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RESEARCH**

APPLICATION NUMBER:

213687Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	213687
Priority or standard	Standard
Submit date(s)	7/31/2019
Received date(s)	7/31/2019
PDUFA goal date	6/30/2020
Division/office	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Review completion date	6/30/2020Click or tap to enter a date.
Established name	Triheptanoin
(Proposed) trade name	Dojolvi
Pharmacologic class	Small Molecule
Code name	Medium-chain triglyceride
Applicant	Ultragenyx
Dose form/formulation(s)	Oral Liquid
Dosing regimen	Up to 35% daily caloric intake (DCI)
Applicant proposed indication(s)/population(s)	(b) (4) for the treatment of adult and pediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD) (b) (4)
Proposed SNOMED indication	39929009 Disorder of fatty acid metabolism
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	Indicated as a source of calories and fatty acids in the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD)
Approved SNOMED indication	39929009 Disorder of fatty acid metabolism

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Glossary

AE	adverse event
AER	annualized event rate
AED	annualized event duration
AG	Andersen and Gill model
AUC	area under the concentration-time curve
BHB	beta-hydroxybutyrate
BHP	beta-hydroxypentanoate
BLQ	below the level of quantitation
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatinine kinase
C _{max}	maximum plasma concentration
CM	cardiomyopathy
CMC	chemistry, manufacturing, and controls
CACT	carnitine-acylcarnitine translocase
CPT	carnitine palmitoyltransferase
DCI	daily caloric intake
EA	expanded access
ECG	electrocardiogram
ECHO	echocardiogram
FDA	Food and Drug Administration
GD	gestation day
GLP	good laboratory practice
GLUT-1	glucose transporter 1
HDPE	high-density polyethylene
IND	investigational new drug
IST	investigator-sponsored trial
KO	knockout
LC-FAOD	long-chain fatty acid oxidation disorders
LCHAD	L-3-hydroxy-acyl-CoA dehydrogenase
LD	lactation day
LVEF	left ventricular ejection fraction
MCE	major clinical event
MCS	mental component score
MCT	medium-chain triglyceride
NBR	negative binomial regression
NDA	new drug application
NOAEL	no observed adverse effect level
OHSU	Oregon Health and Science University
OSI	Office of Scientific Investigation
PCS	physical component score
PD	pharmacodynamics
PK	pharmacokinetics

NDA 213687
Dojolvi (triheptanoin)

PMR	postmarketing requirement
PSS	psychosocial health summary
PVC	polyvinyl chloride
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	status epilepticus
TCA	tricarboxylic acid
TEAE	treatment-emergent adverse event
TEE	total energy expenditure
TFP	trifunctional protein
T _{max}	time to maximum concentration
TK	toxicokinetic
UX007	investigational study drug (triheptanoin)
VLCAD	very long-chain acyl-CoA dehydrogenase

I. Executive Summary

1. Summary of Regulatory Action

The available data are adequate to support the approval of triheptanoin as “a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD).” However, the available data are not adequate to support the Applicant’s proposed claims that triheptanoin reduces major clinical events (MCEs) [REDACTED] (b) (4). The data also do not support the Applicant’s requests for a priority review or a pediatric priority review voucher.

Evidence of efficacy for triheptanoin as a source of calories and fatty acids is based upon one clinical investigation supported by the available scientific knowledge about medium-chain triglycerides (MCTs). The review team concluded that the Gillingham et al. trial was adequate and well-controlled to support the more limited indication of triheptanoin as a source of calories and fatty acids (Gillingham et al. 2017).

Evidence of safety is derived from studies UX007-CL201/UX007-CL202 and is supported by expanded access narratives.

The review team concludes that the benefits of a pharmaceutical grade source of calories and fatty acids outweigh the risks of gastrointestinal symptoms in patients with LC-FAOD. The review team exercised considerable regulatory flexibility in reaching this conclusion. First, the Gillingham trial was underpowered to establish true noninferiority between MCT oil and triheptanoin. Second, knowledge regarding the use of MCTs in the treatment of LC-FAOD is limited, as the use of MCT oil has not been studied in randomized trials apart from the Gillingham trial. The uncertainty regarding benefit is acceptable in this case because of the serious, life-threatening nature of the disease with no current FDA-approved treatment options, and because the uncertainty is balanced by acceptable certainty regarding the safety profile.

The review team concluded that it would be misleading to rely on study UX007-CL201 to claim that triheptanoin reduces major clinical events [REDACTED] (b) (4).

[REDACTED] as study UX007-CL201 was neither adequately conducted nor well-controlled for these purposes. The study did not use a design that permits a valid comparison with a control; did not employ a method of assigning patients to treatment and control groups such as randomization that minimizes bias; and did not take adequate measures such as blinding to minimize bias on the part of the subjects, observers, and analysts of the data. Furthermore, the definitions for clinical events used to assess the subjects’ response to treatment were vague and not well-defined and reliable, and it was unclear whether they were applied consistently across the retrospective and prospective study periods.

FDA does not find it acceptable to rely on the open-label, single-arm design chosen for study UX007-CL201 when designs providing more scientific certainty are potentially feasible.¹ Acceptance of these study designs imposes implications for the next generation of drug development, payer support, and patient access. It is possible that triheptanoin reduces major clinical events (b) (4) but this is a hypothesis that awaits further testing in adequate and well-controlled trials.

The initial review of the new drug application (NDA) for triheptanoin was notable for robust disagreement within the review team regarding whether there was sufficient evidence of efficacy to support filing an NDA given the concerns for bias in study UX007-CL201 and the resulting uncertainty regarding clinical benefit. Drs. Zand, Donohue, Tracy, Russek-Cohen, and Johnson recommended a refuse-to-file action because study UX007-CL201 was not adequate and well-controlled, recommending that the Applicant should have performed a randomized study to compare the occurrence of clinical events in patients receiving triheptanoin to a control group (e.g., patients receiving MCT oil) as originally planned.

The Division and Office Directors, Drs. Roman and Beitz, favored filing the NDA for review and consideration of a more limited nutritional indication for triheptanoin, i.e., as a source of calories and fatty acids. Ultimately, the review team reached consensus that the data from the randomized Gillingham (2017) trial were adequate to support a recommendation for approval for the more limited nutritional indication. Reaching this conclusion regarding efficacy required taking the unusual step of relying exclusively on the efficacy data from the randomized Gillingham study, which was conducted by an academic investigator, funded by a grant from the FDA's Office of Orphan Products Development, and for which the Applicant obtained right of reference, rather than the data collected by the Applicant directly in study UX007-CL201. Since the results from study UX007-CL201 could not be relied upon to support efficacy, the Applicant's requests for Priority Review and a Pediatric Priority Rare Disease Voucher could not be supported. See Section [III.12](#) for the full regulatory history.

Postmarketing Requirement(s)

A pregnancy registry is recommended as a postmarketing requirement (PMR) given the lack of data regarding pregnancy outcomes, dosing, and safety in this population.

¹ Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry (December 2019), see footnotes on 505B2, <https://www.fda.gov/media/133660/download>

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of rare, autosomal recessive disorders caused by defects in nuclear genes that encode mitochondrial enzymes important for the conversion of dietary long-chain fatty acids into energy. Patients with pathogenic variants in these genes are at high risk for catabolism, which can be life-threatening. Clinically, catabolism can manifest as acute rhabdomyolysis, hypoglycemia, and hypertrophic cardiomyopathy. Some patients have more chronic symptoms of pain and fatigue from subacute rhabdomyolysis and progressive cardiomyopathy. - In a January 2019 type C patient engagement meeting, patients shared with the Division that symptoms of fatigue, muscle cramping/muscle pain, and the challenges of living with a chronic disease with recurrent clinical symptoms are the symptoms they find most burdensome and significantly impact their quality of life both physically and emotionally.²	LC-FAOD are serious and life-threatening diseases.

² DARRTS; NDA 213687, Section 1.6.3; Type CLC-FAOD Patient Engagement Meeting, January 9, 2019

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The standard of care for patients with LC-FAOD is careful dietary management under the guidance of dietitians who regularly adjust patients' diets based on age, disease severity, and overall caloric requirements. • Medium-chain triglyceride (MCT) oil is the most commonly used source of medium-chain triglyceride for LC-FAOD patients. As a dietary supplement, the percentage of medium-chain triglycerides (C6, C8, C10, or C12) in each product is not regulated and thus varies. The triglyceride thought to be most useful as an energy source is C8, the percentage of which may vary from 40% to 70% in marketed MCT oils.³ Patients appear to have different levels of tolerability to MCT oil, which may also impact adherence. Gastrointestinal side effects are common. • The degree to which MCT oil tolerability and dietary adherence may reduce the risk of metabolic events due to catabolism is unknown, as neither have ever been studied systematically in randomized trials. Since identification of the underlying genetic defects in 1970, physicians have recommended that patients increase their intake of MCTs with MCT oil, which they can metabolize, and decrease the intake of the long-chain fatty acids that they cannot metabolize (Engel et al. 1970). • Despite careful adherence to dietary recommendations and MCT oil supplementation, many patients still are hospitalized with metabolic events due to underlying catabolism.²	Many patients with LC-FAOD have life-threatening metabolic events, due to catabolism, despite adherence to available therapies such as dietary management and MCT oil supplementation. There are no FDA-approved therapies for LC-FAOD.

³ Source: DARRTS, BLA 213687, Section 2.7.3

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Triheptanoin is an MCT oil that provides 8.3 kcal/mL. • Gillingham et al. (2017) performed a double-blind trial in patients age 7 years to 64 years with mild to moderate LC-FAOD and randomized them to triheptanoin or trioctanoin at a dose of 20% of daily caloric intake (DCI). After 4 months, no clinically meaningful differences were observed between the two treatment groups in metabolic hospitalizations, cardiac function on resting echocardiogram and treadmill ergometry, or metabolic biomarkers including glucose, insulin, lactate, total serum ketones, acylcarnitines, or serum-free fatty acid concentrations. • The Applicant performed an open-label, single-arm study, UX007-CL201, in 29 patients age 11 months to 59 years with moderate to severe LC-FAOD, and treated them with triheptanoin at a dose of up to 35% of daily caloric intake. Patients were followed prospectively for 78 weeks for metabolic hospitalizations, and this was compared to the event rate in a retrospective chart review. However, records regarding dietary management during the retrospective and prospective periods were sparse, and what data are available indicate that patients' diets improved between the two periods. No measures were taken to minimize this or other important potential sources of bias in this nonrandomized study.	• The available chemistry data are adequate to support the efficacy of triheptanoin as a source of calories and fatty acids. • The lack of clinically meaningful differences observed by Gillingham et al. after 4 months of treatment with triheptanoin versus trioctanoin in LC-FAOD patients provides adequate qualitative evidence of efficacy to support the use of triheptanoin as an alternative source of MCT oil in patients with LC-FAOD. While this research study was designed with an exploratory primary endpoint, the Division found the direct comparison of the clinical course of LC-FAOD patients randomized to C8 or triheptanoin (C7) was clinically meaningful. Although purified C8 is not available for commercial use, it is a component of all MCT oils, the current standard of care for dietary management. The degree of uncertainty inherent in this qualitative assessment of benefit is acceptable as no randomized studies of MCT oil versus placebo are available. • The available data are not adequate to support the Applicant's proposed claims that triheptanoin reduces the frequency and duration of hospitalizations for major clinical events because the study was not well-controlled. Study UX007-CL201 did not use a design that permits a valid comparison with a control, did not employ a method of assigning patients to treatment and control groups that minimizes bias, did not take adequate measures to minimize bias on the part of the subjects, observers and analysts of the data, nor did it assess the subjects' response with well-defined and reliable methods.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	- The safety database included 79 patients enrolled in studies UX007-CL201 and UX007-CL202. Patients enrolled in Gillingham et al. were not included in the safety database due to the limitations of information available. Available safety data on 67 patients in expanded access INDs from birth through adulthood were reviewed. As the expanded access IND safety data were limited, it was included descriptively to support the findings from the 79 patients enrolled in studies UX007-CL201/UX007-CL202. These patients aged from 0.3 to 64 years of age and were exposed for a median duration of 22.8 months (Range of 0.1 to 41.3 months). - Adverse reactions reported in at least 5% of triheptanoin treated patients in studies UX007-CL201 and UX007-CL202 included gastroenteritis, gastrointestinal disorder, vomiting and diarrhea. - The available safety profiles from the LC-FAOD expanded access programs and Gillingham et al. were less detailed and described patients on a greater range of doses of triheptanoin, but the adverse event profile observed was similar to what was seen in studies UX007-CL201 and UX007-CL202. - Triheptanoin adheres to gastrostomy tubes (G-tubes) made of polyvinyl chloride (PVC). - Triheptanoin degrades polystyrene. - LC-FAOD patients who are catabolic can experience gastrointestinal symptoms such as nausea, emesis and diarrhea. These GI symptoms may also represent adverse events in a high-fat diet, including the diet recommended with triheptanoin in LC-FAOD patients. - In general, there is limited information on the the management of pregnancy with maternal LC-FAOD. No pregnancies were observed during the studies or expanded access INDs reviewed, so the long-term impact on fetal development is unknown.	- Overall, the safety evaluation is adequate to assess the safety of triheptanoin in patients with LC-FAOD over a dosage range of 25% to 35% DCI. The safety profile is well-characterized and none of the identified safety issues would preclude approval of triheptnaoin. - Labeling Warnings and Precautions (section 5.1) alert concerns with use of gastrostomy tubes (G-tubes) containing polyvinyl chloride and recommend routine monitoring of G-tube function. - As a patient's gastrointestinal symptoms can represent adverse events to triheptanoin or catabolism, product labeling recommends evaluation by a metabolic specialist familiar with LC-FAOD. - The impact of use of a synthetic MCT during pregnancy is unknown, and unable to be predicted from the available nonclinical data. Therefore, the Applicant will complete a 10-year pregnancy study to evaluate fetal risk.

Conclusions Regarding Benefit-Risk

Patients diagnosed with LC-FAOD are at continual risk for life-threatening episodes of catabolism, which can manifest as rhabdomyolysis, cardiomyopathy, and/or hypoglycemia. No drugs or biologics have been approved for the treatment of LC-FAOD, and current management is reliant upon dietary modification directed toward decreased ingestion of long-chain fatty acids, supplementation of medium-chain fatty acids, and sufficient intake of both calories and protein. The most commonly used dietary MCT is MCT oil, and the composition of the oil is variable, as it is not regulated in production.

A randomized, double-blind trial of 4 months compared purified trioctanoin (C8) to triheptanoin (C7) in patients clinically diagnosed with mild LC-FAOD. Patients were dosed at 20% daily caloric intake (DCI) of dietary C8 or C7. Although there were no clinical or laboratory differences between study arms, the study did demonstrate that C7 is a source of calories and fatty acids that can be used to treat LC-FAOD patients without inducing catabolism.

Interpretation of efficacy in an additional 78-week open-label study was impacted by concurrent dietary changes. Therefore, this study was primarily used to determine the long-term safety of triheptanoin in the treatment of severe LC-FAOD patients. Patients received triheptanoin at 25% to 35% DCI. Clinical events associated with catabolism (rhabdomyolysis, cardiomyopathy, hypoglycemia) did not worsen during the study and triheptanoin generally was well tolerated despite the anticipated gastrointestinal adverse events.

Expanded access (EA) narratives also were reviewed. The narratives included 11 molecularly confirmed patients who initiated triheptanoin from birth to 12 months after they were diagnosed with cardiomyopathy related to their LC-FAOD. The narratives did not contain details about diet composition, caloric intake from intravenous fluids, or concomitant medications. However, upon review of the information provided in the narratives, we conclude that triheptanoin is generally tolerated in LC-FAOD patients from birth through adulthood.

With all factors considered, the benefits of triheptanoin as a source of calories outweigh the risks for adverse events and will provide a controlled source of dietary medium-chain triglycerides for the treatment of LC-FAOD.

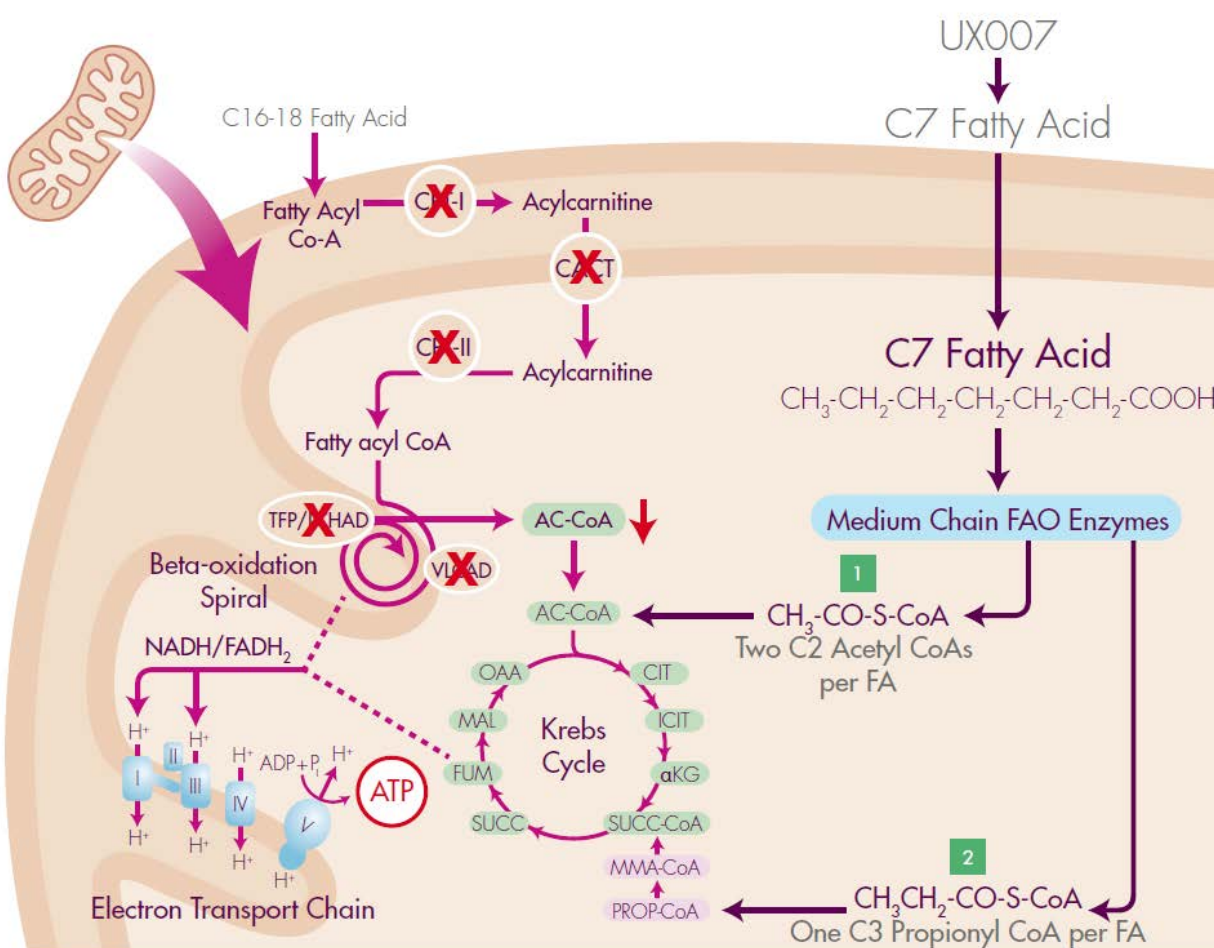
II. Interdisciplinary Assessment

3. Introduction

Drug and Mechanism of Action

Triheptanoin is a synthetic medium-chain triglyceride consisting of three odd-chain seven-carbon length fatty acids (heptanoate), initially used as an additive in butter (Pascual et al. 2014), that provides a source of calories and fatty acids for energy production and replacement.

Figure 1. Mechanism of Action of Triheptanoin in TCA Cycle Intermediates



Source: <https://www.ultragenyx.com/pipeline/UX007-faod/>

Abbreviations: αKG, α-ketoglutarate; AC-CoA, acetyl coenzyme A; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CACT, carnitine acylcarnitine translocase; CIT, citrate; CPT, carnitine palmitoyl transferase; FADH₂, flavin adenine dinucleotide; FAO, fatty acid oxidation; FUM, fumarate; ICIT, isocitrate; LCHAD, L-3-hydroxy-acyl-CoA dehydrogenase; MAL, malate; MMA-CoA, methylmalonyl-coenzyme A; NADH, nicotinamide adenine dinucleotide; OAA, oxaloacetic acid; PROP-CoA, propionyl CoA; SUCC, succinate; SUCC-CoA, succinyl-CoA; TCA, tricarboxylic acid; TFP, trifunctional protein; VLCAD, very long-chain-CoA dehydrogenase

Description of Clinical Condition

Patients diagnosed with LC-FAOD are unable to use long-chain fat obtained from diet or catabolism to create tricarboxylic acid (TCA) cycle substrates (also called anaplerotic substrates). Specifically, this group of autosomal recessive disorders is caused by defects in nuclear genes that encode mitochondrial enzymes important for the creation of anaplerotic substrates. These enzymes transport long-chain fatty acids across the mitochondrial membrane. Ultimately, long-chain fats are metabolized into two-carbon aceto-acetate and converted into energy via the TCA cycle.

In patients diagnosed with LC-FAOD, partial or incomplete oxidation of fatty acids leads to accumulation of potentially toxic fatty acid intermediates, a reduction of anaplerotic substrates and impaired gluconeogenesis. Patients who are unable to metabolize long-chain fatty acids may experience acute life-threatening metabolic crises during times of increased energy demand, such as growth, common infection or moderate exercise. These metabolic crises are caused by catabolism. For the sake of clarity in this review, the term “metabolic crises” refers to metabolic crises due to catabolism. In LC-FAOD patients, these crises most commonly manifest as acute rhabdomyolysis, hypoglycemia, and/or hypertrophic cardiomyopathy and can be precipitous, resulting in life-threatening and rapid deterioration that requires emergency medical management. Patients may also demonstrate chronic symptoms of subacute rhabdomyolysis and progressive cardiomyopathy.

Current Standard of Care

LC-FAOD are a group of inborn errors of metabolism. There are no approved drugs for the treatment of LC-FAOD. Current management is dependent upon dietary modification with a low-fat diet, limitation of ingestion of long-chain fatty acids, and dietary ingestion of MCTs, naturally occurring fat that is not impacted by these metabolic defects. The most commonly used formulation for MCT is as an oil, although infant formulations also contain MCT supplementation.

The most recent dietary guidelines recommend levels of MCT in diet that are stratified by patient age and disease severity (Southeast Regional Genetics Network 2019a) noted in [Table 3](#). Disease severity is assessed by the frequency and severity of metabolic crises, and dietary sufficiency is commonly assessed by multiple factors, including the number of interim metabolic crises since the last assessment, individual patient growth, and biochemical analyses of macronutrient intake (i.e., creatine kinase levels and plasma amino acids).

Table 3. Recommended Fat (Long-Chain, Medium-Chain, and Total), Energy and Protein Intakes for Individuals With VLCAD When Well

Age	Disease Severity	Long-Chain Fat*	Medium-Chain Fat*	Total Fat*	Energy	Protein (g/kg/day)
0-6 months	Severe	10-15	30-45	40-55	EER	≥1.5
	Moderate	15-30	10-30			
	Mild	30-55	0-20			
7-12 months	Severe	10-15	25-30	35-45	EER	≥1.2
	Moderate	15-30	10-25			
	Mild	30-40	0-10			
1-3 years	Severe	10-15	10-30	30-40	EER	≥1.1
	Moderate	20-30	10-20			
	Mild	20-40	0-10			
4-18 years	Severe	10	15-25	25-35	EER with PAL	0.85-0.95
	Moderate	15-25	10-20			
	Mild	20-35	0-10			
>19 years	Severe	10	15-25	20-35	EER with PAL	0.8
	Moderate	15-20	10-20			
	Mild	20-35	0-10			
Pregnancy	Severe	10	15-25	20-35	EER per trimester	1.1
	Moderate	15-20	10-20			
	Mild	20-35	0-10			
Lactation	Severe	10	15-25	20-35	EER	1.3
	Moderate	15-25	10-20			
	Mild	20-35	0-10			

Source: Modified from Recommendation Table 8, Southeast Regional Genetics Network 2019a; Refer to link for greater details: <https://southeastgenetics.org/ngp/guidelines.php/106/tbls/0/0/VLCAD%20Nutrition%20Guidelines/Version%201.0/List%20of%20Tables#topofpage>

* Percent of total energy.

Abbreviations: EER, estimated energy requirement; PAL, physical activity level

MCT oil is the most commonly ingested dietary supplement for patients with LC-FAOD. It is a natural mixture of C6, C8, C10, and C12 triglycerides. As a dietary supplement, the production of and sources for MCT oil are not regulated. Therefore, the composition of each specific fat may vary per product, though it is hypothesized that the component most utilized by LC-FAOD patients is C8. The percentage of C8 identified in commonly available MCT oil formulations provided by the Applicant can range from 40% to 70%.

Regardless of disease severity, patients with LC-FAOD appear to have different levels of adherence and/or tolerability to MCT oil, compounding any underlying risk for catabolism and metabolic crises. Patients with LC-FAOD came for a type C patient engagement meeting on January 9, 2019, to share their own symptoms with the Agency. Fatigue, lethargy, muscle cramps, muscle pain, and difficulty with cognitive “focus” were common symptoms they reported despite diets containing MCT oil. At times, these symptoms were a prodrome to the more severe manifestations of rhabdomyolysis, hypoglycemia and cardiomyopathy. In addition, patients shared about the emotional burden of having a chronic disease with daily management challenges.

As there are no currently approved drugs for the treatment of LC-FAOD, the goal of dietary management is to provide sufficient caloric intake, to limit dietary intake of long-chain and very long-chain fat, and to provide additional sources of medium-chain fat. The rationale for use of medium-chain fat supplementation is that this fat will bypass the need to metabolize longer-chain

fats, which require the specific enzymatic machinery upset by the pathophysiology in LC-FAOD patients.

Regulatory History

The regulatory history of this product is complex and notable for robust disagreement among members of the review team.

Briefly, in 2017, the Agency denied breakthrough designation on the basis of results from the open-label, single-arm study UX007-CL201, citing concerns about potential confounding from concomitant dietary changes, and recommending a controlled study. No additional studies were performed, and 91 patients were treated under expanded access INDs as the Applicant sought unsuccessfully to persuade the Division to accept an NDA based on the results of study UX007-CL201.

Following a request for reconsideration by Ultragenyx, Dr. Beitz accepted the Applicant's proposal to submit an NDA based on the data from study UX007-CL201 and the Gillingham trial. The Applicant submitted the NDA on July 31, 2019, seeking a priority review, a pediatric priority review voucher, and a claim for a reduction in major clinical events based on the results of study UX007-CL201. The clinical and statistical reviewers (Drs. Zand, Donohue, Tracy, Russek-Cohen, and Johnson) recommended a refuse-to-file action, noting that study UX007-CL201 was not an adequate and well-controlled trial. Dr. Beitz acknowledged the limitations of study UX007-CL201 and the recommendations of the clinical and statistical reviewers. However, Dr. Beitz concluded that the available evidence appeared sufficient to file the NDA under a standard review clock for a more limited claim as an alternative source of calories and medium-chain triglycerides. Ultimately, the review team concluded that the evidence from Gillingham (2017) was sufficient to support a recommendation for approval for this more limited nutrition claim.

The FDA is aware that triheptanoin could be categorized as a medical food. However, if a product meets the definition of two or more product categories under the FD&C Act, the manufacturer or Applicant can decide the category under which to market the product, and the Applicant chose to market triheptanoin as a drug.

Triheptanoin was granted orphan drug designation (ODD #154740) April 15, 2015, Fast Track designation March 7, 2019, and rare pediatric disease designation (#RPD-2019-208) March 28, 2019.

The reader is referred to the Appendix ([III.12](#)) for more details regarding the regulatory history for this product.

3.1. Approach to the Review

The review of NDA 213687 is anchored by the current published understanding of LC-FAOD and that dietary management with MCT oil, stratified by age and disease severity, is the current standard of care for LC-FAOD. From clinical experience, review of the literature, and discussions with patients and key opinion leaders in the field, the Division understands that patients who receive insufficient calories or nutrients that they are unable to metabolize (e.g., long-chain fatty acids) risk developing catabolism that manifests as elevated creatine kinase (CK) with acute rhabdomyolysis, acute hypoglycemia, or cardiomyopathy.

NDA 213687
Dojolvi (triheptanoin)

The Applicant submitted four sources of data ([Table 4](#)) to the NDA to support the efficacy and safety of triheptanoin in patients diagnosed with LC-FAOD.

Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations* for Triheptanoin

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	# of Subjects¹	Number of Centers and Countries
Gillingham (2017) (IND 113386 and ROR provided to NDA) NCT01379625	Patients with confirmed diagnosis of LC-FAOD (CPT-2, VLCAD, or LCHAD and/or TFP deficiency) aged 7 years or older who had a history of at least one episode of rhabdomyolysis; stable on a diet using MCT oil	Control type: Active comparator Randomization: 1:1 Blinding: Double-blind Biomarkers: CK Innovative design features: None	Drug(s): -Food grade triheptanoin (C7) or -Purified trioctanoin (C8) Dose: 20% DCI Number treated: 32 Duration: 4 months	Primary: -Cardiac function (ECHO) -Total energy expenditure -Treadmill exercise testing Secondary: Incidence of rhabdomyolysis	32 planned 32 randomized and completed	2 centers in the U.S.
UX007-CL201 (IND117053) NCT01886378	Patients diagnosed with severe LC-FAOD (CPT II, LCHAD, TFP, VLCAD) of at least 6 months of age	Control type: Historical control (attempted; found to be uncontrolled) Randomization: None Blinding: Open-label Biomarkers: None Innovative design features: None	Drug: triheptanoin Dose: 25-35% DCI Number treated: 29 Duration: 78 weeks	Primary: Annualized MCE Event rate Secondary: Annualized MCE duration, annualized event rate and duration for rhabdomyolysis, hypoglycemia and cardiomyopathy	30 planned 29 enrolled 24 completed	10 centers in 2 countries (U.S. and GB)

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	# of Subjects¹	Number of Centers and Countries
UX007-CL202 (IND 117053) NCT02214160	Patients diagnosed with severe LC-FAOD - Previously enrolled in study UX007-CL201 - Other investigator sponsored trials - Treatment naïve who have failed standard of care therapy	Randomization: Nonrandomized Blinding: Open-label Biomarkers: None Innovative design features: None	Drug: triheptanoin Dose: 25-35% DCI Number treated: 75 Duration: Ongoing	Primary: Annualized MCE event rate Secondary: Annualized MCE duration, annualized event rate and duration for rhabdomyolysis, hypoglycemia and cardiomyopathy	150 planned 75 with data at initial cutoff	10 centers in 2 countries (U.S. and GB)
Expanded access (multiple INDs with ROR provided to NDA)	Patients with confirmed diagnosis of LC-FAOD (CACT deficiency, CPT-1, CPT-2, TFP deficiency, LCHAD deficiency or VLCAD deficiency)	Control type: None	Drug(s): triheptanoin (dosages varied)	Primary: disease stability	Questionnaires reviewed from 51 of 67 expanded access INDs	Multiple centers in the U.S. and 10 additional countries

Source: NDA 213687; Section 5

* Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

¹ If no randomization, then replace with "Actual Enrolled"

Abbreviations: CACT, carnitine-acylcarnitine translocase; CPT, carnitine palmitoyltransferase; DCI, daily caloric intake; ECHO, echocardiogram; GB, Great Britain; LC-FAOD, long-chain fatty acid oxidation disorders; LCHAD, L-3-hydroxy-acyl-CoA dehydrogenase; MCE, major clinical events; MCT, medium-chain triglyceride; TFP, trifunctional protein; ROR, right of reference; U.S., United States; VLCAD, very long-chain acyl-CoA dehydrogenase

For the purposes of this review, the Gillingham trial (Gillingham et al. 2017) will be referred to as “Gillingham (2017).” Study UX007-CL201 (Vockley et al. 2019) and the extension study UX007-CL202 will be referred to by study name. The EA narratives submitted with NDA 213687 will be referred to via individual case narrative or as a group.

Determination of Efficacy

The Gillingham (2017) trial was considered adequate, well-controlled, and the most interpretable of all data sources as it was a double-blind, randomized controlled trial with an active comparator arm. The trial compared purified trioctanoin (C8) to food-grade triheptanoin (C7).

The source of triheptanoin used in the Gillingham (2017) trial was food grade, not commercial grade as used in studies UX007-CL201/CL202. However, the chemistry, manufacturing, and controls (CMC) team compared the composition of both products and determined that there were no significant differences. Therefore, the efficacy of the to-be-marketed product can be inferred from the food-grade product used in Gillingham (2017). The trioctanoin (C8) oil in the Gillingham trial was a purified natural product and allowed evaluation of consistent percentages of DCI between the food-grade triheptanoin and trioctanoin. The consistency of C8 or C7 dosages in the Gillingham (2017) trial was important for use in the determination of efficacy.

Neither study UX007-CL201 nor the EA narratives were used to determine the efficacy of triheptanoin. The concern for study UX007-CL201 centered around the study design, a nonrandomized, open-label, single-arm study that compared events retrospectively obtained from the pre-triheptanoin period to events observed on triheptanoin treatment. In addition, there was a significant level of missing data from the retrospective period, variation in approach to the clinical management of LC-FAOD patients prior to enrollment, and concern for confounding from diet prior to triheptanoin exposure. Interpretation of the EA narratives also was impacted by missing data (concomitant medications, information on dietary changes of all dietary components (total kcal/kg/day; protein, etc.) before and after initiation and other medical interventions.

The Gillingham trial differs from studies UX007-CL201 and UX007-CL202 in that the source of even-numbered medium-chain fat in studies UX007-CL201/202 was MCT oil and in the Gillingham trial it was purified food grade C8 oil. Each formulation of MCT oil used in studies UX007-CL201 and UX007-CL202 could vary in its composition with differences in the proportion of C6, C8, C10, and C12. Neither study specified a brand source of naturally-occurring or processed MCT oil, so patient dietary records may reflect these variations. In contrast, the Gillingham trial used a food-grade, purified C8 oil, allowing for a consistent comparison of C8 to C7 among patients. As MCT oil may contain 40% to 70% C8, patients enrolled in study UX007-CL201 may have pretreatment laboratory and clinical evaluations that are reflective of diets consisting of different concentrations of MCT oil. Patient level data of dietary analysis prior to enrollment were not obtained for these patients.

Determination of Safety

Study UX007-CL201 and the open-label extension study UX007-CL202 were reviewed to determine the safety of triheptanoin in patients with LC-FAOD. Both studies prospectively assessed safety and therefore were the most reliable of the data submitted for review. The adverse events reported in the Gillingham (2017) trial were considered supportive, in part

because the dose of triheptanoin was lower (20% DCI compared to 24% to 40% DCI). The inclusion criteria for studies UX007-CL201/202 specified LC-FAOD patients of greater severity than those enrolled in Gillingham (2017); therefore, the adverse events reported in this combined cohort may reflect a greater sensitivity to dietary changes and greater general risk for adverse events. This population would also be the most informative for the safety analysis of triheptanoin. Due to missing data that confounded full clinical interpretation, the adverse events reported in the EA narratives were also considered supportive.

The LC-FAOD diagnoses eligible for enrollment in each study are noted in [Table 5](#). The dietary recommendations for management of these LC-FAODs are the same regardless of the specific diagnosis.

Table 5. Study Enrollment Criteria by LC-FAOD Diagnosis

LC-FAOD Diagnosis	Gillingham (2017) N=32	UX007-CL201 N=29	UX007-CL202 ^a N=75	EA N=67
CACT deficiency	NA ^b	NA	3	9
CPT I deficiency	NA	NA	1	--
CPT II deficiency	12	4	11	9
LCHAD deficiency	10	10	24	24
TFP deficiency (Combined with LCHAD) ^c		3	10	5
VLCHAD deficiency	10	12	26	19
Unknown diagnosis	--	--	--	1

Source: DARRTS; NDA 213687; Section 5.3.5.1, Gillingham package; Section 5.3.5.2, CSR Studies UX007-CL201 and UX007-CL202, Section 5.3.5.4, Table 1 (page 9 of 367)

^a A total of 25 of 29 patients rolled over from study UX007-CL201 into study UX007-CL202. The patients who did not rollover had the following diagnoses: CPT II (1), LCHAD (1) and VLCAD (2)

^b Gillingham (2017) and study UX007-CL201 did not include CPT I and CACT enrollment in their inclusion criteria.

^c The LCHAD protein encodes a subunit needed for TFP activity. Historically, some clinicians have referred to and grouped the two diagnoses as LCHAD/TFP due to their codependent mechanism (Saudubray et al. 2012)

Note: Patients enrolled in the Gillingham (2017) trial, study UX007-CL201 and EA were rolled into study

Abbreviations: CACT, carnitine-acylcarnitine translocase; CPT, carnitine palmitoyltransferase; EA, expanded access;

LC-FAOD, long-chain fatty acid oxidation disorders; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase; NA, not applicable;

TFP, trifunctional protein; VLCHAD, very long-chain L-3 hydroxyacyl-CoA dehydrogenase

4. Patient Experience Data

Table 6. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Section 6.2
☒	Observer-reported outcome	
☐	Clinician-reported outcome	
☒	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	Section 3
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☒	Other: (please specify) <i>Type C Patient Engagement Meeting on January 9, 2019, initiated by the Applicant</i>	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The key clinical pharmacology information of triheptanoin and its active metabolite heptanoate is summarized in [Table 7](#). The pharmacokinetic (PK) parameters were estimated based on the phase 1 study in healthy adult subjects (study UX007-CL101) using a noncompartmental method.

Table 7. Summary of General Clinical Pharmacology and Pharmacokinetics of Triheptanoin and Its Active Metabolite Heptanoate

Characteristic	Drug Information
<i>Pharmacologic activity</i>	
Established pharmacologic class	Medium-chain triglyceride
Mechanism of action	Triheptanoin is a medium-chain triglyceride consisting of three odd-chain 7-carbon length fatty acids (heptanoate) that provide a source of calories and fatty acids.

