in Protocol 1) until they reach the intended dose. Subjects who are unable to tolerate the maximum tolerable dose will be discontinued from the study. The oil

should be taken approximately one hour before meals, and will be mixed with fat-free, sugar-free yogurt or pudding for administration.

5.1.2. Forty-five subjects will be enrolled in a 6 month on/3 month off treatment trial of triheptanoin. Initiation 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 our 14 G1D subjects (1), and a larger group of patients with fatty acid oxidation defects) has failed to reveal any dangerous or permanent adverse effects (9, 11, 12, 14). However, subjects may experience mild gastrointestinal upset or stomach pain, and mild diarrhea (1). 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. Careful monitoring of fat and calorie intake has effectively reversed 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

5.2.1. 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 (see Letter of Support), and/or 2) CKM Corporation headquartered in Racine, Wisconsin with the production facility 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 package the oil for each subject based on oil weight, and provide enough oil for the duration of the study plus a 5% overage to account for spillage and adjustments in dosage. The packaged oil will be given to the research personnel for shipping to the families via FedEx Appointment Home Delivery. This method of delivery provides a confirmed time of delivery and requires an adult signature for delivery. This is a three day shipping time. Subjects will be provided a 4 day supply of C7 oil upon discharge to ensure they have enough to last until the shipment arrives.

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 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.

5.3.3. Precautionary interventions: Dr. Pascual or M.D. co-investigator may direct subjects to adjust the dosing of their oil if necessary for tolerability. If subjects experience acute gastrointestinal distress by self-report during treatment initiation, the amount of oil administered will be decreased to 50% of the dose for 2 days, then gradually increased over less than a week until the desired dose is reached. Subjects who are unable to tolerate the maximum tolerable dose of oil will be discontinued from the trial. If subjects experience gastrointestinal distress during the 6 months of treatment (post treatment initiation), the amount of C7 oil will also be decreased as above. Subjects unable to tolerate a return to the required dose will be discontinued from the study. A dietician will also be available to provide nutritional counseling for subjects who are having difficulties adjusting to the oil, as experience has shown that mixing the C7 oil with an emulsifier, such as yogurt, and other simple dietary interventions can effective and permanently improve tolerability (based on our previous experience with G1D (1)).

5.3.4. Drug treatments during C7 consumption: G1D patients will generally not need to change any concomitant drug treatment as part of this study. Such changes may be initiated by outside local neurologists or by M.D. investigators in this study and prompted by increase seizure frequency or unexpected drug toxicity. While participants will be screened for a stable drug regimen (see Exclusion Criteria) and recognizing that changes in such therapy may occur, the following scenarios will be entertained:

5.3.4.1. No change in type of drug treatment is the planned study conduct. It is likely that this plan will be followed by all subjects because, in clinical practice, the withdrawal of an antiseizure drug on a given patient is usually evaluated only at 2-year intervals, which exceeds the duration of this Protocol. Modest (10-25% dose) changes will be allowed per standard clinical practice in rapidly growing (young) children, whose weigh normally increases on a monthly basis. These children will thus continue to be treated per standard pediatric neurological practice.

5.3.4.2. Addition of a new antiseizure drug. This will be prompted by increased seizures and is equivalent to C7 failure.

5.3.4.3. Discontinuation of an antiseizure drug. This will be prompted by drug adverse events and recorded as such (as outlined below). Such events are very unlikely in patients who have been receiving a stable drug regimen (see Exclusion Criteria).

5.4. Adherence Assessment: The coordinator will call subjects and families once a month to determine adherence (by self-report), remind subjects to go in for the month two lab draw if not already done, and assess amount of oil remaining, and will prompt and procure an answer to any questions that the family may have. If any subjects are having trouble as reported during a call, Dr. Pascual or M.D. co-investigator will be notified and a written plan of action will be developed. Additionally, a nutritional consult will be completed to determine if the C7 dose is still correct. If the subject's caloric intake has changed significantly enough to require a change in the amount of C7 needed, the dietician will consult with PI or M.D. co-investigator, who will contact the family to provide directions for the dose change.

6. CLINICAL AND LABORATORY EVALUATIONS

6.1. Schedule of Evaluations

6.2. Timing of Evaluations

		Visit 1* Pre-Entry and Entry		Monthly Phone Calls	Visit 2 (±7 days) 6 mo. on-oil		Visit 3 (±7 days) 3 mo. off-oil	
Evaluation	Screen -1 month	Day 1 Pre-Entry and Entry	Day 2 Entry	Months 1-5	Day 1 On oil	Day 2 Off oil	Day 1	Day 2
Informed Consent		X						
Documentation of Disease/Disorder	X	X			X		X	
Medical/Treatment History	X	X			X		X	
Clinical Assessment		X			X		X	
Targeted Physical Exam		X			X		X	
Ataxia Scale		X			X		X	
Clinical Global Impression		X			X		X	
Side Effect Assessment		X		X	X		X	
Pregnancy Testing		X			X			
Neuropsychological tests		X	X		X		X	
Nutritional Assessment		X		X	X		X	
Seizure Count		X		X	X		X	
Inpatient		Admit: Noon	D/C: Noon		Admit: Noon	D/C: Noon	Admit: Noon	D/C: Noon
Continuous EEG		X	X		X	X	X	X
Laboratory Evaluations: Hematology, Chemistry on Day 1 or Day 2		X	X	X	X	X	X	X
Blood collection to measure C7 ketones[1]		X	X		X	X		
Triheptanoin Supplementation			Start			End		

[1]Optional

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 informed consent will be obtained only for the purposes of obtaining information regarding age, diagnosis, height, weight, and current dietary therapy. Once

the subject's basic eligibility has been confirmed, the subject will be scheduled a screening visit in order to be consented and to continue the screening process. We will request that subjects keep a seizure log for one month prior to their screening visit. This information will be collected from the subject on the completion of the consent process. Keeping a month long seizure log does not differ from standard of care. A month long seizure log is normally requested of all subjects whether or not they are participating in a research study.

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, medical history, and pregnancy testing if appropriate.

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, ataxia rating, clinical global impression, side effect assessment, pregnancy testing if appropriate, and a seizure count. Neuropsychological testing will be conducted in the afternoon of the same day.

