A Pilot Trial of Triheptanoin for People with Amyotrophic Lateral Sclerosis (PALS)

NCT03506425

Duke IRB Number: Pro00092250

Protocol Version 1.3

December 14, 2017

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1 PURPOSE/HYPOTHESES

1.1 Purpose

The purpose of this pilot study is to determine if Triheptanoin is safe and tolerable in people with ALS, and if it is associated with any promising changes in a clinical measure of disability or biomarkers of cellular energetics or oxidative stress.

1.2 Primary Hypothesis

The primary hypothesis is that Triheptanoin is associated with at least a 20% slowing in disability progression as measured by revised ALS functional rating scale (ALSFRS-R) in people with amyotrophic lateral sclerosis (PALS).

1.3 Secondary Hypotheses

Secondary hypotheses are as follows:

1. Triheptanoin favorably alters MR spectroscopy in PALS
2. Triheptanoin favorably alters serum and urinary biomarkers of mitochondrial function and oxidative stress in PALS
3. Triheptanoin is safe and well tolerated in PALS.

2 BRIEF BACKGROUND

Amyotrophic Lateral Sclerosis (ALS) is a degenerative motor neuron disease characterized by rapidly progressive disability and shortened survival (1). PALS lose about a point per month on a 48-point functional rating scale, and their median survival is 3 years from symptom onset (2). While symptomatic care has improved, there remains no treatment that can meaningfully slow ALS progression or prolong survival (1).

The causes of ALS are largely unknown. However, mitochondrial dysfunction, resulting in impaired energy production, oxidative stress and apoptosis, may play a key role in ALS progression (3). Triheptanoin can improve mitochondrial function and energy production and therefore has potential for slowing ALS progression (reviewed in reference 3). Indeed, triheptanoin slowed motor neuron loss and delayed the onset of weakness in a mutant SOD1 model of ALS (4).

3 DESIGN & PROCEDURES

3.1 Design Overview

This is an open label, prospective cohort study of 10 PALS from the Duke ALS Clinic (5). The first 5 enrolled PALS (Group 1) will receive standard ALS care for the first month, then standard care plus Triheptanoin for the next 5 months. The next 5 enrolled PALS (Group 2) will receive standard ALS care plus Triheptanoin for 6 months (Figure 1). All Group 1 and Group 2 PALS who complete this 6-month study will have an option for Triheptanoin treatment extension for an

additional 12 months. In addition to the PALS, there will also be 5 healthy controls enrolled (Group 3), people that do not have ALS or any other neurodegenerative disease). These participants will not receive any treatment; the only outcome measure they will complete is serum and urine biomarker testing at screening/baseline, month 1 and month 6 (Figure 1).

