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STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 205,060/SN-0000 (SDN 0)
Drug Name: Epanova (omega-3-carboxyl acids) Capsules
Indication(s): Treatment of severe hypertriglyceridemia
Applicant: Omthera Pharmaceuticals, Inc.
Date(s): Received 07/05/13; user fee (10 months) 05/05/14
Review Priority: Standard

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from the EVOLVE trial have demonstrated that Epanova, either 2 g, 3 g, or 4 g dose, were able to significantly reduce TG and non-HDL-C after 12 weeks of treatment when compared with olive oil (placebo) in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. Although not statistically significant, numerically greater mean percent increases in HDL from baseline after 12 weeks of treatment were also observed in all the Epanova dose groups when compared with the olive oil group. For the other efficacy variables such as TC and VLDL-C, all 3 doses of Epanova consistently exhibited greater mean percent reductions from baseline to end of treatment when compared with olive oil. However, Epanova had an unfavorable effect on LDL-C since the mean percent increases in LDL-C in the 3 dose groups were all greater than that in the olive oil group.

Although the 3 doses of Epanova were all effective in reducing TG and non-HDL-C, the dose-response was modest. In fact, the observed treatment effects from the 3 g dose on TG and non-HDL-C lowering were numerically slightly smaller than that from the 2 g dose. Therefore, whether to approve higher doses or not will need to take safety into consideration. In addition, as Figures 4 and 8 (in the main body of the review) depict, the TG and non-HDL-C levels in the Epanova groups seem to turn back up after Week 10. Evaluation of data after Week 12 may be important since the long-term treatment effect of Epanova on these parameters remains to be seen.

Labeling Comments: The sponsor presents the results of (b) (4)

I recommend removing these results from the proposed labeling. Similarly, results of (b) (4); therefore, they should not be presented in the labeling unless there is a clinical reason to. In addition, (b) (4) the proposed labeling presents median for baseline (b) (4). To be consistent with the previous fish oil labels, median is suggested for both baseline and percent change data, and Hodges-Lehmann estimate for treatment difference. The following table is recommended to replace the current Table 3 of the proposed labeling.

| Table 1. Median Baseline (BL) and Median Percent (%) Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥ 500 mg/dL) | | | | | | | | |
|---|------------------------|-------------|-----------------------|-------------|-------------------|-------------|----------------------------|----------------------------|
| Parameter | EPANOVA 2 g N = 100 | | EPANOVA 4 g N = 99 | | Placebo N = 99 | | EPANOVA 2 g vs. Placebo | EPANOVA 4 g vs. Placebo |
| | BL | % Change | BL | % Change | BL | % Change | Treatment Difference | |
| TG | 717 | -25 | 655 | -31 | 682 | -10 | -15 ** | -21 *** |
| Non-HDL-C | 205 | -8 | 225 | -8 | 215 | -1 | -7 * | -10 ** |
| VLDL-C | 123 | -25 | 126 | -35 | 125 | -11 | -14 | -21 |
| TC | 241 | -6 | 254 | -6 | 246 | -0 | -6 | -9 |
| HDL-C | 27 | +7 | 29 | +5 | 29 | +2 | +5 | +4 |
| LDL-C | 77 | +21 | 90 | +26 | 78 | +10 | +13 | +15 |

Placebo = Olive Oil
 Difference = Median of [EPANOVA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
 * for $p < 0.05$; ** for $p < 0.01$; *** for $p < 0.001$ for primary and secondary efficacy endpoints with multiplicity adjustment (p-value obtained from an ANCOVA model on rank-transformed data that included terms for treatment and use of lipid-altering drugs as factors and baseline as a covariate)

1.3 Brief Overview of Clinical Studies

Epanova is a lipid-altering agent containing a complex mixture of polyunsaturated free fatty acids derived from fish oils, including multiple long-chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids. The sponsor is submitting an original NDA seeking approval of Epanova (omega-3-carboxyl acids) capsules for treatment as an adjunct to diet to reduce TG (triglyceride), (b) (4)

_____ levels in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL). The efficacy of Epanova for the proposed indication is determined primarily based on the results from a Special Protocol Assessment (SPA) agreed (issued on 10/22/2010, under IND 107,616) Phase 3 study OM-EPA-003 (EVOLVE). Supportive efficacy is provided by the OM-EPA-004 (ESPRIT) trial where Epanova was studied as an adjunct to diet and statin therapy in high-risk patients with persistent high TG levels (≥ 200 and < 500 mg/dL). Since the target population and indication of interest in the ESPRIT trial are different from those in the EVOLVE trial, this review mainly evaluates the efficacy results from the EVOLVE trial.

The EVOLVE trial was a 12-week, randomized (1:1:1:1), double-blind, placebo-controlled, 4-parallel-group, multicenter (74), multinational (7) study. The three doses of Epanova investigated were 2 g, 3 g, and 4 g. The placebo was an olive oil. Randomization was stratified according to use of permitted lipid-altering drugs (yes or no). The primary efficacy endpoint was the percent change in TG levels from baseline (average of Weeks -2, -1, and 0)

to the end of treatment (average of Weeks 10 and 12). The secondary efficacy endpoints included the percent change from baseline (average of Weeks -2, -1, and 0) to end of treatment (average of Weeks 10 and 12) in serum non-HDL-C and HDL-C. The other lipid variables such as LDL-C, TC, and VLDL-C were tertiary efficacy endpoints.

A total of 399 subjects were randomized to receive olive oil (n = 99), Epanova 2 g (n = 100), Epanova 3 g (n = 101), and Epanova 4 g (n = 99). The overall dropout rate from the study was about 9%. The distributions for the demographic and baseline characteristics such as age, gender, race, ethnic, country, use of statin and/or cholesterol absorption inhibitor (CAI), and baseline TG, non-HDL-C, HDL-C, LDL-C, TC, and VLDL-C values in the randomized population were similar across the 4 treatment groups. The overall mean age at entry was 51 years. Approximately 23% of the randomized subjects were females. White constituted 92% of the population. Approximately 1/3 of the patients in each group used the lipid altering drugs (statin, CAI, or statin-CAI combination) at entry.

1.4 Statistical Issues and Findings

Table 18 in the main body of the review summarizes median baseline, median % change, and least-squares mean (LSM) % change at end of treatment for each study group. As one can see, the decreases in TG, non-HDL-C, TC, and VLDL-C in the olive oil group were all numerically much less than that in each of the 3 Epanova dose groups. Among the 3 Epanova dose groups, the decreases in these parameters were also numerically less in the 3 g dose group than in the 2 g and 4 g dose groups. The dose-response in TG lowering apparently was not in a linear fashion. In fact, the Jonckheere-Terpstra non-parametric test showed that there was no marked association between the percent change data of TG and Epanova doses (nominal two-sided $p = 0.20$). Note that the study was not powered for evaluation of dose-response and between-Epanova-group comparisons.

Nevertheless, as shown in Table 19 in the main body of the review, the percent reductions in TG and non-HDL-C in the 3 Epanova dose groups after 12 weeks of treatment were all statistically significantly greater than that in the olive oil group (all adjusted $p < 0.05$). The treatment differences in mean percent change between each of the Epanova 2 g, 3 g, and 4 g dose groups and olive oil were -21.7%, -21.2%, and -26.6%, respectively for TG, and -10.1%, -9.4%, and -12.2%, respectively, for non-HDL-C based on the natural-log-transformed data. No statistical inferential testing was performed for TC and VLDL-C according to the SAP. The olive oil-adjusted mean percent changes after 12 weeks of treatment were -8.6%, -8.0%, and -10.6% for TC, and -18.0%, -17.9%, and -24.5% for VLDL-C for the corresponding Epanova 2 g, 3 g, and 4 g dose groups. The Hodges-Lehmann median estimates showed similar response patterns in these parameters, but in a slightly less degree of reduction.

Both olive oil and Epanova increased HDL-C and LDL-C after 12-weeks of treatment. The increases in the 3 Epanova dose groups were all numerically greater than that in the olive oil group in either parameter. The treatment differences in mean percent change in HDL-C between each of the Epanova 2 g, 3 g, and 4 g dose groups and olive oil were 5.4%, 1.9%, and 3.8%, respectively, which were not statistically significant. The treatment differences in mean percent change in LDL-C between each of the Epanova 2 g, 3 g, and 4 g dose groups and olive oil were 16.2%, 11.2%, and 16.3%, respectively (no statistical inferential testing performed according to the SAP). As depicted in Figures 23 – 26 in the main body of the review, each of the 4 treatment groups showed that there was a negative correlation between the percent change data of LDL-C and TG; i.e., greater increases in LDL-C were associated with greater reductions in TG.

The percentages of patients with an improved response for TG, non-HDL-C, HDL-C, and LDL-C at end of treatment are shown in Table 20 in the main body of the review. Except for LDL-C, all the percentages were numerically higher in the Epanova groups than in the olive oil group. The percentages of Epanova-treated patients with an improved TG or non-HDL-C (% change < 0) were increased as the doses increased. However, the study was not designed to test for any significant dose-response based on a binary variable. Similar findings were also observed for percentage of patients achieving TG < 500 mg/dL at Week 12.