6.2.2. On-Study/On-Intervention Evaluations

6.2.2.1. Entry Day 1-2

Subjects will be admitted for a 24 hour inpatient stay for treatment initiation and monitoring. Entry evaluations will be done within a day of pre-entry and consist of a blood draw to evaluate hematology, blood chemistry, and lipid panel. We will also obtain 3 mL of blood that is left over from the samples above (if available) or draw an additional 3 mL of blood 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 24 inpatient stay.

Subjects will be started on-intervention on the morning of Day 2 after they fast overnight. We will draw an additional 3 mL of blood to measure C7 ketones. The collection of this blood for measurement of ketones is optional. Subjects will be started on C7 oil at the maximum tolerable dose from Protocol 1, a percentage of age-dependent individual daily caloric intake, divided into 4 doses per day. Subjects will be maintained on continuous EEG for 4-6 hours after the initial C7 administration, then be discharged from their inpatient stay. Subjects will undergo neuropsychological testing on the afternoon of Day 2, ending Visit 1.

6.2.2.2.Months 1-5

Each month between Visit 1 and 2, the research coordinator will contact each family to evaluate adherence and tolerability. Additionally, at month two each subject will complete safety blood work at a local CLIA-certified clinical laboratory and have the

results returned to PI at UT Southwestern Medical Center. Every effort will be made to ensure adherence to the protocol: Subjects who do not comply with the month two blood draw (i.e., those who submit blood work results 10 days or later past the due date) will receive extra guidance via telephone and secure email. The maximum tolerable period for result submission delay is 30 days, after which subjects will be evaluated for termination or, if extenuating circumstances have occurred, may have the delivery of oil delayed until they return to compliance with the protocol. Subjects determined to exhibit greater propensity to delays in the opinion of the research team will receive pre-emptive anticipatory guidance before each blood draw due date and help with local phlebotomy scheduling.

Contingency plans for any pro-epileptogenic effects of C7: This is extremely unlikely since C7 is fully consumed in the TCA cycle as a metabolic fuel source and experience with C7 has failed to show any adverse events, including epilepsy. The EEG in G1D shows preprandial spike-waves in the majority of patients regarding of apparent clinical seizure control, thus providing an individual baseline. To address the potential circumstance that C7 may be associated or coincide with a significant increase in clinical seizure frequency between visits, study exit will be considered. An additional optional procedure will include the performance of a routine outpatient clinical EEG. This procedure will be obtained and reported locally (i.e., in the area of patient residence) in an accredited clinical facility and the report forwarded to the M.D. investigators for the following decisions and interventions after clinical comparison with previous patient EEGs. If the new EEG is deemed significantly more abnormal following clinical neurophysiological evaluation by a board-certified pediatric epileptologist, C7 cessation will be followed by study exit procedures.

6.2.3. Intervention Discontinuation Evaluations

Subjects will return for a discontinuation visit at 6 months after initiation of treatment. Subjects undergo the same set of evaluations completed at enrollment. Subjects will complete a medical history, clinical visit, physical exam, pregnancy test if appropriate, and neuropsychological testing on the first day of the visit. Subjects will undergo a 24 hour inpatient stay with continuous EEG to capture EEG recordings in all states: non-fasting/on oil; fasting/on oil; fasting/off oil; and fasting/on oil. On day 1 or day two, subjects can have blood drawn to evaluate hematology, chemistry, and lipid panel. We will also obtain 3 mL of blood that is left over from the samples above (if available) or draw an additional 3 mL of blood to measure C7 ketones. The collection of this blood for measurement of ketones is optional. Subjects will be administered a final dose of oil on the morning of Day 2 for the purposes of fasting, on oil EEG. At that point, they will be discontinued from the oil and discharged from the inpatient stay.

If subjects wish to discontinue the oil before 6 months, we will ask them to return for a discontinuation visit as soon as feasible and remain on the oil until they return. If subjects wish to discontinue due to intolerable side effects, they will be permitted to do so, and asked to return for a final visit as soon as feasible. Many of our patients come

from out of town, and it could potentially be a matter of weeks to a month before a return visit is possible. Subjects will complete a medical history, clinical visit, physical exam, pregnancy test, and neuropsychological testing on the first day of the exit visit. On day one or day two, subjects will complete a fasting blood drawn to evaluate hematology, chemistry, lipid panel, and specialized metabolites. We will also obtain 3 mL of blood that is left over from the samples above (if available) or draw an additional 3 mL of blood to measure C7 ketones. The collection of this blood for measurement of ketones is optional. Subjects will also have a fasting EEG, and will be discontinued from the study at this visit.

6.2.4 Final On-Study Evaluations

Subjects will return for a 3 month off-intervention visit, which will essentially repeat the Visit 2 discontinuation visit. Subjects will undergo a medical history, clinical evaluation, physical exam, and neuropsychological testing, then be admitted for 24 inpatient continuous EEG. On day 1 or day 2, subjects will undergo blood work (hematology, chemistry, and lipid panel). This stay will complete their participation, and subjects will be discontinued from the study.

6.2.5. Pregnancy

Women who become pregnant while on study will be discontinued from the oil immediately and brought in for a final evaluation as outlined above. If a women becomes pregnant on study, she will be dismissed from the study and will undergo no further study procedures. If a participant becomes pregnant while on study the subject would be instructed to discontinue further study therapy and inform the investigator immediately if she becomes pregnant at any time between the initiation of triheptanoin until 30 days after last receiving the triheptanoin. The investigator would counsel the subject regarding the possible effects of triheptanoin on the fetus and the need to inform the study site PI of the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for classification as an SAE. The PI would follow the procedures for reporting the SAE to both the IRB and FDA. This oil is used as a butter fat marker in Europe and there are no known teratogenic effects. However, no studies have been completed examining the effect of C7 on fetuses or breastfeeding newborns.

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.

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 document to Dr. Pascual. A copy of the signed consent form from both parties will be emailed or mailed back to the family for their records.

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, or PET scan results. Subjects enrolled in Protocol 1 of this study are eligible for this Protocol.

