Population Pharmacokinetics of Heptanoate in Healthy Subjects and Patients With Long-Chain Fatty Acid Oxidation Disorders Treated With Triheptanoin

Sun Ku Lee[1], Nathalie H. Gosselin[2], Claudia Jomphe[2], Kathleen McKeever[1], and Wendy Putnam[1]

Abstract

Triheptanoin is an odd-carbon, medium-chain triglyceride consisting of three fatty acids with seven carbons each on a glycerol backbone, indicated for the treatment of adult and pediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD). A total of 562 plasma concentrations of heptanoate, the most abundant and pharmacologically active metabolite of triheptanoin, from 13 healthy adult subjects and 30 adult and pediatric subjects with LC-FAOD were included in the population pharmacokinetic (PK) analyses. Multiple peaks of heptanoate observed in several subjects were characterized by dual first-order absorption with a lag time in the second absorption compartment. The disposition of heptanoate in human plasma was adequately described by one-compartmental distribution with a linear elimination. The apparent clearance (CL/F) and apparent volume of distribution were allometrically scaled with body weight to describe PK data across a wide range of age groups in subjects with LC-FAOD. The typical CL/F in adult subjects with LC-FAOD was ≈19% lower than that in healthy subjects. Model-estimated elimination half-life for LC-FAOD patients was ~1.7 hours, supporting a recommended dosing frequency of ≥4 times per day. Covariate analyses indicate that age, race, and sex did not lead to clinically meaningful changes in the exposure of heptanoate.

Long-chain fatty acid oxidation disorders (LC-FAOD) are rare, life-threatening genetic diseases associated with defects in metabolic enzymes related to processing dietary long-chain fatty acids into energy within the mitochondria.[1] The disruptions in the metabolic conversion of long-chain fatty acids into energy substrates can result in life-threatening conditions due to metabolic crises requiring high energy demand and physiological stressors such as fasting, illness, and exercise.[2] Clinical manifestations of LC-FAOD include rhabdomyolysis, hypoglycemia, cardiomyopathy, and muscle function impairment.[2–5]

Typically, current management of LC-FAOD includes assiduous avoidance of fasting, maintenance of a low-fat/high-carbohydrate diet, and/or ingestion of commercially available medium-chain triglyceride formulations (MCT) consisting primarily of eight- or 10-carbon fatty acids (ie, even-carbon triglyceride) to minimize the occurrence of metabolic decompensation

[1]Ultragenyx Pharmaceutical Inc., Novato, California, USA
[2]Certara Strategic Consulting, Princeton, New Jersey, USA

Corresponding Author:
Sun Ku Lee, PhD, Ultragenyx Pharmaceutical Inc., 5000 Marina Parkway, Brisbane, CA 94005
(e-mail: skulee@ultragenyx.com)

and associated major clinical events. Since energy requirements and demands vary greatly between individual patients, trained metabolic physicians or dietitians are required to provide appropriate dietary management for individual patients with LC-FAOD.

Triheptanoin, which is also known as UX007, is an odd-carbon, medium-chain triglyceride with three fatty acids including odd-carbons (ie, seven carbons each) attached to a glycerol backbone. Triheptanoin is indicated as a source of calories and fatty acids for the treatment of adult and pediatric patients with LC-FAOD.[6] After an oral administration, triheptanoin is hydrolyzed into glycerol and heptanoate (C7 fatty acids) by pancreatic lipases in the gastrointestinal (GI) tract, minimizing the systemic exposure of triheptanoin. Heptanoate, the major metabolite of triheptanoin, is absorbed from the GI tract and systemically available.[7] Heptanoate is distributed to the body through the bloodstream and transferred to the mitochondria in respective tissues and organs by simple diffusion. In the mitochondria, heptanoate is metabolized to acetyl-CoA and propionyl-CoA by the short- and medium-chain fatty acid oxidation enzymes which bypass the carnitine shuttle and long-chain fatty acid oxidation enzymes deficient in patients with LC-FAOD.[8–10] Acetyl Co-A and propionyl-CoA restore energy metabolism by replenishing intermediates for the TCA cycle and providing substrates for gluconeogenesis.

The pharmacokinetics (PK) of triheptanoin and its metabolites in humans following oral administrations were investigated using the available PK data from two clinical studies and reported previously.[11] Briefly, the systemic exposure of triheptanoin following oral administration was negligible as triheptanoin is hydrolyzed to glycerol and heptanoate before it is absorbed from the GI tract. Heptanoate can be metabolized to four- and five-carbon ketone bodies (ie, beta-hydroxybutyrate [BHB] and beta-hydroxypentoate [BHP]) in the liver and circulated via the bloodstream. Multiple peaks of triheptanoin metabolites were observed in the plasma following oral administrations of triheptanoin, and the time reaching the peaks generally coincided with the time that meals were served. Despite further metabolism in the liver, heptanoate showed the greatest exposure among the triheptanoin metabolites in human plasma.