The missing data rates on the lipid endpoints (average of Weeks 10 and 12) evaluated in this review were 5%, 6%, 13%, and 7% in the olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. All the statistical analyses discussed above were based on the MITT population (i.e., consisting of all randomized subjects who had received at least one dose of investigational product and had at least one post-randomization efficacy assessment) with the LOCF for missing data. Sensitivity analyses using multiple imputation method and MMRM approach to assess the impact of missing data on the analysis results of TG, non-HDL-C, and HDL-C were performed by the sponsor and similar findings were observed (see Tables 6, 7, 9, 10, 12, and 13 in the main body of the review).

Treatment effects on mean percent change from baseline in TG at endpoint for the subgroups of patients defined as age < 65 years, males, White, country (USA or non-USA), baseline TG (< 750 mg/dL or \geq 750 mg/dL), and statin/CAI use (yes or no) were similar to the effects observed based on the overall population (see Table 17 in the main body of the review). Due to the small sample size, the point estimates of the treatment differences for the subgroups of patients defined as age \geq 65 years, females, and non-White were not close to the ones observed in the overall population. Nevertheless, there were no significant interactions of treatment-by-subgroup observed (all $p > 0.10$).

2. INTRODUCTION

2.1 Overview

Epanova is a lipid-altering agent containing a complex mixture of polyunsaturated free fatty acids derived from fish oils, including multiple long-chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids. The sponsor is submitting an original NDA seeking approval of Epanova (omega-3-carboxyl acids) capsules for treatment as an adjunct to diet to reduce TG (triglyceride), (b) (4)

levels in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL). The efficacy of Epanova for the proposed indication is determined primarily based on the results from a Special Protocol Assessment (SPA) agreed (issued on 10/22/2010, under IND 107,616) Phase 3 study OM-EPA-003 (EVOLVE). Supportive efficacy is provided by the OM-EPA-004 (ESPRIT) trial where Epanova was studied as an adjunct to diet and statin therapy in high-risk patients with persistent high TG levels (≥ 200 and < 500 mg/dL). Since the target population and indication of interest in the ESPRIT trial are different from those in the EVOLVE trial (see Table 1 for study highlights), this review mainly evaluates the efficacy results from the EVOLVE trial.

Table 1 – Study Highlights (sponsor’s table)

| Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|-------------------------|--|---|--|--------------------|--|-----------------------|
| <i>Study OM-EPA-003</i> | To evaluate the efficacy and safety of Epanova™ in severe hypertriglyceridemic subjects | Randomized, double blind, olive oil-controlled, parallel group design | Epanova™ 2g QD arm (n=100) Epanova™ 3g QD arm (101) Epanova™ 4g QD arm (n=99) Olive oil (placebo) QD arm (n=99) | 399 | M or F, age ≥ 18 years, with serum TG values at screening in the range ≥ 500 mg/dL and < 2000 mg/dL | 12 weeks |
| <i>Study OM-EPA-004</i> | To evaluate efficacy and safety of adding Epanova™ to statin therapy for lowering non-HDL cholesterol in subjects with persistent hypertriglyceridemia and high-risk for cardiovascular disease. | Randomized, double-blind, olive oil-controlled, parallel group design | Epanova™ 2g QD (n=215); Epanova™ 4g QD (n=216) Olive oil (placebo) QD arm (n=216) | 647 | Subjects at high risk for a future cardiovascular event (with high serum TG ≥ 200 and < 500 mg/dL despite being on a statin for at least 4 weeks prior to screening | 6 weeks |

Source: Table 5.2-1. in sponsor’s tabular-listing.pdf

Unless otherwise stated, all tables and graphs presented in this report were generated by this reviewer.

2.2 Data Sources

The clinical study reports and electronic data files are located in the sub-folders of EDR [\\CDSESUB1\evsprod\NDA205060\0000](#). In response to my request regarding how TG data were log-transformed and analyzed, the sponsor submitted the information to [\\CDSESUB1\evsprod\NDA205060\0023](#). In general, the quality of the electronic data sets and integrity of the study reports were satisfactory.

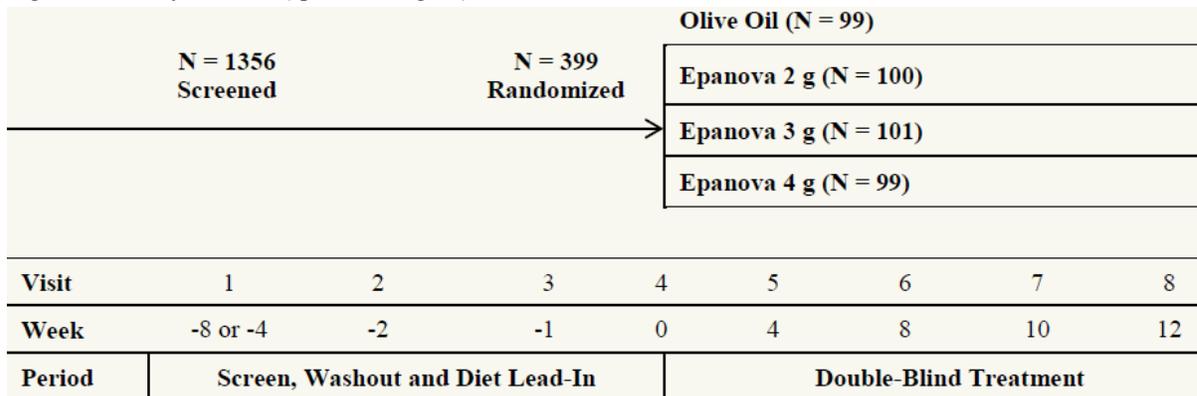
3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study OM-EPA-003 (04/2011 – 02/2012) was a Phase 3, 12-week, randomized, double-blind, olive oil (placebo)-controlled, 4-parallel-group, multicenter (69), multinational (7) trial conducted in adult patients with severe hypertriglyceridemia (TG ≥ 500 mg/dL). Subjects previously on omega-3 drugs/supplements needed to washout for 8 weeks and subjects who required adjustment or addition of a permitted statin, cholesterol absorption inhibitor (CAI), or statin-CAI combination needed to stabilize for 8 weeks before randomization. All other subjects had a washout/diet lead-in of 4 weeks before randomization. Subjects who met the entry criteria at Visit 4 (Week 0) were randomized in a 1:1:1:1 ratio to receive placebo (olive oil, 4 g/day), Epanova 2 g/day (plus 2 g/day placebo), Epanova 3 g/day (plus 1 g/day placebo), or Epanova 4 g/day. Randomization was stratified according to use of permitted lipid-altering drugs (yes or no). Each subject took 4 capsules at one time per day, without regard to meals, for 12 weeks. All subjects were required to follow the National Cholesterol Education Program (NCEP) Therapeutics Lifestyles Changes (TLC) diet throughout the trial. The study schema is shown in Figure 1 below.

Figure 1 – Study Schema (sponsor’s figure)



Source: Figure 9.1 in sponsor’s clinical study report

The primary objective of the study was to evaluate the efficacy and safety of Epanova in subjects with severe hypertriglyceridemia defined as serum TG values ≥ 500 and < 2000 mg/dL. The secondary objectives were to assess the effects of each dose of Epanova on fasting levels of non-HDL-C and HDL-C.

The primary efficacy endpoint was the percent change in TG levels from baseline (average of Weeks -2, -1, and 0) to the end of treatment (average of Weeks 10 and 12). The secondary efficacy endpoints included the percent change from baseline (average of Weeks -2, -1, and 0) to end of treatment (average of Weeks 10 and 12) in serum non-HDL-C and HDL-C. The other lipid, lipoprotein, and plasma fatty acids variables were all tertiary efficacy endpoints. The post-baseline lipid measurements were collected at Weeks 4, 8, 10, and 12. The post-baseline lipoprotein and plasma fatty acids measurements were collected at Week 12 only.

3.1.2 Statistical Methods

The primary, secondary, and tertiary continuous efficacy endpoints were analyzed using an ANCOVA model with treatment and use of lipid-altering drugs (yes or no) as factors and baseline as a covariate. According to the Statistical Analysis Plan (SAP), since the Shapiro-Wilk test conducted on the residuals was significant at the alpha level of 0.01 (i.e., non-normality observed), data were ranked prior to statistical inferential testing. Additionally, as stated in the sponsor's clinical study report (page 42), in order to facilitate clinical interpretation, data were log-transformed to obtain least-squares mean change from baseline.

Pairwise comparisons of each Epanova group to olive oil were performed using the Dunnett's procedure for the primary efficacy endpoint and the Hommel's procedure for the secondary efficacy endpoints to control the type 1 error rate. No multiplicity adjustment was planned for the tertiary endpoints; however, the sponsor used the Dunnett's procedure to adjust p-values for all the tertiary pairwise comparisons in their clinical study report.

The intent-to-treat (ITT) population comprised all randomized subjects. Efficacy analyses were performed on the modified ITT (MITT) population which consisted of all randomized subjects who had received at least one dose of investigational product and had at least one post-randomization efficacy assessment.