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 (15, 16). 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. 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 (15, 16). 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. Ataxia Scale: Brief Ataxia Rating Scale (BARS)

Procedure location: Children's Medical Center Rare Brain Disorders Clinic. Facilitators: Dr. Pascual or physician co-investigators. This assessment takes approximately 15 minutes. The BARS (17) is valid, reliable, and sufficiently fast and accurate for clinical purposes (see Attachment). Items examined include: Gait, Knee-tibia test (decomposition of movement and intention tremor), Finger-to-nose test (decomposition and dysmetria of arm and hand), Dysarthria and Oculomotor abnormalities. Normal score is 0 and most ataxic score is 30.

6.3.6. Clinical Global Impression Scale (CGI)

Procedure location: Children's Medical Center Rare Brain Disorders Clinic. Facilitators: Dr. Pascual or physician co-investigators. The CGI (18) is a 3-item, observer rated scale that provides an overall impression of subject condition based on the clinician's assessment. This assessment takes approximately 5 minutes.

6.3.7. Side Effect Assessment

Side effects will be assessed using the Hague Side Effect Scale (19) and the VA Toxicity Scale (20), 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.

6.3.8. Pregnancy testing

Pregnancy testing will be done via urine or blood draw.. 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. Pregnancy tests can be ordered at any time if clinically necessary.

6.3.9. Neuropsychological Evaluations

The assessment battery, administration time, and data source (i.e., parent or child) is included in Table below. The selection of instruments is based on the NIH Workgroup recommendations. Outcome measures were selected based on clinical relevance, satisfactory reliability, established validity, sensitivity to change, minimal practice effect, and feasibility for administration to children with G1D. The battery is complete in that it measures the major domains of cognitive functioning, including intellectual ability, language, attention, working memory, processing speed, emotional and behavioral functioning, as well as adaptive behavior and quality of life. The primary outcome measure will be attention, as measured by performance on a computerized measure (K-

CPT-2 or CPT-3, as described below) for the two older age groups (see **Table B** of the Proposal) and by performance on a working memory composite (Wechsler Working Memory Index [WMI], as described below) for the youngest age group (see **Table B** of the Proposal). The WMI will be the primary outcome measure for the youngest age group because working memory relies heavily on attention—to the extent that it has been conceptualized as "executive attention" (29) and is increasingly viewed as having significant overlap with core attentional processes (30, 31)—and there are no direct, performance-based measures specific to attention that are normed for the youngest subjects in the present study, whereas the WMI is normed for the entirety of the three age groups described in **Table B** of the Proposal. Attention is a core cognitive function that permits access to other areas of cognition (31) and is commonly impaired in association with seizure disorders. Existing research has indicated that dietary interventions have the potential to promote attention functioning in children with G1D (26, 27).

The neuropsychologist or technician will complete the assessment battery. All instruments are age-appropriate and most are recommended as core or supplemental measures by the NIH Workgroup. Rest breaks will be provided.

Subjects will be administered either the short form of the Wechsler Primary and Preschool Scale of Intelligence, 4th Edition (WPPSI-IV) (*Wechsler, D. (2012). WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition. San Antonio, TX: Psychological Corporation*) or the Wechsler Abbreviated Scale of Intelligence, 2nd Edition (WASI-II) (*Wechsler, D. (2011). WASI -II: Wechsler Abbreviated Scale of Intelligence-Second Edition. San Antonio, TX: Psychological Corporation*), according to the age of subject. Administration takes approximately 20 minutes. These tests provide an estimate of intellectual functioning.

Subjects will be administered the Processing Speed Index Scale (PSI) from either the Wechsler Primary and Preschool Scale of Intelligence, 4th Edition (WPPSI-IV), Wechsler Intelligence Scale for Children, 5th Edition (WISC-V) *(Wechsler, D. (2014). WISC-V: Wechsler Intelligence Scale for Children, Fifth Edition. San Antonio, TX: Psychological Corporation)* or the Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV), *(Wechsler, D. (2008). WAIS-IV: Wechsler Adult Intelligence Scale, Fourth Edition, San Antonio, TX: Psychological Corporation)* according to the age of subject. Administration takes approximately 8 minutes. These tests provide a motor-based estimate of the subject's cognitive processing speed.

Subjects will be administered the Working Memory Index Scale (WMI) from either the Wechsler Primary and Preschool Scale of Intelligence, 4th Edition (WPPSI-IV), Wechsler Intelligence Scale for Children, 5th Edition (WISC-V), or the Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV) according to the age of subject. Administration takes approximately 8 minutes. These tests provide an estimate of the subject's ability to temporarily keep information in mind for a brief period of time in order to use it, which often requires mentally reorganizing the information according to a given rule.

Subjects ages 5 and up will be administered the Purdue Pegboard (Tiffin, 1948). Administration takes approximately 3 to 5 minutes. This test provides an estimate of unilateral and bilateral finger and hand dexterity.

Subjects will be administered either the Conners' Kiddie Continuous Performance Test Second Edition (K-CPT 2) (*Conners, C. K. (2013). K-CPT 2: Conners' Kiddie Continuous Performance Test-Second Edition. North Towanda, NY: Multihealth Systems*) or the Conners' Continuous Performance Test, Third Edition (CPT-3) (*Conners, C. K. (2013). CPT-3: Conners' Continuous Performance Test-Third Edition. North Towanda, NY: Multihealth Systems*) according to age. These tests measure sustained attention and impulsivity; administration takes approximately 7 to 14 minutes depending on age of subject.

Subjects will be administered a Peabody Picture Vocabulary Test, 4th Ed. (PPVT-4) (*Dunn, L.M. & Dunn, D.M. (2007). Peabody Picture Vocabulary Test-Fourth Edition. Minneapolis, MN: Pearson Assessments*) and Expressive Vocabulary Test, 2nd Ed. (EVT-2) (*Williams, K.T. (2007). Expressive Vocabulary Test, Second Edition. Minneapolis, MN: Pearson Assessments*). Combined administration takes approximately 30 minutes, and each test is validated for ages from 2.5 years to adulthood. These tests measure receptive and expressive vocabulary, and incorporate domains of attention, information retrieval, and information expression.