Characteristic	Drug Information																				
Active moieties	Heptanoate (C7 fatty acid)																				
QT prolongation	The Applicant has not conducted a thorough QT prolongation study. Refer to Section 7.6.7 Cardiac Events for more information.																				
General information																					
Bioanalysis	Validated LC/MS/MS method was used to determine the concentrations of heptanoate, and its metabolites, beta-hydroxybutyrate (BHB) and beta-hydroxypentanoate (BHP).																				
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Following oral administration, triheptanoin is extensively hydrolyzed to heptanoate and glycerol by pancreatic lipases in the intestine. PK Parameters of Heptanoate in Healthy Subjects Following Single or Multiple Oral Administrations of Triheptanoin With Food <table><tr><th>Dose</th><th></th><th>Mean (SD) C_{max} (µM)</th><th>Mean (SD) AUC_{0-8h} (µM·hr)</th><th>Median (Range) Time to First Peak Concentration* (h)</th></tr><tr><td>Single dose</td><td>0.3125 g/kg</td><td>178.9 (145)</td><td>336.5 (223)</td><td>0.5 (0.4 to 1.0)</td></tr><tr><td></td><td>0.375 g/kg</td><td>259.1 (134)</td><td>569.1 (189)</td><td>0.8 (0.4 to 6.4)</td></tr><tr><td>Multiple doses</td><td>0.3125 g/kg administered qid for 2 days</td><td>319.9 (164)</td><td>789.8 (346)</td><td>1.2 (0.4 to 2.4)</td></tr></table> * After oral administration of triheptanoin, more than two peak concentrations of heptanoate are observed. Abbreviations: AUC_{0-8h}, area under the curve from 0 to 8 hours; C_{max}, maximum concentration; h, hour; PK, pharmacokinetics; qid, 4 times a day; SD, standard deviation In clinical studies in patients with LC-FAOD, the plasma concentrations of triheptanoin in the majority of PK samples were below the lower limit of quantitation (LLOQ of 0.2µM).	Dose		Mean (SD) C _{max} (µM)	Mean (SD) AUC _{0-8h} (µM·hr)	Median (Range) Time to First Peak Concentration* (h)	Single dose	0.3125 g/kg	178.9 (145)	336.5 (223)	0.5 (0.4 to 1.0)		0.375 g/kg	259.1 (134)	569.1 (189)	0.8 (0.4 to 6.4)	Multiple doses	0.3125 g/kg administered qid for 2 days	319.9 (164)	789.8 (346)	1.2 (0.4 to 2.4)
Dose		Mean (SD) C _{max} (µM)	Mean (SD) AUC _{0-8h} (µM·hr)	Median (Range) Time to First Peak Concentration* (h)																	
Single dose	0.3125 g/kg	178.9 (145)	336.5 (223)	0.5 (0.4 to 1.0)																	
	0.375 g/kg	259.1 (134)	569.1 (189)	0.8 (0.4 to 6.4)																	
Multiple doses	0.3125 g/kg administered qid for 2 days	319.9 (164)	789.8 (346)	1.2 (0.4 to 2.4)																	
Dose-proportionality	Heptanoate exposure increases greater than dose-proportional in the dose range between triheptanoin 0.3125 g/kg and 0.375 g/kg.																				
Bridge between to-be marketed and clinical trial drug products	The to-be-marketed drug product was used in studies UX007-CL101, UX007-CL201 and UX007-CL202. A food-grade triheptanoin product was used in the Gillingham trial. The product quality review team has determined that the food-grade triheptanoin is comparable to that of the to-be-marketed drug product. See section 9 for more information.																				
Absorption																					
Bioavailability	Triheptanoin is minimally absorbed systemically. The absolute bioavailability of triheptanoin has not been characterized.																				
T _{max}	After oral administration of triheptanoin, more than one peak concentration of heptanoate was observed. The first peak was observed between 0.4 hours to 6.4 hours.																				
Food effect (fed/fasted)	In clinical studies, triheptanoin was administered with food; therefore, the PK of triheptanoin and its metabolites was evaluated under fed condition. Triheptanoin is recommended to be administered orally, diluted with food.																				
Distribution																					
Plasma protein binding	Heptanoate exhibited approximately 80% protein binding at the concentration range of 40µM to 400µM in human plasma. Heptanoate increases the unbound fraction of valproic acid by approximately 2-fold.																				
Elimination																					
Clearance	The mean apparent clearance (CL/F) of heptanoate was 6.05 L/hr/kg and 4.31 L/hr/kg, respectively, following single oral dose of triheptanoin 0.3125 g/kg and 0.375 g/kg.																				

Characteristic	Drug Information
Half-life	The half-life of heptanoate could not be determined due to multiple peak concentrations in the PK profiles following oral administration.
Metabolic pathway(s)	Following oral administration, triheptanoin is hydrolyzed to heptanoate in the intestines. After systemic absorption, heptanoate is metabolized following a fatty acid beta-oxidation metabolic pathway. Additional metabolic conversion may occur in liver that forms BHB and BHP (e.g., fatty acid oxidation).
Excretion pathways	Triheptanoin and its metabolites were minimally excreted in urine.
<i>Intrinsic factors and specific populations</i>	
Renal impairment	No dedicated trial of the effect of renal impairment on the PK of triheptanoin was conducted.
Hepatic impairment	No dedicated trial of the effect of hepatic impairment on the PK of triheptanoin was conducted.
<i>Drug interaction liability (drug as perpetrator)</i>	
Inhibition/induction of metabolism	Since triheptanoin is hydrolyzed into heptanoate (C7 fatty acids) by pancreatic lipases in the intestine, pancreatic lipase inhibitors (e.g., orlistat) should not be concomitantly used with triheptanoin. Heptanoate is not a sensitive substrate of CYP or UGT enzymes based on in vitro studies. Heptanoate is not an inhibitor of human CYP isoforms including CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 based on in vitro studies.

Abbreviations: LC-FAOD, long-chain fatty acid oxidation disorders; LC/MS/MS, liquid chromatography-mass spectrometry; LLOQ, lower limit of quantitation; PK, pharmacokinetic

5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical assessment characterizing the effectiveness of triheptanoin (UX007) in LC-FAOD comes from published pharmacodynamic (PD) studies using tissues from in vitro and in vivo animal models.

- In excised rat liver perfused with ¹³C-labeled 1mM heptanoate, it was demonstrated that for every molecule of heptanoate (metabolite of triheptanoin) uptake by the liver, two molecules of acetyl-CoA and one molecule of propionyl-CoA are produced. The acetyl-CoA enters the TCA cycle where it is used for adenosine triphosphate production and ketogenesis (Deng et al. 2009). The effects of a single IV infusion of ¹³C heptanoate were studied in the brains of wildtype mice and compared to those of glucose transporter 1 (GLUT-1)-deficient transgenic mice. Although glucose concentrations were significantly elevated in both wildtype and GLUT-1 knockout (KO) mice following heptanoate infusion, the brain levels of acetyl CoA were higher in the GLUT-1 KO animals than in the wildtype mice. Similarly, although the neurotransmitter glutamine levels were higher than the glutamate levels in the brain of both animals, the glutamine levels were significantly higher in the KO animal brain than in the wildtype animal brain, indicating a potential compensatory mechanism by reactive astrocytes to the lack of GLUT-1 protein. The evidence of labeled substrate and metabolites in both the liver and brain suggests that heptanoate can diffuse across the blood brain barrier and plasma membrane to produce energy for all TCA cycle-dependent cell types (Marin-Valencia et al. 2013).

- The effects of normal long-chain triglyceride diet (5% total fat representing 12% of metabolizable energy), medium-chain triglyceride diet (5% total fat representing 12% of metabolizable energy), or triheptanoin diet (5% total fat representing 12% of metabolizable energy) for 3 months and 12 months were compared in wildtype mice and in very long-chain acyl-CoA dehydrogenase deficient (VLCAD^{-/-}) or KO mice. KO mice fed MCT diet for a year presented with progressive decrease in heart function and chronic energy deficiency, eventually leading to cardiomyopathy without any reversal or attenuation when compared to mice on control diets. In contrast, triheptanoin diet was better tolerated in KO mice and was not associated with progressive decline but stability in cardiac function. Thus, the progressive pathology observed in KO mice fed long-chain triglyceride and MCT diet may not be predictive of the clinical VLCAD enzyme deficiency. Although triheptanoin diet did not significantly improve cardiac function in mice, the lack of progression was notably different from the progressive disease observed in the MCT treated animals (Tucci et al. 2014; Tucci et al. 2017).
- The anticonvulsant effects of dietary heptanoin (35% of daily caloric intake) were studied in two mouse chronic seizure models for a treatment period of up to 7.5. The triheptanoin diet significantly delayed development of kindled seizures in fully kindled mice fed 35% triheptanoin compared to the standard diet. The triheptanoin diet resulted in reversal of tonic extension by 40% in pilocarpine pentylenetetrazole-induced seizure in status epilepticus (SE) model mice (Willis et al. 2010).
- Measurement of blood and brain metabolites in mice demonstrated that epileptic tissue shows changes in metabolism and TCA activity, including significant increases in malonyl-CoA and decreases in propionyl-, acetyl-, and β -hydroxybutyryl-CoA in SE compared to non-SE mouse brain. In addition, aspartate and GABA were decreased compared to non-SE mice. SE mice fed triheptanoin diet had propionyl-CoA but not acetyl-CoA levels restored, whereas methylmalonyl- and HMG-CoA levels were increased in triheptanoin-fed SE mice but not in non-SE mice, showing a connection between the metabolism of triheptanoin and the production of anaplerotic intermediates in tissues. Triheptanoin diet doubled the levels of brain β -hydroxybutyryl-CoA in SE and non-SE mice. Thus, the data indicate that the metabolism of triheptanoin is different in epileptic tissue compared to normal brain (Willis et al. 2010).
- In an isolated heart rat model of cardiac hypertrophy, triheptanoin diet at 7% or 30% of daily caloric intake for 5 weeks improved glucose oxidation and preserved cardiac power, which resulted in the prevention of contractile dysfunction. Tissue doppler measurements showed that left ventricular hypertrophy was significantly reduced, with improved diastolic function in mice fed 30% triheptanoin compared to mice on a control diet. In the isolated working rat heart perfusions, triheptanoin treatment improved myocardial glucose oxidation, but not cardiac fatty acid oxidation. The isolated heart from mice fed the 30% triheptanoin diet showed the highest level of C5-ketone body, beta-hydroxypentanoate (BHP) in blood, compared to the 7% triheptanoin diet or control diet. Triheptanoin treatment, however, did not affect myocardial insulin sensitivity. The study demonstrated that cardiac hypertrophy is likely related to altered anaplerosis (Nguyen et al. 2015).

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Potential Effectiveness

The recommended target daily dose of triheptanoin is up to 35% of the patient's total prescribed DCI, which is determined based on the assessment of the metabolic requirement of the patient. The individual triheptanoin dose should be further determined based on tolerability, medical needs, and other dietary requirement factors such as age and disease severity. The Applicant proposed 25% to 35% DCI as the total daily dose because a majority of patients in studies UX007-CL201 and UX007-CL202 received doses within this range.

The effectiveness and safety of the recommended daily dose of triheptanoin are supported by results of clinical studies UX007-CL201 and UX007-CL202 and the Gillingham trial. A large variability in individual average triheptanoin dose over the treatment duration was noted across these three clinical studies ([Table 8](#)), which generally supported the recommended daily dose of triheptanoin up to 35% DCI.

Table 8. Individual Average Daily Dose (DCI%) of Triheptanoin in Clinical Studies

Study/Cohort	N	Dose (DCI%)
		Median (Min, Max)
Gillingham et al (2017)	16	16.4 (11.3, 22.0)
Study UX007-CL201	29	31.8 (16.6, 35.0)
Study UX007-CL202	75	28.0 (8.0, 48.8)
CL201 rollover	24	30.9 (20.2, 35.0)
IST/other	31	26.3 (8.0, 48.8)
Triheptanoin naïve	20	28.2 (15.6, 33.7)

Source: Reviewer's analysis results based on the article by Gillingham et al (2017) and 'Listing 16.2.5.1.99.1' in clinical study reports of UX007-CL201 and UX007-CL202

Individual average triheptanoin daily dose = sum of (the daily dose * treatment duration) / sum of treatment duration, in each patient
Abbreviations: DCI, daily caloric intake; IST, investigator sponsored trials

Comments: Review of diet in study UX007-CL202 shows that patients received doses of triheptanoin >35% DCI (35% to 49% DCI). These doses did not remain at the same elevation and were commonly titrated downward. However, as dose titration was at the discretion of the investigator, the rationale for each has not been provided for assessment in our review.

Pediatric patients received greater daily doses in grams per kg compared to adult patients in the clinical studies ([Table 9](#)) because pediatric patients require more calories and fat intake per kg for growth than adults do.

Table 9. Body-Weight Adjusted Individual Average Daily Dose (g/kg/day) of Triheptanoin by Age Group in Clinical Studies

Study/Cohort	Individual Average Daily Dose (g/kg/day)			
	Overall	<6 Years	6 to <18 Years	≥18 Years
Study UX007-CL201				
N	29	15	8	6
Median (min, max)	2.04 (0.75, 5.62)	3.16 (1.51, 5.62)	1.20 (0.95, 2.06)	1.00 (0.75, 1.30)
Study UX007-CL202				
N	75	22	32	21
Median (min, max)	1.68 (0.19, 5.43)	3.12 (1.49, 4.69)	1.71 (0.48, 5.43)	0.86 (0.19, 1.25)

Source: Reviewer's analysis results based on adlog.xpt for UX007-CL201 and UX007-CL202

Body-weight adjusted individual average daily dose = sum of (the body-weight adjusted daily dose * treatment duration) / sum of treatment duration, in each patient

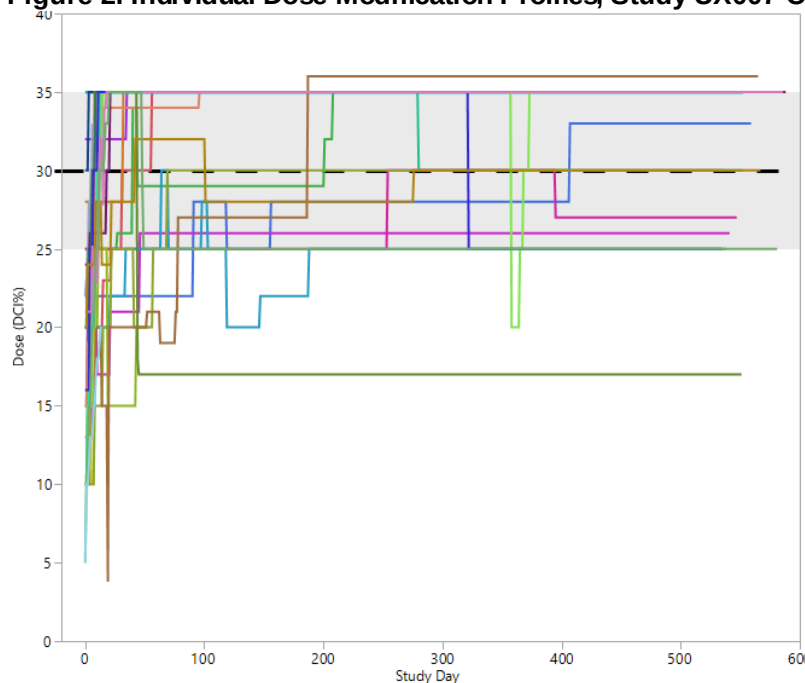
Gillingham (2017) Trial

Triheptanoin was administered to 16 LC-FAOD patients 7 to 64 years of age. Although patients had been instructed to consume 20% DCI of their total caloric needs, they ended up taking 11% to 22% DCI of triheptanoin during the 4-month treatment.

Study UX007-CL201

A total of 29 LC-FAOD patients (10 months to 58 years of age) received triheptanoin. Per the protocol, triheptanoin was to be initiated with 10% DCI or the MCT oil-equivalent dose if the patient had received MCT oil prior to the study. The triheptanoin dose was gradually up-titrated every 2 to 3 days until the target dose range, 25% to 35% DCI, was achieved (refer to UX007-CL201 Study Drug Administration Guideline in UX007-CL201 clinical study report addendum, [Table 55](#) in Section [III.14.1](#) in this document). After dose titration, the majority of patients generally maintained 35% DCI for 78 weeks, although the individual dose was continuously modified throughout the study ([Figure 2](#); also refer to [Figure 11](#) in Section [III.14.1](#) for individual profiles). The rationale for dose modification in individual patients was not recorded, but presumably would be based on tolerability and changes in the caloric needs of each patient. The individual average daily dose ranged from 16.6% to 35.0% DCI, with a median of 31.8% DCI ([Table 8](#)).

Figure 2. Individual Dose Modification Profiles, Study UX007-CL201*



Source: reviewer's plot on the dosing log (adlog.xpt for CL201)

*A total 29 patients, and each line represents a profile of each patient. The grey area represents 25-35% DCI range and the dotted line represents the mean of 30% DCI.

Abbreviations: DCI, daily caloric intake

Baseline diet was modified in many patients enrolled in Study UX007-CL201. Refer to [Table 3](#) for the current (2019) recommended MCT dosing for patients, based on age and clinical assessment of disease severity. In addition, refer to [Figure 5](#), [Figure 11](#), and [Figure 12](#) for individual patient dosing modifications over time during the study.

Study UX007-CL202

A total of 75 LC-FAOD patients (0.3 to 64 years of age) received triheptanoin, of which 24 patients were rolled over from study UX007-CL201, 20 were triheptanoin-naïve (including one patient previously enrolled in Study UX007-CL201 who stopped triheptanoin for 2 years prior to enrollment), and 31 were rolled over from other triheptanoin studies. If patients were rolled over from other triheptanoin studies, they continued the same triheptanoin dose that they had received prior to rollover. For triheptanoin-naïve patients, determination of initial dose and dose up-titration schemes were consistent with those of study UX007-CL201. The individual average doses are summarized in [Table 8](#).

Additional considerations in triheptanoin dosing regimen:

- **Initial dose:** Based on the dosing instruction used in studies UX007-CL201 and UX007-CL202, MCT-naïve patients can start triheptanoin with 10% DCI, and patients receiving another MCT product can switch to triheptanoin at the last tolerated daily dose of MCT.
- **Dose titration:** Based on the dosing instruction used in studies UX007-CL201 and UX007-CL202, the review team recommends a dose up-titration by 5% DCI every 2 to 3

days. Note that the Applicant initially proposed a dose up-titration by 5% DCI every week which would take a longer time to achieve the target dose.

- **Dosing frequency:** The review team recommends that a total daily dose of triheptanoin be divided into four or more doses per day, depending on patient tolerance. In studies UX007-CL201 and UX007-CL202, although most of the patients received triheptanoin four times per day, others used dosing frequencies that ranged widely from once a day to 24 times a day.

6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Trial Design

The studies submitted for review in this NDA differed in their designs. The Applicant intended that the data from study UX007-CL201, a phase 2 study designed as an open-label switch from historical control in patients diagnosed with severe LC-FAOD, would be used to evaluate the efficacy of triheptanoin. However, study UX007-CL201 was not an adequate or well-controlled study due to the amount of missing data and confounding dietary changes that occurred after study enrollment. In contrast, the Gillingham trial was well controlled and the data were adequate given two treatment arms and confirmatory evidence given the underlying chemistry of triheptanoin as medium-chain fatty acid.

Unlike study UX007-CL201, the Gillingham trial enrolled patients with nonsevere but stable LC-FAOD and followed them for only 4 months. The data from these trials are discussed in Section [6.3](#).

Based upon review of the inclusion criteria for the Gillingham trial and study UX007-CL201 ([Table 11](#)) the categorization of nonsevere and severe LC-FAOD patients appears to rely upon each investigator's clinical assessment. The initial Gillingham (2017) protocol submission only required a molecular diagnosis of LC-FAOD for enrollment. However, a protocol amendment required that patients have at least one previous episode of rhabdomyolysis. By comparison, study UX007-CL201 required patients to have at least one predefined clinical- or laboratory-based criteria descriptive of high risk for poor catabolic control.

Gillingham (2017) Trial

This research trial was submitted under IND 113386 and the right of reference was provided to the Applicant. This was a double-blind, randomized (1:1), parallel-design trial to compare the impact of food-grade, purified C8 (trioctanoin) to that of food-grade C7 (triheptanoin). Patients were eligible to participate if they met the following criteria:

- Aged ≥ 7 years
- Diagnosed with the following LC-FAODs:
 - Carnitine palmitoyltransferase (CPT) II deficiency
 - Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
 - Trifunctional protein (TFP) deficiency

- Long-chain-3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency (see [Table 5](#))
- On a stable diet including supplementation with MCT oil
- A history of at least one episode of rhabdomyolysis

Patients were followed at one of two sites in the United States, Oregon Health and Science University (OHSU) or the University of Pittsburgh. The target sample size (n=32) was based on pilot data suggesting a difference in transesophageal echocardiography between patients receiving C7 and those receiving C8. There were 16 patients in each study arm.

At trial initiation, patients were placed on a diet containing 20% of DCI of either purified C8 or food-grade C7 for 4 months. At baseline and at month 4, patients were evaluated for body composition, cardiac function, metabolic response to a test meal, and exercise tolerance. These evaluations included total energy expenditure, heart rate during moderate intensity treadmill testing, cardiac function measured via echo and phosphocreatine recovery, and adverse events such as CK elevation that would suggest rhabdomyolysis. Treatment compliance was assessed via multiple three-day diet records and by measurement of the unconsumed oil at the end of the study.

Comments: While the review team acknowledged the strengths of this trial (i.e., this study was randomized and double-blinded), it was noted that the trial was not intended to be a registration trial. It would have been helpful to document the baseline diet of all enrolled patients to understand if it had changed after randomization. When compared to study UX007-CL201 (below), however, this information is not as essential since the trial included an active comparator (C8) assigned in a double-blind manner, and information about patient course prior to enrollment was not used in the assessment of C7. Because this was a shorter study (4 months) and because the patients enrolled in this study had less severe disease than those enrolled in study UX007-CL201, the impact of C7 in the two studies is not directly comparable.

Study UX007-CL201

Study UX007-CL201 was a phase 2, single arm, multicenter, prospective study to evaluate the impact of triheptanoin in patients 6 years of age and older who had been previously diagnosed with serious clinical manifestations of LC-FAOD despite current management. Eligible patients were to be maintained on current dietary therapy (MCT oil) for 4 weeks (run-in period), after which they were switched over to begin treatment with triheptanoin. Triheptanoin treatment was dose titrated from 25% to 35% of DCI over a 24-week period and then patients were treated for up to 78 weeks. When available, medical events and treatment data covering the 78-week period prior to study enrollment were retrospectively obtained to compare the pre-triheptanoin event rate to the event rate observed during the triheptanoin treatment period. Patients who completed study UX007-CL201 and wished to continue with dietary use of triheptanoin were then eligible to participate in the extension study (study UX007-CL202 described below).

The primary outcome for study UX007-CL201 was the annualized rate of MCEs, defined as rhabdomyolysis, hypoglycemia, or cardiomyopathy that resulted in any visit to the emergency department or admission for hospitalization; emergency room/acute care visit; or emergency intervention (any unscheduled administration of therapeutics at home or in the clinic). The primary analysis compared the annualized rate of MCE during the pre-triheptanoin period (up to 78 weeks prior to enrollment) to the rate during the 78 weeks of triheptanoin.

The review team noted that the protocol lacked a definition of specific clinical findings or a minimal CK level elevation for rhabdomyolysis. In contrast, the protocol did specify that a hypoglycemic event required clinical symptoms or a serum glucose below the clinically important laboratory threshold of 60 mg/dL. Cardiomyopathy events were loosely defined as events assessed via echocardiogram (ECHO) and electrocardiogram (ECG) with additional testing performed if abnormalities were detected or if medically indicated. Refer to [Table 10](#) for MCE-associated clinical symptoms and evaluations.

Table 10. Major Clinical Events (MCEs), Study UX007-CL201

Diagnosis	Organ Pathology	Symptom	Laboratory/Imaging
Rhabdomyolysis	Skeletal myopathy	-Muscle cramping -Weakness -Myoglobinuria	Elevated CK
Hypoglycemia	Hepatic disease	-Altered mental status -Fatigue -Pallor -Palpitations -Sweating -Shakiness	Low blood glucose
Cardiomyopathy	Cardiac myopathy	**	Decreased LVEF

Source: NDA 213687; study UX007-CL201 CSR Section 8.6.2.1

** Protocol UX007-CL201 did not define or refer to specific symptoms related to cardiomyopathy, only how it was to be evaluated. Abbreviations: CK, creatine kinase; LVEF, left ventricular ejection fraction

Comments: The protocol did not specify a specific creatine kinase value for determination of rhabdomyolysis. Similarly, no specific thresholds from echocardiogram, the current standard for diagnosis (Yancy et al. 2017), were required in the definition of cardiomyopathy. The protocol was vague in how these clinical events were defined. Consequently, there is concern that the evaluation and determination of these clinical events varied by clinical site and investigator, and perhaps between study periods.

Secondary outcomes include annualized MCE duration and annualized rates and durations for rhabdomyolysis, hypoglycemia, and cardiomyopathy events separately. Additional secondary endpoints included distance walked in a 12-minute walk test and exercise tolerance measured during a 40-minute cycle ergometry protocol in eligible patients.

Comments: Results from the 12-minute walk test and cycle ergometry were difficult to interpret as baseline and post-treatment initiation data were provided in only seven patients for each test either due to testing ineligibility issues, wheelchair dependency, contraindication due to advanced disease, or other reasons. Consequently, results of these outcomes are not presented in this review.

In summary, study UX007-CL201 was designed as a proof-of-concept study with a target sample size of 30 patients based on feasibility. There was no testable hypothesis in the original protocol or analysis plan.

Comments: Overall, there were multiple limitations of this study design, including the following three that significantly impacted the interpretation of data provided for review:

- 1) Laboratory data and major clinical events were not systematically collected in the same manner during the retrospective period as in the prospective period. Because of this variability, the efficacy outcomes are difficult to interpret and cannot be solely attributed

to triheptanoin. The missing data in the retrospective period is acknowledged by the Applicant.⁴

- 2) The recommended dietary intake during the 78-week pre-triheptanoin period was not systematically collected in most patients. Only limited data were collected on 11 of 29 patients. The pre-triheptanoin data from the 11 patients lacked enough detail to allow for a meaningful comparison with the triheptanoin period. The lack of pre-triheptanoin dietary data for 18 of the 29 patients enrolled in study UX007-CL201 also did not allow for a meaningful comparison.*
- 3) Review of the available data from the pre-triheptanoin period and the run-in evaluations indicate that dietary management varied across study sites and varied from the current nutritional guidelines (Table 3). The Applicant did not provide enough justification for these differences. While the Agency understands there is variability in the practice of medicine, it is unable to determine if all patients received optimized dietary intake prior to enrollment since the MCT administered during the 4-week run-in period ranged from 0% to 33% of DCI and upon switch to triheptanoin the changes in medium-chain fat source increased up to 29% DCI from baseline.*

As the current standard of care for patients with LC-FAOD is dietary modification, the inability to evaluate the diet continuum during this study impacted interpretation of data provided by the Applicant.

Study UX007-CL202

This was an open-label, single arm, multicenter study in patients with one of six diagnoses of LC-FAOD (CPT I, CPT II, CACT, LCHAD, TFP, or VLCAD) who rolled over from previous commercial or investigator-sponsored studies using triheptanoin or in patients who were triheptanoin treatment-naïve. Patients continued on the triheptanoin dose they received prior to rollover or, for the treatment naïve patients, titrated up to a dosage of 25% to 35% DCI. The patients were to be evaluated every 3 months for up to 5 years. The study is ongoing at the time of this review. As with study UX007-CL201, the primary outcome measure is the annualized MCE rate where MCE was the composite of rhabdomyolysis, hypoglycemia and cardiomyopathy clinical events. The same definitions for these events used in study UX007-CL201 applied for this study. Similar to study UX007-CL201, attempts were made to summarize events occurring 18 to 24 months prior to UX007 initiation via retrospective medical record review. For patients with previous triheptanoin exposure through an emergency IND, NCT #01379625, or NCT #01461304, only MCEs occurring after the study UX007-CL202 baseline visit were identified and considered. As in study UX007-CL201, data on treatment history (including MCT history) prior to initiation of triheptanoin are limited or incomplete.

This extension study was designed to collect long-term safety information and noncomparative efficacy and was not designed around a testable hypothesis. Therefore, the sample size was based on expected number of eligible patients from prior investigations.

⁴ NDA 213687; study UX007-CL201 CSR; page 83 of 1260.

Comments: Study UX007-CL201 was restricted to patients with serious clinical manifestations of LC-FAOD despite current management. This was not a requirement for enrollment into study UX007-CL202.

6.2.2. Eligibility Criteria

The eligibility criteria for all three studies (Gillingham (2017), UX007-CL201 and UX007-CL202) are summarized in [Table 11](#) with detailed description below. The following key differences in eligibility criteria are noted:

1. As defined by the inclusion criteria, the patients enrolled in the Gillingham (2017) trial (IND 113386) had nonsevere disease manifestations and those enrolled in study UX007-CL201 had severe disease manifestation. The doses used in each study were reasonably consistent with the current dietary recommendations of medium-chain fat (MCT, food-grade C8 or C7) based upon disease severity [Table 3](#).
2. Prespecified criteria of disease severity were not eligibility requirements for triheptanoin-naïve patients in study UX007-CL202.
3. The diagnoses of carnitine-acylcarnitine translocase (CACT) and CPT I were included in study UX007-CL202 but excluded in study UX007-CL201. It may be that rollover of EA patients into study UX007-CL202 provided the rationale for broadening the diagnoses in the inclusion criteria.
4. Patients eligible to enroll in studies UX007-CL201/UX007-CL202 were younger (minimum of 6 months of age) than those eligible to enroll in the Gillingham (2017) trial.

Comments: The full Office of Scientific Investigation (OSI) report is in Appendix (Section [III.20](#)). The preliminary results of the OSI investigation for inclusion criteria at enrollment demonstrated inconsistencies in compliance for study UX007-CL201 for site 108. Per discussion with the investigator regarding missing documentation to support subject eligibility, it was explained to the inspector that the Applicant did not query eligibility of subjects as they deferred to the investigator's determination for eligibility. Three study sites were inspected (11 of 29 patients), and documentation to support eligibility for most patients enrolled in study UX007-CL201 is unknown.

Inconsistencies in the documentation of how each patient fulfilled enrollment criteria for study UX007-CL201 is one reason why this study is not considered well-controlled or adequate.

Table 11. Key Enrollment Criteria for Clinical Trial/Studies Provided by the Applicant

Gillingham (2017)^a	UX007-CL201	UX007-CL202
- Confirmed diagnosis of CPT II, VLCAD, or LCHAD/TFP - At least 7 years of age - Stable on a diet that includes supplementation with MCT - History of at least 1 episode of rhabdomyolysis	- Confirmed diagnosis of CPT II, VLCAD, LCHAD, or TFP - At least 6 months of age - Severe LC-FAOD as evidenced by any one of the following: - Chronic elevated CK with major clinical events - Episodic elevated CK with reported muscle dysfunction - Highly elevated CK but asymptomatic - Frequent severe major medical episodes - Severe susceptibility to hypoglycemia - Evidence of functional cardiomyopathy	- Confirmed diagnosis of LC-FAOD (all subtypes, including CPT1 and CACT) - At least 6 months of age - Prior participation in a clinical study assessing triheptanoin treatment for LC-FAOD (CL201 Rollover and IST/Other Cohorts) or naive to triheptanoin, failed conventional therapy, and had documented severe unmet need (Triheptanoin-naive Cohort)

Table adapted from Table 5 from summary-clin-efficacy-lc-faod.pdf

^a A protocol amendment dated October 2013 modified inclusion criteria to require a history of MCT oil supplementation and a history of at least one episode of rhabdomyolysis. A total of 17 out of 32 patients were enrolled prior to initiation of the protocol amendment. Abbreviations: CPT, carnitine palmitoyltransferase; LC-FAOD, long-chain fatty acid oxidation disorders; LCHAD, L-3-hydroxy-acyl-CoA dehydrogenase; MCT, medium-chain triglyceride; TFP, trifunctional protein; VLCAD, very long-chain acyl-CoA dehydrogenase

6.3. Statistical Analysis Plan

Gillingham (2017)

Randomization to food grade C7 or C8 in a 1:1 fashion was stratified by medical diagnosis (CPT II, VLCAD, or TFP/LCHAD deficiency) and trial site. This study was initiated as blinded to patients (single blinded) until a study coordinator was identified.⁵ A total of 17 patients were enrolled at the time of the amendment. A randomization table was generated by the study statistician and controlled by the primary research coordinator at OHSU. The primary analyses compared changes from baseline at month 4 in total energy expenditure (TEE), cardiac function, and exercise tolerance using a mixed effects linear model testing for an interaction between time (baseline or follow-up) and treatment group. All models included treatment, medical diagnosis, study site and time (baseline or follow-up) as fixed effects, and included patient as a random effect. Skewed data were log transformed. The analyses were conducted in the intent-to-treat population including all randomized patients.

The target sample size of 16 patients per arm was based on having at least 80% power at a 0.05 significance level to detect a 4.1 mean difference in z-score change TEE calculated using a two-sample t-test. This value was based on results from a prior study in which the mean (SD) z-score was -1.12 (3.12) and 5.22 (1.82) for subjects receiving a high-protein or standard diet, respectively.

⁵ DARRTS; IND 113386; SDN 6; review submitted November 1, 2013.

Comments: Although this was a proof-of-concept trial, the authors prospectively defined the outcome and powered the study around the outcome, which are study strengths. That said, both the sensitivity in measurement of TEE and the clinical relevance of change in TEE are unknown. Hence the echocardiographic outcomes measured in this study are exploratory.

The Applicant obtained patient-level data from the trial authors and performed analyses to validate the published findings noting minor discrepancies. Refer to Section [III.16](#) for a summary of noted differences none of which impact the results or conclusions.

The protocol states that the principle investigator, coinvestigators, all subinvestigators, and patients were blinded to treatment. The OHSU study coordinator, the OHSU investigational pharmacy, and the OHSU metabolic nutritionist were unblinded to treatment. No details were provided on how the treatment blind was implemented or maintained.

Study UX007-CL201

Study UX007-CL201 was designed as an exploratory/proof-of-concept study and not as a registrational study. The target sample size of 30 patients was based on feasibility rather than on a testable statistical objective and hypothesis. The statistical analysis plan (SAP) states that the primary study objective was to evaluate the impact of triheptanoin on acute clinical pathophysiology associated with LC-FAOD following 24 weeks of treatment evaluated by several outcome measures. However, following discussions with the Agency, the Applicant focused primarily on the outcome of MCEs comprising hypoglycemia, rhabdomyolysis, and cardiomyopathy over 78 weeks of treatment, which was an extension period outcome. These MCEs were defined rather broadly but focused upon clinical events of rhabdomyolysis, hypoglycemia, and cardiomyopathy that resulted in any hospitalization, emergency department/acute care visit, or emergency intervention (defined as any unscheduled administration of therapeutics at home or in the clinic).

Comments: Skeletal myopathy, hepatic disease, and cardiac disease are widely reported events of clinical importance in patients with LC-FAODs. The study protocol specifically lists each of these as key efficacy outcomes; however, the composite comprising these events is not explicitly stated in the protocol or SAP as a primary or main outcome. While this is a limitation and is illustrative of the exploratory nature of the study, the combination of these clinical events, each of which represents negative outcomes and are of similar clinical importance, is acceptable. To support the analyses of the composite outcome, the rate and duration of each component were calculated and were presented for the pre-triheptanoin and the triheptanoin periods.

The numbers and durations of MCEs were calculated as the total number of events or total duration of clinical events (days), respectively, and annualized by dividing by duration (days) divided by the total duration (days) of data collection/365.25. The MCE annualized events rates (AER) and event durations (AED) from the retrospective (pre-triheptanoin period) and the triheptanoin period were compared by the Applicant using a paired t-test. Given the absence of randomization, time point zero was defined based on study enrollment.

Per the Agency's guidance, the Applicant also analyzed AER and AED using a negative binomial regression (NBR) model to account for follow-up days less than 78 weeks during the pre-triheptanoin period (for infants less than 18 months of age at time of study) and the correlation among events in the same patient when applicable. The NBR model includes period

(pre-triheptanoin versus triheptanoin) as a covariate and time in each period as an offset (log transformed time (years) on study). Covariate effects were tested using the Wald and score statistics.

Comments: The NBR sensitivity analysis was added after discussion with the Agency and was not specified in the SAP. This is the more-appropriate approach to analyzing the primary outcome, which is a count. The paired t-test submitted by the Applicant assumes differences in annual event rates are normally distributed and this seems inappropriate. As such, the Agency views the results from this analysis as primary when interpreting results of this study. It should also be noted that while the choice of analysis did not impact statistical significance, the interpretation of the results is still a concern.

Additional analyses requested by the Agency during the NDA review included one that accounted for the time-varying nature of triheptanoin dosing during the prospective part of the study while also accounting for the dependence between events occurring in the same patient. This analysis used the model described by Anderson and Gill (AG) (Andersen and Gill 1982), which is a modified Cox proportional hazards model modeling time to MCE that assumes that the correlation between event times for a patient can be explained by a time-varying covariate. In the model for study UX007-CL201, the modeled effect was change (5%, 10%, and 15%) in percent daily caloric intake from pretreatment (baseline) MCT to triheptanoin as a time-varying covariate and included on-treatment diet data (gathered from patient completed diary) and on-study MCEs. The model does not include events occurring during the pre-triheptanoin period as the model effect is change in percent DCI during study. The model includes data collected from 25 of the 29 patients who supplied diet diary data during the study. However, the amount of missing diet-based data for the retrospective period was considerably higher.

