2. SYNOPSIS

NAME OF SPONSOR/COMPANY Omthera Pharmaceuticals, Inc.	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT Epanova™		
NAME OF ACTIVE INGREDIENT Omefas (Omega-3 Free Fatty Acids)		

Title of Study: An Open-Label, 2-Cohort Study to Evaluate the 2-Way Interaction Between Multiple Doses of Epanova™ and a Single Dose of Rosuvastatin (Crestor®), to Assess the Dose Proportionality of Epanova™, and to Compare the Systemic Exposure of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) Following Multiple Doses of Epanova™ and Vascepa® in Healthy Normal Subjects

Investigator([redacted]

Study Centers(s): [redacted]

Publication (Reference): Not Applicable

Studied Period:
(date of first enrollment)
19 September 2013

(**date of last completed**)
12 November 2013

PHASE OF DEVELOPMENT: I

Objectives: The primary objective of this study was to determine the 2-way interaction between multiple oral doses of Epanova™ (omega-3 free fatty acids) and a single oral dose of rosuvastatin (Crestor®) administered after a low-fat meal.

The secondary objective of this study was to assess the dose-proportionality of baseline-adjusted total EPA, total DHA, and total EPA+DHA systemic exposure following multiple administrations of 2 different oral doses (2 g and 4 g) of Epanova™ administered after a low-fat meal.

The tertiary objective of this study was to compare the systemic exposure of baseline-adjusted (primary analysis) and unadjusted (secondary analysis) total EPA, total DHA, and total EPA+DHA following multiple oral doses of Epanova™ (2 g and 4 g once daily [QD]) and Vascepa® (2 g twice daily [BID]) administered after a low-fat meal.

The exploratory objective of this study was to evaluate the percentage changes in lipid parameters (triglycerides [TGs], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], non-high-density lipoprotein cholesterol [non-HDL-C], and apolipoprotein-CIII [apo-CIII]) from baseline following multiple oral doses of Epanova™ (2 g and 4 g QD) and Vascepa® (2 g BID) administered after a low-fat meal.

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Methodology: The study employed an open-label, 2-cohort design in healthy subjects, with 3 treatments in Cohort 1 (a single dose of Crestor® [Treatment A], multiple doses of Epanova™ [Treatment B], and a single dose of Crestor® with multiple doses of Epanova® [Treatment C]) and 1treatment in Cohort 2 (multiple doses of Vascepa® [Treatment D]).

Number of Subjects (Planned and Analyzed): A total of 112 subjects were planned, 114 subjects were enrolled in the study, and 109 subjects completed the study (56 subjects in Cohort 1 and 53 subjects in Cohort 2). Three (3) subjects (Subjects 9, 10, and 16) in Cohort 1 and 2 subjects (Subjects 81 and 83) in Cohort 2 did not complete the study. There were 59 subjects in Cohort 1 included in PK analysis for rosuvastatin, and 56 subjects were included in the analysis of unadjusted and baseline-adjusted plasma total EPA, total DHA, and total EPA+DHA. In Cohort 2, 54 subjects were included in the analysis of total EPA and total EPA+DHA on Day 10 and from 53 subjects on Day 20. One hundred nine (109) subjects from both cohorts were included in the PD analysis. All 114 subjects were included in safety analysis.

Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

Test Product, Dose, Duration, Mode of Administration, and Batch Number: There were 2 comparisons of interest in Cohort 1: (i) determination of the 2-way interaction between multiple oral doses of Epanova™ and a single oral dose of rosuvastatin administered after a low-fat meal, and (ii) to assess the dose-proportionality of baseline-adjusted total EPA, total DHA, and total EPA+DHA systemic exposure following multiple administrations of 2 different oral doses (2 g and 4 g) of Epanova™ administered after a low-fat meal.

In the first comparison, the test products were Crestor® 40 mg tablets ([redacted]) manufactured by IPR Pharmaceuticals, Inc. received from [redacted] and Epanova 1 g capsules (Lot No.: [redacted]) manufactured by Omthera Pharmaceuticals, Inc. and received from [redacted].