Parents or caregivers will be asked to complete the Adaptive Behavior Assessment System-Third Edition (ABAS-3) (*Harrison, P. & Oakland, T. (2015). Adaptive Behavior Assessment System-Third Edition. San Antonio TX: Western Psychological Services*) and the Child Behavior Checklist or Adult Behavior Checklist (as age appropriate) (*Achenbach, T. M., & Rescorla, L. A. (2000). Manual for the ASEBA Preschool Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families*, *Achenbach, T. M., & Rescorla, L. A. (2001). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families*, *Achenbach, T. M., & Rescorla, L. A. (2003). Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families*). These forms take approximately 30 minutes to complete together. Parents or caregivers also will be asked to complete a brief questionnaire (Appendix B: "Patient History Form") that was locally developed to document information related to neuropsychological functioning, including demographic information, other medical history, and academic performance. This data will be collected in order to control for potential confounds affecting performance on the neuropsychological testing battery. This form takes approximately 15 minutes to complete.

The Pediatric Quality of Life Inventory 4.0-Generic Core Scales (PedsQL) (21) will be completed by either the subject or parent/caregiver, depending on age of the subject. At the completion of testing, the neuropsychologist will rate the utility of the completed testing, based on the child's understanding of and ability to do the task. Particularly in the case of our younger subjects, the tests may be validated to their age, but the subject may be too impaired to provide useful testing results.

The Wechsler Primary and Preschool Scale of Intelligence-4th Edition (WPPSI-IV) is an individually administered, norm-referenced instrument for measuring the intelligence of children aged 2-years, 6-months to 7-years, 3-months. The WPPSI-IV is a revision of the Wechsler Primary and Preschool Scale of Intelligence-3rd Edition (WPPSI-III) instrument recommended by the NINDS Common Data Elements (Neuropsychology) for assessing intelligence (22). The WPPSI-III short-form is recommended for research purposes for obtaining an estimate of a child's intellectual status (*Sattler, J. M., & Dumont, R. (2004). Assessment of children: WISC-IV and WPPSI-III supplement. La Mesa, CA: Jerome M. Sattler*); the short-form of the WPPSI-IV thus is utilized for the present study due to its updated normative data. For each item, the subject will either be asked to define words that are read out loud or respond to a question by choosing a picture from four response options and answer questions that address a broad range of general knowledge topics. The subject will also either view an incomplete matrix and select the response option that completes the matrix or use one- or two-color blocks to re-create a design viewed in a model or picture. The reliability and validity of the selected WPPSI-III short-forms is strong across ages with coefficients ranging from of .92 to .93 and .71 to .86, respectively.

The Wechsler Abbreviated Scale of Intelligence-2nd Edition (WASI-II) is an individually administered, norm-referenced assessment of the intelligence of examinees ages 6 years through 90 years. The WASI-II is a revision of the Wechsler Abbreviated Scale of Intelligence (WASI) (*Wechsler, D. (1999). WASI: Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: Psychological Corporation*), recommended by the NINDS for the assessment of intelligence. For each item, the subject will be asked to define words that are read out loud. The subject will also view an incomplete matrix and asked to select the response option that completes the matrix. The overall average reliability for FSIQ-2 (primary index score) is excellent across ages, ranging from .93 to .94. The average test-retest reliability is strong across ages for FSIQ-2, ranging from .89 to .94.

The Processing Speed Index Scale (PSI) is composed of two subtests from either the Wechsler Primary and Preschool Scale of Intelligence-4th Edition (WPPSI-IV PSI): Bug Search and Cancellation; the Wechsler Intelligence Scale for Children, 5th Edition (WISC-V PSI): Coding and Symbol Search; or the Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV PSI): Coding and Symbol Search. The Processing Speed Index Scale (PSI) provides a measure of the examinee's ability to quickly and correctly scan, sequence, or discriminate simple visual information. Young children (ages 4 to <6) will be asked to mark the bug that matches the target bug in a series of search groups and to scan two arrangements of objects (one random, one structured) and mark target objects, both tasks to be completed within separate time limits. Older subjects (ages 6 and older) will be asked to use a key to fill in symbols that correspond with simple geometric shapes and to indicate whether target symbols are present in a series of search groups, both tasks to be completed within separate time limits. For the overall normative sample, the average reliability and stability coefficients range from strong to excellent. The WPPSI-IV PSI has an overall average reliability of .86 and an overall average stability of .84. The WISC-V PSI has an overall average reliability coefficient of .88 and average stability coefficient of .83 across ages. The WAIS-IV PSI has an overall average reliability coefficient of .90 and average stability of .87 across ages.

The Working Memory Index Scale (WMI) is composed of two subtests from either the Wechsler Primary and Preschool Scale of Intelligence-4th Edition (WPPSI-IV WMI): Picture Memory and Zoo Locations; the Wechsler Intelligence Scale for Children, 5th Edition (WISC-V WMI): Digit Span and Picture Span; or the Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV WMI): Digit Span and Arithmetic. The Working Memory Index Scale (WMI) provides a measure of the examinee's working memory abilities. Young children (ages 2:6 to <6) will be asked to select previously viewed pictures from options on a response page and to place previously viewed animal cards in the previously viewed location on a "zoo" template. Older subjects (ages 6 to 16 years) will be read sequences of numbers and asked to recall the numbers in the same order, reverse order, and ascending order and to select previously viewed pictures from options on a response page. Adult subjects (ages 17+) will be read a sequence of numbers and asked to recall the numbers in the same order, reverse order, and ascending order and to mentally solve a series of arithmetic problems. For the overall normative sample, the average reliability and stability coefficients range from strong to excellent. The WPPSI-IV WMI has an overall average reliability of .91 and an overall average stability of .87. The WISC-V WMI has an overall average reliability coefficient of .92 and average stability coefficient of .82 across ages. The WAIS-IV WMI has an overall average reliability coefficient of .94 and average stability of .88 across ages.

The Purdue Pegboard is a norm-referenced test of manual dexterity of examinees ages 5 years through 89 years. The Purdue Pegboard is recommended by the NINDS for the assessment of fine motor speed and manual dexterity (22). The right-hand (RH) and left-hand (LH) subtests of the Purdue Pegboard provide a time-efficient estimate of these functions. For those two subtests, subjects use only the designated hand to place as many pins in holes as possible within 30 seconds. Test-retest reliability ranges from acceptable to good, ranging from .76 to .89.