Study UX007-CL202

The methods used to analyze annualized MCEs observed/reported in study UX007-CL202 were the same as those described for study UX007-CL201. Annualized MCEs are presented by individual study cohort only. No comparative analyses are presented (see comment below) and no inferential testing performed.

Comments: The Applicant compared the MCE annualized event rates between the pre-triheptanoin period and the triheptanoin period in the UX007-CL201 rollover cohort. This analysis comparing the 18-month pre-triheptanoin event rate to the 36-month triheptanoin (combined UX007-CL201/CL202) data suffers from a major limitation, namely that the pre-triheptanoin observation period is one-half the duration of the combined UX007-CL201/CL202 exposure period. For this reason, findings from this biased analysis are not presented in this review.

In addition, the Applicant compared the MCE annualized event rates between the pre-triheptanoin and triheptanoin periods in the triheptanoin-naïve cohort. The analysis is not presented in this review as it is likely confounded by prior treatment (pre-triheptanoin) for which data were not adequately collected and accounted for in the analysis. Essentially, this comparison suffers from the same issues as described for the results presented for study UX007-CL201 and is compounded by the level of disease heterogeneity in the patients enrolled.

6.4. Results of Analyses of Clinical Trials / Studies Intended to Demonstrate Benefit to Patients

Gillingham (2017)

For the reasons noted in Sections 6.2.1 and 6.2.2, this was the only adequate and well controlled trial submitted to NDA 213687. There were no differences in the incidence of clinical events between the purified trioctanoin and food-grade triheptanoin treatment arms.

Thirty-two patients were randomized and treated between two clinical sites located in the United States. Baseline characteristics were generally balanced between treatment arms (Table 12). Males comprised 62% of the study population and the median age was higher in the triheptanoin arm by approximately 8 years, with baseline ages ranging from 7 years to 64 years. All three medical diagnoses were similarly distributed within and between arms and patients generally had unremarkable medical histories. The number of patients diagnosed via newborn screening, in infancy (between 0 years and 2 years), in childhood (2 years to 10 years), and in adulthood (>10 years) were 4 (25%), 4 (25%), 1 (6.2%), and 7 (43.7%) in the triheptanoin arm and 3 (18.7%), 2 (12.5%), 1 (6.2%), and 10 (62.5%) in the trioctanoin arm, respectively. No data were collected on race or ethnicity, preventing assessment by these factors.

Table 12. Baseline Demographic and Clinical Characteristics, Gillingham (2017)

Characteristic	Triheptanoin (N=16)	Trioctanoin(N=16)
Sex, n (%)		
Male	6 (37.5)	6 (37.5)
Female	10 (62.5)	10 (62.5)
Age at enrollment, years		
Mean (SD)	27.2 (15.9)	22.3 (12.7)
Median (min, max)	26.5 (7, 64)	18 (8, 43)
Age at diagnosis, years*		
Mean (SD)	16.5 (19.7)	15.7 (14.2)
Median (min, max)	6.5 (0.04, 63)	14.5 (0.04, 42)
Medical diagnosis, n (%)		
CPT2	5 (31.2)	6 (37.5)
LCHAD/TFP	7 (43.7)	5 (31.2)
VLCAD	4 (25)	5 (31.2)
Baseline height, cm		
Mean (SD)	158.2 (20.8)	161.1 (18.3)
Median (min, max)	164.5 (114.4, 182)	167.6 (121.2, 189.5)
Baseline weight, kg		
Mean (SD)	62.1 (23.5)	67.1 (26.8)
Median (min, max)	64.1 (18.6, 93.8)	67.4 (21.9, 113)
Baseline BMI, kg/m ²		
Mean (SD)	23.5 (5.1)	24.6 (6.0)
Median (min, max)	23.8 (14.2, 32.6)	23.9 (14.9, 34.5)
Site, n (%)		
Oregon Health and Science University	12 (75)	12 (75)
University of Pittsburgh	4 (25)	4 (25)

Characteristic	Triheptanoin (N=16)	Trioctanoin(N=16)
Prior complications, n (%)		
Cardiomyopathy	4 (25)	0 (0)
Hypoglycemia	6 (37.5)	3 (18.7)
Neuropathy	6 (37.5)	4 (25)
Retinopathy	6 (37.5)	4 (25)
Rhabdomyolysis	16 (100)	16 (100)

Source: reviewer created using ADSL.xpt dataset

*Set to 0.04 if newborn screening, infant or birth

Abbreviations: BMI, body mass index; CPT, carnitine palmitoyltransferase; LCHAD, L-3-hydroxy-acyl-CoA dehydrogenase; SD, standard deviation; TFP, trifunctional protein; VLCAD, very long-chain acyl-CoA dehydrogenase

Patients were instructed to record a 3-day diet at the beginning, at week 8 and at the end of the trial. No diet-specific information was collected on the case report forms. Analysis of the diet diary data revealed that only about half of randomized patients completed per-protocol three-day diet diaries. Several patients completed only one or two diet diaries, one in the trioctanoin arm did not return diaries, and the remaining diaries were partially complete. Using reported diary data (no imputation for missing values), the overall average (SD) percent DCI in the triheptanoin (n=16) and trioctanoin arm (n=14) was 16.6% (2.6%) and 14.7% (3.4%), respectively, which is lower than the per-protocol target 20% daily percentage from oil. The dosing observed in this trial is below the Applicant's proposed 25% to 35% DCI, which further complicates interpretation of these data.

As per the publication, no patients were lost to follow-up at the 4-month assessment; however, there were patients excluded from planned analyses because of a lack of, or uninterpretable, data. The lack of ECHO data in six triheptanoin patients and five trioctanoin patients was due to a change in the protocol from cardiac magnetic resonance imaging to ECHO after the randomization of the first seven patients and technical issues that resulted in uninterpretable data in four patients.

Table 13. Patient Disposition and Evaluable Data, Gillingham (2017)

Disposition	Triheptanoin	Trioctanoin
Patients screened	39	
Excluded from study	7 (3 did not meet criteria, 3 declined study, 1 declined in health)	
Randomized	16	16
Lost to follow-up	0	0
Excluded from analyses		
Lipid deposition via MRS	2	3
PCR MRS	8	9
Echocardiogram	6	5
Blood analytes	1	1

Source: Adapted from Gillingham et al. (2017), Supplemental Figure 1

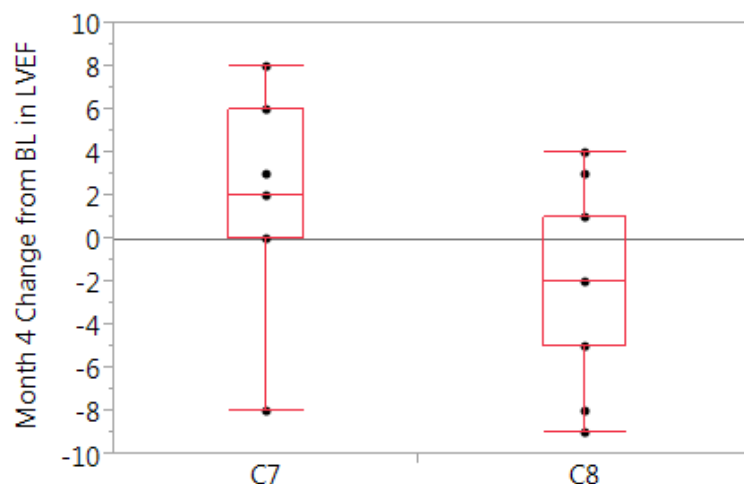
Abbreviations: MRS, ¹H magnetic resonance spectroscopy; PCR, polymerase chain reaction

Change From Baseline in Left Ventricular Ejection Fraction at Month 4

Both baseline and month 4 ECHOs were available for 10 (62.5%) and 11 (68.7%) patients in triheptanoin and trioctanoin arms, respectively. Median (range) left ventricular ejection fraction (LVEF) was 59% (32, 65) and 63% (55, 69) at baseline, and 59.5% (38, 67) and 62% (53, 66) at month 4 in triheptanoin and MCT, respectively. [Figure 3](#) illustrates a relative improvement in LVEF by a reported 7.4%. The improvement was based on small improvements in individual subjects where the baseline values in the cohort were within normal range and the improvements

were also within normal range. These changes were within the test/retest variability normally observed in repeated ECHOs. Thus, the changes in LVEF were not clinically significant. In addition, none of the patients developed cardiomyopathy or had a worsening of cardiac function during the trial.

Figure 3. Month 4 Change From Baseline in LVEF, Gillingham (2017)



Source: reviewer created using ADECHO.xpt dataset

Abbreviations: BL, baseline; C7, triheptanoin; C8, trioctanoin; LVEF, left ventricular ejection fraction

After 4 months, patients in both groups had similar mean fold change from baseline in LVEF and wall mass on resting ECHO and had similar maximal heart rates on treadmill ergometry. As all patients were noted to have normal ECHO evaluations at baseline, the clinical meaningfulness of changes from baseline that are also within normal standards is unclear. The clinical meaningfulness of the heart rate changes also is unclear as they remained within normal ranges throughout the trial assessments.

***Comments:** The review team concludes that no clinically meaningful differences were observed between the two treatment arms. It is reasonable to conclude qualitatively that patients did not worsen on dietary triheptanoin during the four months they were enrolled in the trial.*

Analysis of Total Energy Expenditure (TEE)

Although the Gillingham trial was designed for proof-of-concept and was hence exploratory, the sample size was based on the TEE outcome and therefore assessed in this review ([Table 14](#)). Overall, changes in TEE from baseline to month 4 were modest and did not differ between treatment arms.

Table 14. Summary of Efficacy Outcomes, Gillingham (2017)

Outcome	Triheptanoin (n=16)	Trioctanoin (n=16)
TEE, mean (SD), kg/d		
Baseline	2205.6 (481.1)	2575.1 (645.4)
Month 4 follow-up	2312.1 (695)	2502.4 (745.4)
Change from baseline at 4 months		
Mean (SD)*	100.7 (374.7)	-68.1 (323.7)
Median (range)	-47.7 (-303, 791)	-42.2 (-653.5, 280)
% change from baseline at 4 months	4.0 (18.6)	-2.8 (3.5)
Measures of cardiac function**		
Baseline EF% of LV, mean (SD)	58.4 (7.9)	60.4 (4.6)
Month 4 EF% of LV, mean (SD)	56.3 (9.4)	62.3 (5.2)
Change from BL at month 4, mean (SD)	2.1 (4.4)	-1.9 (4.1)
Baseline wall mass (g), mean (SD) [median]	124.3 (43.7) [120]	91.3 (39.9) [88]
Month 4 wall mass (g), mean (SD) [median]	114.9 (47.9) [88]	102.8 (38.5) [112]

Source: reviewer created using ADENERGY.xpt, ADECHO.xpt and EFF.xpt datasets

*values differ from publication supplementary table 1, which shows means of 107.4 and -72.67. reasons for differences unknown but overall conclusions the same

**includes patients with both a baseline and month 4 assessment

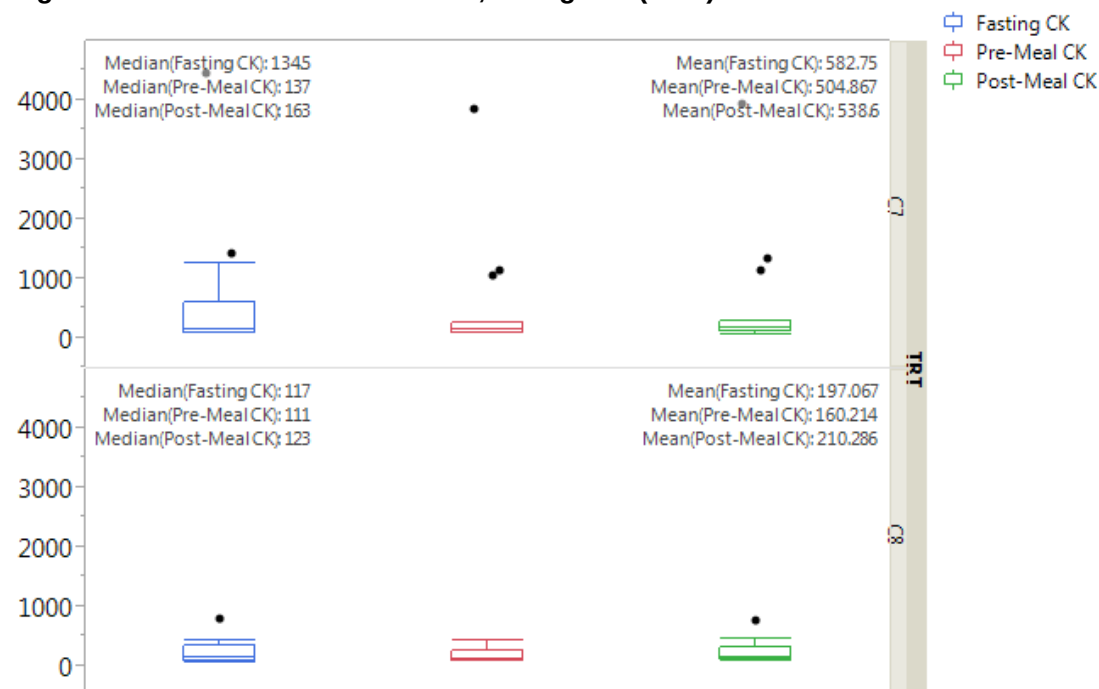
Abbreviations: EF, ejection fraction; LV, left ventricular; SD, standard deviation; TEE, total energy expenditure; g, gram

Analysis of Creatine Kinase (CK) at Month 4

CK was measured after fasting and before and after a meal at the month 4 visit as shown below ([Figure 4](#)). The CK values were similar between treatment arms at each measure; however, there were measures well above the upper-quartile of the data.⁶ Comparisons of median values at each time point suggest no differences between treatment arms.

⁶ CK normal ranges are both age and gender based and may vary slightly by laboratory. The currently published Mayo Clinic Laboratories note that for males >3 months of age, the normal reference range is 39 U/L to 308 U/L, whereas in females >3 months of age the normal reference range is 26 U/L to 192 U/L.
<https://endocrinology.testcatalog.org/show/CK>

Figure 4. Creatine Kinase at Month 4, Gillingham (2017)



Source: reviewer created using EFF.xpt legacy dataset
Abbreviations: CK, creatine kinase

There were seven rhabdomyolysis events in each treatment arm during the 4 months of treatment occurring in five (31.2%) and four (25%) patients in the trioctanoin (C8) and triheptanoin (C7) arms, respectively. Similarly, there were no differences between treatment arms in muscle phosphocreatine use or recovery during the controlled exercise (results not shown). There were no reported cardiomyopathy or hypoglycemia events. Due to the absence of a treatment effect and limited sample size, efficacy analyses by subgroups were not performed.

In summary, the Gillingham (2017) trial was a randomized, double-blind, proof-of-concept trial performed in 32 patients with LC-FAOD with a history of nonsevere disease who were stable at baseline. Patients received an average dose of approximately 15% total DCI of either triheptanoin or trioctanoin. The trial did not demonstrate a difference between treatment arms in the clinical events of interest or in the incidence of rhabdomyolysis. Changes in cardiac function were limited to a small set of patients with evaluable data and were of questionable clinical relevance. Ultimately, labeling reflects that patients in both groups demonstrated a similar mean-fold change from baseline in left ventricular ejection fraction and in wall mass on resting echocardiogram. They also exhibited similar maximal heart rates on treadmill ergometry.

The trial results suggest that stable patients with nonsevere LC-FAOD generally tolerated C7 or C8 treatment without suffering from severe clinical outcomes during the 4 months of treatment. Given the trial's limited duration and negative findings, this study does not provide adequate evidence of efficacy to demonstrate the superiority of triheptanoin over other sources of medium-chain triglycerides for the treatment of LC-FAOD. However, these findings do show that triheptanoin is well-tolerated in patients with LC-FAOD. Qualitatively, no clinically meaningful differences are observed between treatment with triheptanoin and trioctanoin, providing adequate evidence of efficacy to support a recommendation for approval of

triheptanoin as an alternative source of calories and fatty acids for the treatment of patients with LC-FAOD.

Study UX007-CL201

In this single arm, nonrandomized, switch study, 30 patients were screened, and one failed to meet study inclusion criteria. Among the 29 enrolled and treated patients, 24 (82.7%) completed the trial, 4 (13.8%) prematurely discontinued due to treatment-emergent adverse events and 1 (3.4%) withdrew consent for unknown reasons. Two patients, (b) (6), prematurely discontinued on days 2 and 6, respectively. The other three patients prematurely discontinued after 54 days, 58 days, and 538 days of triheptanoin treatment. Baseline characteristics of the 29 enrolled patients are summarized in Table 15. The median age at study enrollment was 5.3 years and ranged from 0.9 to 59 years. Most patients were white, non-Hispanic, were enrolled in the United States, and had an average body mass index of 21.5 kg/m². Note that the Applicant did not categorize patients by LC-FAOD disease severity, so that factor has not been summarized.

Table 15. Baseline Demographics and Characteristics, All Enrolled, Study UX007-C201

Characteristic	Triheptanoin, N=29
Sex, n (%)	
Male	17 (58.6)
Female	12 (41.4)
Age, years	
Mean (SD)	12.1 (13.2)
Median (min, max)	5.3 (0.9, 58.9)
Age at diagnosis, years	
Mean (SD)	5.5 (12.9)
Median (min, max)	0.1 (0, 56.7)
Race, n (%)	
White	25 (86.2)
Asian	21 (6.9)
Black/African American	1 (3.4)
Other	1 (3.4)
Ethnicity, n (%)	
Hispanic	3 (10.3)
Non-Hispanic	26 (89.6)
Country, n (%)	
United States	24 (82.7)
United Kingdom	5 (17.2)
Medical diagnosis, n (%)	
CPT II	4 (13.8)
LCHAD	10 (34.5)
TFP	3 (10.3)
VLCAD	12 (41.4)
Height, cm	
Mean (SD)	126.7 (36.7)
Median (min, max)	118 (71, 186.5)
Weight, kg	
Mean (SD)	42.1 (34.1)
Median (min, max)	22.8 (8.4, 125.6)

Characteristic	Triheptanoin, N=29
BMI, kg/m ²	
Mean (SD)	21.5 (6.8)
Median (min, max)	18.0 (13.8, 37.7)

Source: reviewer created using ADSL.xpt dataset

Abbreviations: BMI, body mass index; CPT II, carnitine palmitoyltransferase II; LCHAD, L-3-hydroxy-acyl-CoA dehydrogenase; TFP, trifunctional protein; SD, standard deviation; VLCAD, very long-chain acyl-CoA dehydrogenase

Missing Data Patterns

A major challenge in interpreting results from study UX007-CL201 is the retrospective nature of the pre-triheptanoin events and nutritional status. Given that the disorders under study are managed through focused modifications to nutritional balance and intake, specifically exogenous fat supplementation, it is essential to understand the dietary details during the pre-triheptanoin period, which was intended to serve as the control against which events during the triheptanoin period are compared. The Applicant attempted to retrospectively obtain diet-specific information from the pre-triheptanoin period covering up to at most 78 weeks prior to enrollment. However, the available data were grossly incomplete such that sparse data were obtained in only 38% of patients (11 of 29).

Table 16. Summary Statistics, Diet Parameters by Study Visit, Study UX007-C201

DCI (kcal/kg/day)	Prestudy	Run-In	Baseline	Week 12	Week 24	Week 48	Week 78
Total DCI							
N	11	29	28	24	25	23	23
% missing	62.1	0	3.4	17.2	13.8	20.7	20.7
Mean (SD)	76.2 (29.9)	60.7 (29.9)	63.4 (31.0)	68.7 (37.9)	73.6 (40.7)	78.9 (39.8)	70.5 (39.8)
Median (range)	84.9 (32.7, 123.8)	57.4 (17.9, 130.2)	63.6 (18.4, 132.5)	69.1 (17.0, 165.8)	70.0 (18.4, 143.5)	68.5 (17.6, 151.4)	63.1 (18.3, 158.0)
Dietary source of % DCI							
MCT fat							
N	11	28	28	24	25	23	24
% missing	62.1	3.4	3.4	17.2	13.8	20.7	17.2
Mean (SD)	24.5 (7.7)	17.9 (7.9)	17.3 (9.8)	28.4 (5.5)	27.6 (5.4)	26.4 (6.6)	27.5 (5.4)
Median (range)	22 (12.7, 36.2)	19.7 (0, 33)	20 (0, 37)	27.8 (17, 38)	26.8 (18.2, 37.0)	27.0 (12.3, 36)	28 (14.4, 36.4)
Total fat							
N	12	29	28	24	25	23	24
% missing	58.6	0	3.4	17.2	13.8	20.7	17.2
Mean (SD)	35.4 (9.6)	30.8 (7.8)	30.8 (9.4)	36.7 (8.9)	38.3 (7.4)	36.9 (6.5)	38.4 (5.9)
Median (range)	31.8 (24.5, 49)	32 (16.8, 48)	30.5 (14.2, 52)	37.9 (7, 50)	36.1 (25, 54)	38 (19, 47)	37.5 (28, 49.7)
Protein							
N	10	29	28	24	25	23	24
% missing	65.5	0	3.4	17.2	13.8	20.7	17.2
Mean (SD)	12.5 (3.4)	13.4 (4.4)	14.0 (4.6)	14.3 (3.7)	14.7 (5.0)	15.6 (4.3)	14.0 (2.8)
Median (range)	12.6 (8.4, 19)	12.2 (7, 28.2)	13.5 (6, 25.2)	14 (7.5, 21)	13 (8, 26)	15 (9, 25.6)	13.6 (8, 19.5)
Carbohydrate							
N	10	29	28	24	25	23	24
% missing	65.5	0	3.4	17.2	13.8	20.7	17.2
Mean (SD)	52.6 (7.8)	55.8 (8.9)	54.8 (10.0)	47.6 (7.5)	46.4 (10.5)	47.0 (7.5)	47.5 (7.9)
Median (range)	54.0 (38.6, 63)	55.0 (38, 75)	55.8 (34, 76)	46.5 (31, 61)	48.7 (24.4, 66)	47 (33, 62)	49 (29.1, 62)

Source: reviewer created using ADDIET.xpt, ADRDIET.xpt and XD.xpt datasets

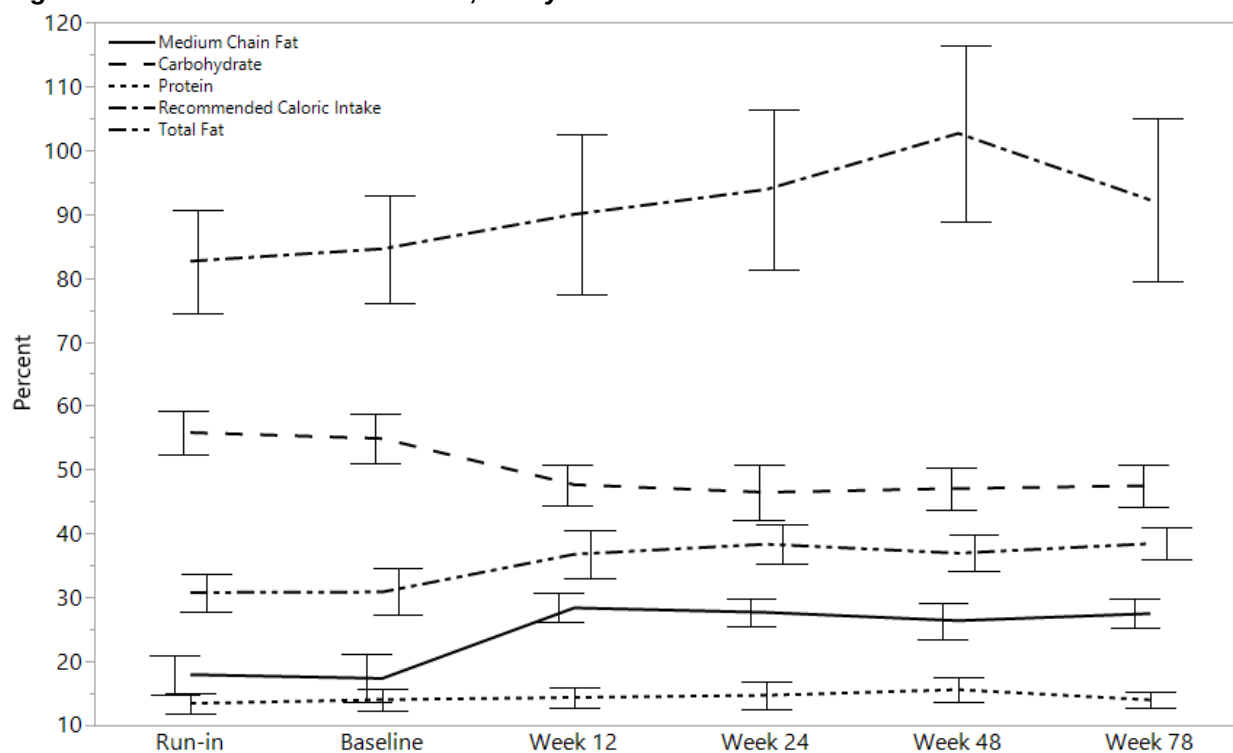
Patients (b) (6) did not receive MCT oil during run-in or at baseline

Abbreviations: DCI, daily caloric intake; MCT, medium-chain triglyceride; SD, standard deviation

Trends in Dietary Parameters

Figure 5 illustrates the percent mean and associated 95% confidence intervals (CIs) for carbohydrate, protein, total fat, MCT, and recommended daily caloric intake by study visit. As illustrated, there was an increase in mean percent total recommended DCI between the run-in period and study week 48, accounting for an increase of approximately 33% in total daily calories over this period. Similarly, as shown in the solid line, the mean (SD) percent DCI from MCT increased from approximately 17% (10%) to 28% (5%). Review of individual dietary records was notable for increases in DCI that increased from baseline DCI to 10% to 45% above baseline. This level of increase in DCI is greater than what would be anticipated by an increase in kcal/kg/day provided solely by medium-chain fat (triheptanoin) and appears to represent an overall optimization of diet after baseline.

Figure 5. Diet Parameters Over Time, Study UX007-CL201



Source: reviewer created using ADDIET.xpt dataset

Note: Dietary Reference Intakes are established by the Institute of Medicine and are calculated using height, weight, age and activity level (<https://www.nal.usda.gov/fnic/dietary-reference-intakes>). They are used to represent dietary needs as a recommended daily allowance (RDA)/daily recommended intake (DRI) in a healthy population and are also utilized as a basis for dietary recommendations in patients with a dietary-dependent inborn error of metabolism. The y-axis represents the percentage of intake compared to the daily recommended intake for total caloric intake and then for the variables listed, the percentage of the individual daily caloric intake compared to the total calories.

(b) (4)

Study UX007-CL202

This study was ongoing at the time of submission of the NDA with 75 enrolled patients by the point of the data cut-off. It included 24 who completed study UX007-CL201 (the rollover cohort), 31 patients with prior triheptanoin treatment from investigator-sponsored trials (ISTs), expanded access, or compassionate use programs, and 20 triheptanoin-naïve patients. The triheptanoin-naïve patients were not required to fulfill the same inclusion criteria as those required for entry in study UX007-CL201, and they were considered for enrollment at the discretion of the site investigator and Applicant. Patients came from the United States or the United Kingdom, were mostly white, non-Hispanic with similar proportions of males and females. Patients with VLCAD comprised the majority (35%) of patients followed by patients diagnosed with LCHAD (32%), CPT II (15%), and TFP (13%). There was a limited number of

patients with a diagnosis of CACT or CPT I. The median age at enrollment was 9.8 years, which was quite high compared to the mean age at diagnosis of less than one year. This difference is explained as most patients were on a prior treatment protocol. As expected, the triheptanoin-naïve cohort included the youngest patients overall ([Table 21](#)).

Table 21. Baseline Characteristics, Study UX007-CL202

Characteristic	Cohorts			
	CL201 Roll Over n=24	IST/Other n=31	Triheptanoin Naïve n=20	All Cohorts N=75
Sex, n (%)				
Male	14 (58.3)	13 (58.1)	12 (60)	39 (52)
Female	10 (41.7)	18 (58.1)	8 (40)	36 (48)
Age, years				
Mean (SD)	13.2 (14.3)	17.6 (14.2)	8.9 (7.8)	13.9 (13.2)
Median (min, max)	6.6 (2.4, 60.2)	14.4 (1.4, 63.3)	7.3 (0.3, 22.0)	9.8 (0.3, 63.3)
Age at diagnosis, years				
Mean (SD)	6.0 (13.9)	6.3 (12.3)	2.7 (5.4)	5.2 (11.5)
Median (min, max)	0.06 (0, 56.7)	7.2 (0, 49.2)	0.06 (0.01, 17.5)	0.09 (0, 56.7)
Race, n (%)				
White	21 (87.5)	29 (93.5)	16 (80)	66 (88)
Asian	1 (4.2)	0	1 (5)	2 (2.3)
Black/African American	1 (4.2)	1 (3.2)	2 (10)	4 (5.3)
Other	1 (4.2)	1 (3.2)	1 (5)	3 (4)
Ethnicity, n (%)				
Hispanic	3 (12.5)	3 (10)	1 (5)	7 (9.4)
Non-Hispanic	21 (87.5)	27 (90)	19 (95)	67 (90.5)
Missing	0	1	0	0
Country, n (%)				
United States	20 (83.3)	31 (100)	18 (90)	69 (92)
United Kingdom	4 (16.7)	0	2 (10)	6 (8)
Medical diagnosis, n (%)				
CPT I	0	0	1 (5)	1 (0.1)
CPT II	3 (12.5)	6 (19.3)	2 (10)	11 (14.7)
CACT	0	1 (3.2)	2 (10)	3 (4)
LCHAD	9 (37.5)	9 (29.0)	6 (30)	24 (32)
TFP	3 (12.5)	4 (12.9)	3 (15)	10 (13.3)
VLCAD	9 (37.5)	11 (35.5)	6 (30)	26 (34.7)
Height, cm				
Mean (SD)	129.3 (29.8)	151.2 (28.0)	121.7 (40.8)	136.3 (34.5)
Median (min, max)	125.3 (88.5, 183)	159.2 (75.6, 186.4)	122.5 (52, 183.1)	137.6 (52, 186.4)
Weight, kg				
Mean (SD)	41.2 (32.5)	58.6 (31.0)	37.7 (32.4)	47.5 (32.8)
Median (min, max)	26.4 (12.2, 121.5)	56 (9.5, 155.5)	24.6 (5.5, 114.2)	37.6 (5.5, 155.5)
BMI, kg/m ²				
Mean (SD)	20.8 (6.9)	23.9 (7.8)	21.0 (7.2)	22.1 (7.4)
Median (min, max)	17.2 (14.2, 36.3)	21.7 (16.0, 56.7)	17.1 (11.9, 37.7)	20.7 (11.9, 56.7)

Source: reviewer created using ADSL.xpt dataset

Baseline characteristics of the UX007-CL201 study rollover cohort are characteristics at time of rollover.

IST = investigator-sponsored trials (Oregon Health & Science University, University of Pittsburgh, and Ultragenyx Pharmaceutical (ClinicalTrials.gov Identifiers: NCT01379625 (n=3), NCT01461304 (n=27)) and n=1 from emergency IND.

Abbreviations: BMI, body mass index; CACT, carnitine-acylcarnitine translocase; CPT I, carnitine palmitoyltransferase I; CPT II, carnitine palmitoyltransferase II; LCHAD, L-3-hydroxy-acyl-CoA dehydrogenase; TFP, trifunctional protein; SD, standard deviation; VLCAD, very long-chain acyl-CoA dehydrogenase

Ten patients (two CL201 cohort, five IST/other cohort, and three triheptanoin-naïve cohort) prematurely discontinued from study UX007-CL202 due to death (n=2), physician decision (n=1), protocol violation (n=1), Applicant decision (n=2), noncompliance (n=2), and withdrawal of consent (n=2). Of the two patients who withdrew consent, one was a rollover patient (b) (6) whose dietary MCT increased 20% from baseline upon enrollment in study UX007-CL201, and the other (b) (6) was a treatment-naïve patient who withdrew after less than one month of enrollment. Further details were not provided.

Duration of exposure to triheptanoin in the extension study/UX007-CL202 at the time of data cutoff was on average 23, 35, and 16 months in the CL201, IST/other, and triheptanoin-naïve cohorts, respectively. Only the IST/other cohort included patients with more than 18 months exposure at baseline. Twenty-four patients enrolled in study UX007-CL201 were rolled over to study UX007-CL202. Of the 24 patients, 22 completed at least 18 additional months of triheptanoin treatment in addition to the 18 months of triheptanoin received during study UX007-CL201 for a total of at least 36 months of exposure. Two patients discontinued after 23 and 26 total months of total exposure, respectively. For the 22 patients who were initially enrolled in study UX007-CL201 and continued to receive triheptanoin in study UX007-CL202 for a total of at least 36 months, the median duration of exposure was 42.4 months (range 36 to 54 months) at the time of data cutoff for the NDA.

Table 22. Duration of Exposure to Triheptanoin, Study UX007-CL202

	UX007-CL201		
Duration of Exposure	Rollover	IST/Other	Triheptanoin Naïve
Duration (months)			
N	24	31	20
Mean (SD)	23.0 (6.2)	34.8 (5.6)	15.7 (11.5)
Median	24.3	35.6	14.5
Range	2.9, 32	18.2, 41.3	6.6, 35.2
Category of duration, n (%)			
<6 months	1 (4.2)	0	5 (25)
6–<12 months	1 (4.2)	0	3 (15)
12–<24 months	9 (37.5)	2 (6.4)	6 (30)
24–<36 months	13 (54.2)	11 (35.5)	6 (30)
36–<48 months	0	18 (58.1)	0
≥18 months	22 (91.7)	31 (100)	7 (35)
≥36 months	0	18 (58.1)	0

Source: reviewer created using ADEX.xpt dataset

Duration only include time on study CL202 (does not include prior time for patients previously treated with triheptanoin)

IST = investigator-sponsored trials (Oregon Health & Science University, University of Pittsburgh, and Ultragenyx Pharmaceutical (ClinicalTrials.gov Identifiers: NCT01379625 (n=3), NCT01461304 (n=27)) and n=1 from emergency IND

Abbreviations: SD, standard deviation

(b) (4)

6.5. Review Issues Relevant to the Evaluation of Benefit

The review team was unable to find conclusive evidence to support superior efficacy of triheptanoin over the current standard of care for the indication proposed by the Applicant with NDA submission. A more limited indication was agreed for triheptanoin “as a source of calories and odd-chain fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD).”

Identified review concerns included the lack of adequate and well-controlled clinical trial data in patients with LC-FAOD, whose disease is not adequately controlled on current management. Those review issues relevant to the evaluation of benefit included insufficient duration and scope of data provided by the Gillingham randomized comparative trial and also included the study design of the Applicant’s phase 2 clinical study UX007-CL201. Due to these concerns, only limited study data were provided in labeling, which was restricted to a global interpretation of Gillingham (2017) and supported by data on treatment from studies UX007-201/UX007-202.

6.5.1. Gillingham Trial

Issues

Lack of long-term natural history data describing the heterogeneity of disease and rate of disease progression

Analysis

Because the Gillingham (2017) trial was a randomized, double-blind, comparative design, the data support the efficacy of triheptanoin in patients with LC-FAOD. An important factor in this evaluation is that the to-be-marketed formulation of triheptanoin is a comparable product to the food-grade triheptanoin used in the trial (IND 113386). Refer to CMC comments in Section 9 for more details.

While this trial provides randomized, comparator data, it is limited in the ability to provide conclusive, long-term data on the efficacy of triheptanoin for the Applicant's proposed dose and indication for the following reasons.

- On average, the triheptanoin in Gillingham (2017) trial dose comprised approximately 17% of total DCI, considerably less than the Applicant's initially proposed 25% to 35% DCI target dose range. These estimates were based on partially complete patient diet diaries collected at three time points during the trial.
- The level of disease in the study population was prespecified as nonsevere, where patients were selected by medical histories without severe or repetitive catabolism or associated sequelae. The Applicant's initially proposed indication for triheptanoin was for the treatment of patients with LC-FAOD (b) (4). In contrast, the Gillingham (2017) trial required stable disease but did not require optimized control.
- The trial duration was only 4 months with in-person assessments occurring at baseline and at month 4. This limited trial duration prevents a complete assessment of long-term treatment maintenance and tolerability.
- This trial was designed as a research trial to objectively assess the effects of triheptanoin on total energy exposure and several other outcomes that are all considered exploratory. Although the trial collected information on incidence of rhabdomyolysis—a clinically-meaningful outcome—the trial was not powered to demonstrate a difference between treatment arms on this outcome.
- The effect of triheptanoin and trioctanoin on cardiac physiology was assessed with resting ECHO and treadmill ergometry. After 4 months, patients treated with triheptanoin and trioctanoin had comparable findings on resting ECHO, with similar mean-fold change from baseline in LVEF and wall mass. Patients in the two treatment groups also had similar maximal heart rates on treadmill ergometry.

Conclusion

The basis for the Division's rationale for changing the indication to "a medium-chain triglyceride indicated as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD)" is the following:

- The data provided from the Gillingham (2017) trial can be used to support the use of triheptanoin in place of MCT oil in patients with LC-FAOD. While this trial only enrolled clinically stable patients, it is supported by the safety profiles of patients enrolled in studies UX007-CL201/UX007-CL202 and EA INDs who were at greater risk for metabolic events due to catabolism. This decision is predicated on the current

understanding that LC-FAOD patients who receive insufficient calories or too much long-chain fatty acid (via oral intake, G-tube or intravenous administration) can experience life threatening metabolic crises within hours to days (Merritt et al. 2018).

- The data do not provide evidence to support triheptanoin use to prevent or to reduce clinical events as this study did not measure such outcomes.

6.5.2. Nonrandomized Study UX007-CL201

Issue

The Applicant's primary study, submitted to demonstrate both efficacy and safety, was not an adequate and well-controlled study.