The LOCF technique was the primary method for missing data handling. The sponsor performed sensitivity analyses using a multiple imputation method and mixed model repeated measures (MMRM) approach to examine the robustness of the analysis results.

3.1.3 Subject Disposition

A total of 399 subjects were randomized to receive olive oil (n = 99), Epanova 2 g (n = 100), Epanova 3 g (n = 101), and Epanova 4 g (n = 99). Of the 399 randomized subjects, 364 (91%) completed the 12-week treatment phase. As shown in Table 2, the Epanova 3 g dose group had the highest withdrawal rate (14%), while the olive oil group had the lowest (5%). The most recorded reason for overall withdrawal was AE/SAE (4.3%). Specifically, there were 7% randomized subjects in the Epanova 3 g dose group and 5% in each of the Epanova 2 g and 4 g dose groups withdrawn due to AE/SAE while none in the olive oil group. As depicted in Figure 2, the proportions of subjects remaining on study treatment over time across the 4 study groups were similar. (Note that there was one placebo-treated withdrawn subject who was randomized in early July, 2011 but discontinued from the study treatment in late October, 2011, resulting in being on the study treatment for 114 days long.)

The ITT population included all the 399 randomized subjects. Of these, 6 did not have post-baseline lipid measurements (1, 1, 4, 0 subjects in the olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively). Therefore, they were excluded from the MITT population according to the SAP. In other words, the MITT population consisted of 393 subjects (98% of the ITT population).

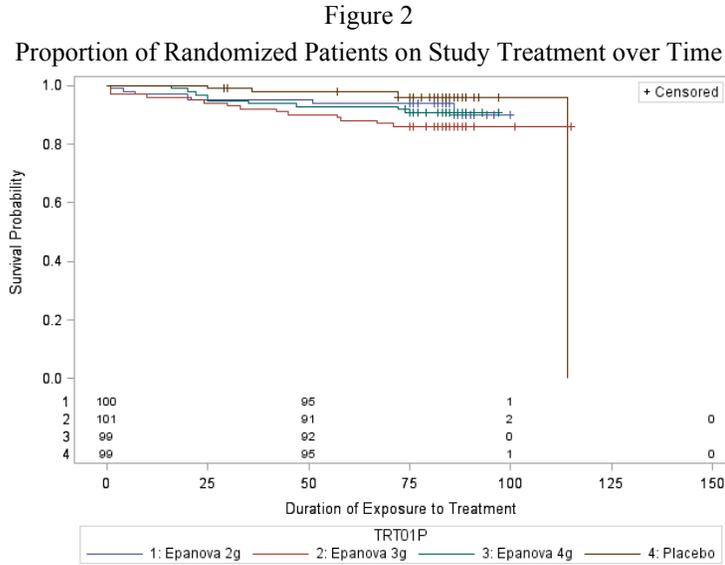
Table 2 – Subject Disposition (sponsor’s table)

| | Olive Oil N (%) | Epanova 2 g N (%) | Epanova 3 g N (%) | Epanova 4 g N (%) | Total N (%) | p-value ¹ |
|---|--------------------|-------------------------|-------------------------|-------------------------|----------------|----------------------|
| Total Randomized | | | | | 399 | |
| Completed Study | 94 (94.9%) | 93 (93.0%) | 87 (86.1%) | 90 (90.9%) | 364 (91.2%) | |
| Discontinued Study | 5 (5.1%) | 7 (7.0%) | 14 (13.9%) | 9 (9.1%) | 35 (8.8%) | 0.146 |
| Primary Reason for Discontinuation | | | | | | |
| AE or SAE | 0 (0.0%) | 5 (5.0%) | 7 (6.9%) | 5 (5.1%) | 17 (4.3%) | |
| Non-compliance | 0 (0.0%) | 0 (0.0%) | 2 (2.0%) | 1 (1.0%) | 3 (0.8%) | |
| Pregnancy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Withdrew Consent | 1 (1.0%) | 1 (1.0%) | 1 (1.0%) | 2 (2.0%) | 5 (1.3%) | |
| Lost to Follow-Up | 1 (1.0%) | 0 (0.0%) | 3 (3.0%) | 0 (0.0%) | 4 (1.0%) | |
| Other ² | 3 (3.0%) | 1 (1.0%) | 1 (1.0%) | 1 (1.0%) | 6 (1.5%) | |

¹p-value from Chi-Square Test.

²“Other” refers to withdrawal from an expected laboratory abnormality in subjects with dyslipidemia that did not result in an adverse event as defined in the protocol.

Source: Table 10.1.1 in sponsor’s clinical study report



3.1.4 Demographic and Baseline Characteristics

As shown in Table 3, the 4 treatment groups were similar with respect to the distributions of demographic and baseline characteristics such as age, gender, race, ethnicity, and use of lipid-altering drugs for the ITT population. The mean age at entry in each group was 51 to 53 years. However, the proportions of subjects aged ≥ 65 years were *imbalanced* among the 4 study groups (11%, 8%, 4%, and 16%, for the olive oil, Epanova 2 g, 3 g, and 4 g dose, respectively). Slightly less than 25% of the randomized subjects were females. White constituted about 92% of the ITT population. Approximately 1/3 of the patients in each group used lipid-altering drugs (statin, CAI, or statin-CAI combination) at entry. In addition, about 28% of the randomized subjects were from USA, 32% from Hungary, 15% from Russia, and 25% from Ukraine, Denmark, Netherland, and India all together.

The baseline TG, non-HDL-C, HDL-C, LDL-C, TC, and VLDL-C are shown in Tables 4, 8, 11, 14, 15, and 16, respectively, for the MITT population. They were all similar across the 4 treatment groups.

Table 3 – Demographic and Baseline Characteristics (extracted from sponsor’s table)

| Characteristic | Olive Oil (N = 99) | Epanova 2 g (N = 100) | Epanova 3 g (N = 101) | Epanova 4 g (N = 99) | Total (N = 399) |
|------------------------------------|-----------------------|-----------------------------|-----------------------------|----------------------------|--------------------|
| Gender, n (%) | | | | | |
| Male | 77 (77.8%) | 80 (80.0%) | 79 (78.2%) | 71 (71.7%) | 307 (76.9%) |
| Female | 22 (22.2%) | 20 (20.0%) | 22 (21.8%) | 28 (28.3%) | 92 (23.1%) |
| Age, years | | | | | |
| N | 99 | 100 | 101 | 99 | 399 |
| Mean (SD) | 50.8 (10.59) | 51.1 (9.79) | 51.2 (8.75) | 52.9 (10.92) | 51.5 (10.04) |
| Ethnicity, n (%) ² | | | | | |
| Hispanic/ Latino | 6 (6.1%) | 8 (8.0%) | 4 (4.0%) | 7 (7.1%) | 25 (6.3%) |
| Not Hispanic/ Latino | 93 (93.9%) | 92 (92.0%) | 97 (96.0%) | 92 (92.9%) | 374 (93.7%) |
| Race, n (%) ² | | | | | |
| White | 95 (96.0%) | 93 (93.0%) | 92 (91.1%) | 88 (88.9%) | 368 (92.2%) |
| Asian | 4 (4.0%) | 5 (5.0%) | 6 (5.9%) | 8 (8.1%) | 23 (5.8%) |
| Multiple | 0 (0.0%) | 1 (1.0%) | 2 (2.0%) | 1 (1.0%) | 4 (1.0%) |
| Black/African- American | 0 (0.0%) | 0 (0.0%) | 1 (1.0%) | 2 (2.0%) | 3 (0.8%) |
| American Indian /Alaskan Native | 0 (0.0%) | 1 (1.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Statin/CAI | | | | | |
| Users | 34 (34.3%) | 35 (35.0%) | 35 (34.7%) | 34 (34.3%) | 138 (34.6%) |
| Non-Users | 65 (65.7%) | 65 (65.0%) | 66 (65.3%) | 65 (65.7%) | 261 (65.4%) |

²Subjects may have reported more than one race or ethnicity.

Source: Extracted from Table 11.2.1 in sponsor’s clinical study report

3.1.5 Efficacy Results and Discussion

In general, I was able to verify the sponsor’s results. TG was the primary efficacy variable. Non-HDL-C and HDL-C were the secondary efficacy variables. LDL-C, TC, and VLDL-C were part of the tertiary variables. (b) (4) I then evaluated all of them in this review. Unless otherwise noted, the following results and discussions are based on my own analyses.

Primary Efficacy Variable – Triglyceride (TG). The observed means and medians of TG over time for the 4 treatment groups are shown in Figures 3 and 4 below, respectively. Figure 5 depicts the distributions of the change data at end of treatment for all the study groups.