The Conners' Kiddie Continuous Performance Test- 2nd Edition (Conners K–CPT 2) is a norm-referenced, computerized measure of sustained attention and impulsivity that has normative data for children ages 4 years through 7 years. The K–CPT 2 uses pictures of objects rather than letters, which are used in the Conners CPT-3. The child is asked to respond to targets (all objects except soccer ball) and refrain from responding to non-targets (soccer ball) that appear on the computer screen. The median split -half reliability estimate across all scores was equal to .87. The median test-retest correlation was .57. These results suggest a good level of test-retest reliability.

The Conner's Continuous Performance Test- 3rd Edition (Conners CPT-3) is a norm-referenced, computerized measure of sustained attention and impulsivity that has normative data for children and adults ages 6 years and older. The CPT-3 requires subjects to press the space bar whenever any letter except the letter 'X' appears on the computer screen. Split-half reliability estimates of the Conners CPT-3 scales were calculated for the normative samples. Results were very strong – across all scores, the median split-half reliability estimate was .92.

The Peabody Picture Vocabulary Test-Fourth Edition (PPVT-4) is a norm-referenced measure of receptive vocabulary that has normative data for ages 2 years 6 months through age 90 years. The PPVT-4 has equivalent Forms A and B, and the PPVT-4 was co-normed with the Expressive Vocabulary Test-2 (EVT-2). For each item, the examiner says a word, and the examinee responds by selecting the picture that best illustrates that word's meaning. Alternate form mean reliability across ages is strong (M=.89), as is test-retest reliability across ages (M=.93). In addition to measuring receptive vocabulary, the PPVT-4 has demonstrated utility as a method for estimating premorbid intelligence (25), which represents an additional rationale for its inclusion in the present study. However, it should be noted that all subjects will participate in neuropsychological testing within the study protocol prior to administration of oil, thus providing baseline/pre-treatment data regarding neuropsychological functioning. It is not possible to obtain truly "premorbid" neuropsychological data in the case of genetic disorders present at birth.

The EVT–2 is an individually administered, norm-referenced instrument that assesses expressive vocabulary and word retrieval for children and adults ages 2 years 6 months through age 90 years. The EVT-2 provides two parallel forms A and B, and is co-normed with the PPVT-4. Alternate form reliability across ages is excellent (M=.87) as is test-retest reliability across ages (M=.95).

Validity and reliability of the PPVT-4 and EVT-2 may be limited for examinees whose primary language is not English or Spanish, but this is predicted to affect a very small number of subjects. At present, all North American patients in the registry have identified English as their primary language. With any neuropsychological measure, individual factors such as language and overall degree of impairment may result in reduced utility of results in select cases, as previously acknowledged on Page 22 of this Protocol.

The Adaptive Behavior Assessment System–Third Edition (ABAS–3) provides a comprehensive norm-referenced assessment of the adaptive skills of individuals ages birth to 89 years. The scale yields assessment of 10 individual adaptive behavior domains (e.g., Self-Care, Home Living) and aggregates into Social, Conceptual, Practical, and General Adaptive Composites. Test-retest reliability for the General Adaptive Composite across ages ranges from .82-.89 and inter-rater reliability across ages ranges from .83-.85.

The Child Behavior Checklist for Ages 1 ½ to 5, Child Behavior Checklist, and Adult Behavior Checklist are parent/caregiver rating scales that assesses competencies, adaptive functioning, and behavioral, emotional, and social problems from age 1½ to over 90 years. Test-retest reliability is excellent, with coefficients for Total Problems scales for the parent/caregiver form falling at .90 for the preschool version, .94 for the school age scale, and .92 for the adult version of the rating scale. Stability correlations are also acceptable at 12 months for the preschool (r=.76) and school age (r=.81) version, and 2-year stability of the adult version falling at an acceptable level (r=.67).

The PedsQL 4.0- Generic Core Scales is a modular approach to measuring health-related quality of life (HRQOL) in healthy children and adolescents and those with acute and chronic health conditions. The PedsQL 4.0 Generic Core Scales consist of 23 items and

covers 4 domains: physical (8 items), emotional (5 items), social (5 items) and school (5 items). It provides a total scales score from 23 items, of which 8 are for physical health summary score and 15 are for psychosocial health summary score. The instrument takes 5 minutes to complete and is translated in multiple international languages including broadcast Spanish. It is usable for parents/guardians of children between the ages of 2 to 18 years (in 4 age groups) and child versions are available for all age groups except the 2-4 years old. Internal consistency reliability for the total scale Score (α = 0.88 child, 0.90 parent report), Physical Health Summary Score (α = 0.80 child, 0.88 parent), and Psycho-social Health Summary Score (α = 0.83 child, 0.86 parent) were acceptable for group comparisons (23). Validity was demonstrated using the known-groups method, correlations with indicators of morbidity and illness burden, and factor analysis. The PedsQL distinguished between healthy children and pediatric patients with acute or chronic health conditions, was related to indicators of morbidity and illness burden, and displayed a factor-derived solution largely consistent with the a priori conceptually-derived scales.

Schedule of Neuropsychological Testing

Instrument/ (Age)	**Test Domain/time**	**Data Source**	**Timepoints**
Wechsler Preschool and Primary Scale of Intelligence, 4th Edition (WPPSI-IV) - short form FSIQ-2 / (2:6 ≤ 5 yrs); Wechsler Abbreviated Scale of Intelligence-2nd Edition (WASI-II) FSIQ-2 / (≥ 6 yrs)	Intellectual ability/ (20');(20')	Subject	**Visit 1:** • Day 1: Pre-entry (non-fasting no-oil) • Day 2: fasting EEG, **Visit 3 (9 mo. off-oil)** • Day 1: non-fasting, off-oil
Peabody Picture Vocabulary Test, 4th Edition (PPVT-4)/ (≥ 2:6 yrs) & Expressive Vocabulary Test 2nd Edition (EVT- 2) / (≥ 2:6 yrs)	Language/ (15'); (15')	Subject	**Visit 1:** • Day 1: Pre-entry (non-fasting no-oil) • Day 2: On treatment (non-fasting on-oil) **Visit 2 (6 mo. on-oil)** • Day 1: non-fasting, on-oil **Visit 3 (9 mo. off-oil)** • Day 1: non-fasting, off-oil
Conners' Kiddie CPT, 2nd Ed. (K-CPT 2) / (4-5 yrs); Conners' CPT, 3rd Ed. (CPT-3) / (6+ yrs)	Attention/ (7.5');(14')	Subject	**Visit 1:** • Day 1: Pre-entry (non-fasting no-oil) • Day 2: On treatment (non-fasting on-oil) **Visit 2 (6 mo. on-oil)** • Day 1: non-fasting, on-oil **Visit 3 (9 mo. off-oil)** • Day 1: non-fasting, off-oil

