Evaluation of OM3-PL/FFA Pharmacokinetics After Single and Multiple Oral Doses in Healthy Volunteers

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ABSTRACT

Purpose: The US Food and Drug Administration has approved several omega-3 (OM3)-containing prescription drugs for the treatment of severe hypertriglyceridemia (HTG). However, there is still a need to develop formulations with high bioavailability irrespective of the fat content and time of the meal. OM3-phospholipid (PL)/free fatty acid (FFA) is an investigational drug for the treatment of severe HTG containing naturally derived krill oil mixture of OM3, mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as PL esters and as FFA. Both forms in OM3-PL/FFA are believed to be readily bioavailable. Per gram, OM3-PL/FFA contains a lower dose of EPA/DHA in comparison with already approved prescription drugs. The study aim was to evaluate OM3-PL/FFA pharmacokinetic (PK) properties after single and multiple oral doses of 1, 2, and 4 g in healthy subjects when receiving a Therapeutic Lifestyle Change (TLC) diet. The dose proportionality of the study drug, the effect of a high-fat (HF) meal on its PK properties and its safety profile after multiple administration were also explored.

Methods: In this Phase I, open-label, randomized, multiple-dose, single-center, parallel-design study, 42 healthy volunteers following a TLC diet were randomly assigned into 1 of 3 treatment groups in a 1:1:1 ratio to receive a single dose at day 1, followed by multiple oral doses of 1, 2, and 4 g/d for 14 days. At day 15, all subjects received a HF breakfast.

Findings: After once-daily dosing, based on graphic assessment, OM3-PL/FFA levels reached steady state within 7−10 days. Exposure of total EPA + DHA, total DHA, and total EPA (C_{max} and AUC) appeared to be approximately proportional over the 1−4 g/d dose range. After 14 days of repeated daily dosing, accumulation was observed and was greater at the higher dose of the study product. When administered after a HF breakfast on day 15, median t_{max}, the geometric mean of AUC_{0-24} and C_{max} were comparable with the values on day 14 across the 3 dose levels.

Implications: OM3-PL/FFA was found to be well tolerated in healthy subjects. The study drug PK properties appeared to be approximately dose proportional over the 1−4 g/d dose range. The bioavailability of OM3-PL/FFA did not appear to be meaningfully affected by the fat content of the meal consumed before dose administration. This is clinically relevant because a low-fat diet is part of the management of patients with HTG. (*Clin Ther.* 2019;41:2500−2516) © 2019 Acasti Pharma Inc. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: docosahexaenoic acid, eicosapentaenoic acid, food effect, OM3 phospholipids, pharmacokinetics single and multiple doses.

INTRODUCTION

Severe hypertriglyceridemia (HTG) is associated with increased risk of acute pancreatitis, a condition with high morbidity and potential mortality.[1−3] It is estimated that ~4 million people aged 20 years and older in the United States have severe HTG (triglyceride concentration [TG] ≥ 500 mg/dL).[2,4−6]

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Several omega-3 (OM3) formulations naturally concentrated or purified from fish oil have been approved by the US Food and Drug Administration (FDA) for the treatment of severe HTG. These formulations provide eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) in either ethly ester (EE) or free fatty acid (FFA) forms. However, there still remains a need to develop formulations with high bioavailability irrespective of the fat content and time of the meal.[7]

CaPre* (NKPL66) is a prescription drug that contains naturally derived krill oil mixture of polyunsaturated fatty acids, primarily composed of OM3 fatty acids, mainly EPA and DHA, that are present in 2 chemical forms, as phospholipid (PL) esters and as FFA. This investigational drug product is being developed as a 1-g hard capsule formulation for oral administration as an adjunctive therapy to reduce TG in adult patients with severe HTG. Each 1-g capsule of this mixture contains ~310 mg of total EPA + DHA (190 mg of EPA and 120 mg of DHA, expressed as FFA).

A single-dose, comparative bioavailability study of OM3-PL/FFA to an EE formulation (Lovaza†) in the fasting and fed states has found that the 2 forms of OM3 (FFA and conjugated to PL) are less affected by the fat content of a meal than the EPA and DHA EEs. In the fasted state, OM3-PL/FFA found greater bioavailability than OM3-EE.[8] Formulations of OM3 with high bioavailability in the low-fat (LF) fed state or fasted state are advantageous because these patients are advised to follow a fat-restricted diet.[7]

Because HTG is a chronic disease, the multiple-dose administration is more representative of the test product regimen, and it is important to describe the pharmacokinetic (PK) properties of EPA and DHA from OM3-PL/FFA in these administration conditions.

The main objective of this study was to evaluate the PK properties of OM3-PL/FFA after single and multiple oral doses of 1, 2, and 4 g/d in healthy subjects when receiving a Therapeutic Lifestyle Change (TLC) diet. Secondary objectives included exploring the dose proportionality of the study drug and the effect of a high-fat (HF) meal on the PK properties of OM3-PL/FFA. The assessment of the safety profile of the study drug after multiple-dose administration was also explored. The tolerability and efficacy of OM3-PL/FFA in the treatment of severe HTG is currently being investigated in 2 Phase III studies (clinicaltrials.gov identifiers: NCT03 398005 and NCT03361501).

SUBJECTS AND METHODS

Study Design and Conduct

This study was a Phase I, open-label, randomized, multiple-dose, single-center, parallel-design study that evaluated the PK properties of OM3-PL/FFA after single and multiple daily doses of 1, 2, and 4 g/d in healthy subjects after a TLC diet. This study was conducted in accordance with Good Clinical Practice, Good Manufacturing Practice; Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95), and International Conference on Harmonization (ICH) guidelines, current views of the Declaration of Helsinki, and in accordance with local regulations. The final clinical study protocol and informed consent form were reviewed and approved by MidLands Institutional Review Board before the initiation of the study. The study population consisted of healthy subjects, so that the outcome of the study would not be influenced by any disease process or concomitant medications. Both male and non-pregnant female subjects were enrolled to represent the target population while ensuring that embryo–fetal exposure to the study drug was avoided. Forty-two healthy male and non-pregnant female subjects who were at least 18 years of age were randomly assigned into 1 of 3 treatment groups in a 1:1:1 ratio. The study drug was administered orally, once daily for 15 sequential days with 240 mL of water, 30 min from the start of breakfast, and the breakfast was eaten in $\leq$30 min.[9] The treatment groups were as follows: (1) one 1-g capsule of OM3-PL/FFA, (2) two 1-g capsules of the study drug, or (3) four 1-g capsules of OM3-PL/FFA. At least 4 female subjects were enrolled into each of the groups.

Informed consent was obtained before screening evaluations, which occurred during the 28-day screening period (day −35 to −7). The study duration for each subject was 20 days, which included a 2-day

* Trademark: CaPre (Acasti Pharma, Laval, QC, Canada).

† Trademark: Lovaza (GlaxoSmithKline, Research Triangle Park, North Carolina).

pre-randomization period (day –2 through day –1), a 17-day treatment period, and a 1-day follow-up. In addition to the pre-randomization days through day 2, all subjects were confined to the clinic on days 13–17. On other study days, procedures were performed on an outpatient basis.