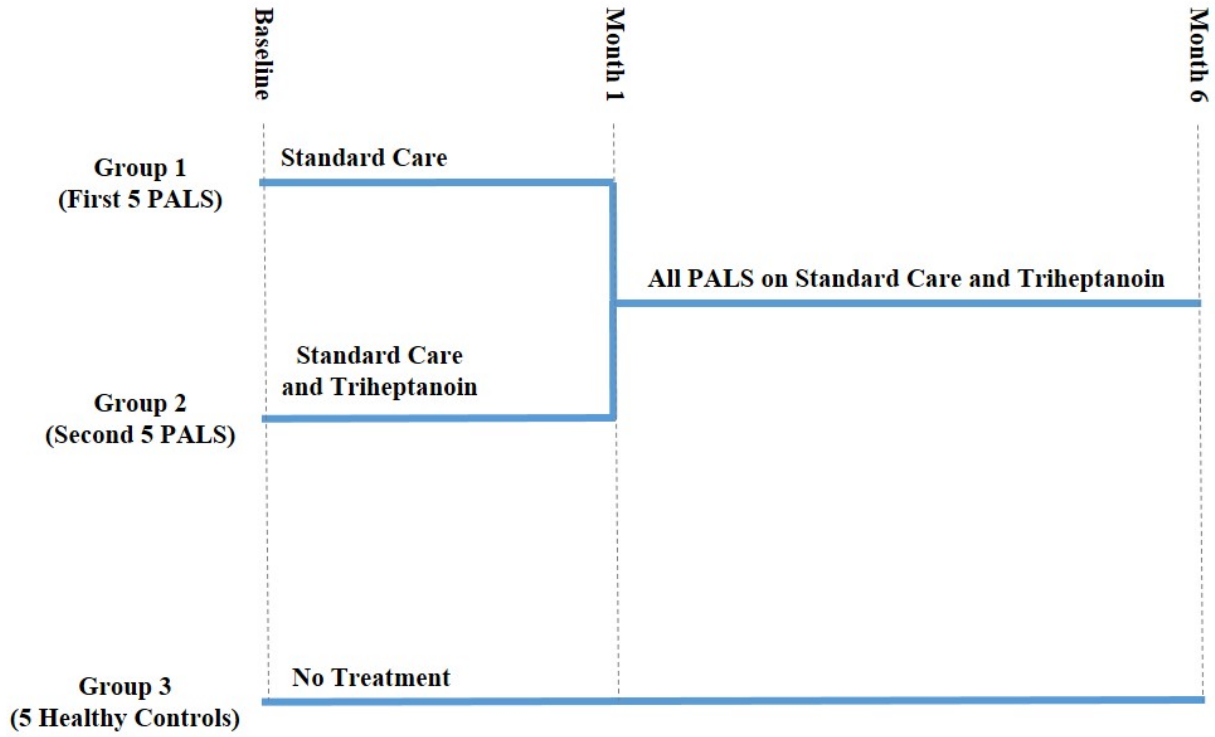

Figure 1: Study Treatment Schema

Human trials with Triheptanoin have demonstrated an excellent safety profile, with only rare associated gastrointestinal side effects (see the provided copy of Ultragenyx's Investigator's Brochure (IB) and references 6-9). However, it has never been studied in PALS. To mitigate the risks of rare gastrointestinal side effects, all our participants will be followed by a nutritionist for the duration of this study.

3.2 Study Population

Participants will be patients in the Duke ALS Clinic that meet the following criteria.

Inclusion:

1. Lab supported probable or more definite ALS by El Escorial Criteria
2. Age greater than or equal to 18 years
3. Willing and able to provide informed consent
4. On riluzole at a stable dose for at least 30d or not taking this
5. On Radicava at a stable dose for at least 30d or not taking this
6. Life expectancy at least 6 months

7. Currently managed on a reasonably stable diet, avoidance of fasting, carnitine or medium chain triglyceride (MCT) oils
8. Must stop any other experimental ALS treatment for at least 30 days prior to screening
9. If sexually active, must agree to use contraceptive or abstinence for duration of treatment with triheptanoin
10. Females of child bearing age must have negative pregnancy test at screening

Exclusion:

1. Unwilling or unable to provide informed consent
2. Previous intolerance or adverse reaction to triheptanoin or MCT
3. Conditions that will prohibit MRI scanning (metal in eye, some surgical implants, claustrophobia, inability to lie supine)
4. Have any other co-morbid conditions that in the opinion of the study investigator, places the participant at increased risk of complications, interferes with study participation or compliance, or confounds study objectives

There will also be 5 healthy controls (adults without ALS or any other neurodegenerative disease) enrolled.