After 12 weeks of double-blind treatment period, all the Epanova dose groups showed a statistically significantly greater mean percent decrease in TG from baseline when compared with the olive oil group (all adjusted $p < 0.05$ based on the sponsor’s rank ANCOVA or my rank ANCOVA on residuals). The olive oil-adjusted treatment differences were -21.7%, -21.2%, and -26.6% for the Epanova 2 g, 3 g, and 4 g dose groups,

respectively, based on the sponsor's natural-log-transformed data (Table 4). I also performed non-parametric test on the percent change data. The Hodges-Lehmann median estimates and the associated 95% CIs were -15.5% (-25.5%, -5.7%), -15.4% (-26.0%, -5.2%), and -20.8% (-31.2%, -11.1%) for the corresponding Epanova 2 g, 3 g, and 4 g dose relative to olive oil. As Figure 6 depicts, approximately 59%, 76%, 80%, and 83% of the olive oil, Epanova 2 g, 3 g, and 4 g treated patients, respectively, showed an improved TG (i.e., % change < 0) at the end of the 12-week treatment period.

Table 4 – Efficacy Results for TG (mg/dL) (extracted from sponsor's table)

| Triglycerides | Olive Oil (N=99) | Epanova | | |
|-------------------------------|---------------------|------------------|------------------|------------------|
| | | 2 g (N=100) | 3 g (N=101) | 4 g (N=99) |
| MITT Population | | | | |
| Baseline (mg/dL) [1] | | | | |
| N | 98 | 99 | 97 | 99 |
| Mean (SD) | 788.5 (305.11) | 790.1 (269.01) | 820.4 (353.15) | 783.6 (335.21) |
| Median | 682.3 | 717.0 | 728.0 | 655.0 |
| Min, Max | 417.7, 2006.5 | 415.3, 1577.8 | 438.7, 2157.7 | 435.3, 2094.7 |
| % Change from Baseline [2] | | | | |
| N | 98 | 95 | 94 | 95 |
| Mean (SD) | 9.5 (76.32) | -20.7 (32.37) | -15.5 (65.89) | -25.0 (34.72) |
| Median | -10.4 | -24.5 | -23.4 | -30.7 |
| Min, Max | -64.2, 424.7 | -88.5, 101.1 | -84.2, 520.1 | -78.4, 105.0 |
| LSM [3] | -4.26 | -25.94 | -25.46 | -30.86 |
| 95% CI | (-13.07, 5.44) | (-32.84, -18.33) | (-32.44, -17.75) | (-37.32, -23.74) |
| LSM Difference from Olive Oil | | -21.68 | -21.19 | -26.60 |
| 95% CI Bonferroni-corrected | | (-40.70, -2.89) | (-40.32, -2.29) | (-45.12, -8.38) |
| P-value [4] | | 0.005 [r] | 0.007 [r] | < 0.001 [r] |

[1] Baseline = Average of Weeks -2, -1 and 0.

[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.

[r] indicates data were ranked prior to performing ANCOVA.

Source: Extracted from Table 11.4.1 in sponsor's clinical study report

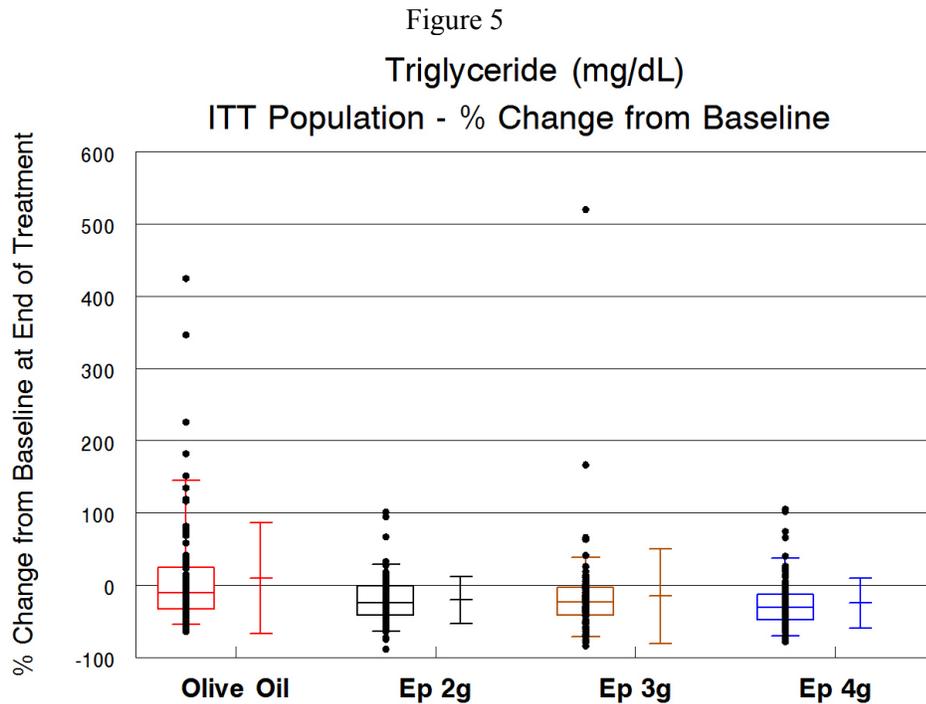
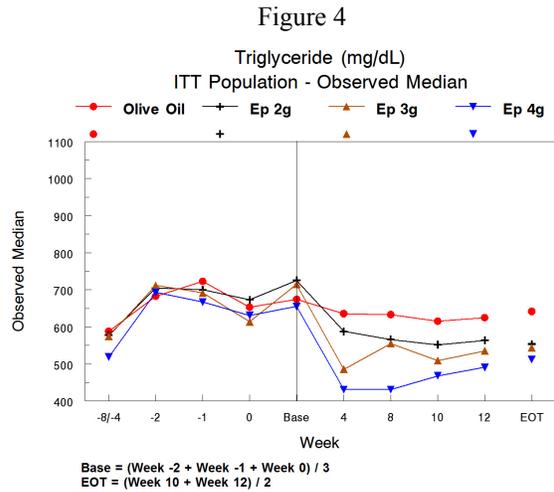
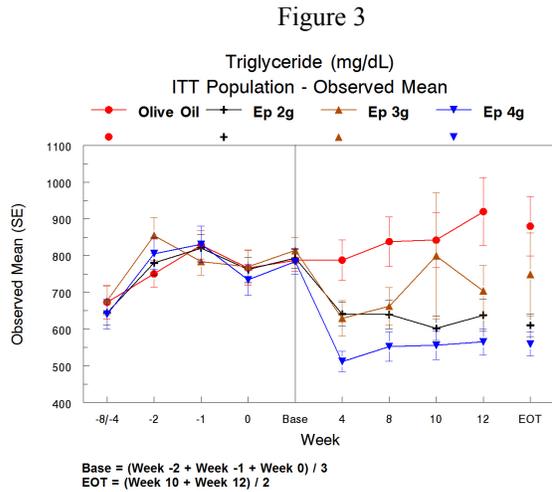
Although determination of dose-response was not the study objective, I performed the Jonckheere-Terpstra non-parametric test as an exploratory analysis to assess the association between the TG lowering and Epanova doses. The test showed that there was no statistically significant correlation indicating that greater reductions in TG were associated with higher Epanova doses (two-sided $p = 0.20$).

Table 5 below shows the proportion of subjects who achieved TG < 500 mg/dL at Week 12 (sponsor's definition for responders). When I treated subjects with missing Week 12 data as non-responders, similar response pattern across the 4 treatment groups was observed (36%, 37%, 42%, and 49% for the olive oil, Epanova 2 g, 3 g, and 4 g dose, respectively).

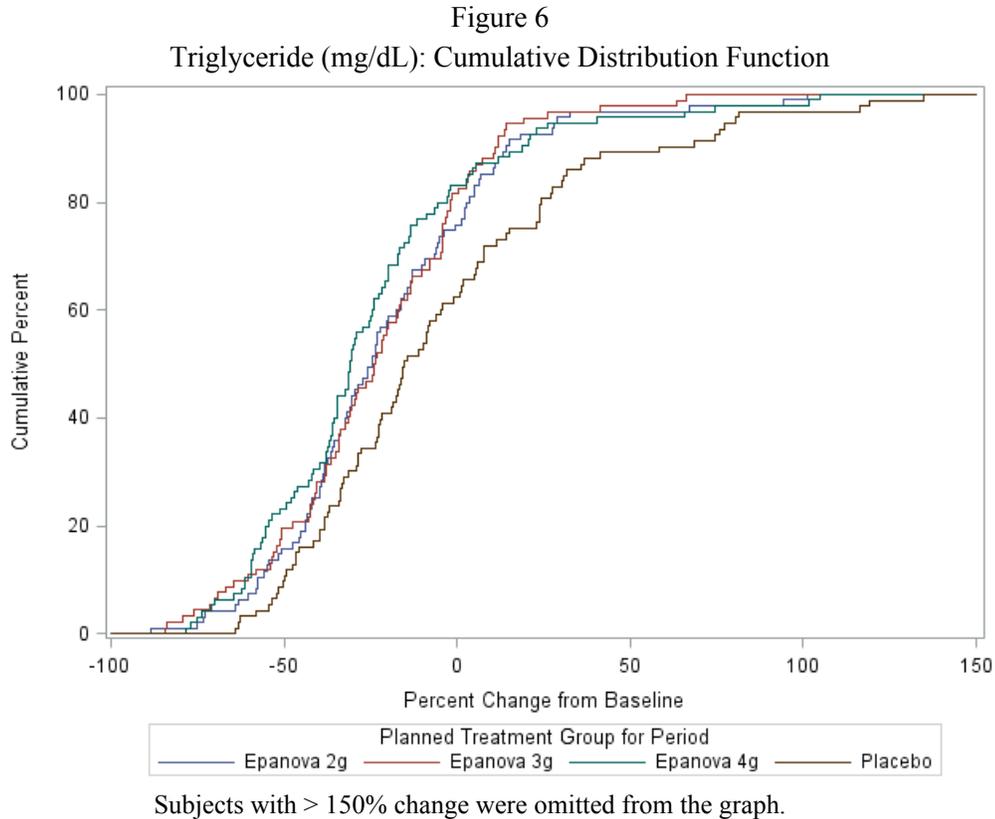
Table 5 – Responder Rate for TG < 500 mg/dL at Week 12