Subjects receiving Treatment A, received 40 mg rosuvastatin (Crestor®) administered as a single oral dose (1 x 40 mg tablet) with 240 mL of water, on Day 1. Subjects receiving Treatment C24 received 4 g of Epanova™ administered as multiple oral doses (4 x 1 g capsules) with 240 mL of water, on Days 14 to 26, and 40 mg rosuvastatin (Crestor®), administered as a single oral dose (1 x 40 mg tablet) with 240 mL of water, on Day 24.

The test treatment in the second comparison consisted of the administration of a 2 g oral dose (2 x 1 g capsules) of Epanova® with 240 mL of water at Hour 0 on Days 4 through 13, compared to the administration of 4 g oral dose (4 x 1 g capsules) of Epanova® with 240 mL of water at Hour 0 on Days 14 through 23 after a low-fat meal.

Duration of Treatment: The duration of the study was approximately 30 days for subjects in Cohort 1 and 24 days for subjects in Cohort 2 (excluding screening).

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Reference Product, Dose, Duration, Mode of Administration, and Batch Number: The reference treatment in Cohort 2 is Vascepa® 1 g capsules (Lot No.: [redacted]), manufactured by [redacted], and received from [redacted].

Subjects in Cohort 2 received 2 g of Vascepa® administered as multiple oral doses (2 x 1 g capsules) with 240 mL of water, every 12 hours, on Days 1 to 20.

Criteria for Evaluation:

Pharmacokinetics: The plasma rosuvastatin $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, C_{max}, t_{max}, $t_{½}$, and k_{el} PK parameters were calculated from individual concentration-time data (using actual blood draw times) using a standard noncompartmental approach.

The unadjusted and baseline-adjusted plasma total EPA, total DHA, and total EPA+DHA $AUC_{0\text{-}tau}$, $AUC_{0\text{-}24}$, $C_{max,ss}$, $C_{min,ss}$, C_{trough}, $t_{max,ss}$, $C_{avg,ss}$, %Flux, and Swing PK parameters were calculated from individual unadjusted and baseline-adjusted plasma concentration-time data (using actual blood draw times) using a standard noncompartmental approach.

Pharmacodynamics: Percent change from baseline in lipid parameters (TGs, HDL-C, LDL-C, non-HDL-C, and apo-CIII) after multiple doses of Epanova™ (2 g and 4 g QD) and Vascepa® (2 g BID) were summarized using descriptive statistics.

Safety: Safety was assessed by adverse events (AEs), vital signs, physical examinations, 12-lead electrocardiogram (ECG), and clinical laboratory tests.

Statistical Methods:
Pharmacokinetics and Pharmacodynamics:

Descriptive Statistics

The plasma concentration and serum lipid concentrations were tabulated and listed by sample time, treatment and study day and were summarized using descriptive statistics (arithmetic mean, standard deviation [SD], standard error of the mean [SEM], coefficient of variation [CV], sample size [N] minimum, maximum, and median).

PK data were tabulated by treatment and study day, and summarized using descriptive statistics (arithmetic mean, SD, SEM, CV, N, minimum, maximum, and median). In addition, geometric mean, geometric SD, and geometric CV were calculated for AUC and C_{max} parameters.

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Analyses of Variance and Covariance

Effect of Multiple Epanova™ Doses on Single-Dose Rosuvastatin:

The drug-drug interaction was assessed by analyzing the ln-transformed PK parameters AUC_{0-t}, AUC_{0-inf} and C_{max}, using mixed-effect analysis of variance (ANOVA) model. The comparison of interest is rosuvastatin and Epanova™ on Day 24 versus rosuvastatin alone on Day 1 (Treatment C24 versus Treatment A). No drug-drug interaction was to be claimed if the 90% confidence interval (CI) for the ratios of least-squares means (LSMs) of the ln-transformed PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} fell within 80% - 125%.