Five days before the admission to the clinic (day –7), all subjects were asked to start a TLC diet and were provided with directions (diet and lifestyle), a diary, and lists of recommended foods and foods that should be avoided. The TLC diet to be followed was low in saturated fat, *trans* fat, and cholesterol, with a recommendation that 25%–30% of total daily calories come from fat and consumption of a daily breakfast that contained <10% fat (TLC breakfast). Subjects received a standardized TLC diet during clinic confinement periods (day –2 through day 2 and days 13 through 17) except on day 15 during which an FDA HF breakfast and standard (non-TLC) meals were provided. Subjects also received a standardized TLC breakfast on days 5, 8, and 11 during outpatient visits. Subjects had to document general compliance with the dietary instructions. No other attempt was made on standardizing any of the meals before clinic admission or during outpatient periods. Figure 1 illustrates the study design.

Study Subjects Inclusion/Exclusion Criteria

Healthy, nonsmoking, men and non-pregnant women of at least 18 years of age with a minimum weight of 50 kg, having a body mass index >18.0 kg/m^2 were enrolled in the study. Subjects who were willing to use an acceptable, effective method of contraception (and to refrain from donating sperm or fathering a child during the study), capable of understanding and complying with the requirements of the study, and giving consent were included in the study. The good health inclusion criteria were determined based on medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests. Furthermore, all subjects were required to abstain from alcohol (48 h before check-in on day –2), caffeine, or methylxanthine intake (48 h before check-in until after the last PK sample was collected before discharge). Participants also agreed not to consume foods fortified (ie, grains, dairy, or juice products) or rich in OM3 FAs (ie, seafood, fish, flaxseed, and walnuts) and OM3 supplements within 14 days of random assignment until after the follow-up visit.

Major exclusion criteria included known history or presence of clinically significant conditions, diseases, drugs, diet, hypersensitivity, or any other condition that would jeopardize the safety profile of the subject or affect the validity of the study. Subjects considering or having surgical procedures during the study or having a history/current alcohol and/or drug abuse, and an excessive caffeine intake were also excluded. The use of any prescribed or nonprescribed medication, including antacids, analgesics other than

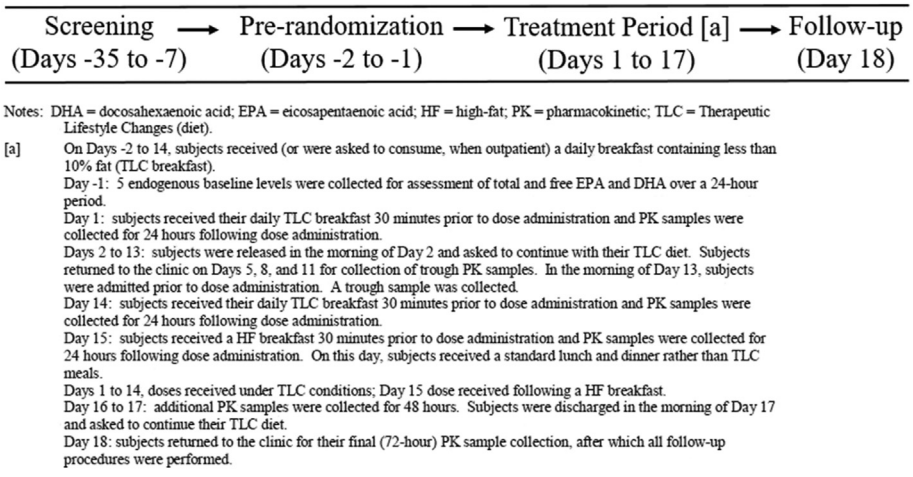

Figure 1. Study design.

paracetamol/acetaminophen, herbal remedies, having another new chemical entity (or participated in another clinical study) was restricted.

Selection and Timing of Dose for Each Subject

A once-daily 4-g and/or twice-daily 2-g regimen are marketed doses for other OM3 FA-containing products. In this study, a dose range of 1, 2, and 4 g once daily was explored to encompass the anticipated therapeutic dose range of the study drug in the treatment of different degrees of mild-to-severe HTG.

On day 1 and day 14, subjects were asked to fast a minimum of 10 h overnight before breakfast and continue to fast for at least 4 h thereafter. Subjects received their assigned dose 30 min from the start of a TLC breakfast that consisted of 14.9% protein, 1.9% of fat, and 83.2% of carbohydrates. On day 15, subjects received their assigned dose 30 min from the start of an FDA-defined HF breakfast (~50% of total caloric content of the meal comes from fat) which consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. They then continued to fast for at least 4 h thereafter.

Subjects also received OM3-PL/FFA in the clinic on day 2 (before release); days 5, 8, and 11 during their outpatient visit; and on day 13. Subjects were asked to consume their dose within ~30 min from start of the breakfast without additional fasting restrictions. On days 3, 4, 6, 7, 9, 10, and 12, subjects took their daily study drug dose at home. Subjects were asked to follow the TLC diet guidelines provided by the clinic and to consume their dose with ~240 mL of water, 30 min from the start of their breakfast.

Once each subject was randomly assigned to receive 1 of the 3 doses of OM3-PL/FFA, the dose variation was not allowed in case of occurrence of an adverse event (AE).

Treatment Compliance

For all doses administered in the clinic, treatment compliance was assured by supervised administration of the study drug by qualified study personnel under the direction of the principal investigator or representative. The dose, date, and time of administration of the study drug were all recorded in the appropriate sections of the electronic case report form.

The date and time of dose administration of all medication (including OM3-PL/FFA) that the subject took on outpatient days were recorded in the subject's study diary, and the information was transferred into the appropriate sections of the electronic case report form. A capsule count for each subject was performed at each visit.

Analysis Variables

PK Sample Collection and Bioanalysis

For the determination of concentrations of EPA and DHA total lipids and FFA in plasma, blood samples (~2 mL) were collected with an indwelling catheter that required 1 mL of waste before each blood draw. The sampling times was before dosing on days –1, 1, 2 (within 1 h of dose administration), 5, 8, 11, 13, and 14 to 15. For day –1, the samples were collected at –25, –23, –19, and –12 h before the schedule dose on day 1. For days 1, 14, and 15, blood samples were collected at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 24 h. The sample at 24 h was identified as the predose value on the next study day. For day 15, additional blood samples were also collected at 36, 48, and 72 h. Plasma was harvested in duplicate samples of ~0.5 mL to allow for a back-up sample.

Baseline-adjusted concentrations were calculated as the dose concentration after day 1 minus mean concentration before the first dose on day 1 (mean of 5 predose values) for EPA and DHA total lipids. If any of the predose values was missing, the baseline was calculated as the mean of the remaining predose concentrations.