Analysis

Study UX007-CL201 was not an adequate and well-controlled study as efficacy outcomes described by MCE were significantly confounded by additional changes in diet made prior to and at the time of introduction of triheptanoin. Therefore, results from study UX007-CL201 cannot serve as the primary evidence to support the efficacy of triheptanoin for the proposed indication and will not be included in section 14 of the label.

As discussed in Section [6.2.1](#), the study design is flawed as patients, on average, received anywhere from 0% to 33% DCI as medium-chain triglycerides during the pre-triheptanoin run-in period. Upon switch to triheptanoin, this amount increased to between 25% and 35% DCI. Therefore, the results are confounded by the change in percentage of medium-chain fat daily calories. Upon starting triheptanoin, there was an average of a nearly 20% increase in total DCI. Because diet is the current standard of care for LC-FAOD, this DCI increase makes it difficult to separate the notable change in total intake of medium-chain fat and total caloric intake from any possible treatment effect from triheptanoin. Furthermore, data on diet management during the pre-triheptanoin period covering up to 78 weeks are grossly lacking in detail except for the data collected during the run-in period covering 4 weeks prior to initiation of triheptanoin.

Though the Applicant reports that study investigators ensured complete medical records for the 18 months prior to triheptanoin initiation upon enrollment, the diet-related data are grossly inadequate. Specifically, data were limited to one or two pre-triheptanoin assessments in only 11 out of 29 patients. Management guidelines by Genetic Metabolic Dietitians International recommend that patients diagnosed with VLCAD are assessed by a metabolic nutritionist and/or a medical provider at least annually when disease is stable and more frequently when disease is unstable (Southeast Regional Genetics Network 2019b). While the guidelines were written for patients diagnosed with VLCAD, they can be applicable for all patients with LC-FAOD. Patients eligible for study UX007-CL201 were required to have a recent history of multiple episodes of acute disease exacerbation or chronic disease exacerbation. The lack of diet-specific data in more than half of this severely affected study population suggests an issue of data quality as it would not be expected given the recommendations for management of disease this severe. Further, the sparseness of the pre-triheptanoin data on dietary intake provided on the 11 enrolled patients calls into question whether these data can be accurately extrapolated to the remaining 18 patients for whom data were not available. Given the variability in LC-FAOD medical diagnoses, patient ages, clinical sites and standards of practice, there is no way to verify that the missing data (n=18 patients) resemble the available data (n=11 patients).

Conclusion

Findings from study UX007-CL201 can be used to infer that the change from MCT oil to triheptanoin appears reasonably safe, as it does not appear to increase the risk of serious adverse events. In patients who were not on any source of MCT oil prior to enrollment, the introduction of triheptanoin into their diet also did not appear to provoke catabolism.

6.5.3. Variability in Clinical Events Assessment (Study UX007-CL201)

Issue

The criteria for hospitalization or emergency department visits due to MCEs were not standardized.

Analysis

In study UX007-CL201, major clinical outcomes experienced prior to treatment with triheptanoin were collected retrospectively, by each investigator, at the time of screening. However, the definitions of each event (rhabdomyolysis, hypoglycemia, and cardiomyopathy) were loosely defined in the study protocol. This allowed for variability across clinical centers and investigators regarding what constituted an event. Specifically, major rhabdomyolysis events were those leading to emergency room/acute care visits, hospitalizations, emergency interventions (at home or in the clinic), or any similar event. The protocol did not specify target creatine kinase values or any other clinical measure to define this outcome, or interventions to be made. Similarly, the evaluation for cardiomyopathy considered ECHO, ECG or additional tests (not specified) as medically indicated. Hypoglycemia was more specifically defined as serum glucose levels <60 mg/dL that occur at home and require treatment.

Conclusion

Given the subjective nature of these definitions for events comprising the primary outcome there is concern that variability by investigator may have been introduced. Therefore, the comparative assessments of the pre-triheptanoin and triheptanoin event rates cannot be viewed as conclusive.

6.5.4. Data Do Not Support the Proposed Indication

Issue

The data submitted in the NDA do not support the Applicant's proposed indication of use for triheptanoin.

Assessment

The Applicant's initially proposed indication was the following: "(b) (4)"
"for the treatment of adult and pediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD)" (b) (4)

Due to the level of confounded dietary data in study UX007-CL201, this proposed indication cannot be considered. However, triheptanoin may be considered a source of dietary calories, as similar to dietary sources of C8, based upon the following:

- During the Gillingham (2017) trial (IND 113386), patients on C8 had sufficient exposure duration to assess their risk of catabolism. Patients on C8 did not immediately go into catabolism or worsen in their disease status, as would be expected if they ingested food that they could not utilize based upon the underlying common mechanisms of LC-FAOD.
- Records from studies UX007-CL201 and UX007-CL202 demonstrated continued growth at anticipated rates after switchover from MCT oil or previous diet, suggesting that the calories supplied by triheptanoin were used similarly as those from MCT oil. Taken together, these data suggest that triheptanoin is an appropriate source of dietary medium-chain fat for patients with LC-FAOD.

Conclusion

The Agency recommends the following indication: Triheptanoin “is a medium-chain triglyceride indicated as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD).”

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

There were no significant safety concerns identified in general toxicology studies conducted following oral administration of triheptanoin in rats and minipigs. Oral administration of triheptanoin for 9-months in minipigs was well tolerated. In the single-dose oral gavage administration of triheptanoin at up to 4.75 g/kg (5.0 ml/kg) to adult male and female Wistar rats, a dose equivalent to 13% daily caloric intake (study CL74-95-1045), there were no animal deaths or signs of toxicity seen for 14 days following dosing.

The chronic (9-month) dietary administration of triheptanoin at 30% (up to 21 g/kg) or 50% (up to 35 g/kg) of diet or soybean oil (control diet) in juvenile (2 months old) male rats was generally well tolerated (Ataíde et al. 2009). There were no significant differences observed in the clinical chemistries and lipid profile or in the urinalysis between the control and treatment groups. However, the relative liver weights were higher in the soybean oil diet group than in the triheptanoin diet group, and all the study animals showed macrovesicular hepatic steatosis upon histopathological examination. There was no correlation of the steatosis to clinical chemistries, suggesting that liver function was not affected. Histopathological changes seen in the small intestine include discrete atrophy or hyperplasia of villi, which did not affect digestive functions. In addition, lymphoid follicular hyperplasia, a case of muco-secreting adenocarcinoma in the duodenum, and four cases of “other alterations” in the duodenum were observed in treated animals, but not in control animals.

The authors stated that similar alterations (adenocarcinoma and two cases of alterations) were also observed in the control animals administered soybean oil. However, the study did not use

any saline or water control, and the relevance of these findings to treatment cannot be ruled out. This was not a good laboratory practice (GLP)-compliant toxicology study, and only a limited number of tissues were examined histologically. The proliferative changes observed in the rat intestine may suggest that oral administration of triheptanoin has a potential for causing tumors in rodents. In addition, in a study conducted by NTP, chronic administration of a similar LCT (tricaprylin, C8) in rats caused increased incidences of fore-stomach and pancreatic adenoma but not carcinoma (National Toxicology 1994).

The chronic (9-month) dietary toxicity of triheptanoin was assessed in juvenile male and female minipigs (the equivalent human age of >2 years) at doses of 10%, 30%, or 50% DCI following dosing (study UX007-PC002). Triheptanoin was well tolerated without any treatment-related toxicity or deaths. Two high-dose animals died from a prolapsed penis and a urinary tract infection, which are common occurrences in minipigs. There were no test article-related changes in body weight, body weight gain, hematology profiles, organ weights, or histopathology, and no target organs of toxicity were identified. The brief inappetence seen in the 30% and 50% DCI dose groups was over in 2 days as the animals ate all their rations afterwards. The observed changes in hematology, clinical chemistry, and lipid parameters were not dose-related, occurred intermittently in one sex or the other, and are secondary to reduced iron and protein content in the dietary admixture. Gross and histopathology assessments did not show any changes in any organ or tissue that could be considered treatment-related. The no observed adverse effect level (NOAEL) for daily administration of triheptanoin for 9 months in minipigs was 50% DCI. The safety margin for clinical dose is approximately 4X, and is based on the area under the concentration time curve (AUC) of heptanoate at the NOAEL in the minipig study and the mean AUC in the clinical study (UX007-CL101) at a dose of 1.25 g/kg/day or 30% DCI.

Triheptanoin was not mutagenic in the Ames assay up to 4800 µg/plate, did not induce chromosomal aberration in vitro in human peripheral blood lymphocytes up to 409 µg/ml, and it was negative in the in vivo rat micronucleus assay at up to 2000 mg/kg/day.

In the segment 1 oral reproductive toxicity study in rats, there were no treatment-related effects on male and female fertility. The slow acceptance of the female rats to triheptanoin (10%, 30%, or 50% DCI) lasted 1 week before adjustment. Body weights were significantly reduced in the 50% DCI dose group in the first week, and body weight gains were reduced in males dosed with 50% DCI and in females dosed with 30% and 50% DCI prior to mating. There were no noteworthy treatment-related necropsy findings in the animals. There were also no treatment effects on mating performance or relative reproductive organ weights. There was no impact on male or female fertility. The NOAEL for fertility and reproductive performance in male and female rats was 50% DCI.

In the segment II oral embryofetal developmental toxicity study in rats dosed with triheptanoin at 10%, 30%, or 50% DCI, there were no clinical signs of toxicity observed over the gestation period of days 6 through 17 except reduced food consumption and reduced body weight. However, gross necropsy observations showed one dam in the 30% DCI dose group with brown fluid in the uterus and another dam in the 50% DCI dose group had red ovaries. Reduced food consumption from inappetence in the 30% and 50% DCI dose group resulted in reduced body weight and body weight gain in the dams during gestation days 6 through 12. Although litter viability and litter weights were not affected, there were incidences of skeletal malformations in the fetuses from dams in the 50% DCI dose group. Skeletal examination of fetuses from the 30% DCI dose groups were unaffected. The alterations seen in the fetuses from the 50% DCI dose

dams were associated with maternal toxicity occurring from reduced body weight and body weight gain. The NOAEL for maternal toxicity of triheptanoin was 10% DCI, while the NOAEL for embryofetal developmental toxicity was 30% DCI. The adverse effects observed in pregnant rats were related to reduced body weights and lower mean body weight gain, indicative of maternal toxicity in both 30% and 50% triheptanoin treated dams. The body weight reductions observed in the pregnant animals was due to reduced food intake, possibly associated with flavor aversion to triheptanoin admixed in the diet which is not a normal constituent of rodent chow. Thus, the adverse effects observed in these animals were attributed to a taste aversion effect triggering a reduced food intake and are not related to the pharmacological effects of triheptanoin or its primary metabolites.

In the segment II oral embryofetal developmental toxicity study in rabbits dosed with triheptanoin at 10%, 20%, or 30% DCI, dietary inappetence was very severe with animals in the 20% DCI dose group consuming 70 g to 90 g out of 120 g of food provided and those in the 30% DCI dose group consuming just 13-20 g out of the 105 g of food provided. However, rabbits in the 10% DCI dose group were unaffected. Consequently, there were both increases and decreases in body weight at these doses. Thus, oral gavage administration of a high dose of triheptanoin oil was not tolerated by the rabbits. Two rabbits in the 30% DCI dose group died on gestation days 13 and 19. One death was due to gavage trauma while the other death was due to inappetence and food aversion. There were clinical evidences of scant feces, abortion, premature delivery, vaginal discharge, red material, and pups/placental discharge in the 30% DCI treatment group. Pre-implantation (0.7% to 8.9%) and post-implantation loss (2% to 8.8%) occurred in all the treated rabbits, while the numbers of corpora lutea of rabbits in the 20% and 30% DCI groups were significantly elevated. High dose (30% DCI) exposure fetuses in two separate full-term gravid litters had skeletal malformations that were related to maternal toxicity. The NOAEL for maternal toxicity was 10% DCI, while the NOAEL for developmental toxicity was 20% DCI of triheptanoin. The decreased body weights observed in rabbits is related to decreased feed intake secondary to forced gavage administration of a large volume of triheptanoin oil and is not relevant to humans.

In the pre- and postnatal development study, the effects of oral dietary administration of triheptanoin (10%, 30%, and 50% DCI) to female rats and their offspring were studied. Triheptanoin dosing in the F0 generation of dams from implantation to gestation and lactation resulted in reduced mean maternal body weight gain during gestation, reduced mean maternal food consumption in all the treated rats during gestation and lactation period, and persistently reduced mean body weight gain in the 30% and 50% DCI dose groups. However, there were no triheptanoin (UX007)-related effects on F0 maternal macroscopic findings, delivery, or litter observations. The observed reductions in mean body weight gain were the effects of initial food aversion in the F0 generation dams. The two deaths of the F0 dams (from the 10% and 50% DCI dose exposure groups) were unrelated to UX007 administration. In the preweaning F1 generation pups, there were no adverse clinical observations, behavioral changes, or necropsy changes. However, reduced mean body weights and changes in sexual maturation and in organ weights were observed through the postpartum days 1 to 28 in the 30% and 50% DCI exposed F1 pups as a result of exposure to UX007. In the F1 pups, minimal to mild alterations in hematology and serum chemistry were observed in the 50% DCI exposure group, and microscopic minimal vacuolation was seen in the liver hepatocytes of the 30% and 50% exposure groups. The observed changes were considered secondary to the reduced food, and probably also secondary

to reduced water consumption. All the F1 generation survived until scheduled euthanasia. Exposure to UX007 was found in day 21 postpartum pups who were also probably exposed to the test article during the gestation or lactation period and via direct consumption. The overall effects of UX007 were seen as weight reduction in treated dams stemming from food aversion, resulting in pups that were smaller and had sexual maturation changes although not behavioral changes. The effects of UX007 seen in the F1 generation were secondary to the maternal toxicities and not considered clinically relevant. The NOAEL could not be determined in the maternal F0 generation, but the NOAEL for F1 generation was 50% DCI of UX007.

In a special toxicity study, dermal sensitization was performed with the intradermal injection of 0.1 ml of triheptanoin in male albino guinea pigs every other day for a total of nine injections. Triheptanoin was not a dermal sensitizing agent in male albino guinea pigs.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Triheptanoin is a colorless, odorless liquid composed entirely from oil. The anticipated risks for this product are gastrointestinal (GI) adverse events, such as diarrhea, emesis/vomiting, and possibly pancreatitis or gall stone formation. Patients with LC-FAOD who become dehydrated due to emesis/vomiting, persistent diarrhea, or poor caloric intake are at additional risk for catabolism, often manifesting as rhabdomyolysis. The review team is aware that while a GI adverse event may create a higher risk for catabolism, there is a need to monitor patients' total caloric intake during dosage titration, especially in patients with gastrointestinal adverse reactions, and to adjust all components of the diet as needed to prevent catabolism.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable. This product has not been approved in the U.S. market or in any foreign market; therefore, no postmarketing experience is available at the time of this review.

7.4. FDA Approach to the Safety Review

The following data were submitted to support the safety of triheptanoin:

- Study UX007-CL201 (29 patients)
- Study UX007-CL202 (75 patients; 24 of these patients rolled over from study UX007-CL201)
- Gillingham (2017) from IND 113386 (32 patients)
- Expanded access, both eIND and SPIND (67 patients including 11 infants: birth to 12 months of age at time of initiation)

However, the safety review focuses upon the adverse events (AEs) reported in studies UX007-CL201 and UX007-CL202, as the patient-level safety data provided from these two studies was more complete than the data provided from expanded access INDs or Gillingham (2017).

- The information about specific dietary or medical interventions made concurrently with administration of triheptanoin was not consistently documented for either emergency or single patient EA INDs, nor was it documented for Gillingham (2017).
- The patients enrolled in study UX007-CL201 generally were dosed at 25% to 35% DCI, but patients who rolled over into study UX007-CL202 received a lower percent DCI of triheptanoin over time. Both protocols stipulated that investigators could change dosing based upon clinical discretion, but there were no requirements to document the specific justification when changing dosing. Therefore, this safety review has limited ability to assess if higher doses of triheptanoin were less tolerated via documentation of specific AEs in conjunction with dosing changes.

Patients enrolled in the Gillingham trial received 20% daily DCI from either purified trioctanoin or triheptanoin, not the dosage proposed by the Applicant for the labeling of triheptanoin (25% to 35% DCI). The triheptanoin used in this study was food-grade, synthesized in (b) (4) for use as a food additive in butter. The manufacturing process of the triheptanoin used in IND 113386 was comparable to that used for the triheptanoin used by the Applicant (refer to Section 9). The documentation from this study collected was less detailed than in studies UX007-CL201 and UX007-CL202, and the reported AEs did not contain narratives or other documentation with justification for dosing changes. Therefore, the AEs from this study could not be evaluated in greater detail than what was reported in the published manuscript (Gillingham et al. 2017). Review of this published data noted that the reported AEs were similar in both type and frequency. Therefore, this data will be considered supportive information to this NDA review.

The EA patient narratives were also reviewed for adverse events. However, these narratives did not contain information regarding triheptanoin dosing over time (dose escalation or dose modification), concomitant medications, diet, or adverse events. In review of the information provided, the reports from the narratives did not suggest risk for AEs other than those anticipated (GI).

In summary, the approach to the safety review focused on patients enrolled in studies UX007-CL201 and UX007-CL202 as the safety information available from these studies was the most complete and the data quality, characterization of adverse events and study conduct were all considered adequate to support a safety review. To better understand the underlying risks for AEs upon exposure to triheptanoin, AEs reported due to GI symptoms were reviewed as provided and after pooling.

7.5. Adequacy of the Clinical Safety Database

The safety database for studies UX007-CL201 and UX007-CL202, characterization of adverse events, and study conduct were all adequate.

Demographics

Table 24. Baseline Demographic and Clinical Characteristics, Safety Population, Studies UX007-CL201 and UX007-CL202

Characteristic	CL201 (N=29)	CL202 (N=75)	Pooled Population (N=79)
Age			
Mean (SD)	12.1 (13.2)	13.9 (13.2)	13.4 (13.2)
Median (min, max)	5.3 (0.9, 58.8)	9.8 (0.3, 63.3)	8.8 (0.3, 63.3)
Sex, n (%)			
Female	12 (41.4)	36 (48.0)	38 (48.1)
Male	17 (58.6)	39 (52.0)	41 (51.9)
Race, n (%)			
Asian	2 (6.9)	2 (2.7)	3 (3.8)
Black or African American	1 (3.4)	4 (5.3)	4 (5.1)
Other	1 (3.4)	0 (0.0)	1 (1.3)
Other (specify)	0 (0.0)	1 (1.3)	1 (1.3)
1/4 pacific islander, 3/4 white	0 (0.0)	1 (1.3)	1 (1.3)
Biracial white/black	0 (0.0)	1 (1.3)	1 (1.3)
White	25 (86.2)	66 (88.0)	69 (87.3)
Ethnicity, n (%)			
Unknown	0 (0.0)	1 (1.3)	1 (1.3)
Hispanic or Latino	3 (10.3)	7 (9.3)	7 (8.9)
Not Hispanic or Latino	26 (89.7)	67 (89.3)	71 (89.9)
Manifest, n (%)			
Unknown	0 (0.0)	50 (66.7)	50 (63.3)
Cardiac disease	2 (6.9)	2 (2.7)	2 (2.5)
Hepatic disease	2 (6.9)	2 (2.7)	2 (2.5)
Skeletal myopathy	24 (82.8)	20 (26.7)	24 (30.4)
Skeletal myopathy, hepatic disease	1 (3.4)	1 (1.3)	1 (1.3)
BMI			
Mean (SD)	21.5 (6.8)	22.1 (7.4)	21.9 (7.2)
Median (min, max)	18.0 (13.8, 37.7)	20.7 (11.9, 56.7)	19.6 (11.9, 56.7)

Source: adsl.xpt; Software: Python

Abbreviations: BMI, Body mass index; SD, standard deviation

The Applicant did not provide detailed information on diet, disease exacerbation, or AEs in all patients for the full duration of the pre-triheptanoin period. Therefore, the AEs reported during this period are not reflective of the baseline diet on MCT oil or underlying disease exacerbation. In addition, as neither study used a control arm, it is difficult to compare this data with AE rates for patients who receive dietary management in accordance with the current standard of care.

Patients treated with triheptanoin for greater than 12 months but less than 24 months (42%) comprised the largest cohort in the safety database. The second largest patient cohort were those treated for greater than 24 months but less than 36 months (38%).

Table 25. Duration of Exposure, Safety Population, Studies UX007-CL201 and UX007-CL202

Parameter	CL201 (N=29)	CL202 (N=75)	Pooled Population (N=79)
Duration of treatment (months)			
Mean (SD)	15.8 (6.1)	25.9 (11.1)	23.1 (10.9)
Median (min, max)	18.1 (0.1, 19.4)	26.0 (0.1, 41.3)	22.8 (0.1, 41.3)
Patients treated, by duration, n (%)			
<12 months	4 (13.8)	10 (13.3)	14 (17.7)
≥12 months	25 (86.2)	17 (22.7)	33 (41.8)
≥24 months	0 (0.0)	30 (40.0)	30 (38.0)
>36 months	0 (0.0)	18 (24.0)	18 (22.8)

Source: adex.xpt; Software: Python
Abbreviations: SD, standard deviation.

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

7.6.1. Overall Adverse Event Summary

Reports of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in patients exposed to triheptanoin are noted in [Table 26](#). All but one patient experienced a TEAE, but less than 6% of them experienced an AE leading to death or discontinuation of the study drug.

Table 26. Overview of TEAEs, Safety Population, Studies UX007-CL201 and UX007-CL202

Categories Subgroups	CL201 (N=29)	CL202 (N=75)	Pooled Population (N=79)
Any TEAE	29 (100.0)	74 (98.7)	78 (98.7)
Grade 3-4	17 (58.6)	48 (64.0)	55 (69.6)
SAE	19 (65.5)	57 (76.0)	63 (79.7)
SAEs with fatal outcome	0 (0.0)	2 (2.7)	2 (2.5)
TEAE outcomes			
Death	0 (0.0)	2 (2.7)	2 (2.5)
Discontinuation of study drug	4 (13.8)	1 (1.3)	5 (6.3)
Modification of study drug	17 (58.6)	17 (22.7)	30 (38.0)
Interruption of study drug	10 (34.5)	8 (10.7)	16 (20.3)
Reduction of study drug	12 (41.4)	9 (12.0)	20 (25.3)
Dose delay of study drug	0 (0.0)	0 (0.0)	0 (0.0)

Source: adae.xpt; Software: Python
Data presented as n (%).

Abbreviations: AE, adverse event; CI, confidence interval; TEAE, treatment-emergent adverse event; SAE, serious adverse event

The TEAEs reported in greater than 10% of the safety population are listed in [Table 27](#). The most commonly reported TEAE is rhabdomyolysis. However, as rhabdomyolysis is a common manifestation of catabolism in LC-FAOD patients, it is unclear if the reports of rhabdomyolysis were always triggered by exposure to triheptanoin or if they were a response to a different disease trigger as these patients were selected for a history of frequent or serious disease exacerbations. Because rhabdomyolysis is a manifestation of catabolism in LC-FAOD patients, this TEAE is also counted by the Applicant as an MCE. Upper respiratory tract infections were the next most commonly reported TEAE and viral upper respiratory tract infections, but their relation to triheptanoin use is unclear. Given that infections are common triggers for catabolism, reports of upper respiratory tract infections may correlate with some episodes of rhabdomyolysis.

Diarrhea, vomiting, gastroenteritis, and gastrointestinal disorders were reported in up to 44% of the pooled safety population. These were the most common treatment-related TEAEs. These GI-related events were anticipated, as large amounts of fat in diet can induce GI dysmotility (Rao et al. 2000; Anitha et al. 2016). Because individual patient dosing was titrated at the discretion of the investigator to optimize anabolism and tolerability, this information considered part of clinical practice and was not recorded. As a consequence, there was insufficient information regarding why triheptanoin dosing was decreased for any attempt to correlate to types of TEAEs to dosing level.

Table 27. TEAEs Most Likely Due to Adverse Reactions, by Descending Incidence, Safety Population, Studies UX007-CL201 and UX007-CL202

Preferred Term	CL201 (N=29)	CL202 (N=75)	Pooled Population (N=79)
Diarrhea	16 (55.2)	23 (30.7)	35 (44.3)
Vomiting	14 (48.3)	26 (34.7)	35 (44.3)
Gastroenteritis	6 (20.7)	17 (22.7)	20 (25.3)
Gastrointestinal disorder	1 (3.4)	18 (24.0)	19 (24.1)
Gastroenteritis viral	10 (34.5)	9 (12.0)	17 (21.5)
Abdominal pain upper	4 (13.8)	12 (16.0)	15 (19.0)
Abdominal pain	8 (27.6)	7 (9.3)	14 (17.7)
Constipation	2 (6.9)	9 (12.0)	11 (13.9)
Nausea	2 (6.9)	9 (12.0)	11 (13.9)

Source: adae.xpt; Software: Python

Data presented as n (%).

Abbreviations: TEAE, treatment-emergent adverse event

Patient-reported TEAEs also included clinical events that may be related to the underlying disease exacerbation. The review team assessed that the reported TEAEs were likely related to the underlying disease exacerbation as shown in [Table 28](#).

Table 28. TEAEs (Occurring ≥10%) Possibly Related to Underlying Disease, by Descending Incidence, Safety Population, Studies UX007-CL201 and UX007-CL202

Preferred Term	CL201 (N=29)	CL202 (N=75)	Pooled Population (N=79)
Rhabdomyolysis	14 (48.3)	46 (61.3)	52 (65.8)
Myalgia	5 (17.2)	13 (17.3)	16 (20.3)
Abdominal pain upper	4 (13.8)	12 (16.0)	15 (19.0)
Headache	9 (31.0)	7 (9.3)	14 (17.7)
Abdominal pain	8 (27.6)	7 (9.3)	14 (17.7)
Dehydration	2 (6.9)	7 (9.3)	9 (11.4)
Pain in extremity	1 (3.4)	8 (10.7)	9 (11.4)

Source: adae.xpt; Software: Python

Data presented as n (%).

Abbreviations: TEAE, treatment-emergent adverse event

In summary, the TEAEs that appear to be associated with the use of triheptanoin are all GI related complaints; GI related complaints are expected given the higher than normal daily caloric intake (DCI) of dietary fat prescribed in these studies. Of the TEAEs more likely to reflect catabolism in LC-FAOD patients, only two preferred terms (abdominal pain upper/abdominal pain) were also considered adverse reactions related to triheptanoin use ([Table 27](#)).

7.6.2. Deaths

No patients died during enrollment in study UX007-CL201 or in the Gillingham trial. Two patients died during enrollment in study UX007-CL202. These deaths were assessed by both the investigators and the Applicant as results of complications from their underlying LC-FAOD and not due to exposure to triheptanoin. Narratives are provided below.

Table 29. Deaths, Safety Population, Studies UX007-CL201 and UX007-CL202

Categories	CL201 (N=29)	CL202 (N=75)	Pooled Population (N=79)
Total deaths	0 (0.0)	2 (2.7)	2 (2.5)
Within 30 days after last dose	0 (0.0)	2 (2.7)	2 (2.5)
Beyond 30 days after last dose	0 (0.0)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis adsl.xpt and addd.xpt; Software: Python
Data presented as n (%).

Narratives of Reported Deaths

- Case reference number (b) (6): This patient was a 9-month-old male (subject (b) (6)) enrolled in study UX0007-CL202 with a diagnosis of TFP and a history of multiple episodes of rhabdomyolysis and cardiomyopathy (ejection fraction of around 20%). The patient was initiated on triheptanoin on (b) (6). By MedWatch report, upon initiation of triheptanoin, the cardiac ejection fraction improved. However, the patient was noted to have worsening apnea, which was described with obstructive and central components. The patient received his last dose of triheptanoin on (b) (6), and was noted to have abdominal distention. Despite deflation via nasogastric-tube, the patient required increased respiratory support and was transferred to the pediatric intensive care unit, where the patient passed that day. Autopsy noted malrotation of the bowel and appendix with concentric hypertrophy of the left ventricle. The investigator assessed the death as the result of cardiorespiratory arrest.
- Case reference number (b) (6): This patient was a 4-year-old female (subject (b) (6)) enrolled in study UX0007-CL202 with a diagnosis of TFP and a history of recurrent rhabdomyolysis, cardiomyopathy, and gastroesophageal reflux disease. The patient was initiated on triheptanoin on (b) (6), via G-tube. The most recent dose prior to the event was provided on January 31, 2017. By MedWatch report, the patient was diagnosed with worsening cardiomyopathy on (b) (6), and was hospitalized on that day. The patient experienced a cardiac arrest on (b) (6), with subsequent development of acute respiratory distress syndrome, a second cardiac arrest, acute liver injury, multifocal intracranial infarction, intraparenchymal hematoma, and subdural hemorrhage with subsequent demise on (b) (6). The investigator assessed the death as the result of the underlying cardiomyopathy related to the diagnosis of TFP.

In review of the MedWatch report, subject (b) (6) may have received triheptanoin up to (b) (6); however, the documentation was not clear.

7.6.3. Serious Adverse Events

Serious adverse events were reported in 80% of patients evaluated in the safety population. Of these SAEs, the events reported in greater than 3% of the total safety population are noted in [Table 30](#).

Table 30. Serious Adverse Events by Descending Incidence, Studies UX007-CL201 and UX007-CL202

Preferred Term	CL201 (N=29)	CL202 (N=75)	Pooled Population (N=79)
Rhabdomyolysis	11 (37.9)	42 (56.0)	47 (59.5)
Gastroenteritis	6 (20.7)	11 (14.7)	16 (20.3)
Gastroenteritis viral	6 (20.7)	7 (9.3)	11 (13.9)
Gastrointestinal disorder	1 (3.4)	9 (12.0)	10 (12.7)
Vomiting	1 (3.4)	5 (6.7)	6 (7.6)
Influenza	0 (0.0)	6 (8.0)	6 (7.6)
Upper respiratory tract infection	2 (6.9)	2 (2.7)	4 (5.1)
Viral upper respiratory tract infection	1 (3.4)	3 (4.0)	4 (5.1)
Gastrointestinal viral infection	2 (6.9)	1 (1.3)	3 (3.8)
Croup infectious	1 (3.4)	3 (4.0)	3 (3.8)

Source: adae.xpt; Software: Python
Data presented as n (%).

As rhabdomyolysis is a manifestation of catabolism in LC-FAOD patients, it is an anticipated SAE in this population, particularly in those patients prone to disease lability. What is unclear from this data is whether and how the rhabdomyolysis may be related to a possible intolerance to triheptanoin, as might be anticipated with SAEs of gastroenteritis, gastrointestinal disorder, and emesis. The frequency of these events was compared with those reported in Gillingham (2017). However, a direct comparison could not be made due to the differences in patients and study protocols:

- The inclusion criteria for Gillingham (2017) describe patients with nonsevere disease by requiring clinical stability and only a single episode of rhabdomyolysis, whereas study UX007-CL201 requires clinical or laboratory demonstration of severity.
- The reports of rhabdomyolysis in studies UX007-CL201 and UX007-CL202 were limited to episodes requiring hospitalization.
- The dosage of food grade triheptanoin used was lower (20%) in Gillingham (2017) than in studies UX007-CL201 and UX007-CL202.

Though not specified as TEAEs or SAEs, all AEs from Gillingham (2017) were submitted for review. Except for emesis/vomiting, patients who received triheptanoin reported similar rates of what the investigator classified as “expected” and “unexpected” AEs as the patients randomized to purified trioctanoin. Refer to [Table 31](#).

Table 31. Reported Adverse Events (AEs), Gillingham (2017)

Adverse Event(s)	Triheptanoin/C7		Trioctanoin/C8	
	# Events	n (of 16)	# Events	n (of 16)
Expected AEs				
Diarrhea/loose stools/steatorrhea	9	5	12	6
Gastrointestinal upset	24	11	38	12
Emesis/vomiting	7	6	0	0
Musculoskeletal pain/cramping/elevated CPK	16	11	18	10
Rhabdomyolysis (hospital admission)	7	5	7	4
Fatigue/lethargy	3	3	2	2
Unexpected AEs				
Headache	17	5	7	3
Viral illness	22	15	17	11
Localized pain not associated with rhabdomyolysis	5	4	2	2
Dermatitis	1	1	4	4

Source: Modified from NDA 213687; Section 5.3.5.1; Gillingham Package, page 28 of 89
Abbreviations: CPK, creatine phosphokinase

Regardless of the source of MCT (triheptanoin or trioctanoin), the highest rates of AEs reported in the Gillingham trial are for elevated CPK levels, GI upset, diarrhea, and rhabdomyolysis that required hospital admission. Emesis/vomiting was only reported in patients who received triheptanoin, not those who received trioctanoin. In general, these AEs support the SAE data from studies UX007-CL201 and UX007-CL202; exposure to triheptanoin is associated with GI complaints that can include emesis, GI upset, and may be associated with an elevated CK.

The literature reports that some patients with LC-FAOD can have feeding aversion, gastrointestinal reflux and resultant emesis. They may also be dependent upon feeding tubes (Karall et al. 2015; Vockley et al. 2015).⁷ Therefore, it is not clear that the lack of emesis in patients treated with trioctanoin/C8 is representative of patient experience while on dietary therapy. It may be more reflective of the selection of patients with nonsevere disease presentation. In addition, patients enrolled in the Gillingham trial were exposed to triheptanoin or trioctanoin for a shorter duration than patients enrolled in studies UX007-CL201 or UX007-CL202. It is this reviewer's (Dr. Zand) clinical understanding that individual patients' acclimation or tolerability to medium-chain fat in diet may vary based upon underlying disease lability and dosage or duration of exposure.

7.6.4. Dropouts and /or Discontinuations Due to Adverse Events

Four patients discontinued study UX007-CL201 due to complaints of gastrointestinal symptoms or pain/myalgia possibly related to disease exacerbation. One patient discontinued study UX007-CL202 due to the development of rhabdomyolysis related to an intercurrent illness (colonic volvulus).

⁷ Medical officer's personal communications with multiple investigators requesting emergency or single patient expanded access INDs

Table 32. Adverse Events Leading to Discontinuation, Studies UX007-CL201 and UX007-CL202

Preferred Term	CL201 (N=29)	CL202 (N=75)	Pooled Population (N=79)
Treatment d/c due to TEAEs ^a	4 (13.8)	1 (1.3)	5 (6.3)
Diarrhoea	1 (3.4)	0 (0.0)	1 (1.3)
Gastroesophageal reflux disease	1 (3.4)	0 (0.0)	1 (1.3)
Myalgia	1 (3.4)	0 (0.0)	1 (1.3)
Pain	1 (3.4)	0 (0.0)	1 (1.3)
Vomiting	1 (3.4)	0 (0.0)	1 (1.3)
Rhabdomyolysis	0 (0.0)	1 (1.3)	1 (1.3)

Source: Reviewer's analysis[adae.xpt; Software: Python]

Data presented as n (%).

¹ Coded as MedDRA preferred terms

^a Some patients discontinued after experiencing more than one TEAE

.Abbreviations: d/c, discontinued; TEAE, treatment-emergent adverse event

7.6.5. Treatment-Emergent Adverse Events

The frequency of TEAEs and their impact on dosage and study discontinuation are evaluated in both study UX007-CL201 and study UX007-CL202. In study UX007-CL201, a similar proportion of patients in the 30% to 35% DCI group experienced a TEAE as did patients in the 25% to 30% DCI group. In study UX007-CL202, the proportions were also similar between the two groups. In general, most patients experienced an interruption and/or dose reduction as a result.

Study UX007-CL201

The incidence of TEAEs as related to the dose of triheptanoin (percent DCI) in study UX007-CL201 was evaluated ([Table 33](#)) and was based upon the data initially provided in the NDA submission.

Table 33. Overview of TEAEs (Subgroup) by Average Daily Caloric Intake (% of DCI) of Triheptanoin, Study UX007-CL201

Type of Adverse Event(s) Subgroup	% of DCI				
	>35% (N=1)	30–35% (N=16)	25–30% (N=8)	20–25% (N=1)	<20% (N=3)
Any TEAE	1 (100.0)	16 (100.0)	8 (100.0)	1 (100.0)	3 (100.0)
Grade 3-4	1 (100.0)	10 (62.5)	5 (62.5)	1 (100.0)	1 (33.3)
SAE	0 (0.0)	12 (75.0)	5 (62.5)	1 (100.0)	1 (33.3)
SAEs with fatal outcome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE outcome					
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation of triheptanoin	0 (0.0)	1 (6.3)	1 (12.5)	0 (0.0)	2 (66.7)
Modification of triheptanoin dose	1 (100.0)	6 (37.5)	8 (100.0)	1 (100.0)	1 (33.3)
Interruption of triheptanoin	0 (0.0)	5 (31.3)	3 (37.5)	1 (100.0)	1 (33.3)
Reduction of triheptanoin	1 (100.0)	3 (18.8)	7 (87.5)	1 (100.0)	0 (0.0)

Source: Reviewer's analysis[adae.xpt; Software: Python]

Data presented as n (%).

Abbreviations: DCI, daily caloric intake; SAE, serious adverse event; TEAE, treatment-emergent adverse event

All 29 patients, reflective of the full spectrum of dosing (less than 20% through greater than 35% DCI) reported TEAEs that were grades 3 or 4. Because the protocol prespecified triheptanoin dosing of 25% to 35% DCI, 24 of 29 patients were in this dose range at the time of TEAE reporting. The reported TEAE resulted in either interruption or reduction of triheptanoin dosing

in 17 of 29 patients, while one additional patient discontinued the study. The protocol allowed dosing to be changed at the discretion of each investigator without documentation of the reason for the change. Therefore, the interruption or reduction of triheptanoin dosing after a TEAE are presumed to be directly related to the TEAE. No patients died during the study.

Comments: In a response to IR, the Applicant provided data to correlate TEAEs temporally to the most recently available dose level. Review of this data did not demonstrate additional or different conclusions.