Working Memory Index Scale (WMI) subtests from either: • Wechsler Preschool and Primary Scale of Intelligence, 4th Ed. (WPPSI-IV; 2:6 to <6 yrs) • Wechsler Intelligence Scale for Children, 5th Ed. (WISC-V; 6 to 16 yrs) • Wechsler Adult Intelligence Scale, 4th Ed. (WAIS-IV; 17+ yrs)	Working memory/ (8')	Subject	**Visit 1:** • Day 1: Pre-entry (non-fasting no-oil) • Day 2: On treatment (non-fasting on-oil) **Visit 2, Day 1** (6 mo. on-oil) **Visit 3, Day 1** (9 mo. off-oil)
Processing Speed Index Scale (PSI) subtests from either: • Wechsler Preschool and Primary Scale of Intelligence, 4th Ed. (WPPSI-IV; 4 to <6 yrs) • Wechsler Intelligence Scale for Children, 5th Ed. (WISC-V; 6 to 16 yrs) • Wechsler Adult Intelligence Scale, 4th Ed. (WAIS-IV; 17+ yrs)	Processing speed/ (8')	Subject	**Visit 1:** • Day 1: Pre-entry (non-fasting no-oil) • Day 2: On treatment (non-fasting on-oil) **Visit 2, Day 1** (6 mo. on-oil) **Visit 3, Day 1** (9 mo. off-oil)
Purdue Pegboard (5+ yrs)	Fine motor speed and dexterity/ (3' to 5')	Subject	**Visit 1:** • Day 1: Pre-entry (non-fasting no-oil) • Day 2: On treatment (non-fasting on-oil) **Visit 2, Day 1** (6 mo. on-oil) **Visit 3, Day 1** (9 mo. off-oil)
Adaptive Behavior Assessment Scale-Third Ed. (ABAS-3) - Parent/Primary Caregiver Form (0-5 yrs); Parent Form (5-21 yrs.)	Adaptive Behavior/ (15' to 20')	Caregiver	**Visit 1, Day 1:** Pre-entry (non-fasting no-oil) **Visit 2, Day 1** (6 mo. on-oil) **Visit 3, Day 1** (9 mo. off-oil)
Child Behavior Checklist (CBCL) /(1 ½ - 5 yrs); Child Behavior Checklist (CBCL) / (6-18 yrs)	Emotional & Behavioral Functioning/ (15' to 20')	Caregiver	**Visit 1, Day 1:** Pre-entry (non-fasting no-oil) **Visit 2, Day 1** (6 mo. on-oil) **Visit 3; Day 1** (9 mo. off-oil)

6.3.10. Nutritional Assessment

At the initial visit, the registered dietician will conduct a complete review of the subject's caloric intake, and work with PI to determine the optimal amount of oil based on the age, current caloric intake and dosing determined in Protocol 1. Additional nutritional counseling will be provided, including instructions on limiting other fats and simple sugars

in the subject's diet to minimize the risk of weight gain. The initial consult will take approximately 60 minutes.

During each monthly phone call, the registered dietician will evaluate the subject's current dietary intake to determine if any changes in amount of C7 administered are necessary. As these are primarily growing children, it is important to evaluate caloric intake regularly, as these needs can change dramatically over even a few months if the child goes through a growth spurt. Any changes in caloric intake, up or down, will be accounted for, and PI will be consulted if the changes are great enough to warrant a change in amount of daily C7 administration. This procedure will take approximately 20 minutes.

6.3.11. Seizure count

For one month prior to each study visit and for each month of participation, parents and caregivers will be asked to track how many observable seizures their child has. Although we have evidence that many patients with G1D have frequent abnormal EEG without observable seizures, seizure count is considered a gold standard in epilepsy research and will be included as a secondary measure.

6.3.12. Electroencephalogram

EEG recordings will be performed with standard 10-20 electrode recording placement and recorded by digital devices with a 1000 Hz sampling rate. Recordings will last for 8 hours during daytime to provide a broad sample of the awake state. The recordings will be stored electronically and locally until they are ready for central review. Prior to transmission for central review the tracings will be de-identified and assigned a unique study number so that the EEG interpretation can be conducted in a blinded fashion. Central EEG review will be done by Dr. Douglas Nordli.

Central EEG readings will be done using an FDA-approved specialized software designed for interpreting recordings from a wide variety of manufacturers (Insight by Persyst). This will permit uniform interpretation of the tracings and will also allow for precise quantitative analysis of the spike-wave discharges. The study will be pruned so that only awake portions are present before the analyses begin and the total duration of the awake recording will be noted.

There will be three measures of the cerebral electrical activity. The first will be a determination of the frequency of the posterior dominant rhythm. This will be measured bilaterally in a non-drowsy portion of the awake recording after eye closure.

The second measure will be the total number of generalized spike-wave discharges will be counted in the awake state only. Computerized automated spike detection will be run on the sample and then the resultant spikes will be analyzed using the spike clustering feature of Insight. This will allow the central reader to reject all detections that are not generalized spikes, and the resultant number of bona fide generalized spikes will be displayed. The ratio of generalized spike-wave discharges per unit time of the awake tracing will be recorded.

The final and third analysis will be of the total number of generalized 3 Hz spike-wave discharges lasting longer than 3 seconds. Here, the rhythmic burst detection system of Insight will be used to identify every burst, and these will be reviewed by the central reader to ensure that they are all accurate detections of the specified time duration. The total number will be recorded and once again compared to the total duration of the awake tracing.