3.3 Treatment Regimen

There will be 2 treatment Groups (Figure 1). Five PALS (Group 1) will be on standard care for 1 month, then standard care and Triheptanoin for 5 months. Five PALS (Group 2) will be on standard care and Triheptanoin for 6 months. The rationale for delaying triheptanoin treatment in one group is to look for differences in MR spectroscopy related to treatment at the 1 month time point. The target triheptanoin dose for this study is 1g/kg/d. This target dose was selected because it was safe and tolerable and altered brain MR spectroscopy in patients with Huntington's Disease (10). Participants will taper up to this dose as follows: start at 0.25g/kg/d for 1 week, then take 0.5g/kg/d for 1 week, then take 1g/kg/d and stay on this dose for the duration of the study. Triheptanoin will be administered orally with food or by gastrostomy tube over 3 divided doses (breakfast, lunch, and dinner). If at any point after week 1 a participant does not appear to be tolerating their current dose, it will be reduced by 0.25g/kg/d. If they cannot tolerate the starting dose of 0.25g/kg/d, the treatment will be discontinued. A dietician will make contact with all participants every month, either in person or by telephone, to try and maximize compliance. All PALS in Groups 1 and 2 who complete the 6-month trial, regardless of their MR spectroscopy results, will have the option for treatment extension for an additional 12 months.

3.4 Trial Procedures and Assessments

The intervention being studied is treatment with Triheptanoin. The procedures and assessments being performed include consent, screening for inclusion and exclusion criteria, dispensing study drug for consented patients who pass screening, obtaining vital signs, obtaining demographics and disease characteristics, obtaining weight, performing a brief physical and neurological exam, adverse event monitoring, review of concomitant medications, safety labs, pregnancy testing, ALSFRS-R, MRI spectroscopy, serum and urine biomarkers of energetics and oxidative stress.

The schedule for these procedures are outlined in Table 1, and a description of why they are important, are provided in the Outcome Measures in Section 3.5.

Table 1: Schedule of Events for Group 1 and 2

	Screening/ Baseline Visit	**Month 1 Visit**	**Month 2 Phone Call**	**Month 3 Visit**	**Month 4 Phone Call**	**Month 5 Phone Call**	**Month 6 Visit**	**Extension Month 6 and 12 Phone Calls**
Consent	X							
Inclusion/ Exclusion	X							
Dispense Drug	(Group 2 only)	X		X			X	
Vitals	X	X		X			X	
Demographics and Disease Characteristics	X							
Weight	X	X		X			X	
Physical Exam	X	X		X			X	
Adverse Event Monitoring*	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	
Neuro Exam	X	X		X			X	
Safety Labs	X	X		X			X	
Pregnancy Test	X	X					X	
ALSFRS-R	X	X	X	X	X	X	X	X
MRS	X	X						
Serum and Urine Biomarkers	X	X					X	

	Screening/ Baseline Visit	Month 1 Visit	Month 2 Phone Call	Month 3 Visit	Month 4 Phone Call	Month 5 Phone Call	Month 6 Visit	Extension Month 6 and 12 Phone Calls
Dietician Contact (may be in person or telephone)	X	X	X	X	X	X	X	

*Adverse event screening will be captured throughout the protocol and the extension period, and continue for an additional 4 weeks following the last dose of study medication.

Table 2: Schedule of Events for Group 3

	Screening/Baseline Visit	Month 1 Visit	Month 6 Visit
Consent	X		
Serum and Urine Biomarkers	X	X	X

3.5 Outcome Measures

3.5.1 Primary Outcome Measure

The primary outcome measure is the ALSFRS-R score obtained monthly for all treated participants (in person at screening/baseline, month 1, month 3 and month 6; via telephone at months 2, 4 and 5). We will also obtain this measure by phone at months 6 and 12 of the extension. For all enrolled PALS in Groups 1 and 2, we will compare the slope of ALSFRS-R progression before enrollment to the slop of ALSFRS-R progression during the trial (see Section 3.6 below). ALSFRS-R is a quickly administered (five minute) ordinal rating scale (ratings 0-4) used to determine patients' assessments of their capability and independence in 13 functional activities. All 13 activities are relevant in ALS. Initial validity was established in ALS patients by documenting their change in ALSFRS-R scores, which correlated with change in strength over time, was closely associated with quality of life measures, and predicted survival (2,11,12). The test-retest reliability is greater than 0.88 for all 13 activities. The ALSFRS-R declines linearly with time over a wide range during the course of ALS. The minimum clinically significant change in this scale is said to be 20% (2,11-13). The measure can be reliably conducted over the phone (13).