Study UX007-CL202

The incidence of TEAEs as related to the dose of triheptanoin (percent DCI) in study UX007-CL202 was also evaluated (Table 34). Similar to study UX007-CL201, almost all patients (74 of 75) reported TEAEs on all doses administered. Because the protocol also prespecified optimal dosing between 25% to 35% DCI, 50 of 75 patients were in this dose range at the time of their TEAE or SAE and were equally distributed between the 25% to 30% DCI and 30% to 35% DCI groups, similar to study UX007-CL201. After their reported TEAE, one patient receiving 20% to 25% DCI triheptanoin discontinued therapy, eight additional patients experienced interruption of therapy, and nine patients had their triheptanoin doses reduced. Two patients died after reported SAEs. Their narratives are noted in Section 7.6.2.

Table 34. Overview of TEAEs (Subgroup) by Average Daily Caloric Intake (% of DCI) of Triheptanoin, Study UX007-CL202

Type of Adverse Event(s) Subgroup	% of DCI				
	>35% (N=2)	30–35% (N=26)	25–30% (N=24)	20–25% (N=10)	<20% (N=13)
Any TEAE	2 (100.0)	25 (96.2)	24 (100.0)	10 (100.0)	13 (100.0)
Grade 3-4	2 (100.0)	17 (65.4)	16 (66.7)	6 (60.0)	8 (61.5)
SAE	2 (100.0)	19 (73.1)	20 (83.3)	8 (80.0)	8 (61.5)
SAEs with fatal outcome	1 (50.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
TEAE outcome					
Death	1 (50.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Discontinuation of triheptanoin	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Modification of triheptanoin dose	0 (0.0)	4 (15.4)	5 (20.8)	3 (30.0)	5 (38.5)
Interruption of triheptanoin	0 (0.0)	3 (11.5)	4 (16.7)	1 (10.0)	0 (0.0)
Reduction of triheptanoin	0 (0.0)	1 (3.8)	1 (4.2)	2 (20.0)	5 (38.5)

Source: Reviewer's analysis[adae.xpt; Software: Python]

Data presented as n (%).

Abbreviations: DCI, daily caloric intake; SAE, serious adverse event; TEAE, treatment-emergent adverse event

In summary, almost all patients experienced a TEAE of grade 3 or 4. Furthermore, due to the prespecified dosing of each protocol, most patients were receiving 25% to 35% DCI of triheptanoin at the time of TEAE report. One patient from study UX007-CL202 who received >35% DCI triheptanoin experienced a fatal SAE (n=1) after discontinuation of therapy. (Refer to Section 7.6.2). Of three patients (n=3) from either study who received >35%, one required a triheptanoin dose reduction. Most patients appeared to tolerate 25% to 35% DCI triheptanoin, though both studies noted that dose reduction or dose interruption was common at these doses.

7.6.6. Laboratory Findings

Routine liver- and muscle-based chemistries were obtained throughout the trial, with particular focus on creatine kinase that correlates clinically with rhabdomyolysis and serum glucose levels that correlate clinically with hypoglycemia.

Table 35. Incidence of Abnormal Lab Parameters, Safety Population, Studies UX007-CL201 and UX007-CL202

Laboratory Parameters	CL201 (N=29)		CL202 (N=75)		Pooled Population (N=79)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
CK (U/L) – increased	26 (89.7)	19 (65.5)	55 (73.3)	30 (40.0)	64 (81.0)	37 (46.8)
ALT (U/L) – increased	17 (58.6)	3 (10.3)	54 (72.0)	18 (24.0)	57 (72.2)	19 (24.1)
AST (U/L) – increased	16 (55.2)	4 (13.8)	49 (65.3)	10 (13.3)	53 (67.1)	12 (15.2)
GGT (U/L) – increased	1 (3.4)	0 (0.0)	14 (18.7)	1 (1.3)	15 (19.0)	1 (1.3)
Triglycerides – increased	9 (31.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (11.4)	0 (0.0)
Chemistry glucose (mmol/L) – decreased	5 (17.2)	0 (0.0)	1 (1.3)	0 (0.0)	6 (7.6)	0 (0.0)

Source: Reviewer's analysis [adlb.xpt; Software: Python]

Data presented as n (%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; GGT, gamma-glutamyl transferase

Greater than 80% of patients in the pooled safety population experienced an elevation of creatine kinase of any grade, and 46% of this population experienced creatine kinase elevation of grade 3 or 4. As creatine kinase elevation correlates with rhabdomyolysis, a clinical symptom of catabolism in patients with LC-FAOD, this is an anticipated underlying disease risk. Comparison of creatine kinase levels before and after triheptanoin could not be assessed in study UX007-CL201 due to the paucity of patient data in the pre-triheptanoin period. An additional consideration in interpretation of creatine kinase levels is that they are affected when the sample was obtained in relation to symptom onset, patient variability and dietary intervention (initiation of fluids and oral/G-tube caloric intake prior to blood draw). Therefore, direct interpretation of the degree of creatine kinase elevation is difficult.

The increases in liver enzymes alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transpeptidase may be reflective of disease pathology in the liver, particularly during times of elevation of creatine kinase.

Six of the 79 patients in the pooled safety population experienced any grade of hypoglycemia, but none were grade 3 or 4. Historically, a smaller portion LC-FAOD patients are at high risk to present with hypoglycemia, particularly in the absence of rhabdomyolysis. However, there is no current methodology to identify those patients who are more prone to hypoglycemia than to rhabdomyolysis.

Given the increase in dietary triglycerides, the increase in serum levels in a subset (n=9) may be anticipated, but it is reassuring that it is not observed in a large proportion of patients and none of the elevations are at the level of grade 3 or 4.

7.6.7. Cardiac Events

One manifestation of LC-FAOD disease pathology is the development of cardiomyopathy. While patients with frequent disease exacerbation report rhabdomyolysis most frequently, there is no

ability to predict which patients will develop cardiomyopathy. Some patients who have developed cardiomyopathy have presented during a protracted duration of intermittent catabolism. Recovery occurs during anabolism, though patients who have already developed cardiomyopathy are at risk for redevelopment in the future. It is not common to identify an arrhythmia not associated with cardiomyopathy in these patients. It is also not common to identify ischemia not associated with cardiomyopathy in these patients.

There is no evidence of an association of clinical events related to QT prolongation with triheptanoin treatment in the available safety data. The Applicant did collect ECGs in both study UX007-CL201 and study UX007-CL202, and no subjects were identified with QTc >480 ms or Δ QTc >60 ms. The unknown timing of ECG collection relative to dosing and the quality of ECG acquisition and measurements limit the data; however, there were no risks identified for cardiac arrhythmia or QT prolongation with triheptanoin use.

No unanticipated adverse cardiac events were identified during this development program.

7.7. Review Issues Relevant to the Evaluation of Risk

7.7.1. Anticipated Risks

Issue

Patients who ingest a large amount of dietary fat are at higher risk for gastrointestinal adverse events.

Assessment

- A retrospective chart review of 20 patients initiated on triheptanoin of up to 35% DCI reported diarrhea in 60% of patients and GI upset in 35% of patients (Vockley et al. 2015), ([Table 7](#)).
- Gastrointestinal symptoms (diarrhea, gastroenteritis, abdominal pain) were the most commonly reported AEs that were not major clinical events in studies UX007-CL201/UX007-CL202.
- This review was not able to determine if triheptanoin related GI events were increased compared to other sources of medium-chain triglycerides, such as MCT oil as studies UX007-CL201/UX007-CL202 did not collect AE data during the retrospective pre-triheptanoin period.
- More GI AEs were reported in patients who were exposed to higher doses of triheptanoin (25% to 35%).

Conclusion

The GI adverse events are anticipated risks to ingestion of triheptanoin. These AEs may be mitigated by changes in the dose of MCT, source of MCT, and other dietary modifications. Labeling will reflect these recommendations.

7.7.2. Risk During Pregnancy

Issue

There are no clinical study data to assess the risk of use of triheptanoin during pregnancy.

Assessment

- Improved newborn screening technologies have increased the rates of LC-FAOD detection in infancy. Early dietary management has improved health and longevity of patients with LC-FAOD, who otherwise might not have survived childhood. These patients, who are diagnosed as adults or managed through adulthood, may now provide an understanding of dietary experience during pregnancy and fetal risk.
- Triheptanoin is a source of medium-chain triglycerides for the treatment of LC-FAOD. Long-term use, and thus, use during pregnancy, is anticipated.

Conclusion

A PMR for a pregnancy registry would inform the use of triheptanoin during pregnancy.

7.7.3. Risks for Use With Specific Plastic Materials

Issue

Feeding tubes containing polyvinyl chloride (PVC) or containers containing polystyrene are not recommended for use with triheptanoin.

Assessment

Triheptanoin may degrade PVC or dissolve polystyrene plastics upon contact.

Conclusion

Labeling reflects these recommendations. Refer to Section [9.1](#) for details.

7.7.4. Long QT Study Waiver

Issue

A designated study to assess the risk for long QT syndrome has not been completed by the Applicant.

Assessment

Triheptanoin is a medium-chain triglyceride and is a source of calories and fatty acids for patients diagnosed with LC-FAOD. It has a low systemic exposure and is ultimately used as a source of dietary fat in this population. Furthermore, a review of the cardiac data did not identify cardiac risks for generalized arrhythmia, QT prolongation, or other cardiac events not associated with catabolism in these patients. Given these factors, the risk for heptanoate and other active metabolites appears low.

Conclusion

A designated long QT study will be waived.

8. Therapeutic Individualization

8.1. Intrinsic Factors

As a caloric source, the total daily dose of triheptanoin should be individualized based on disease severity, metabolic needs, and tolerability. Therefore, all patients treated with triheptanoin should be under the care of a clinical specialist knowledgeable in appropriate disease-related dietary management that is based upon current nutritional recommendations.

Hepatic/Renal Function

The effects of hepatic impairment or renal impairment on exposure of triheptanoin and its metabolites are unknown because there are neither dedicated clinical studies in subjects with such impairments nor clinical data from patients with LC-FAOD who have hepatic or renal impairment. Of note, metabolism of heptanoate primarily occurs in the liver as does energy metabolism, such as beta-oxidation and the TCA cycle. Hepatic disease may alter energy demands and lipid metabolism in the liver, but it is unknown how hepatic impairment affects lipid metabolism and nutritional requirements, including medium-chain fat in patients with LC-FAOD.

On the other hand, urinary excretion of triheptanoin metabolites was minimal, so it is unlikely that renal impairment would significantly affect drug exposure.

Pancreatic Insufficiency

Pancreatic enzymes hydrolyze triheptanoin and release three moles of heptanoate as medium-chain fatty acids in the small intestine. Low or absent pancreatic enzymes may result in reduced absorption of heptanoate, subsequently leading to insufficient supplementation of medium-chain fat in patients with LC-FAOD. Unlike triheptanoin, MCT oil does not require hydrolysis by pancreatic enzyme to be absorbed. Patients with pancreatic insufficiency should avoid administration of triheptanoin.

8.2. Drug Interactions

Triheptanoin is converted into heptanoate (C7 fatty acid) in the intestine by multiple types of pancreatic lipases. Patients should avoid coadministration of triheptanoin with lipase inhibitors (e.g., orlistat) because reduced conversion from triheptanoin to heptanoates leads to insufficient energy supply from C7 fatty acids.

8.3. Pediatric Labeling / Plans for Pediatric Drug Development

Triheptanoin was granted orphan-drug designation on April 15, 2015, for the treatment of fatty acid oxidation disorders. Currently, there are no plans for additional pediatric studies, and triheptanoin is exempt from the Pediatric Research Equity Act (21 U.S.C. 355c). The Applicant has provided sufficient justification and right of reference to INDs where LC-FAOD patients

were initiated on triheptanoin soon after birth. Therefore, triheptanoin will be indicated in patients with LC-FAOD from birth through adulthood.

8.4. Pregnancy and Lactation

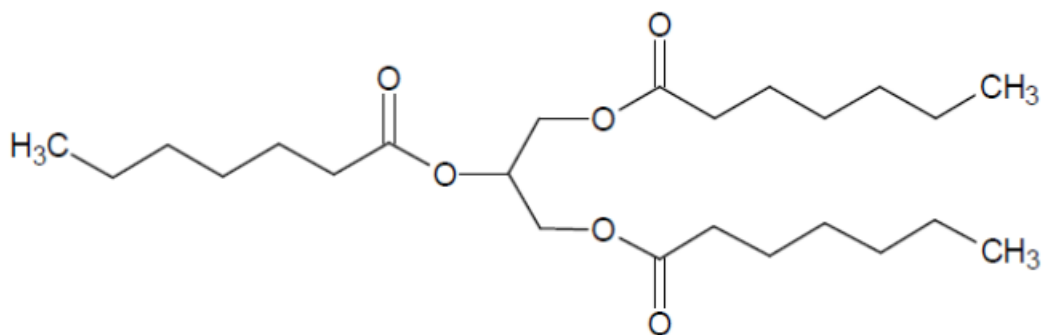
In a segment II embryofetal developmental toxicity study in rats, triheptanoin levels of 30% to 50% DCI correlated with decreased oral intake, resulting in weight reduction and smaller pups with sexual maturation changes. In the segment II embryofetal developmental toxicity study in rabbits, severe anorexia was noted in animals dosed as low as 20% DCI. Refer to Section [7.1](#) for greater detail in the toxicology review.

Currently, there are few documented reports of pregnancy outcomes with maternal LC-FAOD. With improvements in LC-FAOD diagnoses, there is a need to better understand the impact of triheptanoin as a synthetic fat on the risk for fetal anomalies. The Applicant will be asked to conduct a single-arm, pregnancy safety study in women exposed to triheptanoin during pregnancy to assess risks of pregnancy complications and adverse effects on the developing fetus and neonate. Refer to Section [III.22](#).

9. Product Quality

Triheptanoin is the active pharmaceutical ingredient in Dojolvi. Triheptanoin is a triester of heptanoic acid and glycerol. It is a clear, colorless to light yellow liquid and is practically insoluble in water. It does not have any chiral centers or double bonds. The chemical structure of triheptanoin is shown below.

Figure 8. Chemical Structure of Triheptanoin



Triheptanoin

Molecular Weight: 428.6 g/mol

Molecular Formula: C₂₄H₄₄O₆

Triheptanoin is manufactured by (b) (4). The detailed CMC information regarding the raw materials, starting materials, manufacturing process, critical steps, in-process controls, and impurities controls was provided. Its chemical structure was confirmed by many modern analytical methods, such as proton (¹H) and carbon (¹³C) nuclear magnetic resonance spectroscopy, infrared spectroscopy, and mass spectroscopy.

The overall quality of triheptanoin is controlled by its specification for identity, purity, and quality. Based on the stability studies of multiple commercial scale batches, a retest period of (b) (4) months is granted when it is stored in (b) (4) containers with (b) (4) screw caps.

The drug substance reviewer determined that the clinical batches of triheptanoin are pharmaceutical-grade and comparable to the commercial batches because all of these batches were manufactured in similar scale at the same manufacturing facility and met the proposed commercial triheptanoin specification for identity, strength, purity, and quality. As Dojolvi contains only triheptanoin, the clinical batches of Dojolvi are comparable in overall quality to the commercial batches.

Dojolvi (triheptanoin) oral liquid, 100% w/w, is a synthetic medium odd-chain (C7) triglyceride colorless to light yellow liquid. It is supplied in 500 mL (b) (4) glass bottles. Each bottle is closed with a (b) (4) cap (b) (4)

(b) (4) There are no other excipients, antioxidants, or preservatives in this drug product.

Dojolvi (triheptanoin) oral liquid is a medium-chain triglyceride. It is manufactured by (b) (4) The Applicant has provided detailed drug product manufacturing process. The proposed commercial batch size is approximately (b) (4) The overall control strategy for the drug product's identity, strength, purity, and quality is deemed adequate based on raw material controls and drug product specification for identity, strength, purity and quality.

The Applicant has provided adequate microbiology related information regarding the drug product manufacturing process, analytical methods, stability protocol, specification for microbial limits, and labeling.

Based on satisfactory stability study data of multiple commercial scale batches of the drug product, a 36-month of expiration dating period is granted when stored at 20°C to 25°C in the proposed glass bottles sealed with an induction seal and a (b) (4) cap.

The Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Dojolvi (triheptanoin) oral liquid, 100% w/w.

The Office of Pharmaceutical Manufacturing Assessment has made a final overall "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted. The label/labeling is acceptable from the CMC perspective. Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for "Approval."

9.1. Device or Combination Product Considerations

The drug product is orally administered, and in real use situations, patients or caregivers measure a prescribed amount of triheptanoin to be mixed with food and drink. It may also be administered via a feeding tube, either a gastrostomy tube (G-tube) or a nasoenteric feeding tube. The drug product is not copackaged with any associated components or feeding tubes; however, in support

of patient use, compatibility studies were performed with associated components (e.g., measuring cups), G-tubes, and common foods or baby formula.

From the compatibility studies, the following conclusions were supported and, where appropriate, associated labeling was included by the Applicant to address the concerns identified:

- Neat drug product (i.e., without dilution) results in loss of functionality for multiple types of G-tubes. The Applicant includes in section 2.5 of the labeling, ‘Do not administer triheptanoin (b) (4)’. Note, in the labeling, this has been changed to an affirmative statement of “administer DOJOVLI with food or liquids...enterally...”
- PVC feeding tubes are not recommended for enteral feeding with triheptanoin based upon literature describing the potential incompatibility with MCT. MCT can dissolve some plasticizers, such as phthalates, out of the plastic (Sheskey et al. 2017). The Applicant has included statements in the labeling to avoid PVC tubes and further to only use silicone or polyurethane feeding tubes.
- Polystyrene is immediately degraded by the drug product. MCT softens or splits containers and utensils composed of certain plastics, such as polystyrene. Therefore, it is recommended that MCT be stored and used in containers made of metal, glass, ceramics, and unaffected plastics (Sucher 1986). Styrofoam™ is one particular product made from polystyrene. Therefore, based upon the similarity between triheptanoin and MCT, the Applicant has included statements in the labeling to ‘not dose or store in polystyrene containers.’
- Compatibility with foods representing a wide range of acidity (acidic and neutral) and preparation (baking, mechanical mixing, storage temperatures) was adequately performed. No issues were reported.

There was a 9% reduction of triheptanoin when administered through a silicone gastrostomy tube in the dose recovery study at 60 minutes. The Applicant provided information to support their assertion that a 9% reduction was the worst-case scenario, given the gastrostomy tube material used in the study was silicone instead of polyurethane, which demonstrated less loss. Also, the study covered the maximum duration of contact expected during continuous feeding. The Applicant considered the material type and duration of contact as the most relevant factors to dose-recovery. Consideration of a 9% reduction in dose as clinically insignificant was supported by clinical safety data in study UX007-CL201 and by pharmacokinetic data from study UX007-CL202. The clinical sites from both studies were queried by the Applicant as to the types of tubes commonly used in clinical practice, and the results were consistent with the types and size of tubes and with the expected maximum contact time of 60 minutes.

10. Human Subjects Protections / Clinical Site and Other Good Clinical Practice Inspections / Financial Disclosure

Human Subjects Protections

The Applicant stated that the clinical trials were conducted in substantial conformance with International Council for Harmonisation good clinical practice requirements and with applicable

country and/or local statutes and regulations regarding ethical committee review, informed consent, and protection of human subjects participating in biomedical research. The phase 2 studies were conducted according to FDA requirements, under INDs 117053 and 113386. Additionally, FDA clinical site inspections did not reveal evidence of good clinical practice noncompliance.

Clinical Site Inspections

Inspection sites were selected based upon review of the number of patients enrolled at each study site and the largest change in percent DCI of MCT at the run-in stage compared to that at the change to triheptanoin. Only three domestic sites were selected as the most patients enrolled in these sites. The sites enrolled in the Gillingham (2017) trial were not specifically reviewed as this was a research IND funded by a grant from the Office of Orphan Products Development, and the IND had been withdrawn prior to the NDA submission. The clinical site inspection final reports were all classified as No Action Indicated. (Refer to Section [20](#) for more details)

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinic investigators as recommended in the guidance Financial Disclosure by Clinical Investigators (see Section [III.23](#)),⁴ and by 21 CFR 54.4. None of the investigators for studies UX007-CL201/UX007-CL202 or Gillingham (2017) were employed by the Applicant, and none disclosed financial interests with the Applicant. In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

An advisory committee was not held for this application.

III. Appendices

12. Summary of Regulatory History

Refer to Section [II.3](#).

- IND 117053 was opened July 23, 2013 with the protocol for study 201, a phase 2 open-label single arm study in n=29 patients. The Sponsor's general investigational plan called for this study to be followed by a phase 3 randomized, controlled trial comparing triheptanoin with MCT oil in 50 to 100 patients. (See Primary Clinical Review August 16, 2013, Reference ID: 3358658).
- On April 15, 2015, triheptanoin (Ultragenyx) received Orphan Drug Designation (ODD) for the treatment of fatty acid oxidation disorders.
- In response to a request for Breakthrough designation, the Division, including Drs. Zand, Donohue & Roman, concluded the results from Study 201 were insufficient to support

breakthrough designation (See Breakthrough Determination Aug 28, 2017, Reference ID: 4145426). The Medical Policy Council, including Drs. Beitz and Woodcock, agreed with this determination (see meeting minutes August 23, 2017, Reference ID: 4142351). Breakthrough designation was denied Aug 29, 2017, the letter noted concerns about confounding with diet from study 201, and recommended that the sponsor perform a randomized trial (See Deny Breakthrough Therapy Designation letter, August 29, 2017, Reference ID: 4146320).

- December 1, 2017 response to information request regarding feasibility of a phase 3 trial.
- December 12, 2017 End of Phase 2 meeting minutes (Reference ID: 4206249).

•  (b) (4)

- On May 28, 2018, the Division met with the Medical Policy and Program Review Council (MPPRC) and recommended that the Sponsor perform a phase 3 randomized, double-blind, controlled trial to assess the effect of triheptanoin treatment on clinical events. The Council concurred with the Division that the results of study 201 likely were confounded and thus were insufficient to support an NDA filing. However, MPPRC expressed concerns about the feasibility of a phase 3 trial and recommended additional controlled mechanistic studies to support an NDA. “The Council generally agreed with the limitations outlined by the Division but expressed some concerns regarding the challenges of conducting the phase 3 study. The Council agreed that the data submitted based on the current trial was inadequate to support approval of the application and that the sponsor should be encouraged to submit more data before submitting the NDA” (See Reference ID: 4270689 and 05302018 MPPRC Minutes).
- This was conveyed to the Sponsor in a General Advice letter June 2, 2018, noting that “Senior CDER leadership concurred that dietary changes during Study UX007-CL201 confounded interpretation of the study results, and agreed with the need for a new controlled trial.”
- In a teleconference on June 22, 2018, the Sponsor argued that neither the phase 3 trial nor mechanistic studies were feasible (see minutes). “Ultragenyx is not planning to conduct a Phase 3 study, as they do not believe it is feasible ... The FDA also asked about the feasibility of conducting basic physiology studies of energy metabolism in consenting patients to support dosing and even evidence of efficacy, but Ultragenyx opined that such studies cannot be conducted as there are no reliable applicable methodologies currently in use.”
- No additional controlled studies were performed by Ultragenyx. The Sponsor collected some additional open-label extension follow-up and anecdotal data from n=91 patients under expanded access INDs.
- On August 23, 2018, following the Sponsor’s request for reconsideration, Dr. Beitz accepted the Sponsor’s proposal to submit an NDA for triheptanoin based on the data from Study 201. The Sponsor requested that we convene an Advisory Committee meeting to discuss the impact of dietary changes in this study. The Sponsor also

requested that the Agency meet with patients with LC-FAOD; this meeting took place on January 9, 2019.

- The Pre-NDA meeting was held on November 13, 2018. The Agency's first paragraph of the meeting comments noted that "The lack of a randomized, blinded comparator is a significant limitation of your program; whether a valid quantitative assessment of drug effect is possible will be a focus of the review. Thus, a successful NDA submission will thoroughly and systematically address potential confounders, including concurrent administration of drugs or therapy other than the test drug, such as medium chain triglyceride oil and general dietary management." (See Triheptanoin Pre-NDA meeting minutes).
- On March 29, 2019, triheptanoin (Ultragenyx) received Rare Pediatric Disease Designation (RPDD) for the treatment of long-chain fatty acid oxidation disorders (LC-FAOD).
- The NDA was submitted on July 31, 2019.
- During the filing meeting on September 3, 2019, the clinical and statistical reviewers (Drs. Zand, Donohue, Tracy, Russek-Cohen & Johnson) expressed concerns that Study 201 did not appear to be an adequate and well-controlled trial and recommended against filing the NDA. Dr. Beitz preferred to position this question as a review issue rather than a filing issue, recommended filing and consideration of a more limited nutritional indication, citing a precedent approval in the division for Omegaven as a source of calories and fatty acids in patients receiving parenteral nutrition. Dr. Beitz acknowledged the primary review team's concerns and recommended a standard rather than a priority review clock given the considerable degree of uncertainty about whether triheptanoin demonstrated superiority to available therapy.
- During an orientation meeting on September 5, 2019, the Sponsor confirmed that dietary data from the retrospective period of study 201 were not submitted in SAS datasets because they were of insufficient quality to support sensitivity analyses for this important confounder. The Sponsor stated they are "confident" that patients were well-managed by metabolic nutritionists during the retrospective period but acknowledged that they had been unable to locate the medical records typically kept by metabolic nutritionists to support this assumption.

13. Pharmacology Toxicology Assessments and Additional Information

13.1. Summary Review of Studies Submitted Under IND

As per previous agreements, no nonclinical toxicology studies were submitted in the IND (IND 117053). Only published pharmacology studies were submitted in the IND.

13.2. Individual Reviews of Studies Submitted to the NDA

Published in vitro and in vivo PD studies in mice and rats were submitted in support of the proposed indication of triheptanoin. A 9-month repeat dose oral toxicity study in juvenile minipigs was submitted in support of the safety of long-term administration of triheptanoin in adult and pediatric patients. In addition, a published 9-month dietary toxicity study of triheptanoin in rats was submitted in support of the safety in rodents. The Applicant conducted a full battery of genotoxic studies, including the Ames assay, the in vitro chromosomal aberration assay in human peripheral blood lymphocytes, and the in vivo rat micronucleus assay. In addition, reproductive toxicity studies in rats (fertility and early embryonic development study, embryofetal development study, and pre- and postnatal development study) and rabbits (an embryofetal development study) was submitted in the NDA.

The chronic (9-month) dietary toxicity study in juvenile rats (Ataíde et al. 2009), triheptanoin was administered at 30% (growth phase, 21 g/kg; adult phase, 12 g/kg) or 50% (growth phase, 35 g/kg; adult phase, 20 g/kg) concentrations in diet. Soybean oil was used as the control. There were no significant differences observed in the clinical chemistries and lipid profile or in the urinalysis between the control and treatment groups. However, the relative liver weights were higher in the soybean oil diet group compared to the triheptanoin diet group, and the animals in all study groups showed macrovesicular hepatic steatosis upon histopathological examination. There was no correlation of the steatosis to clinical chemistries, suggesting that liver function was not affected. Histopathological changes in the small intestine included discrete atrophy or hyperplasia of villi, which did not affect digestive functions. In addition, lymphoid follicular hyperplasia, a case of muco-secreting adenocarcinoma in the duodenum, and four cases of “other alterations” in the duodenum were observed. The frequency of these alterations ranged from 60% to 70% in all groups. The authors stated that similar alterations were also observed in the control animals administered soybean oil. However, the study did not use any saline or water control, and the relevance of these findings to treatment cannot be ruled out. This was not a GLP-compliant toxicology study, and only limited number of tissues were examined histologically.

13.2.1. Study 13-699

Study description:	9-Month Oral (Dietary) Toxicity and Toxicokinetic Study of Triheptanoin (UX007) in Juvenile Yucatan Minipigs (including a 4-Week Recovery and a 3-Month Interim Sacrifice)
Study report location:	Ultragenyx: UX007 PC002 Volume II Page 1 to 383.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 5, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Triheptanoin (UX007), lot # 302010, 98%.

Key Study Findings

In the dietary administration of UX007 to male and female juvenile minipigs at doses of 0%, 10%, 30%, or 50% DCI for 9 months with a 4-week recovery and a 3-month interim sacrifice, there were no test article-related histopathological findings in the 50% DCI dose group (terminal

or recovery). All findings were considered normal for the age and strain of the minipigs. The two preterm animal mortalities occurred as a result of urinary tract infection/complications and were not considered related to UX007 treatment.

UX007 was well tolerated without any evidence of toxicity in minipigs receiving up to 50% DCI of UX007. The dose-related increase in the primary metabolites (heptanoic acid and C5 ketone bodies) showed systemic exposure to UX007, but no accumulation after 9 months of treatment. The NOAEL for systemic toxicity was the highest administered dose of 50% DCI in minipigs.

Table 36. Study 13-699 Methods

Method	Details
Doses:	0 (control), 10, 30 or 50% of total daily caloric intake in 2 equally divided doses (6 hours apart).
Frequency of dosing:	Daily for a minimum of 91 days and up to 273 consecutive days.
Route of administration:	Oral (dietary admixture)
Dose volume:	5.4 mL/meal (10%), 16.3 mL/meal (30%), 27.2 mL/meal (50%)
Formulation/vehicle:	270-300 g/day/Ground laboratory minipig diet
Species/strain:	Yucatan minipigs
Number/sex/group:	6/sex/group (3/sex/group designated for interim sacrifice after 3 months; 3/sex/group treated for 9 months (terminal sacrifice)).
Age:	6-8 weeks old at dosing initiation.
Weight:	3.86 – 10.125 kg
Satellite groups:	2 animals/sex/group (control and high dose group) were designated as recovery animals after 9 months treatment and 4 weeks recovery period.
Unique study design:	None
Deviation from study protocol:	No deviations that affected the quality of the data occurred.

Observations and Results

Mortality

Animals were observed at least twice daily for moribundity and mortality.

One high-dose (50%) male pig was found dead during week 29. Another high-dose male was found moribund at week 37 and euthanized. Both males had prolapsed penises, and their deaths were related to urinary tract infection and not from test article administration. During the first week of dosing, a control male pig died spontaneously from myocardial necrosis and was replaced.

Clinical Signs

Detailed clinical observations were performed weekly.

There were no treatment-related clinical signs observed in minipigs. Occasionally, vomit was seen in the cage of the pigs, and four pigs (one control, one mid-dose, and two high-dose) were also noted with prolapse of the penises.

Body Weights

Body weights were measured on study day 1 and weekly throughout the study period.

Body weights in the treated animals were similar to controls throughout the study period. A negative body weight gain observed in the male and female minipigs from the 50% dose group on the first week of dosing was only significant in the male animals and likely due to the initial inappetence seen with the UX007 dietary mix introduction.

Feed Consumption

Although animal food was measured before feeding, food consumption was limited to qualitative assessment.

On dosing day 1, the minipigs in the 30% and 50% DCI dosing groups did not eat their food. However, by dosing day 3, the animals began to eat and consumed all of their food.

Ophthalmoscopy

Indirect funduscopy ophthalmic examinations were performed on all animals.

There were no UX007 treatment-related effects noted on examination of the eyes of treated animals.

Hematology

Blood for hematology was collected prior to treatment initiation on study days 30 and 90.

Statistically significant differences of minimal in magnitude were observed predose and at time intervals, but they did not pose any clinical significance.

Clinical Chemistry

Clinical chemistry parameters did not show any adverse treatment-related effects. However, significant differences were seen in some clinical chemistry values of treated animals, especially in the 50% dose groups. The changes observed were likely secondary effects related to the nutritional contents (lower protein) of the treated animals in contrast to the control diet:

- Decreased blood urea nitrogen in the 30% and 50% dose groups
- Decreased total protein, albumin and globulin and globulin in the 30% and 50% treated males at day 90 of the dosing period
- Decreased alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, cholesterol, PO₄, CPK, gamma glutamyl transpeptidase, and creatinine in the treated males and/or females, occasionally, during the study. These changes were not considered toxicologically relevant.

Urinalysis

Urine for urinalysis was collected directly from the urinary bladder in the animals at interim sacrifice.

There were no treatment-related changes seen in measured urinalysis parameters.

Gross Pathology

All animals were fasted prior to the complete necropsy. Tissues collected at necropsy were weighed and preserved.

There were no test article-related findings at gross necropsy. Findings were considered spontaneous in occurrence and not treatment-related. Early deaths in the 50% dosed males were related to urinary bladder dilatation, with or without kidney dilation and enlarged epididymis. In the sacrificed moribund animals, stomach dilation was seen, while the animal found dead had an enlarged heart.

Nodules were seen on the kidney of a female in the 30% dose group and in the pituitary of a female from the 50% dose group. The necropsy observations were considered as common findings for the age and strain of these minipigs.

Organ Weights

Fasted body weight collected from animals prior to scheduled necropsy was used to calculate organ-to-body weight ratios.

There were no treatment related differences in organ weights or organ to body weight ratios.

Histopathology

- Adequate battery: Yes
- Peer review: Yes

Histological Findings

There were no test article-related histopathological findings in the 50% animal dose group (terminal or recovery). All findings were considered normal for the age and strain of the minipigs. The two preterm animal mortalities occurred as a result of urinary tract infection/complications and not because of UX007 treatment.

Toxicokinetics

Blood samples were collected from the toxicokinetic (TK) animals on days 1, 10, and 270 and analyzed for triheptanoin and its metabolites (heptanoic acid, C4 and C5 ketone bodies). Additionally, trough samples were collected monthly at 30, 60, 90, 120, 150, 180, 210, 240, 270, and 298 days from recovery animals.

Systemic exposure to triheptanoin showed a dose-related increase in heptanoic acid, its primary metabolite, as well as a dose-related increase in C5 ketone bodies. The levels of triheptanoin at 10%, 30%, and 50% DCI, as well as the C4 ketone bodies, were not appreciably different from those of controls. The AUC values showed that only heptanoic acid and C5 ketone bodies increased in a dose-related manner similar with the percentage of triheptanoin in the diet. On study day 10, the heptanoic acid AUC values were 4,515 and 4,277 min·µM for the males and

females treated with 10% DCI of triheptanoin, respectively. The levels in the 30% dose group were 48,427 and 66,179 min·µM, and those in the 50% dose group were 288,736 and 285,239 min·µM in males and females, respectively. A similar trend was seen on day 270. The monthly trough plasma concentration values for triheptanoin and the five metabolites in the recovery animals were not substantially above control values or were slightly above in the case of heptanoic acid.

Although the metabolites levels increased in a dose-related manner, no evidence of accumulation was detected after 9 months of dosing or after the 28-day recovery period.

Table 37. Pharmacokinetic Parameters From Mean Heptanoic Acid Plasma Concentrations for Male and Female Minipigs on Days 10 and 270

Gender	Dose Level	Day	T _{max}	C _{max}	AUC _(0-240 min)
			min	µM	min*µM
Male	2-Low	10	30	26.79	4,515
	3-Mid	10	30	334.26	48,427
	4-High	10	180	1,500.90	288,736
	2-Low	270	90	71.51	8,419
	3-Mid	270	60	755.46	122,163
	4-High	270	90	2,640.35	441,770
Female	2-Low	10	30	40.27	4,277
	3-Mid	10	30	630.65	66,179
	4-High	10	90	1,469.28	285,239
	2-Low	270	30	122.88	10,011
	3-Mid	270	90	774.04	106,918
	4-High	273	180	1,177.14	232,148

Note: The Dose Level refers to the dose of test material, Triheptanoin (UX007), administered and expressed as a percentage (10, 30, or 50%) of the daily caloric intake
Abbreviations: AUC_(0-240 min), area under the curve from 0 to 240 minutes (4 hours); C_{max}, maximum concentration; T_{max}, median time to maximum concentration

13.2.2. Study 9600774

Study title:	Bacterial Reverse Mutation Test in <i>Salmonella typhimurium</i> and <i>Escherichia coli</i>
Study report location:	UX007-PC004. Pages 1 to 65
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 16, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	UX007, lot # U4013 (Z847), 98% purity; DMSO, lot # RNBC9842, 100% purity.

Key Study Findings

UX007 at a maximum concentration of 4,800 µg/plate did not produce any mutagenic effect in any of the five bacterial strains tested with and without metabolic activation.

Table 38. Study 9600774 Methods

Methods	Details
Strains:	<i>Salmonella typhimurium</i> strains (TA1535, TA1537, TA98, TA100) and <i>Escherichia coli</i> strain WP2 <i>uvrA</i>
Concentrations in definitive study:	5.0, 15.8, 50, 158, 500, 1581, 4,800 µg/plate
Basis of concentration selection:	Cytotoxicity
Negative control:	Dimethylsulfoxide (DMSO)
Positive control:	Sodium azide (NaN ₃), 9-Aminoacridine hemihydrate (9AC), 2-Nitrofluorene (2NF), 4-Nitroquinoline N-oxide (NQO), 2-Aminoanthracene (2AA), Benzo[a]pyrene (BaP).
Formulation/vehicle:	Dimethylsulfoxide (DMSO)
Incubation & sampling time:	Plates were incubated at 37°C for 65 hours and 23 minutes and counted manually and electronically.

Study Validity

For study validity, the mean revertant colony counts of the vehicle control for each strain should lie close to or within the current historical control range of the laboratory. All positive controls (with S9 mix where required) should produce increases in revertant colony numbers to at least the concurrent vehicle control levels with the appropriate bacterial strain. The study was considered valid.

Results

None of the tested concentrations (ranging from 5.0 to 4,800 µg/plate) of UX007 in any of the five tester strains showed incomplete or absent background lawns of nonrevertant bacteria or substantial reductions in revertant colony counts, indicating that the test item was nontoxic to the bacteria at the levels tested.

At dose level 1,581 µg/plate with strain TA1537, no colonies were present in any of the triplicate plates. This was not dose-related since the higher dose level, the 5,000 µg/plate, showed no indications of toxicity. Therefore, the absence of colonies at 1,581 µg/plate was not considered to be true toxicity. No precipitation was observed in the assay.