Effect of Single-Dose Rosuvastatin on the PK of Multiple Epanova™ Doses:

The drug-drug interaction was assessed by analyzing the ln-transformed PK parameters $C_{max,ss}$ and AUC_{0-tau} of baseline-adjusted (primary analysis) and unadjusted (secondary analysis) total EPA, total DHA, and total EPA+DHA values using a mixed-effect analysis of covariance (ANCOVA) model. The comparison of interest is rosuvastatin and Epanova™ on Day 24 versus Epanova™ alone on Day 23 (Treatment C24 versus Treatment C23). The lack of drug-drug interaction was claimed if the 90% CI for the ratios of LSMs of the ln-transformed PK parameters $C_{max,ss}$ and AUC_{0-tau} of baseline-adjusted values fell within 80% - 125%.

Epanova™ Versus Vascepa®:

The relative systemic exposure to total EPA and total EPA+DHA following multiple-dose administration of Epanova™ versus Vascepa® were assessed by analyzing the ln-transformed PK parameters $C_{max,ss}$, C_{avg}, AUC_{0-tau}, and AUC_{0-24} (AUC_{0-24} for Cohort 2 was calculated by multiplying AUC_{0-tau} x 2) of baseline-adjusted (primary analysis) and unadjusted (secondary analysis) values. Because for Cohort 1 and Cohort 2 each subject had serial concentrations (and consequently derived PK parameters) measured over 2 time intervals (Days 13 and 23 for Epanova™ and Days 10 and 20 for Vascepa®), 2 separate ANCOVA analyses were conducted where each analysis included treatment and group as fixed effects (group was removed if not significant) with the baseline analyte concentration as the value for the covariate. The comparisons of interest were: Epanova™ on Day 13 (Treatment B) versus Vascepa® on Day 10 (Treatment D10), and Epanova™ on Day 23 (Treatment C23) versus Vascepa® on Day 20 (Treatment D20).

Steady-State Analysis:

A steady-state analysis was performed using Helmert contrasts on the ln-transformed predose C_{trough} concentrations of total EPA, total DHA, and total EPA+DHA collected on Days 5 to 13 and Days 15 to 23 of Cohort 1 and Days 2 to 10 and Days 12 to 20 of Cohort 2. The steady-state analysis of Epanova™ and Vascepa® was done separately. Steady state was concluded at the time point where no more statistical differences (using $p > 0.05$) can be observed. Four (4) separate Helmert contrasts were conducted: Days 5 to 13 (Cohort 1), Days 15 to 23 (Cohort 1), Days 2 to 10 (Cohort 2, prior to the morning dose), and Days 12 to 20 (Cohort 2, prior to the morning dose).

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Epanova™ Dose Proportionality:
Dose proportionality was evaluated for baseline-adjusted total EPA, total DHA, and total EPA+DHA following multiple-dose administration of Epanova™ by analyzing the ln-transformed PK parameter $AUC_{0\text{-}tau}$. The results were derived using a mixed-effect ANCOVA model. The comparison of interest is Epanova™ on Day 13 (2 g QD) versus Epanova™ on Day 23 (4 g QD dose normalized to 2 g dose). Dose proportionality was concluded if the 90% CI for the ratio of the LSM of the dose-normalized and ln-transformed PK parameter $AUC_{0\text{-}tau}$ for baseline-adjusted total EPA, total DHA, and total EPA+DHA fall within 80% - 125%.

Lipid Analysis:
The percent changes from baseline in lipid parameters (TGs, HDL-C, LDL-C, non-HDL-C, and apo-CIII) following multiple oral doses of Epanova™ (2 g and 4 g QD, Cohort 1) and Vascepa® (2 g BID, Cohort 2) administered after a low-fat meal were evaluated. Repeated-measures ANCOVA with baseline lipid concentration as a covariate was conducted to compare treatments after 10 days (Day 14 for Epanova™ and Day 11 for Vascepa®) and 20 days (Day 24 for Epanova™ and Day 21 for Vascepa®) for TGs, HDL-C, LDL-C, and non-HDL-C. ANCOVA was also performed on apo-CIII which only had Day 24 measurement for Epanova™ and Day 21 for Vascepa®.

Safety: All clinical safety data were listed by subject. Continuous variables were summarized using N, mean, SD, median, minimum, and maximum. Frequency counts were reported for categorical data.

SUMMARY – CONCLUSIONS

[redacted]

	Geometric LS Means		
[redacted]			