3.5.2 Secondary Outcome Measures

Secondary outcome measures include:

MR Spectroscopy NAA/Cr ratio in motor cortex will be measured at screening/baseline and 1 month time points. This measure declines over time in patients with ALS (14-17). This measure can respond to treatment; it was shown to improve over 3 weeks in patients with ALS on riluzole compared to a group that was not on this treatment (18). We will compare the MR spectroscopy changes over 1 month in Group 1 to the MR spectroscopy changes over 1 month in Group 2.

A Serum and Urine Biomarker Panel will be obtained at screening/baseline, 1 month and 6-month time points and analyzed using liquid chromatography/tandem mass spectrometry. Laboratory, pathologic, and epidemiologic evidence clearly supports the hypothesis that oxidative stress is central in the ALS pathogenic process, particularly in genetically susceptive individuals (19). Oxidative stress biomarkers in cerebrospinal fluid, plasma, and urine are elevated, suggesting that abnormal oxidative stress is generated outside of the central nervous system. Magnitude of lipid peroxidation, measured as non-enzymatic oxidation products of arachidonic acid, F2-isoprostanes, appears the most obvious oxidative stress marker. We will measure urine F2-isoprostane metabolites (class III: iPF2α-III, and 2,3-dinor iPF-2alpha-III, class VI: iPF-2alpha-VI, and 8,12-iso-iPF-2alpha-VI), urine creatinine, and serum and urine glutamate, a-keto-glutarate, NADH, coenzyme A levels in all treated participants and healthy controls at screening/baseline, month 1 and month 6 time points. We will compare the biomarker changes at different time points between Groups 1, 2 and 3.

For safety monitoring: concomitant medications, vital signs, weight, physical exam and safety labs (CBC, CMP, Lipid Profile, GGT, LFT and pregnancy testing for sexually active females with child bearing potential) will be measured at screening/baseline, 1 month, 3 month, and 6-month time points. Adverse events will be monitored continuously throughout the study, as described in Section 5.1.

3.6 Statistical Analysis

The primary analysis is the slope of the revised ALSFRS-R during treatment compared to pre-treatment. Pre-treatment slope for each participant will be estimated as follows: (48-enrollment ALSFRS-R)/months since symptom onset. This frequently used “pre-slope” method is simple and inexpensive, and can predict disease progression as well as more complicated and expensive tools, at least for periods of less than 1 year (20).

Table 3 shows the results for the power analysis assuming that 10 patients are included in the clinical trial. The power of a test is defined as probability of the statistical test to reject a false null hypothesis, thus it quantifies the ability of a test to detect an effect, if the effect actually exists. In Table 3, the power is expressed as a percentage and the standard deviation is given in parenthesis. The number of observations were assumed to occur one per month after the beginning of the trial. The percentage of change in the slope of ALSRFRS-R as function of time is measured against the pre-trial rate of decline. For each combination of slope percentage change and number of observations, 1000 samples were randomly generated assuming the following parameters:

- The ALSFRS-R score at the beginning of the treatment was uniformly distributed in the range [2, 40].
- The pre-trial slope was log-normally distributed with mean 0.90 (per month), and standard deviation 0.27. Thus, the range of pre-trial slopes is approximately [0.25, 3.38].
- The measurement error for the ALSRFRS-R was assumed to be normally distributed with zero mean and standard deviation 0.7. This way the inter-quartile range is approximately [-0.5, 0.5].

Table 3: Power Analysis Based on 10 Patients. Power percentage along with standard deviation in parenthesis for detecting a change in the slope of ALSFRS-R with respect to time using 10 patients in a clinical trial setting. The power is given as function of both the number of observations and the percentage of change in the slope.