Appropriate positive controls (with S9 mix where required) induced increases in revertant colony numbers to at least twice the concurrent vehicle control levels with the appropriate bacterial strain, confirming sensitivity of the test system and activity of the S9 mix.

In conclusion, no substantial increases in the revertant colony counts were obtained with any of the tester strains following exposure to UX007 at any dose level in the presence or absence of S9 mix. Therefore, UX007 was considered to be negative for the induction of mutagenicity in this in vitro assay.

13.2.3. Study 9600775

Study title:	In Vitro Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes
Study report location:	UX007-PC005, Pages 1 to 67
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 17, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	UX007, lot # U4013 (Z847), and 98% purity; DMSO, lot # RNBC9842, 100% purity

Key Study Findings

UX007, at a maximum concentration of 409 µg/ml (in the presence or absence of metabolic activation), did not induce any chromosomal aberration in vitro (human peripheral blood lymphocytes) under conditions where positive controls exerted potent mutagenic effects.

Table 39. Study 9600775 Methods

Methods	Details
Cell line:	Human peripheral lymphocytes primary culture
Concentrations in definitive study:	143 µg/ml to 409 µg/ml
Basis of concentration selection:	Highest concentration of test compound tested was the maximum dose level recommended by the International Council for Harmonisation guideline (1mM).
Negative control:	Dimethylsulfoxide (DMSO)
Positive control:	Mitomycin C (MMC), Cyclophosphamide monohydrate (cyclophosphamide, CP)
Formulation/vehicle:	DMSO
Incubation & sampling time:	21 hrs, and 4 hrs

Study Validity

For study validity, the vehicle/negative control results should lie within or close to the historical control range, while the positive controls should produce a substantial increase in the incidence of aberrant cells (at least twice) compared with the concurrent control with values lying beyond the 99% upper limit of the historical negative/vehicle control range. Based on these criteria, the study was considered valid.

Results

In the definitive study, UX007 at concentrations of 143, 247, and 409 µg/ml did not cause any substantial increases in the proportion of aberrant metaphases.

The positive controls caused substantial increases in the proportion of aberrant metaphases at 11.5% (without S9) and 14.5% (with S9) in the study, confirming the sensitivity of the test system and the effectiveness of the S9 mix.

There were no substantial increases in the incidence of chromatid or chromosome gaps, or polyploidy were observed at any experimental point. No precipitation or toxicity was observed of the assays.

In conclusion, UX007 did not show any evidence of genotoxic activity in this in vitro test for induction of chromosome damage.

13.2.4. Study 9800190

Study title:	Mammalian Erythrocyte Micronucleus Test in Rat Bone Marrow
Study report location:	UX007-PC006, Pages 1 to 72
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 09, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	UX007, lot # U4013 (Z847), 98% purity.

Key Study Findings

UX007 at a maximum dose of 2000 mg/kg/day did not induce chromosome damage in male and female rat bone marrow.

Table 40. Study 9800190 Methods

Methods	Details
Doses in definitive study:	500 mg/kg/day, 1000 mg/kg/day, and 2000 mg/kg/day
Frequency of dosing:	Daily for 2 consecutive days.
Route of administration:	Oral gavage
Dose volume:	0.53 (500 mg/kg), 1.06 (1000 mg/kg), 2.13 (2000 mg/kg)
Formulation/vehicle:	Test article vehicle was not indicated.
Species/strain:	Sprague-Dawley Crl:CD(SD) rats
Number/sex/group:	5/sex/group 3/sex/group; (positive control).
Satellite groups:	None
Basis of dose selection:	Standard limit dose
Negative control:	Ultrapure water
Positive control:	Cyclophosphamide (monohydrate) (CP)

Study Validity

For study validity, the incidence of micronucleated immature erythrocytes for the vehicle control group should fall close to or within the laboratory historical vehicle/negative control range. In addition, the positive control group should show clear unequivocal positive response. Based on these, the study was considered valid.

Results

Rats treated with UX007 did not show any notable increases in the number of micronucleated immature erythrocytes. Therefore, UX007 did not show any evidence of chromosome damage in this assay. Individual and group mean values for animals treated with the negative control or the test item were all within, or close to, the historical range for control animals. Thus, the performance of the negative and positive controls was consistent with a valid assay.

In conclusion, UX007 did not show any evidence of genotoxic activity in the in vivo erythrocyte micronucleus test for the induction of chromosome damage in rat bone marrow, when administered at up to 2000 mg/kg/day.

13.2.5. Study 15-800 Reproductive and Developmental Toxicology

Study title:	Reproductive Toxicity Study (Segment I) of Orally (in Diet) Administered UX007 in Rats
Study report location:	UX007-PC012; page 1 to 558
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 6, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	UX007, lot # U4040 (404011), % purity not given.

Key Study Findings

In the dietary administration of triheptanoin to male (28 days) and female rats (14 days), at doses of 0%, 10%, 30% and 50% DCI, there were no animal deaths, but there was an initial reduction in food consumption in the high dose group, which affected body weight and body weight gain initially in these animals. After mating, the total weight gain was elevated in the female animals. There was no effect of UX007 on mating performance and reproductive organ weights in male or female animals. The NOAEL for reproductive toxicity of dietary administered UX007 was 50% DCI in male and female rats.

Table 41. Study 15-800 Methods

Methods	Details
Doses:	0 (vehicle), 10% DCI, 30% DCI and 50% DCI
Frequency of dosing:	Daily
Dose volume:	0.8 mL, 2.3 mL, or 3.8 mL
Route of administration:	Oral (Dietary)
Formulation/vehicle:	Dietary admixture
Species/strain:	Sprague-Dawley rats
Number/sex/group:	25/sex/group
Satellite groups:	3/sex/group designated as TK group
Study design:	Male rats were dosed daily 7 days/week for 4 weeks prior to and during mating; Females were dosed 7 days/week for 2 weeks prior to mating, during mating and up to gestation day 6 (i.e., implantation)
Deviation from study protocol:	none

Abbreviations: DCI, daily caloric intake, TK, toxicokinetic

Observations and Results

Mortality

Animals were observed at least once daily for morbidity and preterminal deaths. There were no animal deaths during the study.

Clinical Signs

The animals were subjected to a detailed examination during the quarantine period, and at least weekly during the study period.

There were no treatment-related clinical signs seen in any of the animals.

Body Weight

The animals were weighed pretest and weekly until the mating period. Male animals were weighed once prior to their scheduled sacrifice, while dams were weighed on gestation days 0, 3, 6, 9, 12, and prior to their scheduled necropsy (on day 13). Their body weight gains were calculated.

Significantly reduced body weights were seen in the 50% dosed males (ranging from -10 g to -17 g) and females (ranging from -22 g to -26 g) after the first week of treatment and remained lower for the study duration. Significantly reduced body weight gain was observed in some treatment groups prior to mating; among males treated with the 50% dose, body weight gain was reduced by 17 g, and among females, body weight gain was reduced by 7 g among those treated with the 30% dose and by 20 g among those treated with the 50% dose. However, after mating, total body weight gain was significantly elevated in the 50% dosed females (+9 to +13 g). The alterations in body weight gain in treated dams was the consequence of the initial lower food consumption, specifically in the 30% and 50% dose groups.

Feed Consumption

Following treatment initiation, food consumption measurement was performed daily for the first week, and then once/week thereafter (i.e., day 8, 15, 22, and 29 for males, and on days 8 and 15 for females). TK rats were fasted prior to the first dose and prior to the last dose (males on day 28, and females on day 14) to ensure daily food consumption on the days of blood collection.

Initially, the treated females in the low (10% DCI), mid (30% DCI), and high dose (50% DCI) consumed less food than the control animals, but by the end of the first week, they had eaten most of their food ration.

Necropsy

All animals (including dead or moribund ones) were euthanized and necropsied. The following tissue samples from organs were preserved in 10% neutral-buffered formalin, except for the testes and epididymis which were fixed in Bouin's solution:

Table 42. Tissue Samples Collected, Study 15-800

Epididymides*	Cervix
Prostate	Ovaries with oviducts*
Seminal Vesicles	Uterus*
Testes*	Vagina
Coagulating Gland	

No treatment related gross pathology findings were observed in any group.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Epididymal sperm density (count) and sperm morphology parameters were unaffected by treatment with UX007. Sperm motility and progressive sperm were similar across all groups and ranged from 81% to 84% and 22% to 24%, respectively.

Overall, mating performance was unaffected by drug treatment. Absolute and relative reproductive organ weights were also unaffected by treatment. The NOAEL for reproductive toxicity of orally administered UX007 in the diet was 50% of the DCI for both sexes.

Toxicokinetics

Toxicokinetic animals were fasted and bled prior to treatment and 60 min, 240 min, 360 min, 480 min, 1440 min postdose on day 1, and on the last dosing day (day 14 for females, day 28 for males).

The mean plasma triheptanoin concentrations in both males and females were variable, and generally similar for the mid and high dose levels. On day 1, the triheptanoin median time to maximum concentration (T_{max}) occurred between 5 hours and 8 hours for females and between 1 hour and 4 hours for males across doses. On day 14 for female animals, the triheptanoin median T_{max} occurred between 3 hours and 8 hours, and on day 24 in male animals, the T_{max} occurred at 1 hour.

Triheptanoin and related metabolites levels generally increased from the low (10%), to the mid (30%), to the high (50% DCI) dose groups. Heptanoate exposure increases were generally more than dose proportional, but not in a consistent or predictable manner. Overall, no clear gender related trends were observed, and there was no major accumulation over time.

13.2.6. Study 15-799

Study title:	Oral Developmental Toxicity Study (Segment II) of UX007 in Rats
Study report location:	UX007-PC013. p1-422
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 6, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	UX007, lot # U4040 (404011), purity not provided.

Key Study Findings

Administration of UX007 via dietary admixture at dose levels of 0%, 10%, 30%, and 50% DCI from gestation day (GD) 6 to GD 18 to pregnant rats resulted in maternal toxicity (reduced body weight gain) at 30% and 50% DCI, due to initial inappetence to UX007. Uterine and fetal body weights were not affected by the test article, and no gross external, visceral, or cephalic malformations were attributable to UX007. Skeletal variations (fused sternebrae, misshapen thoracic centra, incomplete ossification of the skull, and pelvic girdle) were increased (above control background) in the 50%DCI group, which were considered secondary to maternal toxicity. Seventy eight percent of the control fetus were normal, compared to 85% of the mid-dose (30% DCI) and 55% of high dose (50% DCI). The NOAEL for maternal toxicity of UX007

via dietary administration was 10% DCI, and the NOAEL for developmental toxicity was 30% DCI.

Table 43. Study 15-799 Methods

Methods	Details
Doses:	0 (vehicle), 10% DCI, 30% DCI and 50% DCI.
Frequency of dosing:	Daily
Dose volume:	3.8, 0.8, 2.3 or 3.8 mL
Route of administration:	Oral (dietary)
Formulation/vehicle:	Dietary admixture/water
Species/strain:	Sprague-Dawley rats
Number/sex/group:	23 females/group
Satellite groups:	3 females/group were designated as toxicokinetic (TK) animals
Study design:	4 groups of mated Primiparous female rats were administered graded concentrations of the test article via diet admixture from gestation day (GD 6) through GD 17. Mating was staggered over a minimum of 5 days to obtain a minimum of 5 series. Each series was sacrificed on its respective 21 st day of gestation. TK rats were bled and sacrificed on GD 21, and their pregnancy status assessed. Fetal weights were recorded, and their external morphology examined. Blood was pooled from fetuses in the litter and the dams discarded.
Deviation from study protocol:	No deviations occurred that would affect the quality or integrity of collected data.

Abbreviations: DCI, daily caloric intake

Observations and Results

Mortality

Animals were observed at least once daily for moribundity and mortality during quarantine and observed twice daily on weekdays and once daily on weekends during the study.

Clinical Signs

Animals were observed twice daily on weekdays and once daily on weekends for abnormal clinical signs. A detailed clinical examination was performed on all animals at randomization.

No test article-related clinical signs of toxicity were observed during the study.

Body Weight

Each dam was weighed prestudy and on gestation days 6,7,8,9,12,15,18, and 21.

The mean maternal body weight was significantly lower (at -9 g to -24 g) than controls in the 50% DCI dose group throughout the study duration from GD 7 to GD 21. Body weight gain was lower in the 30% DCI dose group on GD 7 (at -1 g) and also on GD 7, GD 9, and GD 12 (at -5 g to +11 g/interval) in the 50% DCI dose group, even when correction was made for uterine weight. The decreased body weight and body weight gain are indicative of maternal toxicity.

Feed Consumption

Food consumption measurements were obtained daily over GD 6 to GD 18.

Rats dosed at 30% and 50% DCI were noticed to initially consume less food by 22% and 26%, respectively. However, by GD 8 for the 30% DCI dose group and GD 12 for the 50% DCI dose group, the initial inappetence was gone and these animals consumed most of their food ration thereafter.

Toxicokinetics

Blood for TK measurements was collected from dams predose on GDs 6 and 17, and 60, 240, 360, 480, and 1,440-minutes postdose on GD 6 and GD 17. Does were also bled prior to cesarean section on GD 21.

Plasma exposure to triheptanoin and the metabolites heptanoate, 3-hydroxybutanoate, 3-hydroxypentanoate generally increased with increasing dose of UX007 administered. The increase in exposure to triheptanoin and metabolites were more than dose proportional, but not consistently. Plasma triheptanoin concentrations were only seen in animals dosed with 30% and 50% DCI on GD 6 (single dose) or GD17 (repeat dose), whereas plasma heptanoate exposure were seen in all the treated animals. 3-hydroxybutanoate plasma concentrations were measured following single (GD 6) and multiple (GD 17) administration of all UX007 doses, whereas 3-hydroxypentanoate plasma concentrations were only observed in the 50% DCI dosed animals after a single administration (GD 6), and in the 30% and 50% DCI groups after repeated UX007 administration on GD17. Significant accumulation of triheptanoin and heptanoate were seen in the plasma of the 30% and 50% DCI dose groups following single or multiple administration of UX007. On the other hand, accumulation of 3-hydroxypentanoate was seen only in the 50% DCI treated dams following single (GD 6) or multiple dosing (GD 17), and no accumulation of 3-hydroxybutanoate was seen in any of the treated animals. The mean TK parameters of triheptanoin in rats administered UX007 are shown below.

Table 44. Mean TK Parameters for Triheptanoin in Rats

Plasma TK Parameters	Day 6, Mean (%CV)		
	Low UX007 Dose	Mid UX007 Dose (N=3)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	NC	1.330 (131.7)	4.209 (56.7)
C _{max} (μmol/L)	NC	0.4803 (54.2)	0.4553 (28.4)
Plasma TK Parameters	Day 17, Mean (%CV)		
	Low UX007 Dose	Mid UX007 Dose (N=3)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	NC	4.188 (57.2)	12.72 (18.3)
C _{max} (μmol/L)	NC	1.168 (54.8)	2.867 (20.6)

Abbreviations: AUC_{last}, area under the curve to the time of the last concentration; C_{max}, maximum concentration; CV, coefficient of variation; NC, not calculated; TK, toxicokinetics

Table 45. Mean Baseline-Adjusted TK Parameters for 3-Hydroxybutanoate in Rats

Plasma TK Parameters	Day 6, Mean (%CV)		
	Low UX007 Dose* (N=1)	Mid UX007 Dose (N=3)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	429 (NC)	2766 (56.9)	2181 (62.5)
C _{max} (μmol/L)	857 (NC)	658.3 (44.6)	731.0 (49.7)
Plasma TK Parameters	Day 17, Mean (%CV)		
	Low UX007 Dose	Mid UX007 Dose* (N=1)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	NC (NC)	412 (NC)	5545 (121.9)
C _{max} (μmol/L)	NC (NC)	772 (NC)	724.7 (50.7)

* Individual value reported (N=1), not mean parameters

Abbreviations: AUC_{last}, area under the curve to the time of the last concentration; C_{max}, maximum concentration; CV, coefficient of variation; NC, not calculated; TK, toxicokinetics

Necropsy

All animals sacrificed in extremis or on scheduled euthanasia on GD 21 were necropsied. The presence of lesions or abnormalities in the dam and/or fetus were noted, and the uteri were discarded.

All the rats sacrificed on GD 21 were gravid, and no gross necropsy findings related to test article treatments were seen. One dam from the 30% DCI group had a brown fluid in the uterus, and another dam from the 50% DCI dose group had red ovaries.

Cesarean Section Data (Implantation Sites, Pre- and Postimplantation Loss, etc.)

There were no treatment-related differences in litter viability observed. The percent pre- and postimplantation loss was not increased in treated groups relative to controls. The preimplantation loss averaged 3.3% to 4.4%, while the average postimplantation loss averaged 4.1% to 5.5%. The average number of corpora lutea, live, and total implants was similar across groups, although slightly lower in the UX007 50% DCI group. No dead fetuses were observed in any of the litters, and the average number of resorptions/litters was similar across groups at a range of 0.5 to 0.7. A summary of intrauterine parameters assessment is shown in [Table 46](#).

Offspring (Malformations, Variations, etc.)

Fetal weights were similar across groups with no significant difference in litter weights observed. One fetus in the 10% DCI dose group had a threadlike malformed tail, but the incidence of this malformation (0.3%) is within published control ranges (average 0.017% with a maximum of 0.36%). A fetus in the 50% DCI dose group was observed with multiple visceral malformations, including abnormal shaped heart, absent lung lobes, large adrenal, mottled liver, and small spleen.

Fetuses in the 50% DCI dose group had greater incidences of skeletal variations (rudimentary 14th rib, incomplete ossification of the skull and pelvic girdle), whereas the skeletal variations seen in the 30% DCI dose group are similar to that seen in the control animals. Three fetuses in two litters had skeletal malformations. Two fetuses in the 50% dose group had fused sternbrae,

and one had a fused rib. These findings are associated with maternal toxicity. The NOAEL for maternal toxicity of UX007 via diet administration was 10% DCI, while the NOAEL for developmental toxicity was 30% DCI.

A summary of the findings is shown in the tables below.

Table 46. Litter Viability, Oral Developmental Toxicity Study (Segment II) of UX007 in Rats

<u>Parameter</u>	<u>Treatment Group</u>			
	<u>Vehicle Control</u> <u>0%</u>	<u>Low Dose</u> <u>10%</u>	<u>Mid Dose</u> <u>30%</u>	<u>High Dose</u> <u>50%</u>
Live Fetuses/Total Implants	274/290	288/300	278/291	261/276
% Live	94.5	96.0	95.5	94.6
Early Resorptions/Total Implants	16/290	11/300	13/291	15/276
% Early Resorptions	5.5	3.7	4.5	5.4
Late Resorptions/Total Implants	0/290	1/300	0/291	0/276
% Late Resorptions	0	0.3	0	0
Total Resorptions/Total Implants	16/290	12/300	13/291	15/276
% Total Resorptions	5.5	4.0	4.5	5.4
Early Deaths/Total Implants	0/290	0/300	0/291	0/276
% Early Deaths	0	0	0	0
Late Deaths/Total Implants	0/290	0/300	0/291	0/276
% Late Deaths	0	0	0	0
Total Non-Live/Total Implants	16/290	12/300	13/291	15/276
% Non-Live	5.5	4.0	4.5	5.4
Malformed Fetuses/Live Implants	0/274	1/288	0/278	4/261
% Malformed	0	0.3	0	1.5

Table 47. Summary of Fetal Gross External, Visceral, and Cephalic Examinations (Fetal Incidence/Litter Incidence), Oral Developmental Toxicity Study (Segment II) of UX007 in Rats

	Treatment Group			
	Vehicle Control 0%	Low Dose 10%	Mid Dose 30%	High Dose 50%
Gross External Morphology				
	Fetuses/Litters			
Number Examined:	274/23	288/23	278/23	261/23
Number Normal:	274/23	287/23	278/23	261/23
% Normal (fetal):	100	100	100	100
Number Malformed:	0	1	0	0
% Malformed (fetal):	0	0.3	0	0
Thread-like tail (malformation)	0	1	0	0
Visceral Observations				
Number Examined:	137/23	145/23	138/23	126/23
Number Normal:	137/23	142/23	135/23	124/23
% Normal (fetal):	100	98	98	98
Variations # Affected	0	3	2	2
Hydro-ureter/Hydro-nephrosis	0	3	1	0
Short/absent Innominate	0	0	2	1
Number Malformed:	0	0	0	1
% Malformed (fetal):	0	0	0	0.8
Globe Shaped Heart ^a	0	0	0	1
Cephalic Observations				
Number Examined:	137/23	Not Examined	Not Examined	126/23
Number Normal:	137/23	Examined	Examined	126/23
% Normal (fetal):	100			100

^aPup also had no aortic arch or ductus arteriosus, absent lung lobes, large adrenal, mottled liver, and small spleen

13.2.7. Study 15-798

Study title:	Oral Developmental Toxicity Study in Rabbits
Study report location:	UX007 PC014, p1 to 423
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 6, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	UX007, lot # U4025, % purity not given

Key Study Findings

Administration of UX007 via oral gavage at dose levels of 0%, 10%, 20%, and 30% DCI from GD 6 to GD 18 to pregnant rabbits resulted in overt maternal toxicity (inappetence) at 20% and 30% DCI. One rabbit in the 30% DCI dose group died on GD 19 from anorexia, while five rabbits from the 30% DCI dose group delivered or aborted prematurely. Rabbits in the 10% dose group did not show any evidence of maternal toxicity. Three high dose fetuses from two separate full-term gravid litters showed skeletal malformations (fused/forked/extra ribs) that were likely secondarily related to maternal toxicity. Fetal weights in the 30% DCI dose group were significantly lower than controls, whereas the fetal weights in the 10% and 20% DCI dose groups were similar to those of controls. Visceral and cephalic examinations did not show any changes that could be attributed to test article treatment. The NOAEL dose of UX007 for maternal toxicity was 10% DCI, and the NOAEL for developmental toxicity was 20% DCI.

Table 48. Methods, Study 15-798

Methods	Details
Doses:	0 (vehicle), 10% DCI, 20% DCI and 30% DCI
Frequency of dosing:	Daily
Dose volume:	11.3, 3.8, 7.5 and 11.3 mL
Route of administration:	Oral gavage
Formulation/vehicle:	UX007 no vehicle used
Species/strain:	New Zealand white female rabbits
Number/sex/group:	23 females/group
Satellite groups:	3 females/group were designated as toxicokinetic (TK) animals.
Study design:	23 primiparous rabbits/group were administered by oral gavage undiluted UX007 from gestation day (GD) 6 to 18. Blood was collected on GD 6 and 18 for clinical pathology and from TK animals for TK evaluation. Necropsies were performed on animals that died prematurely, and on day 29 on surviving animals. Gravid uterine weights and fetal weights were recorded before external morphological examination.
Deviation from study protocol:	No deviations that would affect the quality or integrity of the data occurred during the conduct of the study.

Abbreviations: DCI, daily caloric intake

Observations and Results

Mortality

Animals were observed at least once daily for moribundity and mortality during quarantine, and twice daily on weekdays and once daily on weekends during the study period.

Two rabbits in the 30% DCI dose group died during the study. On GD 13, one rabbit (#99-524) died of gavage trauma, and on GD 19 one rabbit (#104-551) died from inappetence because it did not eat during the dosing phase of the study.

Clinical Signs

Animals were observed twice daily on weekdays and once daily on weekends for abnormal clinical signs during the study period.

Clinical signs of dose-related scant feces (from reduced food consumption) was observed in all the treated females. In the high (30% DCI) dose group, evidence of abortion (vaginal discharge, red material and/or pups/placentas in excrement pan) was seen in 5 of 23 rabbits. One TK rabbit (211-244) in the 30% DCI dose group showed clinical signs of lethargy, prostrate and irregular breathing, abdominal contractions, and gastric distress on GD 8, GD 9, and GD 14.

Body Weight

Each doe was weighed prior to dosing and on GD 6, GD 7, GD 8, GD 9, GD 12, GD 15, GD 18, GD 21, GD 24, GD 27, and GD 29.

Decreased maternal body weights were observed in the 20% DCI dosed rabbits over GD 12 to GD 15, and with statistical significance in the 30% DCI dosed rabbits over GD 12 to GD 29.

Maternal body weight gain was significantly lower in the 30% DCI dosed animals over GD 8 to GD 15, and they lost weight during the treatment period. However, the weights of the uterus of the full term gravid (nonaborting/nonpremature delivering) does were not significantly reduced in the 30% DCI dose group.

Feed Consumption

Over GD 5 to GD 6, the average daily food consumption was similar across all animal groups. Daily food consumption was also similar during the treatment period in the control and the 10% DCI dosed animal. Dose-related decreased food consumption was observed in the 20% and 30% DCI treated does throughout the dosing phase, resulting in maternal toxicity from inappetence and anorexia. Increased food (rebound) consumption was noticed in the 20% and 30% DCI dosed animals after the dosing stopped, beginning from GD 20 or GD 21.

Toxicokinetics

Blood for TK measurements was collected predose on GDs 6 and GD 18, and at 60 minutes, 360 minutes, 480 minutes, and 1,440 minutes postdose. Does were also bled prior to cesarean section on GD 29. Fetuses were bled for TK after examination, and fetal blood was pooled within litters.

Plasma exposure of triheptanoin and its metabolites (heptanoate, 3-hydroxybutanoate, and 3-hydroxypentanoate) generally increased with increasing dose of UX007 from GD 6 to GD 18. Increases in exposure was not consistent or predictable but was generally more than dose-proportional. Triheptanoin plasma concentration was below the level of quantitation (BLQ) for most of the treated rabbits throughout the study, with detectable levels only occurring in a single high dose rabbit on GD 18 after repeated dosing of 30% UX007. The overall metabolite accumulation over time was only observed for 3-hydroxybutanoate and 3-hydroxypentanoate with the administration of the 30% DCI UX007 dose. Exposure to triheptanoin or its metabolites was not seen in the fetuses. A summary of the TK parameters of triheptanoin metabolites is shown in the tables below.

Table 49. Mean Plasma Heptanoate TK Parameters in Dams

Plasma TK Parameters	Day 6, Mean (%CV)		
	Low UX007 Dose (N=3)	Mid UX007 Dose (N=3)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	130.3 (0.6)	1615 (66.8)	8279 (81.7)
C _{max} (μmol/L)	191.4 (57.7)	731.3 (24.8)	2635 (82.2)
Plasma TK Parameters	Day 18, Mean (%CV)		
	Low UX007 Dose (N=2)	Mid UX007 Dose (N=3)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	148.1 (NC)	1559 (113.8)	6019 (37.7)
C _{max} (μmol/L)	232.7 (NC)	599.0 (58.4)	725.7 (12.1)

Abbreviations: AUC_{last}, area under the curve to the time of the last concentration; C_{max}, maximum concentration; CV, coefficient of variation; NC, not calculated; TK, toxicokinetics

Table 50. Mean 3-Hydroxybutanoate TK Parameters in Dams

Plasma TK Parameters	Day 6, Mean (%CV)		
	Low UX007 Dose (N=2)	Mid UX007 Dose (N=3)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	33.86 (NC)	102.0 (38.3)	149.2 (22.2)
C _{max} (μmol/L)	85.25 (NC)	167.7 (43.7)	274.7 (37.6)
Plasma TK Parameters	Day 18, Mean (%CV)		
	Low UX007 Dose* (N=1)	Mid UX007 Dose (N=2)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	144 (NC)	309.6 (NC)	7372 (45.6)
C _{max} (μmol/L)	228 (NC)	121.0 (NC)	1842 (47.9)

* Individual value reported (N=1), not mean parameters

Abbreviations: AUC_{last}, area under the curve to the time of the last concentration; C_{max}, maximum concentration; CV, coefficient of variation; NC, not calculated; TK, toxicokinetics

Table 51. Mean 3-Hydroxypentanoate TK Parameters in Dams

Plasma TK Parameters	Day 6, Mean (%CV)		
	Low UX007 Dose* (N=1)	Mid UX007 Dose (N=3)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	15.2 (NC)	90.17 (13.6)	123.7 (42.1)
C _{max} (μmol/L)	60.9 (NC)	136.0 (18.6)	265.3 (49.9)
Plasma TK Parameters	Day 18, Mean (%CV)		
	Low UX007 Dose* (N=1)	Mid UX007 Dose (N=3)	High UX007 Dose (N=3)
AUC _{last} (μmol•h/L)	68.0 (NC)	208.0 (139.2)	4557 (42.2)
C _{max} (μmol/L)	92.0 (NC)	96.40 (37.0)	1098 (42.1)

* Individual value reported (N=1), not mean parameters

Abbreviations: AUC_{last}, area under the curve to the time of the last concentration; C_{max}, maximum concentration; CV, coefficient of variation; NC, not calculated; TK, toxicokinetics

Necropsy

All the surviving animals were euthanized on GD 29 prior to undergoing cesarean sections. The presence of lesions or abnormalities in the doe and/or fetus were noted, and the uteri were discarded.

Gross necropsy findings were not remarkable as all the tissues examined appeared normal. The animal found dead from the 30% DCI dose group died from gavage trauma on GD 13. The appearance of red lungs and fluid in the trachea supported the cause of death. The rabbit found dead on GD 19 did not show any gross lesions; however, the inappetence and eating abstention likely contributed to her death.

Cesarean Section Data (Implantation Sites, Pre- and Postimplantation Loss, etc.)

Oral doses of UX007 at 20% and 30% DCI produced maternal toxicity as shown by food inappetence throughout the dosing period. One rabbit from the 30% DCI dose group died on GD 19 from anorexia, while five other rabbits from the 30% dose group delivered or aborted

prematurely. However, rabbits from the 10% dose group did not show any evidence of maternal toxicity.

The rabbit in the 30% DCI dose group that died on GD 19 showed evidence of abortion prior to being found dead. The other five rabbits from the 30% DCI dose group showed signs of abortion/premature delivery likely due to the severe anorexia seen in the group.

Preimplantation loss ranged from 0.7% to 8.9%, while the average percent postimplantation loss ranged from 2% to 8.8%. The average number of corpora-lutea of does in the 20% and 30% DCI dose groups were significantly elevated, while the number of live implants (viable litters) was unaffected by treatment with UX007. The percentage of live fetuses ranged from 91% to 98% for the full-term gravid litters, with the 30% DCI dose group having the lowest percentage of live fetuses at 91%.

Offspring (Malformations, Variations, etc.)

The average fetal weights were significantly lower in the 30% DCI dose group, whereas fetal weights in the 10% and 20% DCI dose groups were similar to controls with no gross external malformations. One control fetus had abnormal flexure of the forelimbs.

The observed visceral and cephalic abnormalities were singular in incidence and randomly distributed across groups, and therefore were considered spontaneous based on their random distribution, and lack of pattern that could be linked to drug treatment.

However, three fetuses had abnormalities; one with dilatation of the ventricles (20% DCI dose group), one with a convoluted retina of the right eye (30% DCI dose group), another with a hypo-plastic brain stem (30% DCI dose group).

Most of the fetuses examined from the mid- and high-dose groups were normal, without any skeletal variations as evidenced by 83%, 86%, and 73% for the control, mid- and high-dose groups, respectively. The most common variation seen were the incomplete ossification of the sternebrae and 13th rib variations, which were considered within the normal range.

The malformations observed were predominantly in the high dose group and of low incidence. Three fetuses in the high dose group and from two separate litters had fused/forked/extra ribs. The third fetus from another litter had fused cervical vertebrae. These malformed skeletal findings in the high dose fetuses are considered secondary effects linked to maternal toxicity. A summary of fetal morphological data is shown in the table below.

Table 52. Summary of Skeletal Observations, Fetal Incidence and (Litter Incidence)

	Vehicle Control		Mid Dose		High Dose	
	0%		20%		30%	
	Fetal	(Litter)	Fetal	(Litter)	Fetal	(Litter)
Number Examined	153	(17)	209	(23)	138	(15)
Normal	127	(17)	179	(23)	101	(15)
% Normal (fetal)	83	N/A ^a	86	N/A	73	N/A
Skulls Examined	103	(17)	140	(23)	93	(15)
Skull (affected)	-- ^b	--	--	--	2	(2)
Incomplete Ossification (IO), Score 1	--	--	--	--	1	(1)
Fontanelle Enlarged, Score 2	--	--	--	--	1	(1)
Sternebrae (affected)	26	(10)	30	(16)	30	(6)
# 5/6 Variation (IO), Score 1	23	(9)	27	(14)	28	(5)
Score 2	1	(1)	2	(2)	--	--
Score 3	--	--	--	--	--	--
Fused, Score 4	--	--	1	(1)	2	(2)
Ribs (affected)	--	--	--	--	4	(3)
12, Normal	65	(16)	93	(19)	15	(6)
13, Normal	57	(14)	85	(19)	100	(15)
13 Normal, with						
Rudimentary/Reduced/Unilateral	29	(13)	31	(16)	18	(9)
Bulbous Rib Score 2	--	--	--	--	1	(1)
Forked/Fused, Score 5	--	--	--	--	3	(2)
Thoracic Centra (affected)	--	--	--	--	3	(3)
Dumbbell, Score 1	--	--	--	--	2	(2)
Misaligned, Score 5	--	--	--	--	1	(1)
Vertebrae (affected)	--	--	--	--	1	(1)
Cervical Fused, Score 5	--	--	--	--	1	(1)

^aN/A = not applicable,

^b-- = zero incidence

Variation, Score 1-4, Malformation, Score 5

13.2.8. Study 20136141

Study title:	An Oral (Diet) Developmental and Perinatal/Postnatal Reproduction Study of UX007 in Rats, Including a Postnatal Behavioral/Functional Evaluation
Study report location:	UX007-PC017. p1-818
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 14, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	UX007, lot # FB0797 (U040022) and FB0757 (U040035), 100% purity.

Key Study Findings

Following oral dietary administration of UX007 at dose levels of 0%, 10%, 30%, and 50% DCI to pregnant rats on GD 6 through lactation day (LD) 20, UX007-related maternal effects included reductions in mean body weight gains at $\geq 10\%$ DCI and mean body weights at 50% DCI during gestation. There was a decrease in maternal food consumption at $\geq 10\%$ DCI during the gestation and lactation periods. Increased piloerection was observed during the gestation and lactation periods in the 50% DCI exposure group. The maternal NOAEL could not be determined because of the persistent reduction in food consumption. There were test article-related effects on preweaning pup body weights at $\geq 30\%$ DCI maternal exposure, but the effect on pup body weight were attributed to the preweaning period when pups were directly eating maternal food. There were no effects of the test article on behavioral assessments, estrous cycling, mating, fertility, or ovarian and uterine content. The NOAEL for the growth and development of the F1 generation postweaning was 50% DCI, with all adverse effects in the F1 generation deemed to be secondary to the initial reduction in weight gain at the end of the preweaning period.

Table 53. Study 20136141 Methods

Methods	Details
Doses:	0 (control), 10% DCI, 30% DCI and 50% DCI.
Frequency of dosing:	Daily
Dose volume:	3.8, 0.8, 2.3 or 3.8 ml/day
Route of administration:	Oral (Dietary)
Formulation/vehicle:	Dietary admixture
Species/strain:	Crl:CD(SD) Rats
Number/sex/group:	22 females/group
Satellite groups:	3 females/group (control), 6 females/group for the treatment groups were designated as toxicokinetic (TK) animals.
Study design:	Mated female rats were administered the test article in diet once daily from gestation day (GD) 6 through day 20 postpartum or lactation day (LD) 20. All the animals could deliver and rear their offspring to LD 20. For the F0 generation TK animals, the test article was provided via the diet once daily on GD 6 through LD 21. The F1 generation were not directly provided the test article through diet but were possibly exposed <i>in utero</i> or via maternal milk during lactation period.
Deviation from study protocol:	None.

Abbreviations: DCI, daily caloric intake

F₀ Dams

Survival

The animals were observed twice daily for mortality or moribundity.

There was no UX007-related mortality at any exposure level. One 10% DCI (female #3726) and one 50% DCI (female # 3788) F0 generation rat was found dead on LD 12 and LD 8, respectively. The deaths were not dose dependent, were of low incidence, and were not considered treatment related. The female rat #3726 had no macroscopic findings at necropsy, had a litter consisting of one stillborn pup and five viable, normal pups. Female rat #3788 showed tan discoloration on the right cardiac lobe and right diaphragmatic lobe of the lungs, an enlarged spleen, and an enlarged discolored liver at necropsy. Its litter consisted of 14 pups with six found dead. Six pups were normal at necropsy examination, and two pups were euthanized early due to adverse clinical signs.

Clinical Signs

There were no UX007-related clinical signs in the 10% and 30% DCI dose groups. Clinical signs of piloerection were observed in six dams in the 50% DCI dose group during gestation and lactation period. The piloerection was not dose dependent.

Body Weight

There were reduced mean maternal body weights observed in rats at $\geq 10\%$ DCI from GD 6 to GD 9 as a result of initial taste aversion to the test article. Mean body weight gain in the 10% DCI dose group was also reduced from GD 6 to GD 9 at 73% of the control value, but thereafter was similar to controls throughout the gestation period. The mean body weight gain was

significantly reduced in the 30% DCI dose group at 27% of controls, and a mean body weight reduction of 2.2 g in the 50% DCI dose group from GD 6 to GD 9. Overall, mean body weight gain were significantly reduced over the interval of GD 6 to GD 21 in the 30% and 50% DCI dose groups, with a body weight gain difference of more than 10% from the controls. There were also sporadic significant differences in mean maternal body weight throughout the lactation period in the 30% and 50% DCI dosed dams.

Feed Consumption

Food consumption in rats were recorded daily from GD 6 through LD 20 for main study animals, and up to LD 21 for TK animals.

The relative maternal food consumption was significantly reduced in all the treated dams during the gestation period. This reduced food consumption also persisted throughout the lactation period in all treated dams.

Uterine Content

On LD 28, all surviving F0 dams were euthanized, the reproductive tract was dissected, and the number of implantation sites and corpora lutea was recorded.