Here, we present the population PK of heptanoate in healthy subjects and patients with LC-FAOD following oral administrations of triheptanoin. As heptanoate was the most abundant, pharmacologically active metabolite of triheptanoin in human plasma, the current analyses aimed to characterize the PK of heptanoate in healthy subjects and patients with LC-FAOD, and evaluate the covariates that potentially affect the exposure of heptanoate.

Methods

Clinical Studies and Data Collection

All clinical studies were conducted in accordance with the US Code of Federal Regulations (CFR), Good Clinical Practice (GCP), 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization harmonized tripartite guideline regarding GCP, and the ethical requirements referred to in the European Union directive 2001/20/EC. The study protocols were approved by relevant local institutional review boards or ethics committees at the investigative sites.

PK samples were collected from a total of 47 subjects who participated in three clinical studies including two studies where serial blood samples had been collected and PK results were previously reported by noncompartmental analyses.[11] Data from two subjects were excluded from the population PK analysis due to inaccurate clinical records on meal duration. Additionally, two subjects participated in two clinical studies and contributed PK samples in each study. In the combined population PK analysis, these subjects received unique subject IDs irrespective of clinical studies. The quantitation of heptanoate in human plasma was conducted by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Details of the bioanalytical assays were reported previously.[11] The descriptions of clinical studies, dose regimen, PK sampling schedule, and number of subjects are presented in Table S1.

Population PK Analyses

Population PK analyses were conducted to characterize the PK of heptanoate by nonlinear mixed effect (NLME) modeling using the pooled concentration–time data from three clinical studies. The analyses were performed using Phoenix NLME v8.1 (Pharsight – A Certara Company) with a first-order conditional estimation (FOCE with INTERACTION) algorithm. The exploration of dataset, and the generation of figures and tables were performed using R v3.5.2 with a comprehensive R archive network (CRAN) and Certara Strategic Consulting (CSC) package.

The analyses were conducted in the following steps: base model development, random effect model development, covariate model development, and model validation. As subjects were administered triheptanoin doses mixed with food to reduce GI-related adverse events, the duration of the meal was included in the population PK dataset. Concentration levels below the lower limit of quantitation (BLQ) were treated as missing. Dose levels of triheptanoin were converted from g/kg to μmol/kg based on the molecular weight of triheptanoin (428.61 g/mol). Creatinine clearance (CRCL) at

baseline was calculated using the Schwartz equation in pediatric subjects and the Cockcroft and Gault approach in adolescents and adults, respectively.[12,13]

Multiple structural models describing the absorption and disposition of heptanoate were tested and the final model was selected based on the model diagnostics and goodness-of-fit (GOF) criteria. The disposition model parameters (apparent clearance [CL/F] and apparent volume of distribution [V/F]) were scaled with body weight to appropriately describe the PK across a wide range of body weights in adult and pediatric subjects with LC-FAOD. Between-subject variability (BSV) was incorporated using the exponential variance model assuming that the respective individual PK parameters follow a log-normal distribution. The residual variability was incorporated after evaluating a combined (ie, proportional + additive) error model or a log-additive error model. At all stages, diagnostic plots reflecting a GOF, residual plots, shrinkage, and precision of the parameter estimates were evaluated to assess model adequacy, which is a common approach in population PK modeling.[14]

Covariate analyses were conducted to evaluate the effects of demographics and disease status on the PK of heptanoate. The relationships between covariates and PK parameters were explored graphically to obtain information on covariates likely to affect the PK of heptanoate. The selected covariates based on the graphical evaluations were further tested in the population PK model using a stepwise approach with forward inclusion with criteria of $P < 0.05$ and backward elimination with criteria of $P < 0.01$.

Internal model validations with the interim and final models were conducted by performing a visual predictive check (VPC) on observed concentrations of heptanoate. Based on the estimates of the models, concentration–time profiles of heptanoate after single and multiple doses of triheptanoin in each population (ie, healthy subjects versus patients with LC-FAOD) were simulated using 1000 replicates of the subjects in each group of stratification. The median and 95% confidence intervals (CIs) of concentrations within each bin were computed and compared with the observed data in each population. A nonparametric bootstrap analysis was conducted to evaluate the stability of the final model and to estimate CIs for the model parameters. A total of 420 datasets generated by random resampling of subjects from the original dataset with stratification by the study were used to re-estimate the parameters of the final model. The 90%CIs were calculated based on the distribution of the parameter estimates from the bootstrap runs.