Laboratory Evaluations

Hematological and chemical profiles (including blood cell count, comprehensive metabolic panel, lactate, lipid panel, urine and or blood pregnancy test if appropriate, 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. Measurement of C7 ketones will be conducted by a collaborating research laboratory.

6.3.13. Triheptanoin Initiation

Triheptanoin initiation 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.

6.3.14. Adherence Assessments

Adherence will be evaluated during a monthly phone call. Parents will be asked to rate adherence on a scale of 1 to 10. Quantity of oil remaining will also be assessed via the phone call.

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 are no definitive data available on how frequent the following side effects occur.

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 treatment initiation may, at the direction of Dr. Pascual or M.D. co-investigator, reduce the dose of C7 oil to 50% for 2 days, then increase the daily dose back to the recommended level within a week. If subjects cannot tolerate the recommended dose, they will be discontinued from the study.

Weight gain: Subjects who experience weight gain (defined as any weight gain greater than 5% of the total body weight expected if the individual percentile were followed in the standard weight growth curve; CDC Standard Growth Curves, 2001) will be re-counseled about the dietary changes recommended while taking the C7 oil supplement. Subjects will have a dietician consult prior to treatment initiation and during treatment initiation, to discuss these changes (primarily reduction in other dietary fat). If subjects continue to experience weight gain, they will undergo a dietary assessment. If subjects have made recommended changes and continue to gain weight, they will be removed from the study and an adverse event will be reported.

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 clinically relevant blood cell count abnormality develops
Non-compliance occurs
Severe intercurrent illnesses 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

In the proposed single-arm phase II trial, we define favorable impact on the neurocognitive outcome as at least 0.5 standard deviation (SD) improvement in performance on attention measures (measured as described above) after administration of C7. That is, impact on the outcome is determined by whether a treatment causes at least 0.5 SD improvement on the primary attention measure for that age group in a single arm trial and the interest is **primarily focused on reaching a decision on whether to progress with C7 to a future larger trial**. (Note: The SD is a normative parameter provided with the testing instruments). The evidence to make this decision is evaluated by testing the null hypothesis that the true efficacy rate is less than or equal to some pre-specified value. It is desirable to achieve this goal whilst minimizing the number of subjects exposed to a novel agent. Here, we use the Simon's optimal two-stage design that yields the smallest expected sample size when the null hypothesis is true.

We apply Simon's optimal two-stage design (24) using as primary outcome attention performance for each of three age groups. At least 0.5 SD improvement in performance on the primary attention measure after the administration of C7 is considered a favorable outcome. The measurement of 0.5 SD improvement is commonly accepted as the cutoff for a minimally clinically important difference, as described in various studies (e.g., 32, 33).

This protocol will yield data that allow a clear **go/ no-go decision** regarding whether C7 should proceed to an efficacy trial:

- If a favorable outcome occurs in less than 50% of subjects, we will recommend that C7 not proceed to an efficacy trial.

- If a favorable outcome occurs in at least 80% of subjects, we will recommend that C7 proceed to an efficacy trial.

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

If an intermediate number of subjects (51 – 79%) exhibit a favorable primary attention outcome, the rest of outcomes, including the long-term, 6-month responses, will be considered for the go/ no-go decision on the basis of impact on these outcomes and the disease process, in addition to tolerability and safety indicators.

Clinical significance and meaningfulness of the primary neurocognitive (attention) outcome: Attention is a core cognitive function that permits access to other areas of cognition and is commonly impaired in association with seizure disorders. Existing research has indicated that dietary interventions have the potential to promote attention functioning in children with G1D (26, 27). With regard to long-term outcomes, research in the field of childhood absence epilepsy has shown that even after attaining seizure freedom, attention deficits may remain (28). In other words, even normal EEG findings may not correspond to functional neuropsychological improvements. These findings in the field of childhood absence epilepsy are significant for the present study given that EEG seizures are more common than observable seizures in children with G1D. Additionally, these findings with regard to childhood absence epilepsy may help explain why language functioning improvements in children with G1D after administration of triheptanoin were not statistically significant in a previous trial (1). Again, attention is a core cognitive function that permits access to other areas of cognition (including language) and is commonly impaired in association with seizure disorders. For all of these reasons, attention functioning as measured by neuropsychological testing (described below in 6.3.9) may be a more relevant primary outcome for the present study than EEG findings. As noted above, the measurement of 0.5 SD improvement is commonly accepted as the cutoff for a minimally clinically important difference, as described in various studies (e.g., 32, 33), and thus in the present study we will look for this degree of improvement in performance on the primary measure of attention to answer the go/no-go decision for each age group.

Clinical significance and meaningfulness of the secondary EEG outcome: A specific (but variable across studies) percentage in EEG seizure reduction is a generally accepted outcome in epilepsy trials. The spike-wave and other EEG changes investigated above in this trial have the potential to reflect a meaningful disease burden reduction to patients that would be associated, if realized, with considerably fewer observable seizures, since EEG seizures are significantly more frequent than overt seizures in G1D (1). In this publication (1) we observed that, on average, a reduction in seizure rate comparable to the reduction sought above is associated with a significant acute (hours to days) impact on neuropsychological performance as well as sustained (months) quality of life and neuropsychological scores (1). As described in the proposal, this rate allowed many patients to significantly increase school performance, social interactions, autonomy and a decrease in or a cessation of antiseizure drugs. Every patient who participated in (1) experienced improvement in terms of one or more of these aspects and most improved in all of them. Thus, the expected reduction in EEG spike-wave burden after C7 treatment may be highly medically significant, but the definitive implications of this will be established only in more advance-phase trials. Therefore, we will attempt to relate attention scores (primary outcome) with EEG recordings (used here as a surrogate marker of the disease and a secondary outcome) to seek such correlations. The long-term aspects of the treatment, which may be expected to illustrate sustained or additional benefits as in (1) are also captured on the 6-month on-treatment study design.