| ITT Population | Olive Oil | Epanova 2 g | Epanova 3 g | Epanova 4 g |
|-------------------------|-------------|--------------|--------------|-------------|
| Sponsor's | 36/98 (37%) | 37/95 (39%) | 42/94 (45%) | 49/95 (52%) |
| Reviewer's ¹ | 36/99 (36%) | 37/100 (37%) | 42/101 (42%) | 49/99 (49%) |

¹ Subjects with missing data at Week 12 were treated as non-responders.



The box shows the range between the 25th and 75th percentiles with a horizontal line at the median value. The whiskers extend from the edge of the box to the 5th and 95th percentile of the data. Mean and SD are drawn next to the box.



The missing data rates on the TG endpoint (average of Weeks 10 and 12) were 5%, 6%, 13%, and 7% in the olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. Unless otherwise noted, all the statistical analyses discussed above were based on the MITT population with the LOCF single imputation method for missing data. The sponsor performed sensitivity analyses using a multiple imputation method (Table 6) and a MMRM approach (Table 7) to assess the impact of missing data on the primary analysis results of TG; similar findings were observed.

Table 6 – Sensitivity Analysis using Multiple Imputation for TG (sponsor’s table)

| | Visit | | Estimate | Standard Error | 95% CI | P-value[1] |
|----------------------|---|-------------------------|----------|----------------|----------------|------------|
| Triglyceride (mg/dL) | Treatment Effect | | | | | <0.001 |
| | Estimates of differences between means for Epanova and Olive Oil at Week 12 | Epanova 2 g - Olive Oil | -29.1 | 8.9 | (-46.5, -11.6) | |
| | | Epanova 3 g - Olive Oil | -18.8 | 9.5 | (-37.6, -0.1) | |
| | | Epanova 4 g - Olive Oil | -34.9 | 9.0 | (-52.5, -17.3) | |

[1] Missing data was imputed using a multiple imputation method. A total of 10 imputations were generated. Pooled p-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model using the multiply imputed data. P-values for each iteration were adjusted by Dunnett’s procedure for multiple comparisons. Source: Extracted from Table 14.2.8.2 in sponsor’s clinical study report

Table 7 – Sensitivity Analysis using MMRM and Non-parametric test for TG (sponsor’s table)

| | | | Estimate | Standard Error | P-value[1] | P-value[2] |
|----------------------|---|-------------------------|----------|----------------|------------|------------|
| Triglyceride (mg/dL) | Time | | | | <0.001 | |
| | Treatment Effect | | | | 0.004 | |
| | Treatment by Time | | | | <0.001 | |
| | Estimates of differences between Means for Epanova and Olive Oil at Week 12 | Epanova 2 g - Olive Oil | -283.7 | 92.5 | | |
| | | Epanova 3 g - Olive Oil | -219.5 | 93.9 | | |
| | | Epanova 4 g - Olive Oil | -354.2 | 92.9 | | |
| | Non Parametric Analysis [Median shift on %Change] | Epanova 2 g - Olive Oil | -15.5 | | | 0.002 |
| | | Epanova 3 g - Olive Oil | -15.4 | | | 0.003 |
| | | Epanova 4 g - Olive Oil | -20.8 | | | <0.001 |

Missing data was not imputed for the Mixed Model repeated measures procedure on this table.

[1] P-value from a Mixed Model repeated measures procedure that includes terms for treatment, time, and time by treatment interaction, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model using the unstructured covariance structure for correlation between measures at different times on the same subject using full data without imputation. For the time variable, actual Week was used, for example, baseline value as time=0 and Visit 8 as time=12.

[2] P-value from Wilcoxon-Mann-Whitney test using percent change from baseline at week 12 using the LOCF data. The median shift and the 95% confidence interval were from the Hodges-Lehmann procedure.

Source: Extracted from Table 14.2.8.1 in sponsor’s clinical study report

Secondary Efficacy Variable – non-High-Density Lipoprotein Cholesterol (non-HDL-C).

The observed means and medians of non-HDL-C over time for the 4 treatment groups are shown in Figures 7 and 8 below, respectively. Figure 9 depicts the distributions of the change data at end of treatment for all the study groups.

After 12 weeks of double-blind treatment period, all the Epanova dose groups showed a statistically significantly greater mean percent decrease in non-HDL-C from baseline when compared with the olive oil group (all adjusted $p < 0.05$ based on the sponsor’s rank ANCOVA or my rank ANCOVA on residuals). The olive oil-adjusted treatment differences were -10.1%, -9.4%, and -12.2% for the Epanova 2 g, 3 g, and 4 g dose groups, respectively, based on the sponsor’s natural-log-transformed data (Table 8). I also performed non-parametric test on the percent change data. The Hodges-Lehmann median estimates and the associated 95% CIs were -7.2% (-12.6%, -2.1%), -6.5% (-12.7%, -1.0%), and -10.3% (-16.1%, -4.7%) for the corresponding Epanova 2 g, 3 g, and 4 g dose relative to olive oil. As Figure 10 depicts, approximately 53%, 61%, 62%, and 73% of the olive oil, Epanova 2 g, 3 g, and 4 g treated patients, respectively, showed an improved non-HDL-C (i.e., % change < 0) at the end of the 12-week treatment period.

Table 8 – Efficacy Results for non-HDL-C (mg/dL) (extracted from sponsor’s table)

| Non-HDL Cholesterol | Olive Oil (N=99) | Epanova | | |
|-------------------------------|---------------------|-----------------|-----------------|-----------------|
| | | 2 g (N=100) | 3 g (N=101) | 4 g (N=99) |
| MITT Population | | | | |
| Baseline (mg/dL) [1] | | | | |
| N | 98 | 99 | 97 | 99 |
| Mean (SD) | 220.2 (54.37) | 221.0 (62.30) | 228.3 (74.10) | 235.3 (72.77) |
| Median | 214.5 | 205.3 | 215.3 | 225.0 |
| Min, Max | 109.3, 379.7 | 106.0, 517.0 | 115.3, 609.3 | 106.7, 536.0 |
| % Change from Baseline [2] | | | | |
| N | 98 | 95 | 94 | 95 |
| Mean (SD) | 7.5 (37.43) | -5.2 (19.62) | -3.9 (28.10) | -7.9 (19.63) |
| Median | -0.9 | -7.7 | -3.6 | -7.7 |
| Min, Max | -49.3, 201.0 | -53.3, 78.6 | -70.4, 206.2 | -55.4, 55.6 |
| LSM [3] | 2.53 | -7.61 | -6.89 | -9.63 |
| 95% CI | (-2.31, 7.61) | (-12.02, -2.97) | (-11.35, -2.21) | (-13.95, -5.09) |
| LSM Difference from Olive Oil | | -10.14 | -9.42 | -12.16 |
| 95% CI Bonferroni-corrected | | (-21.01, 0.71) | (-20.34, 1.48) | (-22.92, -1.43) |
| P-value [4] | | 0.017 [r] | 0.019 [r] | 0.001 [r] |

[1] Baseline = Average of Weeks -2, -1 and 0.