The exposures of heptanoate in individual subjects were derived based on the steady-state concentration–time profiles simulated with posterior Bayes PK parameters at 1.25 g/kg/day (2916 μmol/kg/day) of triheptanoin administered four times a day (corresponding to ∼30% of daily caloric intake [DCI] in adults), assuming an 8-hour pause during the night. The following individual plasma exposure parameters were estimated at steady-state conditions: daily area under the concentration–time curve (AUCday), maximum concentration (Cmax), and minimum concentration (Cmin). Terminal elimination half-life ($T_{1/2}$) values were computed based on simulated PK profiles after the last dose of administration.

The clinical relevance of covariates in patients with LC-FAOD was assessed based on their effects on the individual subject's AUCday and Cmax. AUCday and Cmax in each virtual subject were divided by the corresponding medians in the overall LC-FAOD study population. Distributions of those ratios were presented in a forest plot by category of the covariates of interest (ie, quartiles of age, quartiles of body weight, hepatic function, race, and sex). A covariate effect was deemed potentially relevant if the point estimate of the effect size on PK exposure levels, AUCday, and Cmax, was outside of the 80%–125% range.

Results

Patient and PK Sample Disposition

A total of 692 blood samples were collected from subjects treated with triheptanoin (13 healthy subjects and 30 with LC-FAOD), with 562 measurable concentrations of heptanoate, as shown in Table S2. Key categorical and continuous baseline demographics are provided in Tables 1 and 2, respectively. In subjects with LC-FAOD, the majority were pediatric subjects consisting of five infants (6 months to <2 years), 13 children (2 to <12 years), and five adolescents (12 to <18 years). Most subjects were White, and males and females were almost evenly distributed in the combined dataset. Mean baseline levels of aspartate aminotransferase (AST) and CRCL in subjects with LC-FAOD were greater than those in healthy subjects, as presented in Table 2. Elevated AST and CRCL have been associated with rhabdomyolysis or muscle damage, which are known disease manifestations in patients with LC-FAOD.[15,16] Therefore, elevated levels of AST and CRCL at baseline appear to be the accompanying phenomena related to rhabdomyolysis or muscle damage, rather than malfunctions in liver or kidney.

Model Development

A schematic of the structural model is presented in Figure 1. The absorption of heptanoate from the GI tract following the hydrolysis of triheptanoin was characterized by dual first-order absorption with a lag time in the second absorption compartment. The

Table 1. Summary of Continuous Demographic Data at Baseline

	Mean (CV%), N = 43		
		Subjects with LC-FAOD, n = 30	
Continuous Covariates at Baseline	Healthy Volunteers, n = 13	Pediatric Subjects, n = 23 (76.7%)	Adult Subjects, n = 7 (23.3%)
Age (years)	39.1 (31.1%)	7.41 (76.7%)	33.6 (55.6%)
Weight (kg)	73.8 (17.6%)	35.0 (79.3%)	83.6 (24.2%)
Height (cm)	174 (5.1%)	121 (30.3%)	170 (6.6%)
Body mass index (kg/m^2)	24.9 (15.6%)	18.8 (20.0%)	28.0 (16.7%)
Body surface area (m^2)	1.87 (10.0%)	1.04 (55.3%)	1.94 (14.2%)
Albumin (g/L)	41.2 (6.3%)	44.5 (8.1%)	44.6 (5.5%)
Aspartate aminotransferase (U/L)	21.4 (37.3%)	66.0 (94.5%)	53.9 (44.1%)
Total bilirubin (mg/dL)	0.631 (51.5%)	0.217 (53.1%)	0.271 (27.9%)
Creatinine clearance age <12 years old (mL/min/1.73 m^2) age ≥12 years old (mL/min)	112 (18.0%)	205 (47.4%)	163 (15.9%)
Serum creatinine (mg/dL)	0.872 (14.0%)	0.430 (47.2%)	0.657 (26.3%)