Analysis of plasma for EPA and DHA total was performed by InVentiv Health Clinique (Quebec, QC, Canada). The concentrations of EPA and DHA total were determined from the plasma samples with the use of a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) analytical method. Total EPA and total DHA were extracted from a 0.040-mL aliquot of human EDTA K_3 plasma with the use of a protein precipitation, followed by basic hydrolysis and dilution, then 10 µL is injected into a LC-MS. The separation was performed on a Zorbax Extend C18 (50 × 4.6 mm, 3.5 µm) column. The mobile phase consisted of Milli-Q Type water/methanol with ammonium acetate and ammonium hydroxide. The Sciex Atmospheric Pressure Ionization Triple Quadruple (API 4000) LC-MS/MS system (Applied Biosystems/AB Sciex, Framingham, Massachusetts) was used to acquire and process data

with the use of the Analyst software package (AB Sciex; Version 1.6.1). The reference standards were either free or ethyl forms of EPA and DHA. For quality control sample preparation in human plasma, ethyl forms of EPA and DHA were used as reference standard to mimic actual study samples. The precursor ion and product ion for EPA were 301.100 Da and 257.100 Da, respectively. The precursor ion and product ion for DHA were 327.100 Da and 283.200 Da, respectively. The internal standards were EPA-d5 and DHA-d5. Quantitation is based on peak area ratio of analyte versus their stable labelled internal standards. A weighted ($1/C^2$) linear regression is performed to determine the concentration of the analyte. Because the high level of analytes naturally found in human samples cannot easily be removed by the usual charcoal stripping procedure, the calibration standards were prepared with 2% bovine serum albumin (BSA) in potassium-buffered saline (PBS) as surrogate matrix, and the quality control samples were prepared in both 2% BSA in PBS and human EDTA K_3 plasma.

The bioanalytical facility had validated the method for lower and upper limits of quantitation, linearity, recovery, reproducibility, specificity, accuracy, and stability. In addition, day-to-day performance of the methods was assessed by monitoring quality control samples and standard curve summaries and through incurred sample analysis. The coefficient of determination r^2 was $\geq$0.9951 and 0.9963 for total EPA and DHA, respectively. The calibration curve range was 2−100 μg/mL and 10−200 μg/mL for EPA and DHA, respectively. The between-run precision and accuracy for total EPA ranged from 3.17% to 8.61% and −5.09% to −0.75%, respectively, in 2% BSA in PBS and from 5.18% to 7.20% and −5.66% to −5.12%, respectively, in human EDTA K_3 plasma. The between-run precision and accuracy for total DHA ranged from 2.63% to 4.62% and −2.78% to −1.63%, respectively, in 2% BSA in PBS and from 4.45% to 6.68% and −6.21% to −4.89%, respectively, in human EDTA K_3 samples. The lower limit of quantitation was a signal-to-noise ratio at 2.03 μg/mL equal to 57 and a signal-to-noise ratio at 10.03 μg/mL equal to 141 for total EPA and DHA in 2% BSA in PBS, respectively. The recovery of total EPA in 2% BSA in PBS and in human EDTA K_3 plasma ranged from 83.37% to 85.28% and 72.81%−78.89%, respectively. The recovery of total DHA in 2% BSA in PBS and in human EDTA K_3 plasma ranged from 83.00% to 85.63% and 69.65%−78.79%, respectively.

All samples were analyzed within a time frame for which the stability of EPA and DHA in the samples had been validated and found to be acceptable.

PK Analysis

Concentrations for plasma observed and baseline-adjusted EPA and DHA total lipids and EPA + DHA total lipids were listed and summarized by study day, dose, and treatment group/scheduled time with the use of appropriate descriptive statistics (eg, number, arithmetic mean, SD, minimum, median, maximum, CV%, and geometric mean [GM]). Below the limit of quantitation concentrations were treated as zero for the computation of descriptive statistics. Concentrations assigned a value of missing were omitted from the calculation of descriptive statistics. For observed EPA and DHA total lipids, below the limit of quantitation concentrations were treated as zero for the computation of descriptive statistics, for the computation of the baseline-adjusted concentrations, and for the computation of EPA + DHA total lipids.

The total EPA + DHA total lipids concentrations were calculated by the following equation and expressed in μmol/L: [(EPA total lipids concentration/EPA MW) + (DHA total lipids concentration/DHA MW)] × 1000; where the molecular weights (MWs) for EPA and DHA were 302.451 and 328.48828, respectively.

All PK parameters and computations were derived with non-compartmental methods with Phoenix WinNonlin Version 6.3 (Pharsight, St. Louis, Missouri), or SAS Version 9.2 (SAS Institute, Inc, Cary, North Carolina). Graphics were prepared with SAS Version 9.2; SigmaPlot 12.5 (Systat Software, Inc, San Jose, California). The AUC_{0-24} was calculated by linear up/log down trapezoidal summation.

PK parameters for plasma baseline-adjusted EPA and DHA total lipids and baseline-adjusted EPA + DHA total lipids were listed and summarized by study day, dose, and treatment group with the use of appropriate descriptive statistics (eg, n, arithmetic mean, SD, minimum, median, maximum, GM, and

CV%). Arithmetic mean, SD, GM, and CV% were not calculated for t_{max}.

Primary PK variables included AUC_{0-24} and C_{max} for baseline-adjusted EPA and DHA total lipids and baseline-adjusted EPA + DHA total lipids. All other parameters were secondary variables.

Safety Variables and Analysis

Safety profile was monitored throughout the study, and results of vital signs, clinical laboratory evaluations, 12-lead ECGs, physical examinations, and AEs were analyzed. Clinical laboratory evaluations were conducted by the Physicians Reference Laboratory (Overland Park, Kansas). Serious AEs were collected from the time the subject signed the informed consent. AEs were collected from day −1 through the follow-up visit at day 18. AEs that had not resolved at the follow-up visit were followed until resolution or until medically stable. All safety assessment, including AEs, clinical laboratory evaluations, vital signs, 12-lead ECG results, and physical examinations, were listed and when appropriate summarized with descriptive statistics. No formal statistical hypothesis was performed for safety profile and tolerability.

Statistical Analysis

The PK analysis set included all subjects who receive at least 1 administration of CaPre* and have at least 1 scheduled after dose PK measurement without important protocol deviations, violations, or events thought to significantly affect the PK properties of the investigational product.

Effect of a Single HF Meal During Multiple Dosing on the PK of OM3-PL/FFA

For EPA total lipids, DHA total lipids, and EPA + DHA total lipids, the effect of a single HF meal during multiple dosing (HF on day 15 versus LF [TLC diet] on day 14 comparison) was assessed for each dose level separately with the use of a repeated-measures (ANOVA on the natural log transformed PK parameters (AUC_{0-24} and C_{max}) with fixed-repeated effect for day. For each OM3-PL/FFA dose level, the least-square (LS) means plus 95% CIs for each day and the difference between the days (day 15 [HF] – day 14 [LF]) plus 90% CIs were estimated. Transformed back from the logarithmic scale, GMs with corresponding 95% CIs for C_{max} and AUC_{0-24} were presented. Ratios of GMs (day 15/day 14 [HF/LF]) with corresponding 90% CIs were presented.