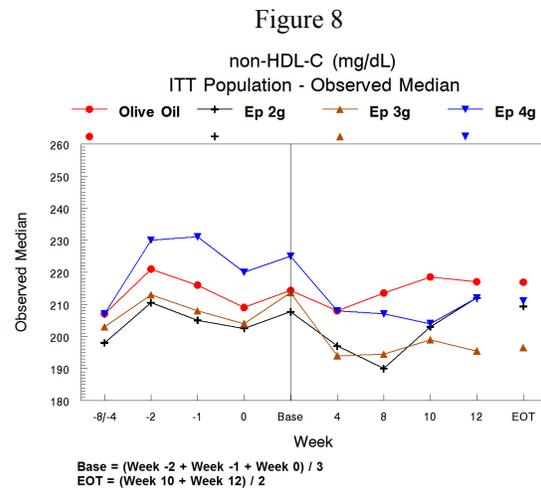
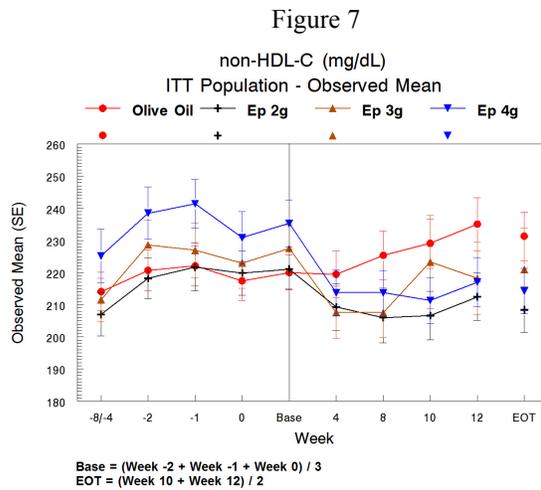
[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

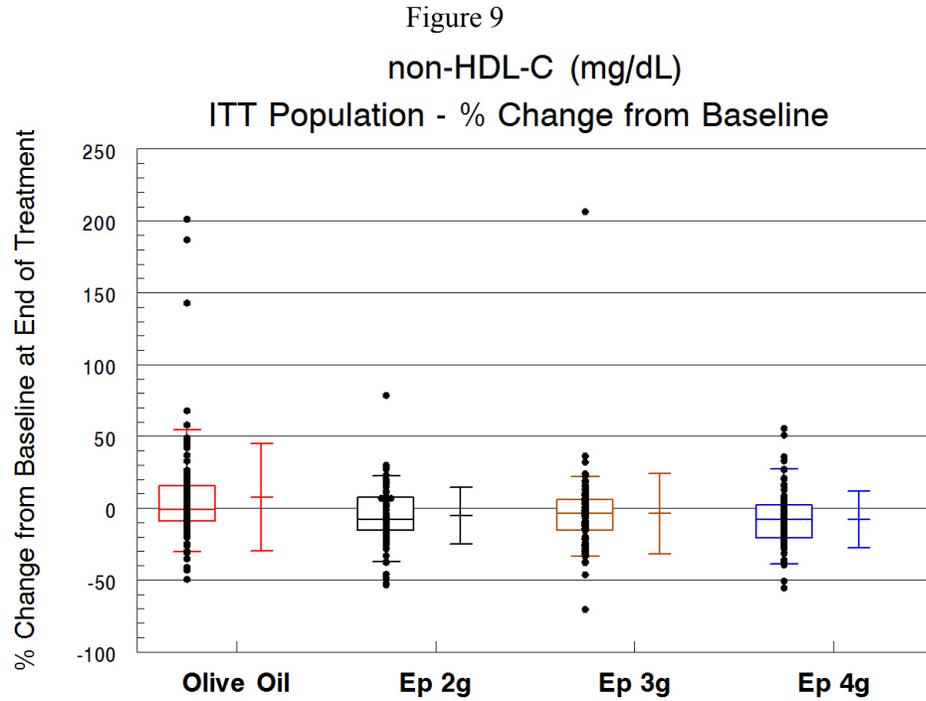
[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Hommel’s procedure for multiple comparisons of each Epanova vs. olive oil.

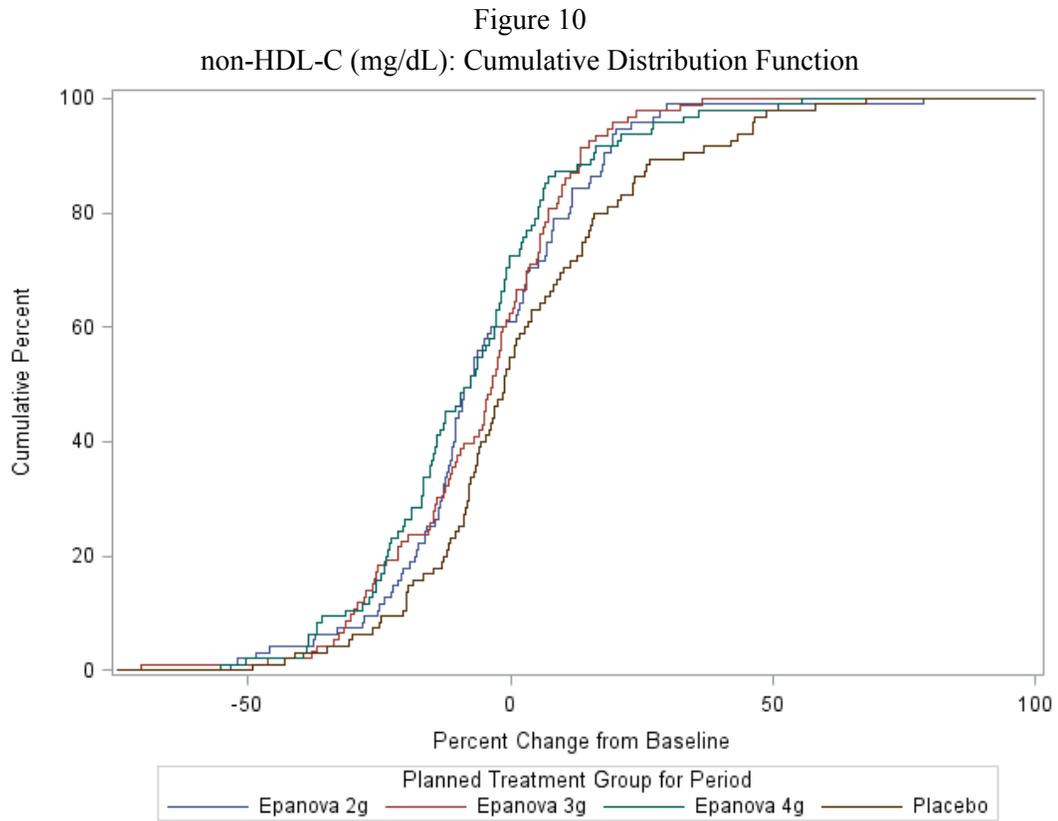
[r] indicates data were ranked prior to performing ANCOVA.

Source: Extracted from Table 11.4.2 in sponsor’s clinical study report





The box shows the range between the 25th and 75th percentiles with a horizontal line at the median value. The whiskers extend from the edge of the box to the 5th and 95th percentile of the data. Mean and SD are drawn next to the box.



Subjects with > 100% change were omitted from the graph.

The missing data rates on the non-HDL-C endpoint (average of Weeks 10 and 12) were 5%, 6%, 13%, and 7% in the olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. All the statistical analyses discussed above were based on the MITT population with the LOCF single imputation method for missing data. The sponsor performed sensitivity analyses using a multiple imputation method (Table 9) and a MMRM approach (Table 10) to assess the impact of missing data on the analysis results of non-HDL-C; similar findings were observed.

Table 9 – Sensitivity Analysis using Multiple Imputation for non-HDL-C (sponsor’s table)

| | Visit | | Estimate | Standard Error | 95% CI | P-value[1] |
|-----------|---|-------------------------|----------|----------------|---------------|------------|
| Non-HDL-C | Treatment Effect | | | | | <0.001 |
| | Estimates of differences between means for Epanova and Olive Oil at Week 12 | Epanova 2 g - Olive Oil | -12.4 | 4.0 | (-20.2, -4.5) | |
| | | Epanova 3 g - Olive Oil | -10.2 | 4.1 | (-18.2, -2.2) | |
| | | Epanova 4 g - Olive Oil | -15.5 | 4.1 | (-23.5, -7.5) | |

[1] Missing data was imputed using a multiple imputation method. A total of 10 imputations were generated. Pooled p-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model using the multiply imputed data. P-values for each iteration were adjusted by Dunnett’s procedure for multiple comparisons. Source: Extracted from Table 14.2.8.2 in sponsor’s clinical study report

Table 10 – Sensitivity Analysis using MMRM and Non-parametric test for non-HDL-C (sponsor’s table)

| | | | Estimate | Standard Error | P-value[1] | P-value[2] |
|-----------|---|-------------------------|----------|----------------|------------|------------|
| Non-HDL-C | Time | | | | <0.001 | |
| | Treatment Effect | | | | 0.587 | |
| | Treatment by Time | | | | 0.012 | |
| | Estimates of differences between Means for Epanova and Olive Oil at Week 12 | Epanova 2 g - Olive Oil | -22.9 | 12.5 | | |
| | | Epanova 3 g - Olive Oil | -16.6 | 12.6 | | |
| | | Epanova 4 g - Olive Oil | -18.3 | 12.5 | | |
| | Non Parametric Analysis [Median shift on %Change] | Epanova 2 g - Olive Oil | -7.2 | | | 0.007 |
| | | Epanova 3 g - Olive Oil | -6.5 | | | 0.019 |
| | | Epanova 4 g - Olive Oil | -10.3 | | | <0.001 |

Missing data was not imputed for the Mixed Model repeated measures procedure on this table. [1] P-value from a Mixed Model repeated measures procedure that includes terms for treatment, time, and time by treatment interaction, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model using the unstructured covariance structure for correlation between measures at different times on the same subject using full data without imputation. For the time variable, actual Week was used, for example, baseline value as time=0 and Visit 8 as time=12. [2] P-value from Wilcoxon-Mann-Whitney test using percent change from baseline at week 12 using the LOCF data. The median shift and the 95% confidence interval were from the Hodges-Lehmann procedure. Source: Extracted from Table 14.2.8.1 in sponsor’s clinical study report

Secondary Efficacy Variable – High-Density Lipoprotein Cholesterol (HDL-C). The observed means and medians of HDL-C over time for the 4 treatment groups are shown in Figures 11 and 12 below, respectively. Figure 13 depicts the distributions of the change data at end of treatment for all the study groups.