CV, coefficient of variation; LC-FAOD, long-chain fatty acid oxidation disorders; N, n, number of subjects.
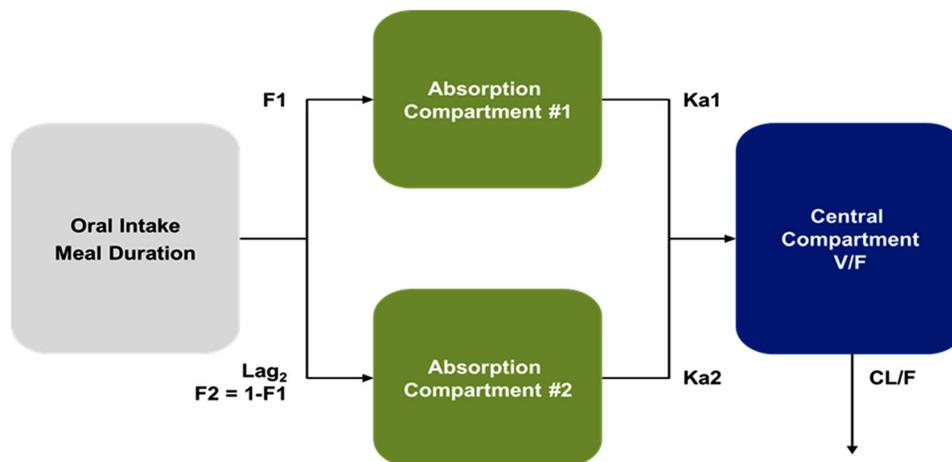
Figure 1. Model schematic. CL/F, oral-dose apparent clearance; F1, fraction of absorbed dose in absorption compartment #1; F2, fraction of absorbed dose in absorption compartment #2; GI, gastrointestinal; Ka1, first-order rate constant in absorption compartment #1; Ka2, first-order rate constant in absorption compartment #2; Lag2, lag time of absorption in absorption compartment #2; V/F, oral-dose apparent volume of distribution.

disposition of heptanoate in human plasma was adequately described by one-compartmental distribution with a linear elimination. Incorporation of time-dependent changes in the CL/F of heptanoate into the model was necessary to describe an apparent systemic accumulation of heptanoate following the multiple dosing of triheptanoin.

Exploratory analyses indicated that no obvious trends were observed for the random effects of PK parameters with most covariates once the body weights (WT) were allometrically scaled with CL/F and V/F, as presented in Figure S1. However, random effects of CL/F showed distinct trends with disease popula-

tion (healthy vs LC-FAOD), CRCL, and bilirubin, thus those trends were formally evaluated based on a stepwise covariate analysis as described in Methods. The incorporation of these covariates into the model did not lead to statistically significant improvement of model diagnostics. Despite the lack of statistical significance, the effect of disease on CL/F was retained in the final model considering a clinical relevance.

The PK parameters for the final model are presented in Table 3. The bootstrap results evaluating the robustness of final PK parameters are presented in Table S3. The model indicates that approximately 56% of heptanoate in the systemic circulation was absorbed via

Table 2. Summary of Categorical Demographic Data Included in the Population PK Analyses (N = 43)

Categorical Demographics	Healthy Volunteers, n = 13	Subjects with LC-FAOD, n = 30	
		Pediatric Subjects, n = 23 (76.7%)	Adult Subjects, n = 7 (23.3%)
Sex			
Male	6 (46.2%)	15 (65.2%)	2 (28.6%)
Female	7 (53.8%)	8 (34.8%)	5 (71.4%)
Race			
White	10 (76.9%)	18 (78.3%)	7 (100%)
Black or African American	2 (15.4%)	2 (8.7%)	0 (0%)
Asian	0 (0%)	1 (4.3%)	0 (0%)
Native Hawaiian/Pacific Islander	1 (7.7%)	0 (0%)	0 (0%)
Other	0 (0%)	2 (8.7%)	0 (0%)
Age group			
Adults (≥18 years)	13 (100%)	0 (0%)	7 (100%)
Adolescents (≥12 to <18 years)	0 (0%)	5 (21.7%)	0 (0%)
Children (≥2 to <12 years)	0 (0%)	13 (56.5%)	0 (0%)
Infants (6 months to <2 years)	0 (0%)	5 (21.7%)	0 (0%)
NCI-ODWG Hepatic Dysfunction Category			
Mild	2 (15.4%)	10 (43.5%)	5 (71.4%)
Normal	11 (84.6%)	13 (56.5%)	2 (28.6%)

AST, aspartate aminotransferase; BIL, total bilirubin; LC-FAOD, long-chain fatty acid oxidation disorders; N, number of subjects; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; PK, pharmacokinetic; ULN, upper limit of normal.
Note: NCI-ODWG liver dysfunction category.[27]
Normal: BIL ≤ ULN and AST ≤ ULN.
Mild: BIL ≤ ULN and AST > ULN or ULN < BIL ≤ 1.5 × ULN.

the first absorption compartment and the absorption process for this compartment was expected to be almost completed prior to the beginning of the second phase of absorption (ie, lag time of 3.74 hours). Because one molecule of triheptanoin contains three heptanoate moieties, the final estimates of heptanoate CL/F and V/F were corrected by a factor of 3. The estimated population mean parameters for CL/F and V/F indicate that heptanoate is extensively distributed into the body and rapidly eliminated from the body.