Assessment of Dose Proportionality of OM3-PL/FFA

For EPA total lipids, DHA total lipids, and EPA + DHA total lipids, dose proportionality of C_{max} and AUC_{0-24} on day 1, day 14, and day 15 were analyzed statistically with the use of a power model ($[C_{max}$ or $AUC_{0-24}] = \alpha \times dose^{\beta}$) for each of the primary PK parameters AUC_{0-24} and C_{max} (day 1, day 14, and day 15) on log scale as the dependent variable and the logarithm of the dose as the independent variable. The model parameters (slope and intercept) were estimated with LS regression. Point estimates and corresponding 2-sided 90% CIs for the slope parameter (β) and the intercept parameter (α) were provided. Dose proportionality for the 1−4 g/d dose range were assessed separately for treatment day 1, day 14, and day 15, based on whether a 90% CI constructed for the estimate of β lies within the interval (0.84, 1.16). This interval ensured that a doubling of dosage was associated with no more than a 20% deviation from doubling of exposure over the 4-fold dose range for this study. A minimum of 3 values per dose level must have been available for a given parameter to estimate dose proportionality with the power model.

Assessment of Steady State of OM3-PL/FFA

Achievement of steady state during the LF treatment period (day 1 through day 15 predose concentrations) was assessed graphically and evaluated statistically with the use of the linear mixed model ANOVA. For each dose level, a repeated-measures linear mixed model was fitted to all valid predose concentrations on the natural log scale with day as a fixed-repeated effect. From this model, contrasts were formed between the concentration mean at each study (early-day) day and the concentration means for all of the following study days (latter-day). These contrasts were statistically compared with zero at the 5% significance level, with the 1-sided alternative that the later-day mean was higher than the early-day mean. Assessment of the time to reach steady state from the statistical analysis was based on the earliest day at which a contrast was determined to be not statistically significant. For reporting of steady state comparisons, the contrasts were back-transformed to

the original scale, to yield the ratio of earlier-day mean concentration to later-day mean concentration. Similarly, the 90% CI for the ratio of means was calculated and reported with the *P* value of the contrast. The graphic assessment of steady state was considered as the primary assessment of steady sate.

RESULTS

Study Population

Subject demographic characteristics and disposition are shown in Table I.

A total of 42 healthy male and female subjects were randomly assigned into the appropriate groups

Table I. Subject demographic characteristics and disposition.

Demographic Characteristic	OM3-PL/FFA*			All Subjects (N = 42)
	1 g/d (N = 14)	2 g/d (N = 14)	4 g/d (N = 14)	
Sex, n (%)				
Male	5 (35.7)	5 (35.7)	6 (42.9)	16 (38.1)
Female	9 (64.3)	9 (64.3)	8 (57.1)	26 (61.9)
Race, n (%)				
White	8 (57.1)	5 (35.7)	11 (78.6)	24 (57.1)
Black or African American	6 (42.9)	9 (64.3)	3 (21.4)	18 (42.9)
Ethnicity, n (%)				
Not Hispanic or Latino	13 (92.9)	14 (100.0)	12 (85.7)	39 (92.9)
Hispanic or Latino	1 (7.1)	0 (0.0)	2 (14.3)	3 (7.1)
Age, y				
Mean [SD]	32 [12]	32 [12]	37 [21]	33 [15]
Median	26	28	28	28
Range	19–52	19–55	18–75	18–75
Height, cm				
Mean [SD]	171.9 [7.8]	166.8 [7.3]	170.9 [10.6]	169.9 [8.8]
Median	170.1	168.5	168.4	169.5
Range	154.2–183.2	150.9–177.0	156.5–193.8	150.9–193.8
Weight, kg				
Mean [SD]	70.7 [9.1]	70.9 [12.3]	75.1 [13.9]	72.2 [11.8]
Median	71.8	70.1	73.4	71.8
Range	54.3–84.6	50.1–92.9	52.7–101.9	50.1–101.9
BMI, kg/m^2				
Mean [SD]	23.96 [2.96]	25.36 [3.04]	25.55 [2.89]	24.96 [2.98]
Median	23.93	25.65	25.90	25.23
Range	18.18–29.97	19.48–29.65	20.87–29.40	18.18–29.97
Subject disposition, n (%)†				
Total screened	14	14	14	42
Total randomized	14	14	14	42
Completed study	14 (100.0)	14 (100.0)	14 (100.0)	42 (0.0)
Prematurely withdrawn	0 (0)	0 (0)	0 (0)	0 (0)

BMI = body mass index; FFA = free fatty acid; OM3 = omega-3; PL = phospholipid.
* OM3-PL/FFA was administered as 1-g capsule.
† Percentages for the reasons for discontinuation are based on the number of subjects who prematurely withdrew from the study. All other percentages are based on the number of subjects randomly assigned to treatment.

receiving the treatment. Of all the subjects enrolled, 16 subjects (38.1%) were men and 26 (61.9%) were women. The overall average age was 33 years, ranging between 18 and 75 years. More than one-half of the subjects were white/Caucasian (57.1%), followed by 42.9% black or African Americans. In terms of ethnicity, 92.9% were not Hispanic or Latino, with only 3 subjects of Hispanic or Latino descent. The overall mean weight across the 3 dose levels was 72.2 kg with an average body mass index of 24.96 kg/m^2, ranging between 18.18 and 29.97 kg/m^2. All subjects completed the study, and none of them were excluded from the safety profile, PK populations. No relevant medical history was reported for these subjects during the study.

Of the 42 enrolled subjects, 12 subjects (28.6%) received concomitant medications during the study treatment. Birth control was the most common medication received. Only 1 subject received medication for menorrhagia that was reported as an AE in the study.

PK Results of OM3-PL/FFA After Single and Multiple Doses

EPA + DHA Total Lipids After 14 Days of TLC Diet

The mean plasma concentration–time profiles for baseline-adjusted total EPA + DHA on day 1 and day 14 with LF breakfast is illustrated in Figure 2. A summary of key PK parameters for total EPA + DHA on day 1, day 14, and day 15 is presented in Table II. After single-dose administration, levels of mean total EPA + DHA slowly increased; the most pronounced increase in mean EPA + DHA total lipid concentrations was observed at times later than 4 h after the dose. Similarly, after multiple-dose administration, the most pronounced increase in mean EPA + DHA total lipid concentrations was observed at times later than 4 h after the dose. However, the overall fluctuation of mean concentrations over the 24-h dosing period was much less pronounced. After administration of single and multiple 1, 2, or 4 g/d doses of OM3-PL/FFA, median t_{max} values for total EPA + DHA ranged between 7.51 and 12 h, indicative of a slow absorption. The EPA + DHA systemic exposure (GM of AUC_{0-24} and C_{max}) tended to increase with ascending doses in an approximately proportional fashion over the 1–4 g/d doses on day 14. An increase with ascending doses on day 1 and day 14 was also observed for the mean baseline-adjusted plasma concentrations of total EPA + DHA (Figure 2). Accumulation of EPA + DHA total lipids was observed on day 14, after 14 days of once-daily dosing. The comparison of PK parameters AUC_{0-24} and C_{max} for total EPA + DHA found an accumulation for which the extent appeared to depend on dose because it was greater at the higher dose. The mean accumulation ratio ranged from 2.6-fold at 1 g/d to 4.26-fold at 4 g/d for AUC_{0-24} and 1.84-fold at 1 g/d to 2.82-fold at 4 g/d for C_{max}. Finally, graphic assessment found that steady state for total EPA + DHA appeared to be reached within 7 days of dosing (Figure 3). The statistical assessment found that steady state for total EPA + DHA was reached within 2–11 days of dosing (data not shown).

EPA Total Lipids After 14 Days of TLC Diet

A summary of key PK parameters for total EPA on day 1, day 14, and day 15 is presented in Table III.