After 12 weeks of double-blind treatment period, all the Epanova dose groups showed a numerically greater mean percent increase in HDL-C from baseline when compared with the olive oil group (but not statistically significant since all adjusted $p > 0.05$ based on the sponsor's rank ANCOVA or my rank ANCOVA on residuals). The olive oil-adjusted treatment differences were 5.4%, 1.9%, and 3.8% for the Epanova 2 g, 3 g, and 4 g dose groups, respectively, based on the sponsor's natural-log-transformed data (Table 11). I also performed non-parametric test on the percent change data. The Hodges-Lehmann median estimates and the associated 95% CIs were 5.1% (0.4%, 10.3%), 4.4% (-0.2%, 8.6%), and 3.6% (-0.6%, 7.8%) for the corresponding Epanova 2 g, 3 g, and 4 g dose relative to olive oil. As Figure 10 depicts, approximately 55%, 65%, 68%, and 64% of the olive oil, Epanova 2 g, 3 g, and 4 g treated patients, respectively, showed an improved HDL-C (i.e., % change > 0) at the end of the 12-week treatment period.

Table 11 – Efficacy Results for HDL-C (mg/dL) (extracted from sponsor's table)

| HDL Cholesterol | Olive Oil (N=99) | Epanova | | |
|-------------------------------|---------------------|----------------|----------------|----------------|
| | | 2 g (N=100) | 3 g (N=101) | 4 g (N=99) |
| MITT Population | | | | |
| Baseline (mg/dL) [1] | | | | |
| N | 98 | 99 | 97 | 99 |
| Mean (SD) | 29.2 (7.93) | 28.0 (6.87) | 29.0 (7.93) | 29.9 (9.22) |
| Median | 28.7 | 27.3 | 28.0 | 28.7 |
| Min, Max | 14.0, 60.0 | 13.3, 47.3 | 15.3, 58.7 | 12.7, 69.3 |
| % Change from Baseline [2] | | | | |
| N | 98 | 95 | 94 | 95 |
| Mean (SD) | 5.1 (29.94) | 9.8 (22.22) | 6.0 (19.69) | 7.3 (17.88) |
| Median | 2.2 | 7.0 | 6.9 | 5.0 |
| Min, Max | -48.3, 226.2 | -31.8, 102.5 | -50.0, 66.7 | -36.4, 61.7 |
| LSM [3] | 1.92 | 7.35 | 3.78 | 5.77 |
| 95% CI | (-1.98, 5.98) | (3.18, 11.68) | (-0.27, 7.99) | (1.65, 10.06) |
| LSM Difference from Olive Oil | | 5.42 | 1.86 | 3.85 |
| 95% CI Bonferroni-corrected | | (-4.00, 14.86) | (-7.42, 11.14) | (-5.51, 13.23) |
| P-value [4] | | 0.076 [r] | 0.091 [r] | 0.091 [r] |

[1] Baseline = Average of Weeks -2, -1 and 0.

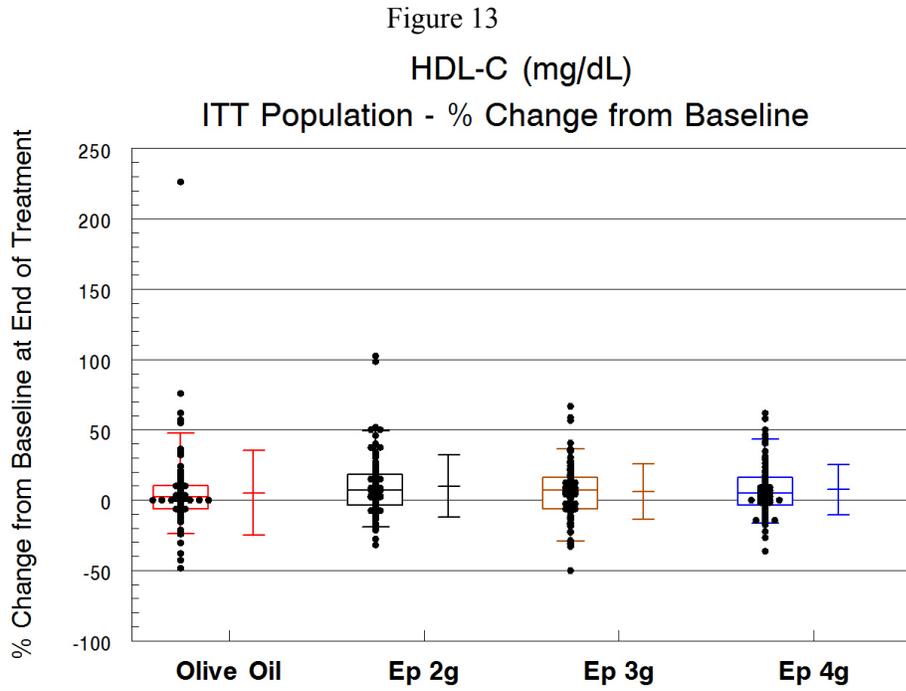
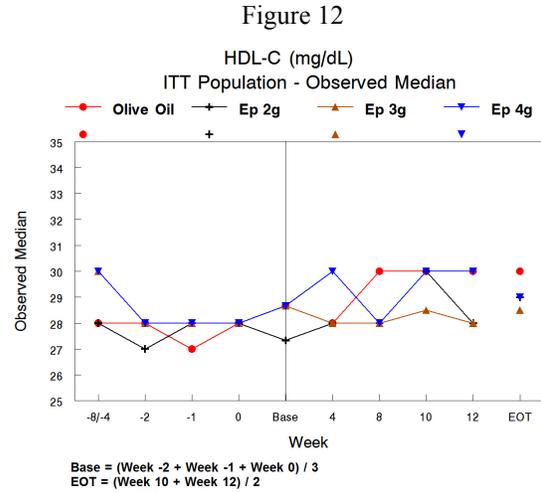
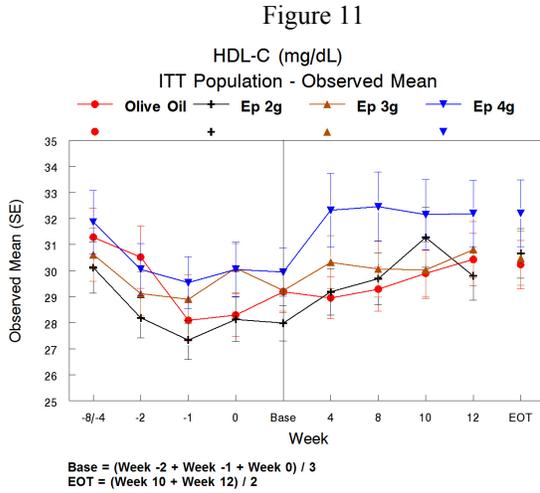
[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

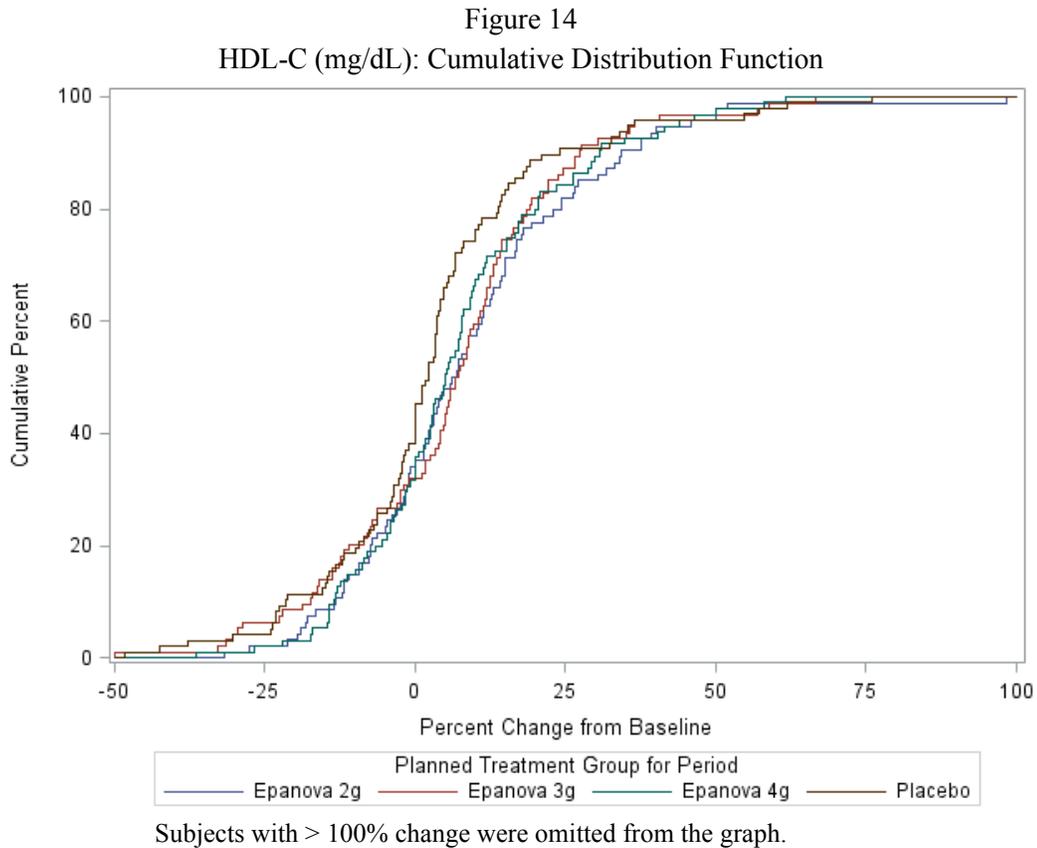
[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Hommel's procedure for multiple comparisons of each Epanova vs. olive oil.