Number of observations (per patient)	Slope percentage change (compared to pre-trial rate of decline)				
	10%	20%	30%	40%	50%
4	5.8 (0.7)	21.6 (1.3)	49.4 (1.6)	78.8 (1.3)	94.8 (0.5)
5	9.7 (0.9)	44.6 (1.6)	81.8 (1.2)	97.2 (0.5)	99.6 (0.7)
6	19.4 (1.3)	69.9 (1.5)	97.5 (0.5)	99.9 (0.1)	100.0 (0.0)
7	30.3 (1.5)	88.2 (1.0)	99.7 (0.2)	100.0 (0.0)	100.0 (0.0)

The results indicate that a 20% change in the slope, compared to pre-trial rate of decline, can be detected with power 88.2% (1.0%) with 7 observations (six months trial - baseline observation plus one observation monthly).

4 STUDY DRUG

Triheptanoin is a medium chain triglyceride (MCT) that can improve mitochondrial function and energy production and therefore has potential for slowing ALS progression (reviewed in reference 3). Indeed, triheptanoin slowed motor neuron loss and delayed the onset of weakness in a mutant SOD1 model of ALS (4). The Triheptanoin we will use is a colorless to light yellow oil. The target triheptanoin dose for this study is 1g/kg/d. This target dose was selected because it was safe and tolerable and altered brain MR spectroscopy in patients with Huntington's Disease (10). Participants will taper up to this dose as follows: start at 0.25g/kg/d for 1 week, then take 0.5g/kg/d for 1 week, then take 1g/kg/d and stay on this dose for the duration of the study. Triheptanoin will be administered orally with food or by gastrostomy tube over 3 divided doses (breakfast, lunch, and dinner). If at any point after week 1 a participant does not appear to be tolerating their current dose, it will be reduced by 0.25g/kg/d. If they cannot tolerate the starting dose of 0.25g/kg/d, the treatment will be discontinued. A dietician will make contact with all participants every month, either in person or by telephone, to try and maximize compliance.

Additional details about this drug are available in the accompanying IB.

5 SAFTEY & ADVERSE EVENTS

5.1 Adverse Events Monitoring

All adverse events (AEs), whether observed by the Investigator, elicited from the participant or volunteered by the participant, and whether ascribed to the drug or not, will be recorded. This will include the following: a brief description of the event, the date of onset, the date of resolution, the duration and type of the event, the severity, contributing factors and any action taken with respect to the study drug. This recording will commence following informed consent, and with the initiation of protocol-specific procedures and continue at each study visit or telephone contact until 4 weeks following the last study related visit.

For each adverse event, the relationship to the study drug will be recorded as one of the choices on the following scale:

DEFINITE Causal relationship is certain (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated and the event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge procedure if necessary).

PROBABLE High degree of certainty for causal relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge [re-challenge is not required] and other causes have been eliminated or are unlikely).

POSSIBLE Causal relationship is uncertain (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, de-challenge/re-challenge information is either unknown or equivocal and while other potential causes may or may not exist, a causal relationship to the study drug does not appear probable).

UNLIKELY Not reasonably related, although a causal relationship cannot be ruled out (i.e., while the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug).

NOT RELATED No possible relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible).

The severity of each adverse event must be recorded as one of the choices on the following scale:

MILD	No limitation of usual activities
MODERATE	Some limitation of usual activities
SEVERE	Inability to carry out usual activities

The expectedness of an AE must be indicated when reporting adverse events. An unexpected adverse event is any adverse experience for which the specificity or severity of the event is not consistent with the current IB.