The effects of body weight on CL/F and V/F were tested with PK data collected in subjects with a wide range of body weight from 8.23 to 121 kg, enabling adequate estimation of exponent parameters showing relationships between body weights and those PK parameters. The precision estimates (% relative standard error [RSE]) of most final model parameters based on the bootstrap analyses were below 30%, and the range of the 95%CIs for most model parameters was generally narrow, consistent with %RSE (Table S3). These results indicate that the final model parameters were reliably estimated without overparameterization.

The estimated BSV for CL/F was ~60% but the estimated BSV for Ka1 exceeded 100%, suggesting that the absorption rate constant is highly variable among indi-

vidual subjects. The diagnostic plots and VPC for the final model are presented in Figures 2 and S2, respectively. Overall, the final model adequately described the observed concentration–time profiles of heptanoate in patients with LC-FAOD without biases, despite a slight underprediction at the highest bin (95th percentile) presented in the VPC plots (Figure S2). The predicted concentrations tended to be lower than observed concentrations at the higher concentration range presented in Figure 2. Most of those concentration data represented samples collected within 30 minutes following a single-dose administration of triheptanoin in healthy subjects.

Model Application

Due to an individualized dosing regimen based on DCI, the estimated PK exposure from the population PK model cannot be directly compared across subjects. Thus, PK simulations were conducted using the posterior Bayes parameters obtained from the final population PK model for each subject with LC-FAOD at the dosing regimen of 1.25 g/kg/day (2916 μmol/kg/day) triheptanoin, administered four times per day assuming an 8-hour pause during the night. This dose level is close to ~30% of DCI in typical healthy adults and was used in the healthy subject study. The clinical significance
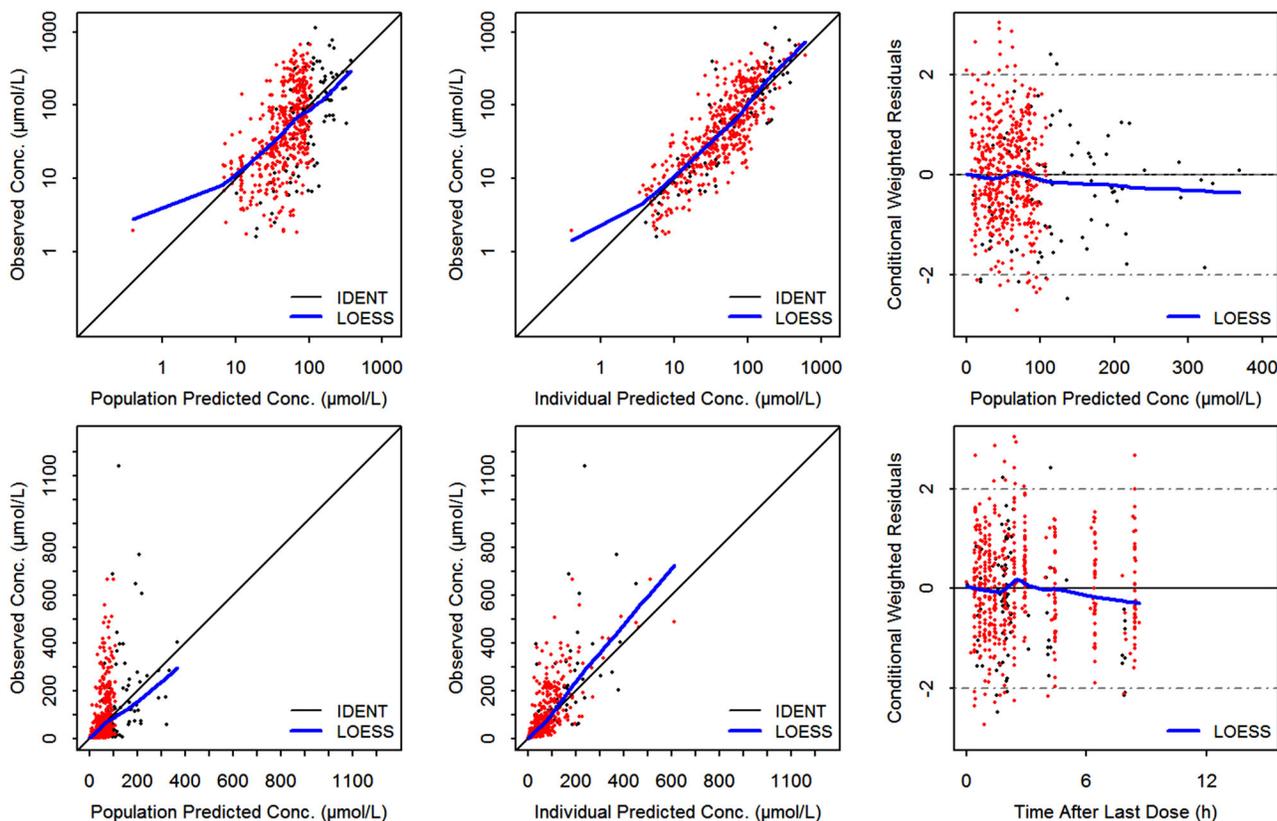
Figure 2. Diagnostic plots of the final population PK model of heptanoate. Conc, concentration; IDENT, identity; LC-FAOD, long-chain fatty acid oxidation disorders; LOESS, locally weighted scatter plot smoothing. Red dots represent healthy subjects and black dots represent LC-FAOD. Black lines and blue lines indicate IDENT and LOESS lines, respectively. Horizontal dotted lines indicate the boundary of conditional weighted residuals from −2 to 2.