Although a variety of designs were considered, including crossover designs for non-ketogenic diet subjects and randomization to C7 or ketogenic diet, several factors contributed to the development of an open-label design. The G1D population, while hypothesized to be greater than previously realized, is currently a relatively small population and the number of patients needed to adequately power a cross over study could be difficult to recruit. This holds true for a head to head comparison of C7 and ketogenic diet, although the increasing availability of genomic testing may increase the available population in the next few years. Finally, and most importantly, the safety and tolerability of C7 has not been rigorously proven in G1D. Therefore, this issue needs to be addressed before entering into advanced clinical trials.

A six-month, on-supplement follow up time period was chosen in order to provide long-term safety and tolerability data for triheptanoin. Additionally, we consulted with Dr. Holland (co-investigator), an established pediatric neuropsychologist expert in G1D. It is general practice to wait a minimum of 6 months after ischemic insult to the brain (such as traumatic brain injury or stroke) before assessing neurocognitive changes. This time period is consistent with how long it takes the brain to demonstrate performance improvement after these insults. Because chronic seizures can also induce long-term brain changes, 6 months was chosen to allow sufficient time for the brain to exhibit improvement that could be captured by the outcome measure tools.

The three-month exit visit allows us to assess whether changes in brain wave activity and other neurocognitive measures persist after withdrawal of oil.

9.2. Outcomes

9.2.1. Primary outcome

9.2.1.1. Attention performance

C7 provides a spectrum of short-term (hours to days) and long-term (over 6 months) benefits in subjects with G1D as measured by a 0.5 SD improvement in performance on the primary attention measure both in the acute and long-term.

Subjects receiving C7 supplementation will experience a significant (0.5 SD) improvement in performance on the primary attention measure for each subject's age group.

9.2.2. Secondary outcomes

9.2.2.1. EEG

C7 provides a spectrum of short-term (hours to days) and long-term (over 6 months) benefits in subjects with G1D as measured by a decrease in abnormal EEG activities as defined above both in the acute and long-term.

9.2.2.2. Other neuropsychological and neurological performance, such as ataxia.

Subjects undergoing C7 supplementation will experience improvements in neuropsychological and neurological performance over the long term. Subjects will experience an increase in vocabulary expression and recall in both the acute (days) and long term (months) time frames. Subjects will also experience decreases in ataxia and other neurological symptoms measured on the neurological assessment.

9.2.2.3. Safety

C7 supplementation is safe when used over the long term (6 months) period. Subjects will experience no clinically significant changes in standard laboratory measures (blood cell count, blood electrolytes, AST, ALT, blood urea nitrogen, creatinine, lipid panel, plasma glucose and beta-hydroxybutyric acid.) and exhibit no evidence of toxicity as measured by the VA Toxicity Scale.

9.3. Sample Size and Accrual

We estimated the sample size using the primary outcome (attention) for each of three age groups. The same method will be applied for sample size estimation in each of three age groups. An improvement of 0.5 SD or more on the primary attention measure

after the administration of C7 is considered a favorable outcome. This study will yield data that allow a clear go/no-go decision regarding whether C7 should proceed to an efficacy trial: If a favorable outcome occurs in less than 50% of subjects, we will recommend that C7 not proceed to an efficacy trial. If a favorable outcome occurs in at least 80% of subjects, we will recommend that C7 proceed to an efficacy trial.

The sample size was estimated using Simon's optimal two-stage design (24). The null hypothesis that the proportion of favorable outcome is 50% will be tested against a one-sided alternative hypothesis that the proportion of favorable outcome is 80%. In the first stage, 7 subjects will be accrued. If there are 4 or fewer favorable outcomes in these 7 subjects, the study will be stopped, and we will recommend that C7 not proceed to an efficacy trial. Otherwise, 6 additional subjects will be accrued for a total of 13 subjects. If 8 or fewer favorable outcomes are observed in 13 subjects by the end of stage two, then no further investigation of C7 is warranted. This design yields a type I error rate of 0.1 and power of 80% when the true favorable outcome occurs in 80% of subjects. We plan to recruit 15 subjects with an expected 15% dropout rate resulting in 13 subjects for each age group. That is, we will recruit a total of 45 subjects for this protocol.

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.

Data and safety 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

Summary descriptive statistics: 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 and medians and semi-interquartile 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.

Primary Aim: The primary aim is demonstrating the benefit of C7, as measured by a change in performance on the primary attention measure for each age group. The proportion of subjects who achieved favorable outcome will be estimated along with the corresponding 95% confidence interval using an exact binomial method. We will also investigate if there will be significant differences in the proportions of favorable outcomes among three age groups using Fisher's exact test. We will make every effort to minimize the missing data. We expect minimal amount of missing data. If missing data occurs, missing data will be imputed using multiple imputation techniques. Generalized estimating equation (GEE) analysis will be used to examine if C7 positively affects other neuropsychological (e.g., IQ, language, processing speed) and neurological performance, such as ataxia over time (baseline, 6 months, and 9 months).

Secondary Aim: A secondary aim is to evaluate the effect of C7 supplementation of a regular diet on an EEG activity and to evaluate the safety of C7 supplementation. EEG will be analyzed in 3 ways (spike-wave duration, total number of seizures and background of the EEG as described above). GEE analysis will be used to examine if there are significant changes in EEG activity and safety over time. GEE analysis will be also conducted to investigate whether attention neuropsychological scores correlate with the EEG findings.

Study end. Statistical analyses at the end of the study will examine the initial measures at baseline, 6 months, and 9 months. Repeated measurement data will be analyzed using the generalized estimating equation (GEE) approach. The GEE method has been widely used for the analysis of repeated measurement data because of its robustness to random missing and misspecification of the true correlation structure.

SAS V9.4 (SAS Institute, Inc. SAS V9.4, Cary, NC, 2014) will be used to analyze the data.

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 completed at Children's Medical Center, and neurological evaluations done at each visit) 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.

Neuropsychological test forms are not part of the medical records. Results from these tests will become part of the subject's research record, but source documents will be maintained by the Department of Psychology at Children's Medical Center in accordance with internal privacy laws, and are subject to a greater level of confidentiality than the primary medical record.

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; see Attachment). 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 serious 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's Center for Devices and Radiological Health 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 product(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 (Appendix I) 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 at every visit in order to monitor for any changes in patient health status.

Benefits potentially include a reduction in daily seizure activity, 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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