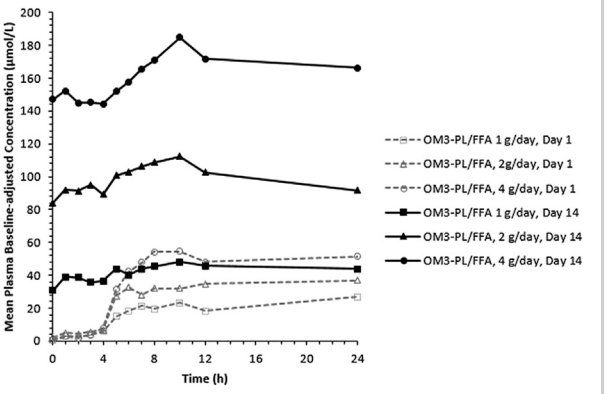

Figure 2. Mean baseline-adjusted total eicosapentaenoic acid (EPA) + docosa hexaenoic acid (DHA) concentration time profiles for all treatments (n = 14) after omega-3 phospholipid/free fatty acid (OM3-PL/FFA) on day 1 and day 14 with low-fat breakfast. All treatments were given orally for 15 days. Day 1–14: Therapeutic Lifestyle Change diet; Day 15: high-fat breakfast.

Table II. Summary of key pharmacokinetic parameters reflecting EPA + DHA total lipid exposure after administration of OM3-PL/FFA in healthy volunteers during 15 days.

Dose*	n	$AUC_{(0-24)}$ (μmol*h/L)		C_{max} (μmol/L)		t_{max}†, h	$t_{1/2}$, h
		GM	CV, %	GM	CV, %		
Day 1 (TLC diet)							
1 g	14	387	45.3	30.77	42.1	10.00	NA
2 g	14	644	30.8	44.43	28.9	12.00	NA
4 g	14	891	42.2	69.30	30.3	10.00	NA
Day 14 (TLC diet)							
1 g	14	914	42.7	52.05	34.5	7.51	NA
2 g	14	2250	22.8	118.65	24.7	8.00	NA
4 g	14	3540	41.3	182.46	37.1	10.00	NA
Day 15 (HF breakfast diet)							
1 g	14	1100	42.2	58.98	35.9	8.00	(30.4, 87.0)‡
2 g	14	2610	24.1	127.48	23.7	12.00	41.3§
4 g	14	3770	42.2	185.73	42.5	11.0	44.1‖
		Mean ARAUC		Mean ARC_{max}			
Day 14/day 1							
1 g	14	2.60		1.84		—	—
2 g	14	3.57		2.77		—	—
4 g	14	4.26		2.82		—	—

AR = accumulation ratio; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FFA, free fatty acid; GM, geometric mean; HF = high-fat; n = number of non-missing observations; NA = not applicable; OM3 = omega 3; PL = phospholipid; TLC = Therapeutic Lifestyle Change.

*Treatment A was oral OM3-PL/FFA at 1 g, once daily for 15 days (days 1–14: TLC diet; day 15: HF breakfast). Treatment B was oral OM3-PL/FFA at 2 g, once daily for 15 days (days 1–14: TLC diet; day 15: HF breakfast). Treatment C was oral OM3-PL/FFA at 4 g, once daily for 15 days (days 1–14: TLC diet; day 15: HF breakfast).

† t_{max} presented as median.

‡ n = 2 (minimum, maximum) are presented.

§ n = 6.

‖ n = 10.

Total EPA was slowly absorbed when administered as single and multiple 1, 2, or 4 g/d doses of OM3-PL/FFA after LF breakfast, with median t_{max} ranging from 8 to 12 h. GM (AUC_{0-24} and C_{max}) of total EPA increased with ascending doses on day 1 and day 14 in the 1–4 g/d OM3-PL/FFA oral dosage range. Total EPA accumulated after once-daily dosing with OM3-PL/FFA. The mean accumulation ratios ranged from 2.89 to 3.68 for AUC_{0-24} and 2.33 to 2.85 for C_{max}. After once-daily dosing, graphic assessment found that total EPA reached steady state within 4–7 days (data not shown). The statistical assessment revealed that the steady state for total EPA was reached within 5–8 days (data not shown).

DHA Total Lipids After 14 Days of TLC Diet

A summary of key PK parameters for total DHA on day 1, day 14, and day 15 is presented in Table IV.

Total DHA was slowly absorbed when administered as single and multiple 1, 2, or 4 g/d doses of OM3-PL/FFA after LF breakfast, with median t_{max} ranging from 7 to 12 h. GM (AUC_{0-24} and C_{max}) of total DHA increased with ascending doses on day 1 and day 14 in the 1–4 g/d OM3-PL/

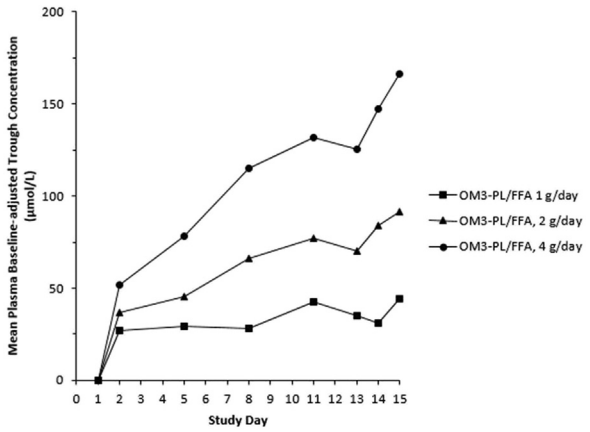

Figure 3. Mean baseline-adjusted total eicosapentaenoic acid (EPA) + docosa hexaenoic acid (DHA) trough plasma concentrations versus study days for all treatments (n = 14) on a linear scale. All treatments were given orally for 15 days. Day 1−14: Therapeutic Lifestyle Change diet; Day 15: high-fat breakfast. FFA = free fatty acid; OM3 = omega-3; PL = phospholipid.

FFA oral dosage range. Total DHA accumulated after once-daily dosing with OM3-PL/FFA. The extent of accumulation appeared to depend on dose, with greater accumulation at the higher dose. The mean accumulation ratios ranged from 2.36 (1 g/d) to 6.34 (4 g/d) for AUC_{0-24} and 1.54 (1 g/d) to 3.14 (4 g/d) for C_{max}. After once-daily dosing, based on graphic assessment, total DHA appeared to reach steady state within 10 days of dosing (data not shown). The statistical assessment revealed that the steady state for total DHA was reached within 2−11 days of dosing (data not shown).

Effect of a HF Meal on the PK of OM3-PL/FFA

At day 15, all subjects received a HF breakfast. The mean plasma concentration−time profiles for baseline-adjusted total EPA + DHA on day 1, day 14, and on day 14 and 15 are presented in Figures 2 and 4, respectively. A summary of key PK parameters for total EPA + DHA, total EPA, and total DHA on day 1, day 14, and day 15 is presented in Tables II−IV, respectively.