5.1.1 Reporting of Serious Adverse Events

A serious adverse drug event (SAE) is defined as any adverse event that occurs during the study that results in any of the following outcomes: death, a life-threatening adverse event (i.e., the participant was at immediate risk of death from the event as it occurred; does not include an event, that had it occurred in a more severe form, might have caused death), inpatient hospitalization or prolongation of existing hospitalization (hospitalizations scheduled before enrollment for an elective procedure or treatment of a pre-existing condition which has not worsened during

participation in the study will not be considered a serious adverse event), a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions), a congenital anomaly/birth defect, a medically important event or required medical intervention to avoid one of the above outcomes. In addition to the above procedures for AEs, all SAEs will be reported to the IRB within 24 hours of recording. All serious adverse event information will be followed until resolution or an appropriate end point is reached. This may involve contacting other clinicians responsible for the participant's care to obtain information on diagnoses, investigations performed and treatment given.

Institution and Sponsor-Investigator are responsible for the identification, collection, reporting and documentation of SAEs in patient(s) participating in the Protocol. Institution and Sponsor-Investigator are responsible for complying with all Applicable Laws concerning the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the IRB and regulatory authorities (FDA), in accordance with 21 CFR 312.32, in connection with the Protocol. Notwithstanding the foregoing, Institution and Sponsor-Investigator shall comply with IRB reporting instructions and all Applicable Laws regarding SAE reporting.

The Sponsor-Investigator shall collect AEs and SAEs for patient(s) receiving Investigational Product at the Institution as per protocol. Sponsor-Investigator shall record seriousness, causality and expectedness assessments for each AE as per Institution's policies. All SAEs provided to Ultragenyx must have the Sponsor-Investigator's assessment of seriousness, causality and expectedness. Events not listed in the Investigator Brochure (IB) are considered "unexpected" and events listed in the IB are considered "expected." The Institution and/or Sponsor-Investigator is responsible for determining the reportability of each assessed SAE. All SAEs considered by the Sponsor-Investigator as unexpected per the IB, and Investigational Product related, must be reported as a SUSAR by the Sponsor-Investigator to the FDA and IRBs in accordance with Applicable Laws.

All SUSARs shall be reported to FDA and Ultragenyx by completing and submitting MedWatch 3500A form. Safety reports must be as complete as possible, at minimum including the SAE term(s), patient identifier, seriousness criteria, date of event onset, causality and expectedness assessment between each reported SAE term and Investigational Product, and name of the reporter (Sponsor-Investigator). Information not available at the time of the initial report shall be documented on a follow-up report and submitted to Ultragenyx (and/or regulatory authorities, IRBs, accordingly) as specified in Table 4. Additional information shall include SAE stop date(s), outcome for each reported SAE, dates when Investigational Product was first received and the last dose prior to event onset, and action taken with Investigational Product as a result of the SAE. If applicable, the Institution and/or Sponsor-Investigator protocol number shall be included in all MedWatch Form 3500A or CIOMS I reports.

SAEs with fatal and/or life-threatening outcomes occurring during treatment, regardless of causality or expectedness shall be reported to Ultragenyx within 7 calendar days of event knowledge. In addition, SAEs meeting SUSAR criteria, as defined by Applicable Laws and regulations, occurring during treatment, shall be reported to FDA and Ultragenyx within 15 calendar days of event knowledge. The Sponsor-Investigator must also notify the IRB of the SAEs in accordance with IRB requirements and Applicable Laws and regulations.

Institution and/or Sponsor-Investigator shall submit all initial and follow-up SUSAR reports to the FDA, IRBs, and Ultragenyx within regulatory defined timeframes. Final versions of the initial fatal and/or life-threatening SUSAR reports will be submitted as soon as possible but no later than 7-calendar days of first knowledge of the event, and follow-up information will be submitted within an additional 8-calendar days to the FDA, IRB and Ultragenyx. All other SUSARs will be submitted to the FDA, IRB and Ultragenyx within 15-calendar days of first knowledge of the event. Reports shall not be delayed due to incomplete information, which can be supplied as follow-up at a later time. Sponsor-Investigator shall record non-serious adverse events per Institution's clinical procedures. Where there is any doubt or debate relating to whether an AE is serious or non-serious, the AE shall be treated as an SAE until information is received to clarify seriousness. Sponsor-Investigator shall cooperate with Ultragenyx in any request for information on SAE reporting related to the Protocol. Ultragenyx will not be responsible for reporting safety information from treatment of patient(s) by Sponsor-Investigator or Institution to the Health Authorities.