of key intrinsic factors on the exposure of heptanoate was evaluated with the simulated data at 1.25 g/kg/day (2916 μmol/kg/day). A graphical representation of the magnitude and variability of covariate effects is presented in Figure 3. Simulated PK parameters are presented in Table S4. Clinically relevant differences in daily AUC at steady state (AUCday) were not observed for age, hepatic function based on NCI-ODWG classification, race (White vs non-White), sex, and body weight since all point estimates of AUCday were within the 80%–125% range. Similarly, Cmax appears not to be affected by race, sex, or NCI-ODWG category, with all point estimates of Cmax falling within the 80%–125% range. Only the upper groups of body weight and age (ie, 73.1–126 kg and 17.6–62.1 years of age) showed moderately higher Cmax than the reference values (ie, 1540 μmol × h/L for AUCday and 195 μmol/L for Cmax) by 146% and 130%, respectively. These minor differences do not appear to be clinically meaningful. Overall, these results suggest that the exposure of heptanoate is not significantly affected by age, race, sex, or mild hepatic impairment (based on NCI-ODWG classification). Model-estimated Tmax and $T_{1/2}$ were simi-

lar between pediatric and adult patients with LC-FAOD (Table S4).

Discussion

The objectives of the current population PK analyses were to describe the PK of heptanoate, the most abundant and pharmacologically active metabolite of triheptanoin, and to estimate the effects of covariates on the variability in PK parameters. The PK of heptanoate in healthy subjects and patients with LC-FAOD were adequately described by the one-compartmental, linear-elimination model with dual first-order absorption and a lag time for the second absorption compartment.