There were no UX007-related effects on natural delivery parameters at any exposure level. Pregnancy was confirmed in 21, 22, 22, and 21 dams in the 0%, 10%, 30%, and 50% DCI dose groups, respectively. All the pregnant rats delivered their litters. The numbers of implantation sites per delivered litters, gestation index, and dams with stillborn pups were all similar across all the exposure groups. There were no dams with total litter loss in any exposure group.

There were no UX007-related effects on any litter parameter, including viability index, lactation index, surviving pups per litter, sex ratio, and live litter size at any of the treatment levels. There was a significant decrease in the lactation index for the 50% DCI dose group due to a maternal death (female #3788) that had six pups found dead and two euthanized pups on LD 8. This finding was secondary to the maternal death and not related to UX007 exposure.

Necropsy Observation

On LD 28, all surviving F0 dams were euthanized and examined for gross lesions. Rats that died prematurely were examined for cause of death and necropsied.

There was no UX007-related maternal macroscopic observation seen at necropsy.

Toxicokinetics

Blood was collected from TK animals on GD 17 at time 0 (fresh food change) and at approximately 1 hour, 4 hours, 6 hours, 8 hours, and 24 hours following the provision of fresh food.

T_{max} was reached at 8 hours and 4 hours postexposure in pregnant rats on GD 17 at 30% and 50% DCI exposures, respectively. For the metabolites, T_{max} was 24 hours postexposure for 3-hydroxybutanoate, 6 hours and 1 hour postexposure for 3-hydroxypentanoate at 30% and 50% DCI respectively, and 1 hour to 6 hours postexposure for heptanoate at all exposure levels. The

exposure to UX007 increased with increasing dose in a dose-proportional manner between 30% and 50% DCI.

F₁ Generation

Survival

Litters were examined twice daily for survival. Pups in each litter were counted and pups examined for morphological abnormalities.

There were no UX007-related effects on any litter parameters, including the viability index, lactation index, surviving pups/litter, sex ratio, and live litter size at any of the treatment levels.

Clinical Signs

Clinical observations were recorded daily in litters, including the day of birth. Postweaning, rats were observed for general appearance at least once weekly.

There were no UX007-related clinical signs in the F1 generation pups in any group during the preweaning phase.

Body Weight

Body weights of the pups were recorded on day 1 (birth), day 4, day 7, day 10, day 14, day 17, and day 21 postpartum. Postweaning, body weight in male and female rats were recorded once weekly, and in female rats on GD 0, GD 3, GD 7, GD 10, and GD 13 (terminal weight).

There were no UX007-related effects on mean body weights in the F1 generation pups at the 10% exposure level. The mean pup body weights were reduced in the 30% DCI maternal exposure group on day 17, day 21, and 28 days postpartum (88% and 92% of controls), and in the 50% DCI maternal exposure group on day 1 through day 28 postpartum (59% to 93% of controls).

Feed Consumption

Food consumption in the male and female rats were recorded once weekly until cohabitation, and in the female rats on GD 0, GD 3, GD 7, GD 10, and GD 13.

There were reductions in mean food consumption in the 50% DCI maternal exposure group. From days 29 to 85 postpartum, the mean food consumption was 103%, 98%, and 86% of controls in the 10%, 30% and 50% DCI groups, respectively.

Physical Development

Litters were evaluated for normal developmental parameters (surface righting reflex, negative geotaxis, acoustic startle).

There were no UX007-related effects on any reflex development parameters in the F1 generation in any maternal exposure groups. In the 50% DCI dose group, there was a significant decrease in the percentage of pups that achieved acoustical startle on day 13 postpartum, at 81.7% compared to control rat response at 91.2%.

Neurological Assessment

On days 24 and 31 postpartum, each rat was tested twice for passive avoidance evaluation. On day 70 postpartum, each rat was given the M-shaped water maze test.

There were no UX007-related effects on learning, short-term retention, long-term retention, or response inhibition in the F1 generation male and female rats, as evaluated by performance in a passive avoidance test. There were no UX007-related effects on coordination, swimming ability, learning, and memory in the F1 generation rats at any exposure level in the M-shaped water maze tests.

Reproduction

Rats within each exposure group were paired (one male per one female) randomly on day 90, day 91, day 92, or day 93 postpartum, with the exclusion of sibling pairings. The pairings lasted for 16 days, and females observed with spermatozoa in a smear of the vaginal contents and/or copulatory plug were considered to be at GD 0. After the completion of the cohabitation period, F1 generation male rats were euthanized and examined for gross lesions. On GD 13, F1 female rats were also euthanized and examined for gross lesions.

There were no UX007-related effects on F1 generation mating or fertility. The male and female fertility indices were 85% to 100% and 86.4% to 100%, respectively.

14. Clinical Pharmacology Assessment: Additional Information

14.1. In Vivo Studies

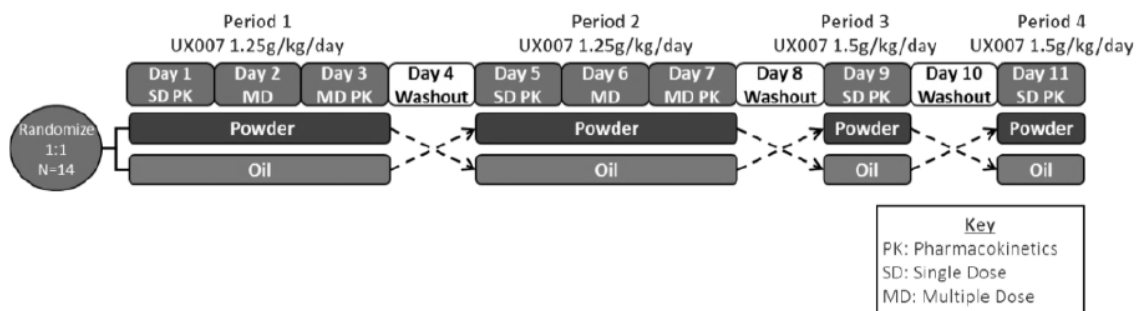
UX007-CL101

Description: A phase 1, randomized, crossover, pharmacokinetic, safety, and tolerability study of triheptanoin formulations in healthy volunteers

A total of 13 healthy adult male and female subjects completed the study. A schema of the study design is provided in [Figure 9](#). This study characterized single dose and multiple-dose PK of triheptanoin and its metabolites such as heptanoate, beta-hydroxybutyrate (BHB), and beta-hydroxypentanoate (BHP) after oral administration of triheptanoin. Plasma PK samples were collected at predose, the end of meal, 0.25, 0.75, 1, 1.5, 2, 2.5, 4, 6 and 8-hour postdose.

Since BHB is an endogenous ketone body, PK analyses were conducted after subtracting the predose level in each subject.

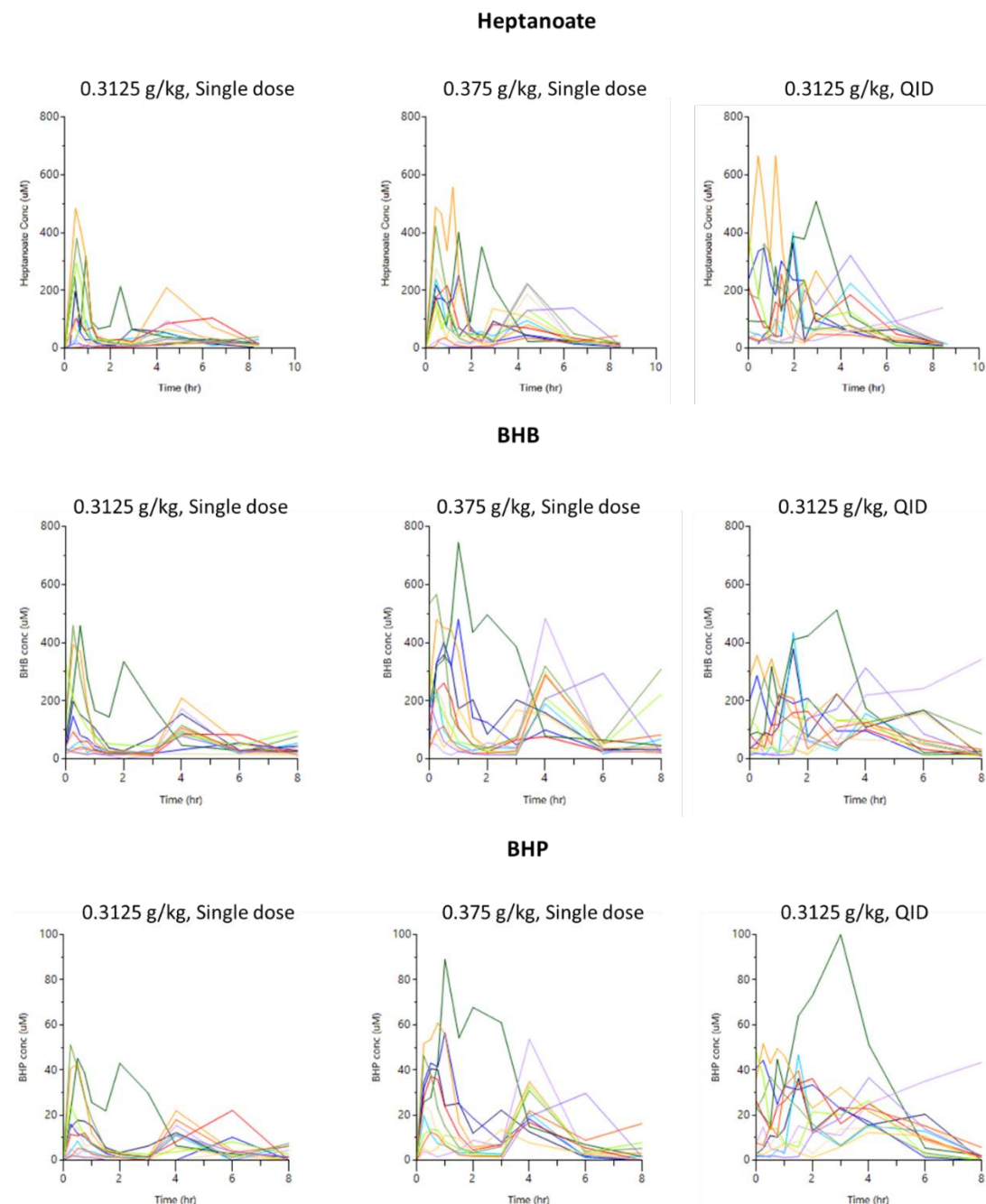
Figure 9. UX007-CL101 Study Schema



Source: Clinical Study Report of UX007-CL101

The plasma concentrations of triheptanoin were below the lower limit of quantitation ($\leq 0.2\mu\text{M}$). Individual plasma concentration-time profiles of heptanoate, BHB, and BHP after single dose of 0.3125 g/kg and 0.375 g/kg and multiple doses of 0.3125 g/kg four times a day for 2 days are presented in [Figure 10](#). The PK profiles show multiple peaks after dosing, with large between-subject variability in terms of peak concentrations and time to achieve the peak concentrations.

Figure 10. Individual Plasma Heptanoate, BHB, and BHP Concentration-Time Profiles, Study UX007-CL101



Source: Reviewer's plots based on the PK dataset under Section 5.3.3.5 (listing.xpt)
Abbreviations: BHB, beta-hydroxybutyrate; BHP, beta-hydroxypentanoate; QID, four times a day

PK parameters of heptanoate, BHB, and BHP are summarized in [Table 54](#), which also indicate large variability (%CV) ranging from 33% to 115% for AUC_{0-8h} and from 49% to 101% for C_{max} . The exposure of triheptanoin metabolites after single dose increases greater than dose-proportional in the dose range between triheptanoin 0.3125 g/kg and 0.375 g/kg.

Table 54. PK Parameters for Heptanoate, BHB and BHP Following Either a Single Dose or Multiple Dose Administration of Triheptanoin Oil to Healthy Subjects, Study UX007-CL101

Triheptanoin Dose						
Analytes	C _{max} (µM)	T _{max} (h)	C _{1st peak} * (µM)	T _{1st peak} * (h)	AUC _{0-8h} (µM·h)	CL/F (L/h/kg)
0.3125 g/kg single-dose						
Heptanoate	179 (145) [81.0]	0.67 (0.42-6.47)	172 (151) [87.9]	0.50 (0.42-0.97)	337 (223) [66.2]	6.05 (2.80) [46.4]
BHB	141 (142) [101]	0.67 (0.42-4.42)	141 (142) [101]	0.67 (0.42-4.42)	180 (207) [115]	NA
BHP	20.2 (16.8) [83.1]	0.70 (0.42-6.42)	19.3 (17.1) [88.7]	0.70 (0.42-1.20)	42.5 (42.6) [100]	NA
0.375 g/kg single-dose						
Heptanoate	259 (134) [51.6]	1.17 (0.42-8.33)	243 (149) [61.3]	0.82 (0.42-6.40)	569 (189) [33.3]	4.31 (1.02) [23.8]
BHB	317 (219) [69.0]	0.72 (0.0-1.42)	278 (186) [67.1]	0.53 (0.0-0.92)	408 (412) [101]	NA
BHP	41.3 (20.2) [49.0]	2.90 (0.67-6.40)	34.2 (24.3) [70.9]	0.92(0.50-6.40)	116 (47.4) [40.9]	NA
0.3125 g/kg, 4 times per day (1.25 g/kg/day)						
Heptanoate	320 (164) [51.1]	1.42 (0.0-8.42)	240 (174) [72.5]	1.17 (0.0-2.42)	790 (346) [43.9]	NA
BHB	238 (122) [51.4]	1.42 (0.0-8.42)	188 (117) [62.2]	0.67 (0.0-4.42)	447 (386) [86.4]	NA
BHP	45.4 (25.0) [55.1]	1.92 (0.0-8.42)	30.8 (24.2) [78.5]	0.42 (0.0-1.92)	152 (59.6) [39.2]	NA

Source: UX007-CL101 Clinical Study Report Addendum, Table 1 to Table 3

Presented data are arithmetic mean (standard deviation) [CV%] except for T_{max} and T_{1st peak} which are presented in median (min-max).

*After oral administration of triheptanoin, more than one peak concentration of heptanoate was observed. C_{1st peak} and T_{1st peak} refer to concentration at the 1st peak and time to reach the 1st peak, respectively.

Abbreviations: AUC_{0-8h}, area under the curve from 0 to 8 hours; BHB, beta-hydroxybutyrate; BHP, beta-hydroxypentanoate; CL/F, apparent clearance; C_{max}, maximum concentration; PK, pharmacokinetic; T_{max}, median time to maximum concentration

UX007-CL201

Description: An open-label phase 2 study to assess safety and clinical effects of triheptanoin in subjects with LC-FAOD.

A total of 29 patients with LC-FAOD received triheptanoin. After the initial dose, triheptanoin doses were up-titrated by 5% DCI every 2 to 3 days to a target dose of 25% to 35% DCI following the dosing guideline in the protocol ([Table 55](#)).

Table 55. Study Drug Administration Guideline, Study UX007-CL201

The table is a guide for how to titrate subject to 35% of caloric intake or the maximum tolerated dose if it is < 35%. Some discretion and flexibility can be used by the Principal Investigator based on each subject.

Dose Day	Caloric Intake	If tolerability issues arise
Day 1-2	~10%*	N/A
Day 3-5	~15%	N/A
Day 6-8	~20%	N/A
Day 9-11	~25%	Down-titrate to 20% for 3 more days, then continue to titrate up if possible
Day 12-14	~30%	Down-titrate to 25% for 3 more days, then continue to titrate up if possible
Day 15 - study duration	~35%**	Down-titrate to 30% for 3 more days, , then continue to titrate up if possible

Source: UX007-CL201 clinical study report addendum, Appendix 1

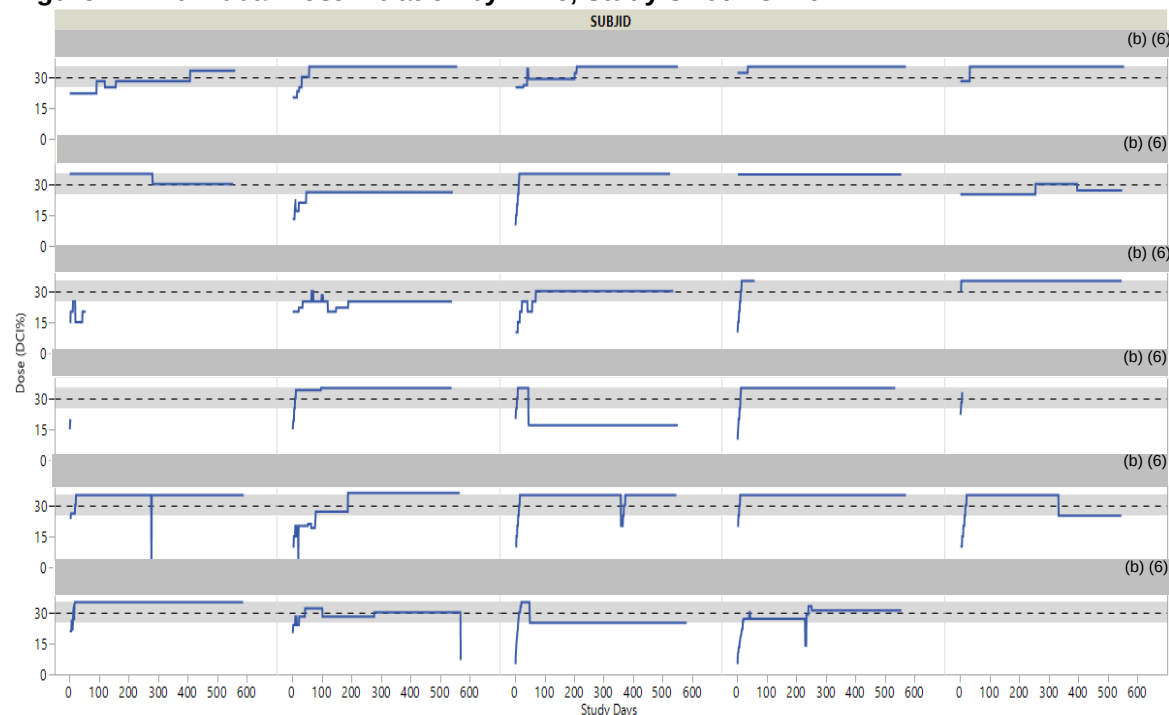
* If the subject has been receiving and tolerating MCT during the screening and run-in period, sites may consider initiated UX007 treatment at the same dose of MCT rather than at 10%. In those cases, UX007 Should be titrated up ~5% of the subject's daily caloric intake every 2-3 days until 35% of caloric intake, or the maximum tolerated dose, is reached.

** Some subjects may not be able to tolerate up to 35% of daily caloric intake, despite down titration and re-titrating up. For those subjects, their individual maximum tolerated dose, as determined by the Principal Investigator, will be administered for the duration of the study.

Abbreviations: N/A, not applicable

Aside from four patients who discontinued the study, the majority of patients achieved 25% to 35% DCI and maintained the dose until the study completed while some patients modified the dose during the study after the initial dose titration ([Figure 11](#)). Even though the rationale for dose modification in individual patients was not recorded, it was presumably determined based on tolerability and changes in caloric needs of each patient.

Figure 11. Individual Dose Titration by Time, Study UX007-CL201



Source: Reviewer's plots based on the dosing log (adlog.xpt for UX007-CL201).

*The grey area represents 25-35% DCI range and the dotted line represents the mean of 30% DCI.

Abbreviations: DCI, daily caloric intake

Plasma PK samples were collected at baseline and at approximately 2 hours postdose at week 4, week 12, week 24, week 48, and week 78 or early termination. As anticipated, triheptanoin concentrations were BLQ ($<0.2\mu\text{M}$) in virtually all samples. The bioanalytical method (GC-MS/MS) used in this study was not sensitive enough to quantify plasma heptanoate, BHB and BHP concentrations. For heptanoate, 20% to 59% of samples between week 4 and week 48 were BLQ. For BHB, 48% to 80% of samples were BLQ and for BHP, more than 90% of plasma samples were BLQ ($<50\mu\text{M}$). Note that the Applicant later improved the sensitivity of the bioanalytical method (LC-MS/MS) that was used in study UX007-CL101. Plasma concentrations of triheptanoin, heptanoate, BHB, and BHP are summarized in [Table 56](#).

Table 56. Summary of Plasma Heptanoate, BHB and BHP Concentrations, Study UX007-CL201

Visit	Statistics	Heptanoate	BHB	BHP
Week 4 (N=27)				
	BLQ, n (%)	16 (59.3)	20 (74.1)	25 (92.6)
	Mean (SD), uM	104.4 (164.7)	71.8 (155.3)	5.3 (19.3)
Week 12 (N=23)				
	BLQ, n (%)	10 (46.5)	15 (65.2)	22 (95.7)
	Mean (SD), uM	124.8 (180.4)	84.7 (137.7)	2.6 (12.5)
Week 24 (N=25)				
	BLQ, n (%)	11 (44.0)	12 (48.0)	4 (80.0)
	Mean (SD), uM	119.8 (137.5)	90.3 (133.5)	4.3 (14.8)
Week 48 (N=5)				
	BLQ, n (%)	1 (20.0)	4 (80.0)	5 (100.0)
	Mean (SD), uM	83.4 (62.2)	21.6 (48.3)	0.0 (0.0)

Source: UX007-CL201 CSR, Table 11.1.1. and Table 11.1.2.

Abbreviations: BLQ, below the lowest level of the quantitation (<50.0uM); BHB, beta-hydroxybutyrate; BHP, beta-hydroxypentanoate; SD, standard deviation

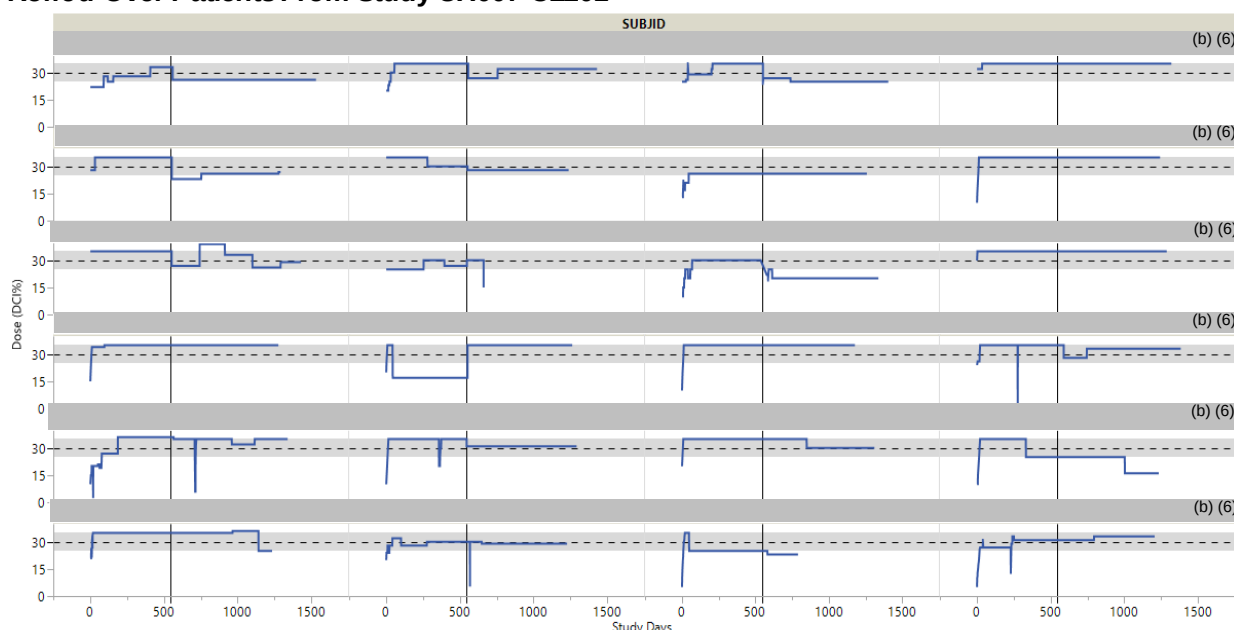
UX007-CL202

Description: An open-label, long-term safety and efficacy extension study in subjects with LC-FAOD previously enrolled in UX007 or triheptanoin studies.

A total of 75 subjects were enrolled in the study, of which 24 were rolled over from study UX007-CL201, 31 were enrolled over from other ISTs or other studies with triheptanoin treatment, and 20 were enrolled as triheptanoin-naïve subjects. Patients who had received triheptanoin from the previous studies continued the same dose of triheptanoin. Triheptanoin-naïve patients initiated triheptanoin based on the dosing guideline used in study UX007-CL201 ([Table 55](#)).

As shown in [Figure 12](#), almost 50% patients who were rolled over from study UX007-CL201 changed the dose after the enrollment to study UX007-CL202. Although the rationale for the dose modification in individual patients were not recorded, dose titration was at the discretion of the investigator based on tolerability and changes in caloric needs of each patient.

Figure 12. Individual Dose Titration Before and After the Enrollment to Study UX007-CL202 for Rolled-Over Patients From Study UX007-CL201



Source: Reviewer's plots based on the dosing log (adlogr.xpt for UX007-CL202).

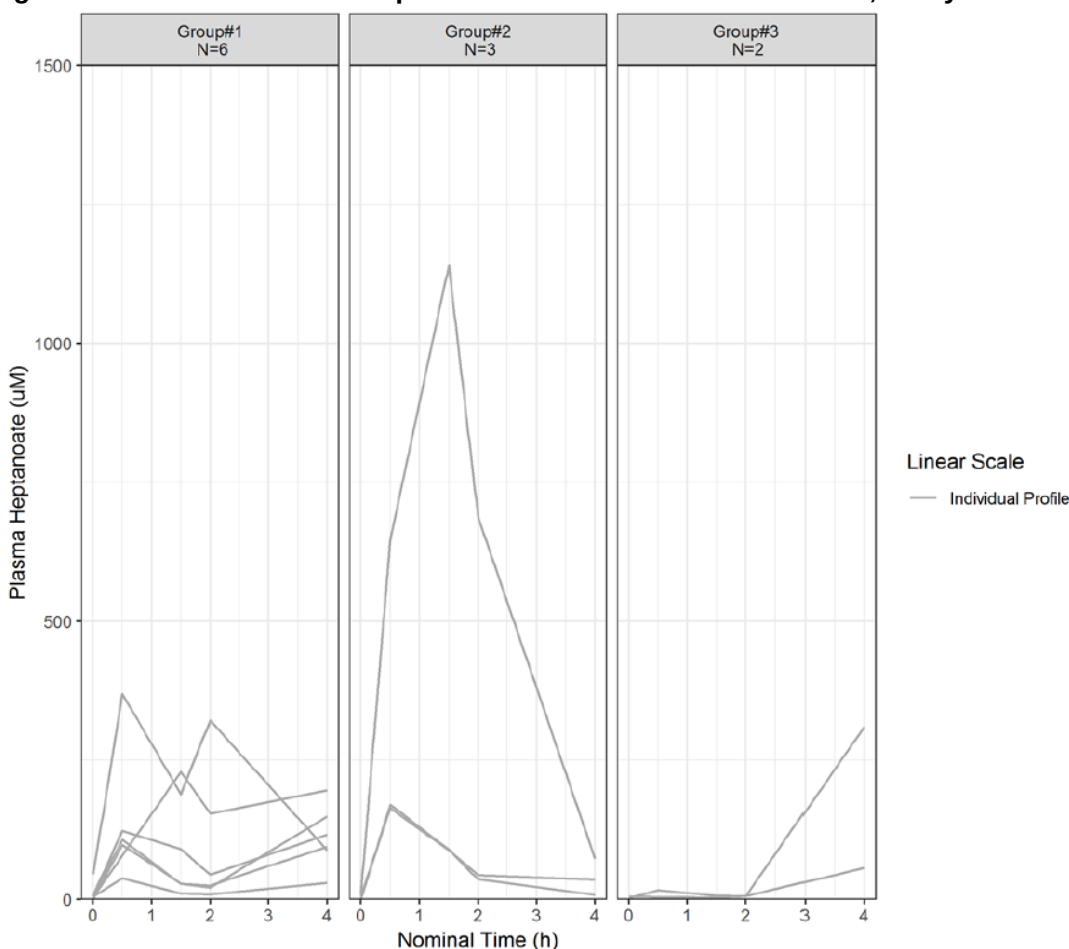
* Grey area means 25% to 35% DCI range and dotted lines mean 30% DCI. Grey area means 25% to 35% DCI range and dotted lines mean 30% DCI. Black vertical lines on X-axis stand for the time of rollover from UX007-CL201 to UX007-CL202.

Abbreviations: DCI, daily caloric intake

Blood samples were collected from patients in the PK substudy at predose (within 15 minutes prior to start of a meal) and at 0.5, 1.5, 2, and 4 hours after finishing the meal at two consecutively scheduled PK visits. At the data cutoff for this clinical study report, data were available from 11 subjects with LC-FAOD (five adults and six pediatrics) at the first PK visit.

The individual heptanoate concentration-time profiles are presented in [Figure 13](#). The PK results show a wide range of peak concentrations within 4 hours after the meal.

Figure 13. Individual Plasma Heptanoate Concentration-Time Profiles, Study UX007-CL202



Source: Figure 2 in the PK report for UX007-CL202

Group#1 includes concentration-time profiles with two peaks; Group#2 corresponds to concentration-time profile showing a single early peak and Group#3, a single late peak. PK samples were collected up to 4 hours post-dose to characterize concentration-time profiles of heptanoate at steady state

Source: Clinical Study Report of UX007-CL202, Figure 11.1.1

14.1.1. Population PK Analysis

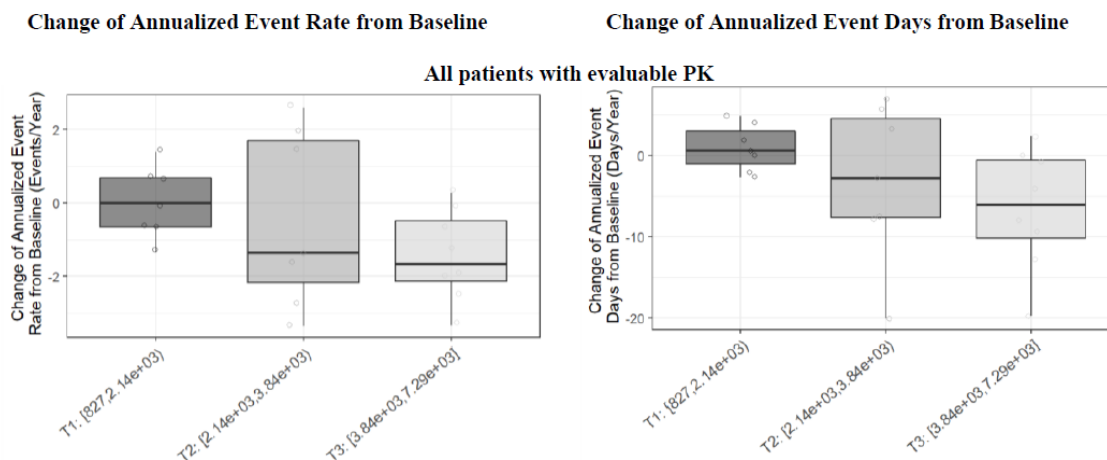
Pharmacokinetic data from aforementioned clinical studies showed a large between-subject variability. Also note that plasma heptanoate concentrations do not show a typical linear absorption and elimination kinetics after oral administration of triheptanoin. The Applicant's population PK analysis (Population PK Study Report, ULTR-PMX-UX007-852) is limited by insufficient PK data due to sparse PK sampling in a small number of patients with LC-FAOD, and may not be adequate to describe PK of heptanoate. Therefore, PK parameters in study UX007-CL101, estimated by a noncompartmental method, are used to inform PK of triheptanoin in the label (see Section II.5).

14.1.2. Exposure-Response Analysis

The Population PK Study Report (ULTR-PMX-UX007-852) included the exploratory exposure-response analyses with study UX007-CL201 data. The Applicant claimed that this exposure-response analyses indicated that clinical effectiveness was positively correlated to the exposure

of heptanoate ([Figure 14](#)). The clinical effectiveness was represented in terms of the annualized rate or annualized duration of major clinical events such as rhabdomyolysis, hypoglycemia, or cardiomyopathy. The exposure of heptanoate was represented in AUC per day at the last visit in $\mu\text{M}\cdot\text{h}$, which was estimated using the population PK model.

Figure 14. Applicant's Exploratory Exposure-Response Analysis of Relationship Between Heptanoate Exposure Levels ($\mu\text{M}\cdot\text{h}$) and Change From Pretreatment of Major Clinical Events in Patients With LC-FAOD, Study UX007-CL201

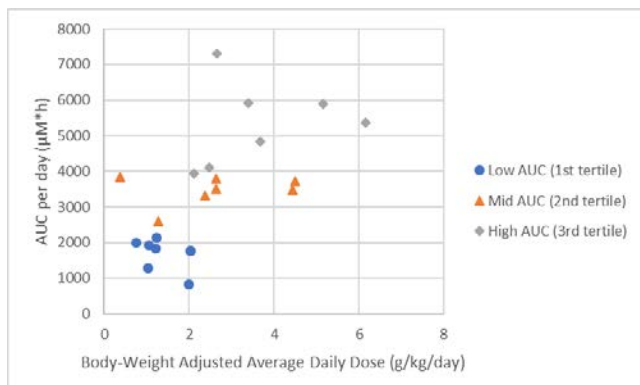


Source: The Population PK Study Report (ULTR-PMX-UX007-852), Figure 19
Abbreviations: LC-FAOD, long-chain fatty acid oxidation disorders; PK, pharmacokinetic

However, the review team considers this exposure-response analysis inconclusive due to the following limitations:

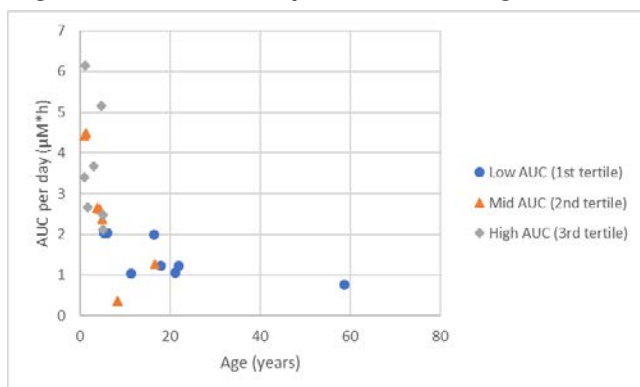
- The measure of the clinical response in UX007-CL201 (i.e., change from baseline in annualized major clinical events) is deemed confounded by modification in dietary management after initiation of triheptanoin. Refer to Section [I.1](#) “Summary of Regulatory Action.”
- The measure of the drug exposure (i.e., AUC per day at the last visit) does not accurately represent the overall drug exposure in the study because most patients frequently titrated the dose during the study period. Additionally, the values of AUC per day may not be reliably generated, as the population PK model used is deemed limited by insufficient PK data (see Section [14.1.1](#)).
- As tertiles of AUC per day appears to be confounded by age, the exposure-response analysis should have been conducted by age groups. However, the subgroup analysis by age may not be viable given its small sample size. As shown in [Figure 15](#), the AUC per day tends to increase as the body weight adjusted to daily dose (in g/kg/day) increases. Pediatric patients received greater daily dose in g/kg compared to adult patients, because they require more calories for growth (see [Table 9](#) in Section [II.6.1](#)). In other words, the younger a patient was, the greater the AUC per day they had ([Figure 16](#)).

Figure 15. Relationship Between Body-Weight Adjusted Individual Average Daily Dose (g/kg/day) and AUC Per Day ($\mu\text{M}\cdot\text{h}$), Study UX007-CL201



Source: Reviewer's analysis results based on adlog.xpt for UX007-CL201 and erdatset.xpt for the Population PK Study
Abbreviations: AUC, area under the curve

Figure 16. Relationship Between the Age and AUC Per Day ($\mu\text{M}\cdot\text{h}$), Study UX007-CL201



Source: Reviewer's analysis results based on adlog.xpt for UX007-CL201 and erdatset.xpt for the Population PK Study
Abbreviations: AUC, area under the curve

14.2. In Vitro Studies

Protein Binding Studies

Study UX007-PC020: Protein Binding of Heptanoate

In the human plasma, heptanoate exhibited moderately high human plasma protein binding (~80% at the range of 40 μM to 400 μM).

Study UX007-PC018: Protein Binding of Valproic Acid in the Presence of Heptanoate

In the presence of 400 μM heptanoate, the unbound fraction of valproic acid increased about twofold, suggesting that heptanoate may competitively displace valproic acid from binding to plasma proteins. Presence of valproic acid did not affect the protein binding of heptanoate.

Metabolism

Study UX007-PC015: Lipase-Mediated Metabolism

The in vitro evaluation of lipase-mediated metabolism showed that triheptanoin was hydrolyzed by three lipases tested (pancreatic triglyceride lipase, pancreatic triglyceride lipase-related protein 2, and carboxyl ester lipase).

Study UX007-PC023: Metabolic Stability of Heptanoate in Human Hepatocytes

In vitro metabolism of heptanoate was investigated using human hepatocytes. The mean half-life of heptanoate was estimated to be 28 minutes in the human hepatocytes. The in vitro-in vivo scaled hepatic clearance of heptanoate in humans was estimated to be 18.5 mL/min/kg, corresponding to ~90% of human hepatic blood flow.

Study UX007-PC019: CYP and UGT-Mediated Metabolism

Based on the in vitro evaluation in the human microsomes, neither heptanoate nor BHP was a sensitive substrate of human CYP or UGT enzymes.

Study UX007-PC025: Identification of Metabolites in Human Liver Microsomes

In vitro metabolites of heptanoate from human liver microsomes, no oxidation metabolites of heptanoate were detected, indicating that heptanoate is not a sensitive substrate of CYP enzymes. A direct glucuronide conjugate of heptanoate was observed, but the amount of this metabolite was negligible (~0.08 ppm).