The following timeframes shall apply to both initial and follow-up reports unless otherwise specified:

Sponsor-Investigator shall send to Ultragenyx final copies of initial and follow-up SAE reports within the timeframes specified in Table 4 using FDA MedWatch Form 3500A.

Table 4: Reporting Timeframe from Sponsor-Investigator to Ultragenyx

Type of Report	Reporting Timeframe from Sponsor-Investigator to Ultragenyx	Format
Suspected Unexpected Serious Adverse Reactions – Fatal and Life-threatening	Final report no later than **7 calendar days** from Sponsor-Investigator event knowledge with an additional 8 calendar days for follow-up report.	FDA MedWatch 3500A)
Suspected Unexpected Serious Adverse Reactions – other serious criteria	Final report no later than **15 calendar days** of Sponsor-Investigator event knowledge.	FDA MedWatch 3500A
Suspected Unexpected Serious Adverse Reactions – Follow-up reports	No later than **15 calendar days** after Sponsor-Investigator receipt of follow-up information (see follow-up requirements above for fatal/life-threatening SUSAR)	FDA MedWatch 3500A
Non-SUSAR SAEs - regardless of relatedness to the Product	No later than **30 calendar days** from Sponsor-Investigator event knowledge	FDA MedWatch 3500A and SAE line listing

Type of Report	Reporting Timeframe from Sponsor-Investigator to Ultragenyx	Format
Annual Safety Report	Provided in parallel with submission to regulatory authorities	Annual Safety Report

Ultragenyx shall provide the Institution and/or Sponsor-Investigator copies of SUSARs received from other clinical trials or expanded access using the same Investigational Product as specified in Table 5.

Table 5: Reporting Timeframe from Ultragenyx to Institution and/or Sponsor-Investigator

Type of Report	Reporting Timeframe from Ultragenyx to Institution and/or Sponsor-Investigator	Format
Suspected Unexpected Serious Adverse Reactions – Fatal and Life-threatening*	No later than **7 calendar days** from Ultragenyx event knowledge	FDA MedWatch 3500A
Suspected Unexpected Serious Adverse Reactions – other serious criteria*	No later than **15 calendar days** from Ultragenyx event knowledge	FDA MedWatch 3500A
Suspected Unexpected Serious Adverse Reactions – Follow-up reports*	No later than **15 calendar days** after Ultragenyx receipt of follow-up information	FDA MedWatch 3500A
Investigational Product Investigator Brochure (including safety attachments, as appropriate)	Within **15 calendar days** of final update	Email to Sponsor-Investigator

*SUSARs from Ultragenyx-sponsored studies using the same Investigational Product (cross-reporting to Sponsor-Investigators)

Should Ultragenyx require additional information on a SAE, Ultragenyx may send a request to the Institution and Sponsor-Investigator for follow-up as appropriate. Institution and Sponsor-Investigator shall use reasonably diligent efforts to conduct follow up activities on SAE reports in accordance with their standard operating procedures and in compliance with all Applicable Laws.

Institution and Sponsor-Investigator shall transmit to Ultragenyx the information required pursuant to the above provisions by facsimile, e-mail or other agreed-upon electronic means. If the volume of pages is deemed too large for reasonable electronic transmission, the information will be sent by expedited courier service.

All SUSARs and SAEs shall be documented and provided to Ultragenyx/designee using the FDA MedWatch Form 3500A or CIOMS I form (non-US) within the timeframes set forth in Table 4.