Figures 2 and 4 shows that overall mean baseline-adjusted plasma concentrations of EPA + DHA total lipids were generally similar between day 14 (TLC diet) and day 15 (HF breakfast). Similar findings were obtained for other baseline-adjusted analytes (EPA total lipids, DHA total lipids when evaluated separately). When administered after a HF breakfast on day 15, median t_{max} values of total EPA + DHA (range, 8−12 h), total EPA (range, 10−12 h), total DHA (range, 7−17 h) were similar to those on day 14 (TLC diet). The GM AUC_{0-24} and C_{max} values were also similar to the values on day 14 (TLC diet) across the 3 dose levels for total EPA + DHA, total EPA, and total DHA. As for day 14, total EPA + DHA, total EPA, and total DHA appeared to be slowly eliminated. However, at day 15, total EPA + DHA and total EPA $t_{1/2}$ appeared to be independent of dose (GM ranged between 41.3 and 44.1 and 32.6 and 37.5, respectively). For DHA, the $t_{1/2}$ could not be reliably estimated because the PK sampling was not sufficiently long to adequately characterize the $t_{1/2}$ in this study.

The statistical analysis of the effect of a single HF meal on key parameters of total EPA + DHA is summarized in Table V. Systemic exposure (C_{max} and AUC_{0-24}) of total EPA + DHA after 2 or 4 g/d multiple doses of OM3-PL/FFA was not affected by the fat content of the meal consumed before dose administration. This is because the 90% CIs for the ratio of GMs (day 15/day 14 [HF/LF] for C_{max} and AUC_{0-24} were completely within the 80%−125% boundaries.[9]

After multiple 1 g/d doses of OM3-PL/FFA, similarly C_{max} of total EPA + DHA was not affected by the fat content of the meal consumed before dose administration. For the comparison of total exposure AUC_{0-24} at the 1 g/d study drug dose level, treatment differences were slightly higher with a 90% CI between 109.87 and 131.02.

Statistical Assessment of Dose Proportionality

The statistical assessment of dose proportionality for total EPA + DHA is presented in Table VI.

After a single-dose administration, systemic exposure (C_{max} and AUC_{0-24}) of total EPA and total DHA increased in a less than dose proportional manner on day 1 over the 1−4 g/d dose range.

Table III. Summary of key pharmacokinetic parameters reflecting EPA total lipid exposure after administration of OM3-PL/FFA in healthy volunteers during 15 days.

Dose*	n	$AUC_{(0-24)}$ (μmol*h/L)		C_{max} (μmol/L)		t_{max}†, h	$t_{1/2}$, h	CV, %
		GM	CV, %	GM	CV, %			
Day 1 (TLC diet)								
1 g	14	75.7	51.2	4.80	46.7	10.00	NA	—
2 g	14	124	29.5	7.56	30.6	12.00	NA	—
4 g	14	193	40.4	13.36	30.3	10.00	NA	—
Day 14 (TLC diet)								
1 g	14	189	37.2	9.89	34.4	10.00	NA	—
2 g	14	409	21.6	20.91	21.8	8.00	NA	—
4 g	14	688	35.8	35.18	34.6	10.00	NA	—
Day 15 (HF breakfast diet)								
1 g	14	212	42.0	10.83	38.2	10.00	32.6‡	32.9
2 g	14	453	22.3	21.54	24.6	12.00	37.5‡	30.3
4 g	14	742	34.6	36.41	34.5	11.04	35.6‡	22.0
		Mean ARAUC		Mean ARC_{max}				
Day 14/day 1								
1 g	14	2.89		2.33		—	—	—
2 g	14	3.40		2.85		—	—	—
4 g	14	3.68		2.72		—	—	—

AR = accumulation ratio; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FFA = free fatty acid; GM = geometric mean; HF = high-fat; n = number of non-missing observations; NA = not applicable; OM3 = omega-3; PL = phospholipid; TLC = Therapeutic Lifestyle Change.

*Treatment A was oral OM3-PL/FFA at 1 g, once daily for 15 days (days 1−14: TLC diet; day 15: HF breakfast). Treatment B was oral OM3-PL/FFA at 2 g, once daily for 15 days (days 1−14: TLC diet; day 15: HF breakfast). Treatment C was oral OM3-PL/FFA at 4 g, once daily for 15 days (days 1−14: TLC diet; day 15: HF breakfast).

† t_{max} presented as median.

‡ n = 12.

Considering the slow absorption of EPA and DHA, AUC_{0-24} may not be fully representative of total exposure and the uncharacterized terminal portion of the concentration profile may differ across dose levels.

Similarly, after multiple-dose administration, dose proportionality for total EPA + DHA could not be statistically concluded because the 90% CI for slope estimate did not lie within the predefined CI of (0.84−1.16) on day 14 and day 15. However, the CIs included 1 and the slope estimates indicated that total EPA + DHA exposure increased approximately proportional over the 1−4 g/d dose range on days 14 and 15. Similar results were obtained for total EPA and total DHA when evaluated separately.

Safety Profile and Tolerability

No deaths or serious AEs and no AEs leading to discontinuation were reported. Table VII shows an overview of all reported AEs (all causalities) during the study. The most frequently reported AE was headache (9.5%); 3 subjects in the dose levels of 1 g/d OM3-PL/FFA and 1 subject in the dose level of 4 g/d of study drug. All treatment-emergent AEs were mild in intensity. Three subjects (7.1%) reported treatment-related AEs in the study. Treatment-related AEs, as assessed by the principal pnvestigator, were headache (OM3-PL/FFA 1 g/d, n = 1), eructation (OM3-PL/FFA 2 g/d, n = 1), and increased alanine aminotransferase (ALT) (OM3-PL/FFA 4 g/d, n = 1)

Table IV. Summary of key pharmacokinetic parameters reflecting DHA total lipid exposure after administration of OM3-PL/FFA in healthy volunteers during 15 days.

Dose*	n	$AUC_{(0-24)}$ (μmol*h/L)		C_{max} (μmol/L)		t_{max}†, h	$t_{1/2}$, h
		GM	CV, %	GM	CV, %		
Day 1 (TLC diet)							
1 g	14	46.7	48.0	5.06	38.4	9.00	NA
2 g	14	73.4	50.6	7.06	32.7	12.00	NA
4 g	14	81.1	52.3	8.53	39.7	9.00	NA
Day 14 (TLC diet)							
1 g	14	73.9	73.2	6.22	54.1	7.00	NA
2 g	14	284	33.2	17.01	33.8	8.13	NA
4 g	14	346	52.1	21.48	45.2	7.00	NA
Day 15 (HF breakfast diet)							
1 g	14	114	66.1	8.26	44.9	4.00	ND‡
2 g	14	354	34.8	19.31	29.3	7.00	ND‡
4 g	14	380	54.4	22.41	49.2	17.00	ND‡
		Mean ARAUC		Mean ARC_{max}			
Day 14/day 1							
1 g	14	2.36		1.54		—	—
2 g	14	4.16		2.58		—	—
4 g	14	6.34		3.14		—	—

AR = accumulation ratio; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FFA = free fatty acid; GM = geometric mean; HF = high-fat; n = number of non-missing observations; NA = not applicable; ND = not done; OM3 = omega-3; PL = phospholipid; TLC = Therapeutic Lifestyle Change.