LC-FAOD affects the metabolism of fats with long-chain fatty acids greater than 12 carbons, resulting in a deficit of reducing equivalents for mitochondrial oxidative phosphorylation.[17] The disruption of fatty acid metabolism compromises energy homeostasis and potentially increases toxic fatty acid intermediates.[18] Thus, providing adequate nutrients unrelated to the metabolism of long-chain fatty acids could compensate
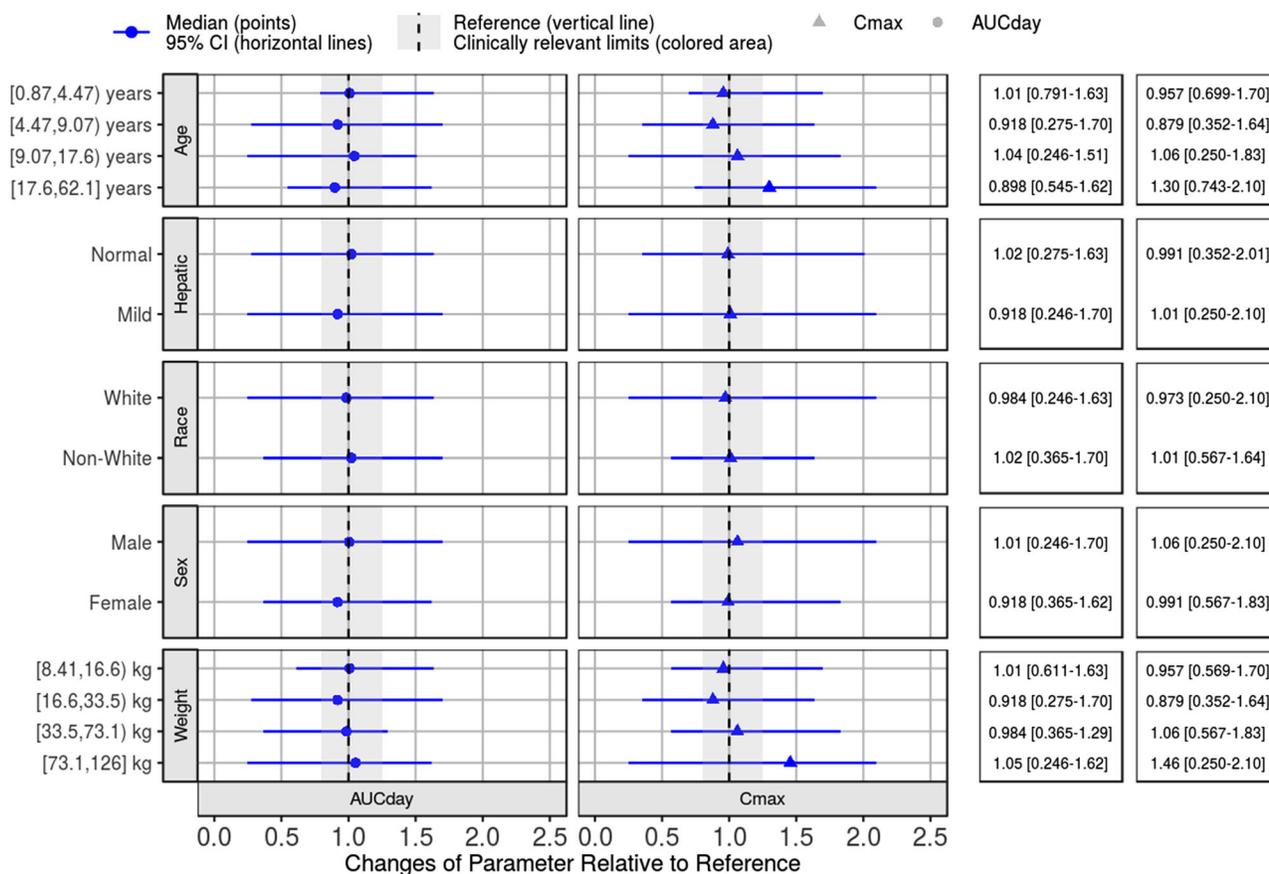
Figure 3. Covariate effects on AUCday and Cmax in patients with LC-FAOD. Dots and horizontal segments represent individual median and range of covariate effect relative to the median values of the overall population of patients with LC-FAOD (ie, 1540 μmol $\times$ h/L for AUCday and 195 μmol/L for Cmax). The shaded area represents effect size of 80%–125%. AUCday, daily area under the concentration time curve accounting for dosing frequency; Cmax, maximum concentration; LC-FAOD, long-chain fatty acid oxidation disorders.

for the energy deficiencies in patients with LC-FAOD. From this mechanistic perspective, MCT oil has been used to treat patients with LC-FAOD.[19] However, clinical symptoms in many patients with LC-FAOD persisted following MCT treatment, partly due to the depletion of key TCA cycle intermediates. As MCT is composed of even-chain fatty acids, the end-product of beta-oxidation for even-chain fatty acids is acetyl-CoA. Acetyl-CoA is an important substrate for the TCA cycle but cannot replenish TCA cycle intermediates, which can be easily depleted. In contrast, triheptanoin is hydrolyzed to heptanoate in the GI tract and the end-product of beta-oxidation for heptanoate is acetyl-CoA and propionyl-CoA. Propionyl-CoA is further metabolized to succinyl-CoA and succinate, resupplying the TCA cycle intermediates.[20] Thus, triheptanoin can continuously compensate for the energy deficiencies without the depletion of TCA cycle intermediates, while also providing substrates for gluconeogenesis.

Incorporation of the dual absorption compartments was necessary to describe the multiple peaks of

heptanoate observed in clinical studies. PK models incorporating dual absorption compartments have been used to describe complicated absorption kinetics.[21–23] The model-estimated proportion in the first absorption compartment was 56% and an estimated lag time in the second absorption compartment was ~3.7 hours. These results suggest that the absorption of heptanoate is staged with approximately 50% of heptanoate absorbed from the GI tract immediately after the dosing and the remaining portion absorbed approximately 4 hours later when the next meal is served. An enterohepatic recirculation model was tested to describe the multiple peaks of heptanoate following oral administrations of triheptanoin. However, the model was not successfully optimized due to instability of the model and the limitations of the available data such as the imputation time of next meal. Healthy subjects showed wide variation in the timing of the second peaks (1–4 hours post-dose). The earlier second peaks do not support the enterohepatic recirculation process. Furthermore, triheptanoin is not metabolized by UDP-glucuronosyltransferases,