Drug-Drug Interactions

Study UX007-PC021: Potential CYP Inhibition

The potential for heptanoate or BHP to elicit drug-drug interactions via an inhibition of CYPs was investigated in an in vitro study. At 40 and 400 μ M of heptanoate or 10 and 50 μ M of BHP, neither heptanoate nor BHP showed appreciable inhibition of the major human CYP isoforms tested: CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

14.3. Bioanalysis

In study UX007-CL101, plasma concentrations of triheptanoin and its three metabolites (heptanoate, BHB, and BHP) were measured using validated bioanalytical methods with LC-MS/MS. Method validations were adequate to support the study UX007-CL101.

The performance and validation parameters for plasma concentrations of heptanoate, BHB, and BHP are summarized in [Table 57](#). The performance and validation parameters for plasma triheptanoin concentrations are not included in this review because most concentrations of triheptanoin were below LLOQ ($\leq 0.2\mu$ M).

Table 57. Summary of the Performance and Validation Parameters of the Bioanalytical Method For the Quantitation of Heptanoate, BHB, and BHP in Human Plasma

Method description	Drug extracted using protein precipitation from K2EDTA human plasma and quantitated using LC-MS/MS method				
Materials used for calibration curve, QCs & concentration	Human plasma, K2EDTA				
Validated assay range	Heptanoate: 1.0 - 250µM; BHB: 8.0 - 800µM; BHP: 1.0 - 100µM				
Validation parameters	Method validation summary	Heptanoate	BHB	BHP	Acceptability
Calibration curve performance	No of standard calibrators	8	8	8	Yes
	Cumulative accuracy (%bias)	-3.7% to 9.9%	-8.9% to 3.5%	-1.8% to 0.8%	Yes
	Cumulative precision (%CV)	≤2.9%	≤2.1%	≤1.5%	Yes
QCs performance during accuracy and precision	Cumulative accuracy (%bias) in 4 QCs	-2.4% to 4.7%	-4.1% to 7.0%	-2.6% to 2.7%	Yes
	Interbatch %CV	≤6.6%	≤6.5%	≤5.6%	Yes
Selectivity & matrix effect/Interference & specificity	Six individual blank matrix samples tested. No interference peaks (>20.0% of the LLOQ calibration standard response; >5.0% of the internal standard peak response)				Yes
Dilution linearity	Linear within 10-fold				Yes
Bench-top/process stability	Stable on wet ice for 3 hours in whole blood Stable at room temperature for 6 hours in plasma Stable under refrigeration for 12 hours (heptanoate) or 34 hours (BHB and BHP) in processed-sample				Yes
Freeze-thaw stability	Up to 3 cycles at -80°C				Yes
Long-term storage	6 months at -80°C and -20°C				Yes
Carry over	No evidence of carryover				Yes
Method performance in study UX007-CL101					
Assay passing rate	There were 46 runs (including incurred sample reanalysis), out of which, 40, 38, and 39 runs met the method acceptance criteria for heptanoate, BHB, and BHP, respectively.				Yes
Standard curve performance	Heptanoate: %bias: -1.0 to 2.3%; %CV ≤6.4% BHB: %bias: -8.3 to 4.6%; %CV ≤4.0% BHP: %bias: -2.2 to 1.8%; %CV ≤3.3%				Yes
QC performance	Heptanoate: %bias: 1.5 to 4.1%; %CV ≤5.2% BHB: %bias: -0.8 to 0.9%; %CV ≤5.5% BHP: %bias: 2.7 to 4.5%; %CV ≤4.8%				Yes
Method reproducibility (incurred sample reanalysis)	55 out of 958 samples (5.7%) reanalyzed.100% of the repeat results and original results were within 20.0% of the mean of the two values				Yes
Study sample analysis/stability	All samples were analyzed within 83 days of collection following storage at -80°C within established stability				Yes

Source: Validation Report TA-VP007-00; Bioanalytical Report of UX007-CL101

Abbreviations: BHB, beta-hydroxybutyrate; BHP, beta-hydroxypentanoate; CV, coefficient of variation; LLOQ, lower limit of quantitation; QC, quality control

15. Trial Design: Additional Information and Assessment

Table 58. Protocol Synopsis, Gillingham (2017)

Applicant	Melanie Gillingham Ph.D., R.D. (Right of reference to this IND was provided to NDA 213687)
Compound	Triheptanoin and octanoin
Protocol title	Study of triheptanoin for treatment of long-chain fatty acid oxidation disorder
Protocol number	IND 113386
Clinical phase	Research
Study state/end date	June 23, 2011/March 23, 2017
Ethics	An IRB at each clinical site renewed and approved the protocol and ICF prior to study initiation. The study was designed, conducted and recorded in accordance with the principles established by the 18 th World Medical Association General Assembly (Helsinki, 1964).
Trial centers	This study was conducted at two centers in the United States (Oregon Health Sciences University; University of Pittsburgh)
Design	Double-blind, randomized controlled trial with a comparator arm (trioctanoin) for four months duration. <u>Note:</u> The initial trial was a single-blind (subjects blinded) study. A protocol amendment received October 8, 2013 changed the trial design to a double-blind study due to the addition of a dedicated study coordinator. At the time of receipt of the amendment, 17 patients were enrolled.
Trial status	Completed
Study objectives	The primary objective of the study was to: The primary analyses to compare change in energy expenditure, cardiac function, and exercise tolerance between triheptanoate and trioctanoate supplementation will be based on intention-to-treat (ITT).
Eligibility criteria	Inclusion criteria: - Confirmed diagnosis for one of the following LC-FAOD disorders: carnitine palmitoyltransferase (CPT II) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency, and trifunctional protein (TFP) deficiency via: - History of disease specific elevations of acylcarnitines on a newborn blood spot or in plasma - History of low enzyme activity in cultured fibroblasts - At least one significant episode of rhabdomyolysis - At least 7 years of age at screening - Ability to travel and to be admitted to the clinical research center for the treatments - Ability to follow the protocol Exclusion criteria: - Hgb <10 g/dl - Peripheral neuropathy that limits ability to complete treadmill studies - Inclusion in another research study that alters macronutrient intake - Pregnant females - History of myocardial infarction or cardiovascular disease

	Note: A protocol revision dated October 8, 2013, added the following two inclusion criteria: • Currently managed on a stable treatment regimen (including diet) that may include a low fat/high carbohydrate diet, no fasting, carnitine and/or MCT oil for at least the prior 60 days. • Willingness to maintain current regimen upon switching to UX007.
Study hypothesis	No formal hypothesis. Sample size was based on feasibility.
Treatment/exposure	Patients will receive a baseline assessment a 4-day assessment that includes blood/urine sample, exercise treadmill, meal tolerance analysis, DEXA scan and cardiac analyses. Subsequently patients were randomized to triheptanoin or octanoate and discharged home for four months with repeat testing over a three-day period. Dietary records (3-day) will be obtained in the interim.
Study endpoints	Efficacy endpoints: The primary analyses to compare change in energy expenditure, cardiac function, and exercise tolerance between triheptanoate and MCT supplementation will be based on ITT. Safety endpoints: Safety endpoints included assessment of muscle pain, urinary assessment of myoglobin and serum CK /myoglobin levels.
Analytical considerations	This was a research study, so results were essentially descriptive in nature.
Abbreviations: CK, creatine kinase; Hgb, hemoglobin; MCT, medium-chain triglyceride; DEXA, dual-energy X-ray absorptiometry	
Table 59. Protocol Synopsis (Vockley et al. 2019), Study UX007-CL201	
Applicant	Ultragenyx Pharmaceutical Inc., Novato, CA, USA
Compound	Triheptanoin
Protocol title	An open-label phase 2 study to assess safety and clinical effects of UX007 in subjects with long-chain fatty acid oxidation disorders (LC-FAOD)
Protocol number	UX007-C201
Clinical phase	2
Study state/end date	February 6, 2014/August 25, 2016
Ethics	An IRB at each clinical site renewed and approved the protocol and ICF prior to study initiation. The study was designed, conducted and recorded in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964).
Trial centers	This study was conducted at 10 centers: seven in the United States and three in the United Kingdom
Design	Open-label, phase 2 study in patients with serious clinical manifestations of LC-FAOD despite current management.
Trial status	Completed
Study objectives	Primary objective: To evaluate the impact of UX007 on acute clinical pathophysiology associated with LC-FAOD (following 24 weeks of treatment) Secondary objectives: • To evaluate the safety of UX007 treatment in subjects with LC-FAOD • To evaluate the effect of UX007 on energy metabolism in LC-FAOD The objective of the Treatment + Extension Periods (following 78 weeks of treatment) of the study was: • To evaluate the impact of UX007 on major clinical events associated with LC-FAOD

Eligibility criteria	Inclusion criteria: • Confirmed diagnosis for one of the following LC-FAOD disorders: carnitine palmitoyltransferase (CPT II) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency, and trifunctional protein (TFP) deficiency • At least 6 months of age at screening • Currently managed on a stable treatment regimen (including diet) that may include a low fat/high carbohydrate diet, no fasting, carnitine and/or MCT oil for at least the prior 60 days. Willingness to maintain current regimen upon switching to UX007. • Have severe FC-FAOD as shown by any one of the following: - Chronic elevated CK with major clinical events: Elevated mean CK levels over the last 6 months -1 year (defined as $\geq 2X$ upper limit of age/gender-matched normal, or ≥ 500 units/L if age-matched reference not established) not associated with an acute rhabdomyolysis event, AND at least two major clinical events (as defined in the protocol) in the last year, or at least four major clinical events over the last two years - Episodic elevated CK with reported muscle dysfunction: Episodes of elevated CK levels over the last 6 months -1 year (defined as $\geq 2X$ upper limit of age/gender-matched normal, or ≥ 500 units/L if age-matched reference is not established), AND patient report of frequent muscle fatigue, exercise intolerance, or limitation of exercise - Highly elevated CK but asymptomatic: More seriously elevated mean CK levels (defined as $\geq 4X$ upper limit of age/gender-matched normal, or ≥ 1000 units/L if age-matched reference is not established) consistent with substantial chronic muscle rupture over the last 6 months-1 year, regardless of frequency of hospitalizations or ER events, - Frequent severe major medical episodes: (at least three within the past year, or five within two years) of hypoglycemia, rhabdomyolysis, or exacerbation of CM, requiring ER/acute care visits or hospitalizations, - Severe susceptibility to hypoglycemia: (serum glucose < 60 mg/dL) after short periods of fasting (less than 4 to 12 hours, depending on age), with at least two events in the last year that require ongoing prophylactic management, OR recurrent symptomatic hypoglycemia (blood glucose levels or clinical symptoms of hypoglycemia) at home requiring intervention $\geq$ two times per week, - Evidence of Functional CM: (with echocardiogram (ECHO) within past 90 days documenting poor EF) requiring ongoing medical management Exclusion criteria: • Diagnosis of carnitine-acylcarnitine translocase (CACT) deficiency, or CPT I • Diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, short- or medium-chain FAOD, ketone body metabolism defect, propionic acidemia or methylmalonic acidemia • Enrolled in a clinical study involving concurrent use of an investigational drug product within the last 30 days, or unwilling to discontinue use of a prohibited medication or other substance that may confound study objectives • Have any comorbid conditions, including unstable major organ-system disease(s) that in the opinion of the Investigator, places the subject at increased risk of complications, interferes with study participation or compliance, or confounds study objectives
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Study hypothesis	No formal hypothesis. Sample size was based on feasibility.
Treatment/exposure	Run-in (4 weeks prior to switch to triheptanoin): patients continued their current standard management regimen for LC-FAOD, including MCT if used. Following the run-in period, subjects entered the treatment period (24 weeks), where they discontinued MCT after the baseline visit and began treatment with daily open-label UX007 while maintaining their other dietary restrictions. Following completion of assessments at week 24, subjects continued treatment in the extension period for an additional 54 weeks (total of 78 weeks treatment).
Study endpoints	Efficacy endpoints: • Major rhabdomyolysis events: - Number and duration of events (ER visits, hospitalizations or emergency interventions) related to rhabdomyolysis • Hypoglycemia events: - Number of symptomatic or clinically important events (serum glucose <60 mg/dL) needing treatment at home each week, reported in a diary - Number and duration of major events (ER visits, hospitalizations or emergency interventions) related to hypoglycemia or its effects • Major CM events: - Number and duration of events (ER visits, hospitalizations or emergency interventions) for decompensation of CM Major clinical events: composite of rhabdomyolysis, hypoglycemia, and cardiomyopathy events Changes from baseline in measures of exercise tolerance: • Cycle ergometry at week 24 • 12-minute walk test (12MWT) at week 18 Changes from baseline in health-related quality of life at week 24 • Functional disability and cognitive development (PDMS-2, PEDI-CAT and SF-10/SF-12v2, as age appropriate) Safety endpoints: • Treatment-emergent adverse events (TEAEs), including treatment-related and serious TEAEs and TEAEs leading to discontinuation • Clinical laboratory parameters and changes from baseline values, electrocardiograms, echocardiograms, height, weight, and BMI.
Analytical considerations	Annualized event rates for major clinical events over 78 weeks of triheptanoin treatment was compared to the pre-triheptanoin period using a paired t-test. Sensitivity analyses of AER using negative binomial regression model. Changes over time for 12MWT, cycle ergometry, and QoL analyzed using generalized estimation equation models

SF-10: 10-Item Short Form Health Survey for Children

SF-12v2: 12-Item Short Form (Adult) version 2

PDMS-2: Peabody Developmental Motor Scales– 2nd Edition

PEDI-CAT: Pediatric Evaluation of Disability Inventory – Computer Adaptive Test

Abbreviations: AER, annualized event rate; BMI, body mass index; CK, creatine kinase; CM, cardiomyopathy; EF, ejection fraction; ER, emergency room; ICF, informed consent form; IRB, institutional review board; MCT, medium-chain triglyceride; QoL, quality of life

Table 60. Protocol Synopsis, Study UX007-CL202

Applicant	Ultragenyx Pharmaceutical Inc., Novato, CA, USA
Compound	Triheptanoin
Protocol title	An Open-label Long-Term Safety and Efficacy Extension Study in Subjects with Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD) Previously Enrolled in UX007 or Triheptanoin Studies
Protocol number	UX007-C202
Clinical phase	2
Study state/end date	December 9, 2014/June 1, 2018 (data cutoff)
Ethics	An IRB at each clinical site renewed and approved the protocol and ICF prior to study initiation. The study was designed, conducted and recorded in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964).
Trial centers	This study is being conducted at 10 centers: eight in the United States and two in the United Kingdom
Design	Ongoing, open-label, phase 2 study assessing the long-term safety and efficacy of UX007 treatment in subjects with LC-FAOD. Subjects could have participated in the prior clinical study, CL201; or had failed conventional therapy and had documented severe unmet need (triheptanoin naïve); or, participated in other programs, such as compassionate use, with triheptanoin.
Trial status	Ongoing
Study objectives	The primary objective of the study was to: - Evaluate the long-term safety and efficacy of triheptanoin in subjects with LC-FAOD The secondary objectives of the study were to: - Evaluate the effect of triheptanoin on energy metabolism in LC-FAOD - Evaluate impact of triheptanoin on clinical events associated with LC-FAOD The objective of the PK substudy was to: - Characterize the steady-state PK of triheptanoin and triheptanoin metabolites in subjects with LC-FAOD
Eligibility criteria	Inclusion criteria: - Male and female patients ≥6 months of age with a confirmed diagnosis of LC-FAOD (CACT, CPT I, CPT II, LCHAD deficiency, TFP deficiency, or VLCAD deficiency) who: - Previously completed study UX007-CL201 - Were previously enrolled in other trials (Gillingham et al., Investigator sponsored trials including expanded access INDs). - Were treatment naïve and identified by an Investigator as having severe symptoms of disease despite conventional therapy. Exclusion criteria: - Patients - Diagnosed with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, short- or medium-chain FAOD, ketone body metabolism defect, propionic acidemia or methylmalonic academia, - Are eligible for another clinical trial of triheptanoin in LC-FAOD.

Study hypothesis	No formal hypothesis
Treatment/exposure	Target dose of 25% to 35% daily caloric intake (DCI)
Study endpoints	Primary efficacy endpoint: - The annualized LC-FAOD major events rate (also referred to as MCE rate) inclusive of skeletal myopathy (rhabdomyolysis), hepatic (hypoglycemia), and cardiomyopathy events Secondary efficacy endpoints: - Cardiomyopathy and cardiac function endpoints as measured by ECHO: ventricle size, - Ejection fraction (EF), and shortening fraction (SF) - Annualized duration rate (annualized event days) of all MCEs, where duration is defined as the total duration in number of days of MCEs - Number and duration of each type of MCE (i.e., rhabdomyolysis, cardiomyopathy, and hypoglycemic events): - Annualized event and duration rates of rhabdomyolysis MCEs - Annualized event and duration rates of cardiomyopathy MCEs - Annualized event and duration rates of hypoglycemic MCEs Exploratory efficacy endpoints: - Functional disability and cognitive development endpoints were: - SF-10 (for subjects aged 6 through 17 years) PHS and PSS scores* - SF-12v2® (for subjects aged 18 years and older) PCS and MCS scores - Clinical biomarkers endpoints were serum CK, fasting serum glucose, ALT, AST, and GGT age, head circumference - PK endpoints were plasma levels and PK parameters of triheptanoin and its metabolites, including heptanoate, beta-hydroxypentanoate (BHP), and beta-hydroxybutyrate (BHB) Safety endpoints: - Incidence and severity of TEAEs (primary safety endpoints) - Vital signs - Incidence of laboratory abnormalities - Concomitant medications
Analytical considerations	Annualized event rates for major clinical events over all weeks of triheptanoin treatment, and 18-month intervals. The annualized MCE rate was summarized using descriptive statistics with mean, SD, median, quartiles, minimum and maximum values.

SF-10: 10-Item Short Form Health Survey for Children

SF-12v2: 12-Item Short Form (Adult) version 2

*PSS and PHS scores were analyzed for SF-10. The SF-10 was evaluated for subjects 5 years to 17 years of age
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CACT, carnitine-acylcarnitine translocase; CPT, carnitine palmitoyltransferase; ECHO, echocardiogram; FAOD, fatty acid oxidation disorder; GGT, gamma glutamyl transpeptidase; LCHAD, L-3-hydroxy-acyl-CoA dehydrogenase; ICF, informed consent form; IND, investigational new drug; IRB, institutional review board; MCE, major clinical event; MCS, Mental Component Score; PCS, Physical Component Score; PHS, Physical Summary Score; PSS, psychosocial summary; PK, pharmacokinetic; TFP, trifunctional protein; SD, standard deviation; TEAE, treatment-emergent adverse event; VLCAD, very long-chain acyl-CoA dehydrogenase

16. Efficacy Assessment Additional Information and Assessment

(b) (4)

17. Clinical Safety Assessment Additional Information and Assessment

Refer to Section [II.7](#).

18. Mechanism of Action / Drug Resistance Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations Additional Information

Not applicable.

20. Data Integrity-Related Consults (OSI, Other Inspections)

Because the Gillingham (2017) trial was submitted to a research IND, withdrawn in February 2016, no OSI consults were made for this study.

Based upon the number of patients enrolled, the amount of change in medium-chain triglyceride dietary dosing study UX007-CL201 and the available growth records, three sites were chosen for inspection from study UX007-CL201.

- Site 108 (six of 29 patients)
- Site 119 (three of 29 patients)
- Site 136 (two of 29 patients)

One of these sites, site 108, was one of two sites for the Gillingham trial.

Clinical data from an open-label phase 2 study was submitted as a 505(b)(2) supplement to NDA 213687 to the Agency in support of the above proposed indication for triheptanoin. Three clinical investigators, Dr. Kimberly Chapman (site 136), Dr. John Phillips (site 119), and Dr. Gerard Vockley (site 108) were selected for clinical inspections. The inspections verified the reported primary efficacy measures with source data at the clinical investigator sites. Dr. Vockley's site (site 108) was found to have a few protocol deviations. Specifically, one patient (subject (b) (6)) was found not to have met the eligibility criteria, which was not reported to the sponsor as a protocol violation.

Overall, the data generated by these clinical investigator sites, which were submitted by the Applicant, appear to be acceptable and supportive of this NDA.

21. Labeling Summary of Considerations and Key Additional Information

INDICATIONS AND USAGE

The indication proposed by the Applicant was management of clinical outcomes of LC-FAOD disease:

DOJOLVI is indicated (b) (4) for the treatment of adult and pediatric patients with LC-FAOD (b) (4)

The review team determined the submitted clinical trials did not support a claim of (b) (4) and the indication was revised to a nutritional support indication:

DOJOLVI is indicated as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed LC-FAOD.

The Established Pharmacologic Class is “medium-chain triglyceride.”

DOSAGE AND ADMINISTRATION

The total daily dosage is divided for times per day diluted 1:1 with semi-solid foods, liquids, or formula and is supported by studies UX007-CL201 and UX007-CL202.

As patients may require an increase in their total fat intake, it is recommended that patients treated with DOJOLVI should be under the care of a clinical disease specialist knowledgeable of current nutritional recommendations for patients with LC-FAOD. The neonatal population may require higher fat intake and current nutritional recommendations should also be considered when dosing the neonatal population.

The proposed target daily dosage of (b) (4)% DCI was revised to up to 35% DCI to reflect dosing in studies UX007-CL201 and UX007-CL202 (see Section [II.6.1](#) of the Integrated Review). A formula is provided to convert the total daily dosage to a volume of DOJOLVI.

Based upon studies UX007-CL201 and UX007-CL202, the dosage titration recommendations were revised because the data was not supportive of the Applicant’s proposal for a long titration period (see Section [II.6.1](#) of the Integrated Review). Information on how to titrate the dosage based on tolerability was also added. Patients with gastrointestinal adverse reactions may need dosage reduction.

Detailed preparation and administration instructions for administration orally or enterally via a feeding tube were added, including compatibility information with various materials. Examples of semi-solid foods and liquids that were used in clinical trials or stability studies were included. Stability studies supported storage of the mixture for up to 24 hours in refrigerated conditions (see Section [II.9.1](#) of the Integrated Review). An Instructions for Use document also developed to describe step-by-step for the patient/caregiver how to prepare and administer the drug.

Administer DOJOLVI mixed with semi-solid food or liquids orally or enterally via a silicone or polyurethane feeding tube.

Prepare or administer DOJOLVI using containers, dosing syringes or measuring cups made of compatible materials such as stainless steel, glass, high density polyethylene (HDPE), polypropylene, low density polyethylene, polyurethane and silicone.

DOJOLVI is not compatible with certain plastics. Do not prepare or administer DOJOLVI using containers, dosing syringes or measuring cups made of polystyrene or polyvinyl chloride (PVC) plastics.

Regularly monitor the containers, dosing components or utensils that are in contact with DOJOLVI to ensure proper functioning and integrity.

Instructions on how to administer the product for patients receiving bolus delivery versus continuous feeds were provided by the Applicant upon request:

- Flush the feeding tubes with between 5 mL to 30 mL of water. Flush volume should be modified based on specific patient needs and in cases of fluid restriction.
- Administer DOJOLVI over 15 to 20 minutes for patients receiving bolus delivery of enteral feeds. For patients receiving continuous feeds, administer DOJOLVI over 30 to 60 minutes alternating with formula alone.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

There are no contraindications. A Warning and Precaution was added to address the potential safety concern of feeding tube dysfunction. During the clinical trials, adverse events of G-tube dysfunction were reported in patients receiving triheptanoin. The contribution of the product to the events was not clear, but MCT oil is known to degrade certain plastics (polystyrene) and triheptanoin adheres to PVC. The Applicant asserts that there is no evidence that plastic degrades triheptanoin. The compatibility studies support lack of degradation in silicone feeding tubes for up to 60 minutes. While causality cannot be established, the contribution of the drug cannot be ruled out. Therefore, it is recommended that healthcare providers regularly monitor the feeding tube to ensure proper functioning and integrity.

A Warning and Precaution was also added to describe the risk of intestinal malabsorption of heptanoate in patients with pancreatic insufficiency. Dojolvi should be avoided in patients with pancreatic insufficiency because it is not possible to monitor pharmacodynamic or clinical response to triheptanoin to guide dosing.

ADVERSE REACTIONS

The review team based the safety evaluation on 79 patients and includes patients enrolled in studies UX007-201/UX007/202 (as discussed in Section [II.7.5](#) of the Integrated Review). This population allowed for long-term assessment of most patients in study UX007-201 and was considered the most informative population. Adverse reactions reported in these patients were gastrointestinal in nature.

DRUG INTERACTIONS

Triheptanoin is hydrolyzed to heptanoate by pancreatic lipases in the intestine. Therefore, coadministration with pancreatic lipase inhibitors (e.g., orlistat) may reduce exposure to heptanoate and thereby potentially reduce the clinical effect of triheptanoin and is not recommended (see Section [II.5](#) of the Integrated Review).

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on triheptanoin use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal reproduction studies conducted in pregnant rats and rabbits administered triheptanoin during the period of organogenesis, the primary toxicological effect (reduced body weight gain) was considered to be specific to decreased food consumption related to taste aversion in animals, and therefore is not relevant to clinical use in the intended populations (see Section [II.7.1](#) of the Integrated Review).

The Applicant will be required to conduct a pregnancy safety study collecting pregnancy outcome data (see Section [22](#)). Women are advised to report pregnancies to the Applicant.

Lactation

There are no data on the presence of triheptanoin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Studies in animals have not been conducted to assess the excretion of triheptanoin in the milk, and systemic exposure of triheptanoin or its metabolites was not detected in nursing rat pups.

Pediatrics

The product is recommended for approval in all age groups (birth through adult).

Geriatrics

There were no patients 65 years of age or older in the clinical trials or the safety database.

CLINICAL PHARMACOLOGY

The mechanism of action was limited to triheptanoin providing a source of calories and fatty acids, which serve as a substrate for energy production. Other claims attributed to the chemical composition as an MCT consisting of three odd-chain 7-carbon length fatty acids (heptanoate) have not been substantiated.

No formal pharmacodynamic studies have been conducted.

Triheptanoin is hydrolyzed to heptanoate which can be measured in the plasma and the pharmacokinetic characteristics after single and multiple doses in healthy subjects are described.

NONCLINICAL TOXICOLOGY

Triheptanoin is not genotoxic and has no effect on fertility. Nonclinical findings of tumorigenicity in the gastrointestinal tract of rats are described.

CLINICAL STUDIES

As described in Section [II.6.2.1](#), Gillingham (2017) (referred to as study 3 in the PI), was considered an adequate and well-controlled study to support use of triheptanoin as a source of calories and fatty acids and is the only clinical data described in this section. (b) (4)

Descriptive results from Gillingham (2017) considered acceptable to include were the number of events of rhabdomyolysis. Metabolic markers of metabolism (e.g., glucose, insulin, lactate) were described in terms of no differences between the treatment groups. Cardiovascular indices of left ventricular ejection fraction and wall mass on echocardiography and maximal heart rate on treadmill ergometry were described as similar.

The product studied in Gillingham (2017) was not the to-be-marketed formulation of DOJOLVI; therefore, the product is referred to by the nonproprietary name of triheptanoin in this section.

HOW SUPPLIED/STORAGE AND HANDLING

The incompatibility of triheptanoin with various materials is emphasized by instructions not to dose or store it in polystyrene or PVC containers and to alert the pharmacist to dispense it only in glass or HDPE bottles.

22. Postmarketing Requirements and Commitments

The following PMRs apply to triheptanoin.

PMRs

- PMR #1 - Conduct a worldwide, single-arm, pregnancy safety study in women exposed to DOJOLVI during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. Results will be analyzed and reported descriptively.
 - Rationale: The ability to identify patients with long-chain fatty acid oxidation disorders (LC-FOADs) has improved. Standard of care has relied upon dietary modifications to include higher dosing of naturally occurring medium-chain fat. With improved diagnosis and management of LC-FAOD, there is now a greater possibility that women with LC-FAOD may become pregnant. Ingestion of dietary fat is needed for normal fetal development. As triheptanoin is a synthetic fat not found naturally, it is important to understand the risk of fetal anomalies due to use in pregnancy. Pregnant patient.
 - As LC-FAODs are rare, this information is unlikely to be obtained in a clinical trial. Therefore, a 10-year (of up to 40 pregnancies) assessment for fetal anomalies is

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proposed. This would provide reasonable time and number to identify a high risk for specific patterns of teratogenesis.

Draft Protocol Submission: 08/2020

Final Protocol Submission: 04/2021

Study Completion: 01/2032

Interim: 09/2024

Interim: 09/2027

Final Report Submission: 01/2033

23. Financial Disclosure

Table 65. Covered Clinical Studies: Study UX007-CL201, Study UX007-CL202 and Gillingham (2017)^a

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 183		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

^a The Gillingham (2017) study was funded by an FDA Office of Orphan Product Development grant (FD-R03895-01), Form FDA 3455 was not submitted for this study

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25. Review Team Acknowledgements

Table 66. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Jenny Doan, MSN, BSN
Nonclinical Reviewer	Emmanuel Akinshola, PhD
Nonclinical Team Leader	Sushanta Chakder, PhD
Office of Clinical Pharmacology (OCP) Reviewer	Sojeong Yi, PhD
Office of Clinical Pharmacology Team Leaders	Jie (Jack) Wang, PhD Lian Ma, PhD
Clinical Reviewer	Dina J. Zand, MD
Clinical Team Leader	Kathleen M. Donohue, MD
Statistical Reviewer	LaRee Tracy, MA, PhD (retired)
Statistical Team Leader	Estelle Russek-Cohen, PhD (retired)
Cross-Disciplinary Team Leader	Kathleen Donohue, MD
Associate Director of Labeling	Joette Meyer, PharmD
Division Director (OCP)	Michael Pacanowski, PhD
Division Director (OB)	Laura Lee Johnson, PhD
Office Director	Julie Beitz, MD

Table 67. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Sam Bain, PhD, and Donna Christner, PhD (DS); Caroline Strasinger, PhD, and Moo Jhong Ree, PhD (DP) Peter Krommenhoek, PhD, and Aditi Thakur, PhD (OPF) Raanan Bloom, PhD (EA) Hitesh Shroff, PhD (ATL) Oumou Barry, PharmD(RPM)
Microbiology	Yan Zheng, PhD, and Jesse Wells, PhD
OPDP	Adewale Adeleye (OPDP); Kelly Jackson, PharmD, and Marcia Williams, PharmD (DMPP)
OSI	Zana Handy Marks, MD and Karen Bleich, MD
OSE/DEPI	Monisha Billings, PhD, and Catherine Callahan, PhD
OSE/DMEPA	Sarah Vee, PharmD, and Idalia Rychlik, PharmD
OSE/DRISK	Ingrid Chapman, PharmD, and Donella Fitzgerald, PhD
Other	DCRP (cardiology): Fred Senatore, MD, PhD

OPQ = Office of Pharmaceutical Quality

OPDP = Office of Prescription Drug Promotion

OSI = Office of Scientific Investigations

OSE = Office of Surveillance and Epidemiology

DEPI = Division of Epidemiology

DMEPA = Division of Medication Error Prevention and Analysis

DRISK = Division of Risk Management

See attached signature page.

Table 66. Reviewers of Integrated Assessment

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Cross-Disciplinary	Jenny Doan, MSN, BSN	OND/ORO/Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine	25 ☒ Authored ☐ Approved
Project Manager	Signature:		
Pharmacology/Toxicology	Babatunde Akinshola, PhD	OND/ORP/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine	5, 7.1,13 ☒ Authored ☐ Approved
Primary Reviewer	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Sushanta Chakder, PhD	OND/OII/Division of Pharm/Tox for Immunology and Inflammation	5, 7.1, 13 ☒ Authored ☒ Approved
Secondary Reviewer	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Sojeong Yi, PhD	OTS/OCP/Division of Inflammation and Immune Pharmacology (DIIP)	5, 6.1, 8.1, 8.2, 14 ☒ Authored ☐ Approved
Primary Reviewer	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Jie (Jack) Wang, PhD	OTS/OCP/Division of Translational and Precision Medicine (DTPM)	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Team Leader	Signature:		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology/Pharmacometrics	Lian Ma, PhD	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Team Leader	Signature:		
Clinical Pharmacology	Michael Pacanowski, PhD	OTS/OCP/Division of Translational and Precision Medicine (DTPM)	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Division Director	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Dina J. Zand, MD	OND/ORPURN/Division of Rare Diseases and Medical Genetics	1,2,3,4,6,7,8,10,11,12,15,16, 17, 20, 21,22,23,24 ☒ Authored
Primary Reviewer	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Kathleen M. Donohue, MD Director (Acting)	OND/ORPURN/Division of Rare Diseases and Medical Genetics	All ☒ Authored ☒ Approved
Cross-Disciplinary Team Lead	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Cross-Disciplinary	Joette Meyer, PharmD	OND/ORPURN/Division of Rare Diseases and Medical Genetics (Acting)	9.1, 21 ☒ Authored ☒ Approved
Associate Director for Labeling	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Biometrics	LaRee Tracy, PhD (retired)	OB/Division of Biometrics IV	6, 15, 16 ☒ Authored ☐ Approved
Primary Reviewer	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Estelle Russek-Cohen, PhD (retired)	OB/Division of Biometrics VII	6, 15, 16 ☒ Authored ☐ Approved
Secondary Reviewer	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Laura Lee Johnson, PhD	OB/Division of Biometrics III	6, 15, 16 ☐ Authored ☒ Approved
Division Director	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Product Quality	Hitesh Shroff, PhD	OPQ/ONDP	9 ☒ Authored ☐ Approved
Team Leader	Signature:		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Cross-Disciplinary	Julie Beitz, MD	OND/Office of Immunology and Inflammation	All ☐ Authored ☒ Approved
Signatory Authority	Signature:		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary.

Table 66. Reviewers of Integrated Assessment

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Cross-Disciplinary	Jenny Doan, MSN, BSN	OND/ORO/Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine	25 ☒ Authored ☐ Approved
Project Manager	Signature: Jenny Doan -S Digitally signed by Jenny Doan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jenny Doan -S, 0.9.2342.19200300.100.1.1=0010124444 Date: 2020.06.24 20:22:45 -04'00'		
Pharmacology/Toxicology	Babatunde Akinshola, PhD	OND/ORP/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine	5, 7.1, 13 ☒ Authored ☐ Approved
Primary Reviewer	Signature: Babatunde Akinshola -S Digitally signed by Babatunde Akinshola -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000342685, cn=Babatunde Akinshola -S Date: 2020.06.29 12:32:17 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Sushanta Chakder, PhD	OND/OII/Division of Pharm/Tox for Immunology and Inflammation	5, 7.1, 13 ☒ Authored ☒ Approved
Secondary Reviewer	Signature: Sushanta K. Chakder -S Digitally signed by Sushanta K. Chakder -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144003, cn=Sushanta K. Chakder -S Date: 2020.06.25 17:43:50 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Sojeong Yi, PhD	OTS/OCP/Division of Inflammation and Immune Pharmacology (DIIP)	5, 6.1, 8.1, 8.2, 14 ☒ Authored ☐ Approved
Primary Reviewer	Signature: Sojeong Yi -S Digitally signed by Sojeong Yi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sojeong Yi -S, 0.9.2342.19200300.100.1.1=2002075079 Date: 2020.06.25 09:38:07 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Jie (Jack) Wang, PhD	OTS/OCP/Division of Translational and Precision Medicine (DTPM)	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Team Leader	Signature: Jie Wang -S Digitally signed by Jie Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jie Wang -S, 0.9.2342.19200300.100.1.1=2000739081 Date: 2020.06.25 09:51:48 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology/Pharmacometrics	Lian Ma, PhD	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Team Leader	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2020.06.24 21:21:38 -04'00'		
Clinical Pharmacology	Michael Pacanowski, PhD	OTS/OCP/Division of Translational and Precision Medicine (DTPM)	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Division Director	Signature: Michael Pacanowski -S Digitally signed by Michael Pacanowski -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000350707, cn=Michael Pacanowski -S Date: 2020.06.25 09:56:10 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Dina J. Zand, MD	OND/ORP/Division of Rare Diseases and Medical Genetics	1,2,3,4,6,7,8,10,11,12,15,16, 17, 20, 21,22,23,24 ☒ Authored
Primary Reviewer	Signature: Dina Zand -S Digitally signed by Dina Zand -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Dina Zand -S, 0.9.2342.19200300.100.1.1=0012675847 Date: 2020.06.25 12:55:00 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Kathleen M. Donohue, MD Director (Acting)	OND/ORP/Division of Rare Diseases and Medical Genetics	All ☒ Authored ☒ Approved
Cross-Disciplinary Team Lead	Signature: Kathleen Donohue, M.D. Digitally signed by Kathleen Donohue, M.D. DN: cn=Kathleen Donohue, M.D., o=FDA, ou=DGIEP OND CDER, email=Kathleen.Donohue@fda.hhs.gov, c=US Date: 2020.06.29 11:55:11 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Cross-Disciplinary	Joette Meyer, PharmD	OND/ORP/Division of Rare Diseases and Medical Genetics (Acting)	9.1, 21 ☒ Authored ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Biometrics	LaRee Tracy, PhD (retired)	OB/Division of Biometrics IV	6, 15, 16 ☒ Authored ☐ Approved
Primary Reviewer	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2020.06.29 11:51:41 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Estelle Russek-Cohen, PhD (retired)	OB/Division of Biometrics VII	6, 15, 16 ☒ Authored ☐ Approved
Secondary Reviewer	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2020.06.29 11:52:34 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Laura Lee Johnson, PhD	OB/Division of Biometrics III	6, 15, 16 ☐ Authored ☒ Approved
Division Director	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011413414, cn=Laura L. Johnson -S Date: 2020.06.29 11:53:14 -04'00'		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Product Quality	Hitesh Shroff, PhD	OPQ/ONDP	9 ☒ Authored ☐ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Cross-Disciplinary	Julie Beitz, MD	OND/Office of Immunology and Inflammation	All ☐ Authored ☒ Approved
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¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary.

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/s/

JENNY N DOAN
06/29/2020 05:31:18 PM

JULIE G BEITZ
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