*Treatment A was oral OM3-PL/FFA at 1 g, once daily for 15 days (days 1−14: TLC diet; day 15: HF breakfast). Treatment B was oral OM3-PL/FFA at 2 g, once daily for 15 days (days 1−14: TLC diet; day 15: HF breakfast). Treatment C was oral OM3-PL/FFA at 4 g, once daily for 15 days (days 1−14: TLC diet; day 15: HF breakfast).

† t_{max} presented as median.

‡ $t_{1/2}$ was not calculated because the terminal phase of the concentration−time profile could not be determined in any subjects.

which were reported as of mild intensity. Only the increased ALT remained ongoing at the end of the study, the other 2 treatment-related AEs were resolved. There were no clinically significant anomalies observed in the vital signs and EGC readings. No other safety concerns were identified during the study.

DISCUSSION

The main objective of this study was to evaluate the PK parameters of OM3-PL/FFA after single and multiple doses of 1, 2, and 4 g/d in healthy subjects after a TLC diet. The study also aimed to explore the dose proportionality of the study drug, the effect of a HF meal on its PK parameters, and its tolerability after multiple-dose administration.

When administered after a LF meal, OM3-PL/FFA indicated a slow rate of absorption (t_{max} values for total EPA + DHA ranged from 7.51 to 12 h). After once-daily dosing, the study drug appeared to be approximately dose proportional over the 1−4 g/d dose range. The steady state was reached within 7−10 days of dosing. The extent of accumulation of OM3-PL/FFA at steady state was observed after 14 days of once-daily dosing and appeared to depend on dose. This is thought to be mainly because of the apparent nonlinear PK parameters of DHA after single-dose administration but not at steady state

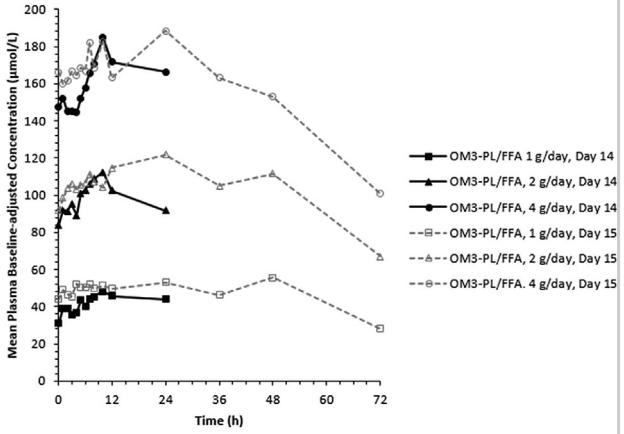

Figure 4. Mean baseline-adjusted total eicosapentaenoic acid (EPA) + docosa hexaenoic acid (DHA) concentration time profiles for all treatments (n = 14) after omega-3 phospholipid/free fatty acid (OM3-PL/FFA) on day 14 with low-fat breakfast and day 15 with high-fat breakfast. All treatments were given orally for 15 days. Day 1−14: Therapeutic Lifestyle Change diet; Day 15: high-fat breakfast.

after 14 days of multiple dosing. These findings suggests that the PK profile of OM3-PL/FFA is predictable, offering a possibility of titration without tolerability concerns because no saturation of absorption and elimination was observed with increasing doses. For OM3-EE, a dose-dependent increase in serum EPA was observed; however, the increase was found to be less pronounced and not dose dependent for serum DHA.[10] This disproportionate effect of DHA was not observed with OM3-PL/FFA.

In the Epanova Compared to Lovaza in a PK Single-Dose Evaluation study (Eclipse II), at steady state, after a 4 g once-daily dosing administration of Epanova‡ (OM3-FFA) and OM3-EE with a LF meal after 14 days, the total extent and peak exposure of the baseline-adjusted total EPA + DHA for OM3-EE (GM AUC_{0-24} = 3320; GM C_{max} = 206.7) were similar to those achieved by OM3-PL/FFA in the present study (GM AUC_{0-24} = 3540; GM C_{max} = 182.5) even though the total quantity of total EPA + DHA administered was ~2.5-fold lower (1240 mg for OM3-PL/FFA versus 3060 mg for OM3-EE).[11] In addition, the total extent and peak exposure of total EPA + DHA (GM AUC_{0-24} = 2250; GM C_{max} = 118.7) for OM3-PL/FFA at the 2-g dose was 68% and 57%, respectively, that of OM3-EE (GM AUC_{0-24} = 3320; GM C_{max} = 206.7) at 4 g/d.[11] This is indicative that the 2 forms of OM3 in the study product (FFAs and PL esters) are more readily bioavailable than the OM3-EE form. These findings could be explained because PL esters of OM3 have micelle-forming ability and emulsification properties that facilitate the access and binding of hydrolyzing enzymes and hence the digestion and absorption of lipids.[12] The positive impact of the pre-emulsification and micelle-forming capacity on the bioavailability of OM3-EE were evaluated in several studies.[13−16] OM3-EE with emulsification capacities and micelle-forming capacity found improved bioavailability in comparison with standard OM3-EE. However, FFA forms of OM3 do not require any digestive step nor any fat for absorption which improves their bioavailability.[7,11,17,18] The similar systemic exposure after multiple 4-g doses between the study drug and OM3-EE, a proven efficacious drug, suggests the attainment of therapeutic EPA + DHA blood levels with OM3-PL/FFA and supports the exploration of this dose in future clinical development.

However, in ECLIPSE II, at steady state, after a 4-g once-daily dosing administration with a LF meal, the total extent and peak exposure of the baseline-adjusted of total EPA + DHA for OM3-FFA (GM AUC_{0-24} = 19110; GM C_{max} = 1350) was 5-fold and 7-fold higher than OM3-PL/FFA (GM AUC_{0-24} = 3540; GM C_{max} = 182.5), respectively.[11] These results are expected because the OM3-FFA contains 2.5-fold higher dose of total EPA + DHA, 6-fold higher dose of OM3-FFA, and its bioavailability is not affected by the fat content of a meal like OM3-EE.[11] However, it should be noted that in the Epanova for Lowering Very High Triglycerides (EVOLVE) trial, OM3-FFA at 2, 3 and 4 g/d dosages reduced TG levels from baseline by a percentage

‡ Trademark: Epanova (AstraZeneca, London, United Kingdom).

Table V. Statistical assessment of effect of single HF meal on key pharmacokinetic parameters of total EPA + DHA.