Table 3. PK Parameters for the Final Population PK Model

Parameters[a]	Estimates	BSV[b] (Shrinkage %)
F1	0.562	1.09 (46.7%)
Ka1 (h^{-1})	0.425	134% (45.0%)
Ka2 (h^{-1})	0.507	N/A
Lag2 (h)	3.74	N/A
CL/F (L/h)[c]		
CL/F$_0$	471 (LC-FAOD subjects)	60.1% (26.7%)
	584 (healthy subjects)	
Expo_CL	1.07	N/A
MAX	0.450	N/A
T50	86.7	N/A
V/F (L)[d]		
V/F$_0$	5.56	N/A
Expo_V	1.13	N/A
Log-additive error	0.764	N/A

BSV, between-subject variability; F1, fraction of absorbed dose in absorption compartment #1; Ka1, first-order rate constant of absorption in absorption compartment #1; Ka2, first-order rate constant of absorption in absorption compartment #2; Lag2, lag time of absorption of compartment #2; CL/F, oral-dose apparent clearance; LC-FAOD, long-chain fatty acid oxidation disorders; nF1, individual random effect of F1; tvF1, typical value of F1; V/F, oral-dose apparent volume of distribution. The typical parameter values are presented for a subject of 58 kg, which is the median WT of the overall PK population; Expo_CL, allometric exponent of CL/F; Expo_V, allometric exponent of V/F; N/A, not applicable.
[a] Conversion from one mole of triheptanoin into three moles of heptanoate was considered to derive CL/F and V/F.
[b] Variability of F1 represents variance with F1 = exp(tvF1 + nF)/(1 + exp(tvF1 + nF)) and for other parameters BSV was derived with %BSV = $\sqrt{\exp(w^2) - 1} \times 100\%$.
[c] CL/F = CL/F$_0$ × (WT/58)$^{Expo\_CL}$ × (1 − MAX × TIME/[T50 + TIME]), where MAX is maximum effect, T50 is time to reach 50% of maximum effect, TIME is time in hours, and WT is time-varying actual body weight (kg) at dosing.
[d] V/F = V/F$_0$ × (WT/58)$^{Expo\_V}$.

a common mechanism for enterohepatic recirculation. Thus, there is no supportive mechanistic basis to apply the enterohepatic recirculation model.

The estimated typical CL/F of heptanoate is 544 L/h in heathy subjects, which exceeds a typical blood flow rate in the human liver (∼90 L/h).[24] This result suggests that an extrahepatic metabolism plays a significant role in the overall metabolic elimination of heptanoate. This result is consistent with the proposed major elimination pathway via beta-oxidation occurring in most tissues and organs containing mitochondria.[10,11] The estimated CL/F in patients with LC-FAOD is ∼19% lower than that in healthy subjects, but the difference appears to be minor considering the observed BSV and clinically insignificant. The model-estimated elimination T$_{1/2}$ in patients with LC-FAOD was ∼1.7 hours, supporting the proposed dosing frequency (four times or more per day).

Further model-based evaluations indicate that age, race, and sex do not lead to clinically meaningful changes in the exposure of heptanoate based on the results that the point estimates of AUCday were within the 80%–125% range. These results suggest that dose adjustment is not necessary for these intrinsic factors. The incorporation of body weight into the CL/F and V/F via allometric scaling adequately described the PK data across a wide range of age groups in adult and pediatric subjects with LC-FAOD (ie, 0.870–17.9 years old and 19.2–62.1 years old in pediatric and adult subjects, respectively). At the same body weight-adjusted dose level, the exposure of heptanoate in pediatric patients is expected to be similar to that in adults. This simulation result was consistent with the observed PK data reported previously.[11] Once body weight was allometrically scaled with CL/F and V/F, body mass index did not affect these parameters. These results suggest that the tissue distribution and further metabolism of heptanoate may not be affected by the weight status. Overall PK results support the consistent clinical outcomes observed in patient studies.[25,26]

In conclusion, the PK characteristics of heptanoate in healthy subjects and patients with LC-FAOD were adequately described by a one-compartmental, linear-elimination model with dual first-order absorption and a lag time for the second absorption compartment. Age, race, and sex do not lead to clinically meaningful changes in the exposure of heptanoate, suggesting that dose adjustment is not necessary for these intrinsic factors.

Conflicts of Interest

Sun Ku Lee, Kathleen McKeever, and Wendy Putnam are employees and shareholders of Ultragenyx Pharmaceutical Inc. Nathalie H Gosselin and Claudia Jomphe are employees of Certara Strategic Consulting.

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