Contact information:
Ultragenyx Pharmaceutical/designee
eFax: 1.415.930.4033
email: Ultragenyx@PrimeVigilance.com

For other safety related correspondence including providing of annual safety reports:

Contact information:
Ultragenyx Drug Safety and Pharmacovigilance
eFax: 415.299.8985 or 1.888.866.5771
email: DrugSafety@ultragenyx.com

The Sponsor-Investigator is also responsible for providing Ultragenyx all final SAE and SUSAR reports submitted to regulatory authorities via the contact information listed above. The report must be completed on a FDA MedWatch Form 3500A. Ultragenyx reserves the right to review SUSAR reports, SAE reports or source documents pertaining to Protocol safety reports in response to any regulatory authority inquiries received.

SUSARs shall not be considered addendums to the IB until a formal update to the IB is made by Ultragenyx.

As per Applicable Laws, the Institution and/or Sponsor-Investigator are responsible for the development and submission of annual safety reports to regulatory health authorities and IRBs as it pertains to the overall conduct of the specific Protocol. The Institution and/or Sponsor-Investigator shall provide Ultragenyx a copy of the annual safety report in parallel to its submission to regulatory authorities.

Ultragenyx shall provide the Institution and/or Sponsor-Investigator a copy of the IB and any revisions within the specified timeframe (Table 5).

Ultragenyx will be responsible for the conduct of surveillance and safety signal detection activity using the Global Safety Database and ad-hoc reports in accordance with Ultragenyx sponsored study procedures and will notify Sponsor-Investigator of safety signals that do, or may, affect the safety profile of the Investigational Product, taking into consideration the urgency of the matter and the Applicable Laws.

Ultragenyx and Sponsor-Investigator shall promptly inform each other of all adverse event information relating to Investigational Product, including but not limited to, safety issues that either party becomes aware of or material safety-related regulatory queries from regulatory authorities taking into consideration the urgency of the matter and the Applicable Laws. The Sponsor-Investigation will submit an IND Safety Report for any SUSARs, according to 21 CFR 312.32, when informed of such event by Ultragenyx. Ultragenyx may request assistance from Sponsor-Investigator to evaluate and investigate such safety information and Sponsor-Investigator undertakes to use reasonably diligent efforts to promptly investigate and respond to Ultragenyx's requests.

Sponsor-Investigator shall be solely responsible for regulatory submissions of AEs and SAEs in regards to the Sponsor-Investigator's regulatory health authority approval and IRB in accordance with the Applicable Laws.

5.2 Data & Safety monitoring

Adverse events will be continuously tracked throughout the study as described above and below. There is no formal safety monitoring plan or DSMB, nor are there any formal stopping rules. Patients who do not tolerate triheptanoin (as described in Section 3.3) will be encouraged to continue in the protocol off-treatment. PI will review and sign off on all adverse events and promptly report these to the IRB.

5.3 Good Clinical Practices and Human Subjects Protection Training

The investigator and coordinator involved with the conduct of this study will be certified in Good Clinical Practices (GCP) and Human Subjects Protection training. Human Subjects Protection training certification will be obtained by completing approved training, such as the online computer based training offered by the NIH Office of Human Subjects Research (*http://ohsr.od.nih.gov*).

6 DATA COLLECTION AND MANAGEMENT

6.1 Database

Data will be collected on paper case report forms. Each participant's paper case report forms will be stored in a paper binder. Data from paper forms will be transferred to electronic case report forms (eCRFs) in a newly created RedCap electronic database.

6.2 Data Handling and Record Keeping

The Site Investigator (SI) is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the eCRF derived from paper case report forms should be consistent with these and discrepancies should be explained.

6.3 Confidentiality and Storage

Participants will be assigned unique study identification numbers. All forms and samples will be identified only by these numbers. The identification key and all study binders will be kept in a locked office. The study database will be password protected, and stored on a password protected computer. No identifiable information on study participants will leave Duke University.

7 REFERENCES

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