Fat Content per Dose	n	Geometric LS Mean	95% CI	Comparison of HF/LF	
				Ratio, %	90% CI
1 g					
AUC_{0-24}, µmol*h/L					
LF (day 14)	14	914.4	(684.6−1221)		
HF (day 15)	14	1097	(827.7−1454)	119.98	(109.87−131.02)
C_{max}, µmoL/L					
LF (day 14)	14	52.045	(41.220−65.715)		
HF (day 15)	14	58.984	(46.766−74.393)	113.33	(106.89−120.16)
2 g					
AUC_{0-24}, µmol*h/L					
LF (day 14)	14	2246	(1963−2569)		
HF (day 15)	14	2614	(2277−3003)	116.41	(109.55−123.69)
C_{max}, µmoL/L					
LF (day 14)	14	118.645	(101.899−138.143)		
HF (day 15)	14	127.482	(110.947−146.482)	107.45	(100.96−114.36)
4 g					
AUC_{0-24}, µmol*h/L					
LF (day 14)	14	3540	(2734−4585)		
HF (day 15)	14	3774	(2875−4954)	106.60	(99.71−113.96)
C_{max}, µmol/L					
LF (day 14)	14	182.463	(145.689−228.519)		
HF (day 15)	14	185.735	(142.856−241.484)	101.79	(94.48−109.67)

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HF = high-fat; LF = low-fat (ie, Therapeutic Lifestyle Change diet); LS = least squares.

change of LS GM (95% CI) of 25.9% (−32.8% to −18.3%), 25.5% (−32.4% to −17.8%), and 30.9% (−37.3% to −23.7%), respectively. This suggests that there is no dose/response relationship between the exposure of EPA and DHA (2, 3, and 4 g/d) of OM3-FFA and the efficacy in lowering TG levels.[19] Therefore, a higher exposure does not necessarily imply a higher efficacy.

The bioavailability of the study drug did not appear to be meaningfully affected by the fat content of the meal consumed before dose administration. These results are consistent with a previous study in which OM3-PL/FFA was found to provide improved bioavailability of total EPA and DHA compared with an OM3-EE formulation under fasting and fed states after a 4 g/d single dose.[8] These results can be explained because the digestion and the absorption of the 2 forms of OM3 (OM3-PL and OM3-FFA) in the study drug is independent from the coingested fat.[7,11,12,17,18,20,21] The present study suggests preserved exposure and perhaps retained efficacy of OM3-PL/FFA after single and multiple administration irrespective of the meal's fat content.

Overall, OM3-PL/FFA was found to be well tolerated in healthy male and female subjects after multiple-dose administrations. All subjects completed the study, indicating that no AEs led to discontinuation from the study. Only 3 AEs were reported, and these were considered mild and possibly related to OM3-PL/FFA (ie, headache, eructation, increase in laboratory test ALT).

The principal limitations of this study must be considered. The design of PK parameters of OM3-PL/FFA did not include an OM3 comparator to evaluate

Table VI. Statistical assessment of dose proportionality for EPA + DHA total lipids.

Parameter	n	Slope			Intercept			Rsq
		Estimate	SE	90% CI	Estimate	SE	90% CI	
Day 1								
C_{max}, µmoL/L	42	0.59	0.09	(0.43−0.74)	3.41	0.08	(3.27−3.55)	0.50
$AUC_{(0-24)}$, µmol*h/L	42	0.60	0.11	(0.42−0.79)	5.99	0.10	(5.82−6.15)	0.43
Day 14								
C_{max}, µmoL/L	42	0.90	0.10	(0.74−1.07)	4.02	0.09	(3.87−4.17)	0.67
$AUC_{(0-24)}$, µmol*h/L	42	0.98	0.11	(0.78−1.17)	6.89	0.10	(6.72−7.06)	0.65
Day 15								
C_{max}, µmoL/L	42	0.83	0.10	(0.65−1.00)	4.14	0.09	(3.99−4.30)	0.61
$AUC_{(0-24)}$, µmol*h/L	42	0.89	0.12	(0.69−1.09)	7.08	0.10	(6.91−7.26)	0.59

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HF = high-fat; LF = low-fat; Rsq = coefficient of determination; SE = standard error.

Table VII. Summary of AEs and TEAEs by each treatment (all casualties − safety population) by preferred term.

Preferred Term	OM3-PL/FFA Treatment Group, n (%)			Total (N = 42)
	1 g/d (N = 14)	2 g/d (N = 14)	4 g/d (N = 14)	
Subjects with AEs	5 (35.7)	2 (14.3)	3 (21.4)	10 (23.8)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (7.1)*	1 (2.4)*
Catheter site pain	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Dizziness	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Dizziness postural	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Eructation	0 (0.0)	1 (7.1)*	0 (0.0)	1 (2.4)*
Feeling hot	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Headaches	3 (21.4)†	0 (0.0)	1 (7.1)	4 (9.5)†
Menorrhagia	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Musculoskeletal discomfort	0 (0.0)	1 (7.1)	0 (0.0)	1 (2.4)
Nausea	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Neck pain	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)
Ocular hyperaemia	1 (7.1)	0 (0.0)	0 (0.0)	1 (2.4)
Vessel puncture site bruise	1 (7.1)	0 (0.0)	0 (0.0)	1 (2.4)
Vomiting	0 (0.0)	0 (0.0)	1 (7.1)	1 (2.4)

AE = adverse event; FFA = free fatty acid; OM3 = omega-3; PL = phospholipid; TEAE = treatment-emergent adverse event.
* AE was considered as treatment related.
† One headache was considered as treatment-related.

how its bioavailability compares with other OM3 products in the same setting. However, this was performed in a different study in which a single 4-g dose of OM3-PL/FFA was found to provide improved bioavailability of total EPA and total DHA compared with a 4-g single dose of OM3-EE under fasting and fed states.[8] Although trials are similar in design, the researchers acknowledge limitations of

such cross-trial comparisons. In addition, because of the long half-life of EPA and DHA, AUC_{0-72} would have been a more appropriate parameter of total exposure than AUC_{0-24}. However, because the t_{max} for EPA and DHA is within 24 h across all doses, no major impact is expected on the findings of this study. Greater than 85% of subjects included in all treatments groups were Not Hispanic or Latino. Because ethnicity appears to influence the uptake of OM3 from the diet, the generalization of the results of the present study to other demographic characteristics may be limited.[22] The tolerability and efficacy of OM3-PL/FFA in Hispanic and Latino persons is currently being investigated in the Phase III study that is being performed in Mexico (clinicaltrials.gov identifiers: NCT03361501).

CONCLUSIONS

OM3-PL/FFA was found to be well tolerated in healthy subjects when administered as multiple oral doses of 1, 2, and 4 g/d. The study drug PK parameters appeared to be approximately dose proportional over the 1−4 g/d dose range. After 14 days of repeated daily dosing with OM3-PL/FFA, the steady state was reached within 7−10 days, whereas accumulation was observed and was greater at the higher dose of the study drug. The bioavailability of OM3-PL/FFA did not appear to be meaningfully affected by the fat content of the meal consumed before dose administration. The present study suggests preserved exposure and perhaps retained efficacy of OM3-PL/FFA after single and multiple administration irrespective of fat content of the meal. This is clinically relevant because a LF diet is part of the management of patients with HTG. The similar systemic exposure observed between the study drug and a proven efficacious drug supports future clinical development to assess efficacy.

DISCLOSURES

This research and its publication were sponsored by Acasti Pharma Inc. The sponsor was involved in the study design, interpretation of data, in the writing of the report, and in the decision to submit the article for publication. J.-F. Lapointe, S. Aziz and P. Lemieux are employed by Acasti Pharma Inc. L. Harvey is a former employee of Acasti Pharma Inc. R.A. Hegele reports grants and personal fees from Acasti, personal fees from Aegerion, personal fees from Amgen, personal fees from Gemphire, personal fees from Sanofi, grants from Regeneron, grants from Boston Heart Diagnostics, grants and personal fees from Akcea/Ionis, outside the submitted work. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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