[r] indicates data were ranked prior to performing ANCOVA.

Source: Extracted from Table 11.4.3 in sponsor's clinical study report



The box shows the range between the 25th and 75th percentiles with a horizontal line at the median value. The whiskers extend from the edge of the box to the 5th and 95th percentile of the data. Mean and SD are drawn next to the box.



The missing data rates on the HDL-C endpoint (average of Weeks 10 and 12) were 5%, 6%, 13%, and 7% in the olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. All the statistical analyses discussed above were based on the MITT population with the LOCF single imputation method for missing data. The sponsor performed sensitivity analyses using a multiple imputation method (Table 12) and a MMRM approach (Table 13) to assess the impact of missing data on the analysis results of non-HDL-C; similar findings were observed.

Table 12 – Sensitivity Analysis using Multiple Imputation for HDL-C (sponsor’s table)

| | Visit | | Estimate | Standard Error | 95% CI | P-value[1] |
|-------|---|-------------------------|----------|----------------|--------------|------------|
| HDL-C | Treatment Effect | | | | | 0.693 |
| | Estimates of differences between means for Epanova and Olive Oil at Week 12 | Epanova 2 g - Olive Oil | 3.8 | 3.4 | (-2.9, 10.5) | |
| | | Epanova 3 g - Olive Oil | 1.4 | 3.5 | (-5.4, 8.1) | |
| | | Epanova 4 g - Olive Oil | 1.6 | 3.4 | (-5.1, 8.3) | |

[1] Missing data was imputed using a multiple imputation method. A total of 10 imputations were generated. Pooled p-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model using the multiply imputed data. P-values for each iteration were adjusted by Dunnett’s procedure for multiple comparisons. Source: Extracted from Table 14.2.8.2 in sponsor’s clinical study report

Table 13 – Sensitivity Analysis using MMRM and Non-parametric test for HDL-C (sponsor’s table)

| | | | Estimate | Standard Error | P-value[1] | P-value[2] |
|-------|---|-------------------------|----------|----------------|------------|------------|
| HDL-C | Time | | | | <0.001 | |
| | Treatment Effect | | | | 0.293 | |
| | Treatment by Time | | | | 0.061 | |
| | Estimates of differences between Means for Epanova and Olive Oil at Week 12 | Epanova 2 g - Olive Oil | -0.9 | 1.5 | | |
| | | Epanova 3 g - Olive Oil | 0.9 | 1.6 | | |
| | | Epanova 4 g - Olive Oil | 1.6 | 1.6 | | |
| | Non Parametric Analysis [Median shift on %Change] | Epanova 2 g - Olive Oil | 5.1 | | | 0.032 |
| | | Epanova 3 g - Olive Oil | 4.4 | | | 0.058 |
| | | Epanova 4 g - Olive Oil | 3.6 | | | 0.090 |

Missing data was not imputed for the Mixed Model repeated measures procedure on this table.

[1] P-value from a Mixed Model repeated measures procedure that includes terms for treatment, time, and time by treatment interaction, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model using the unstructured covariance structure for correlation between measures at different times on the same subject using full data without imputation. For the time variable, actual Week was used, for example, baseline value as time=0 and Visit 8 as time=12.

[2] P-value from Wilcoxon-Mann-Whitney test using percent change from baseline at week 12 using the LOCF data. The median shift and the 95% confidence interval were from the Hodges-Lehmann procedure.

Source: Extracted from Table 14.2.8.1 in sponsor’s clinical study report

Tertiary Efficacy Variable – Low-Density Lipoprotein Cholesterol (LDL-C). The observed means and medians of LDL-C over time for the 4 treatment groups are shown in Figures 15 and 16 below, respectively. Figure 17 depicts the distributions of the change data at end of treatment for all the study groups.

After 12 weeks of double-blind treatment period, all the Epanova dose groups showed a numerically greater mean percent increase in LDL-C from baseline when compared with the olive oil group. Since the Statistical Analysis Plan did not call for formal inferential testing with multiplicity adjustment for LDL-C, I did not perform any statistical test for pairwise comparisons. The olive oil-adjusted treatment differences were 16.2%, 11.2%, and 16.3% for the Epanova 2 g, 3 g, and 4 g dose groups, respectively, based on the sponsor’s natural-log-transformed data (Table 14). The Hodges-Lehmann median estimates were 13.1%, 8.8%, and 15.3% for the corresponding Epanova 2 g, 3 g, and 4 g dose relative to olive oil. As Figure 18 depicts, approximately 36%, 19%, 26%, and 22% of the olive oil, Epanova 2 g, 3 g, and 4 g treated patients, respectively, showed an improved LDL-C (i.e., % change < 0) at the end of the 12-week treatment period.

Table 14 – Efficacy Results for LDL-C (mg/dL) (extracted from sponsor’s table)

| Lipid Parameter | Olive Oil (N=99) | Epanova | | |
|-------------------------------|---------------------|----------------|----------------|---------------|
| | | 2 g (N=100) | 3 g (N=101) | 4 g (N=99) |
| LDL Cholesterol | | | | |
| Baseline (mg/dL) [1] | | | | |
| N | 98 | 99 | 97 | 99 |
| Mean (SD) | 81.5 (31.49) | 83.0 (32.86) | 84.7 (38.74) | 90.3 (38.86) |
| Median | 78.2 | 77.3 | 81.0 | 90.3 |
| Min, Max | 22.7, 160.8 | 19.7, 181.7 | 19.7, 213.0 | 11.7, 223.0 |
| % Change from Baseline [2] | | | | |
| N | 98 | 95 | 94 | 95 |
| Mean (SD) | 11.7 (38.39) | 25.5 (32.69) | 20.3 (31.66) | 26.2 (35.80) |
| Median | 9.8 | 21.4 | 16.6 | 26.2 |
| Min, Max | -81.6, 224.2 | -39.9, 129.1 | -62.7, 168.6 | -65.7, 170.0 |
| LSM [3] | 3.00 | 19.20 | 14.25 | 19.35 |
| LSM Difference from Olive Oil | | 16.20 | 11.25 | 16.35 |

[1] Baseline = Average of Weeks -2, -1 and 0.

[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

Source: Extracted from Table 11.4.4 in sponsor’s clinical study report

Figure 15

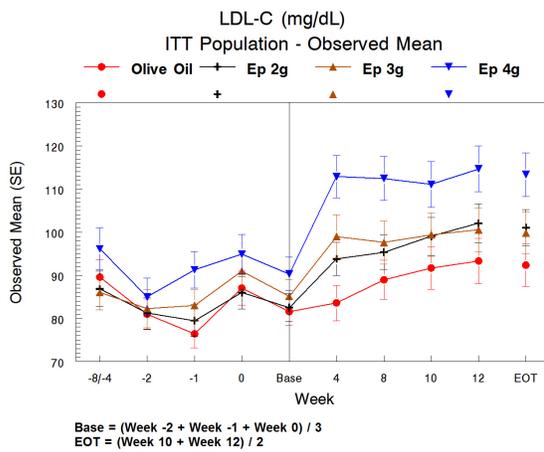


Figure 16

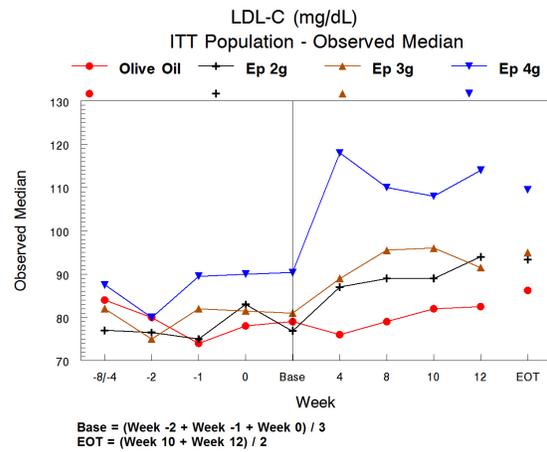
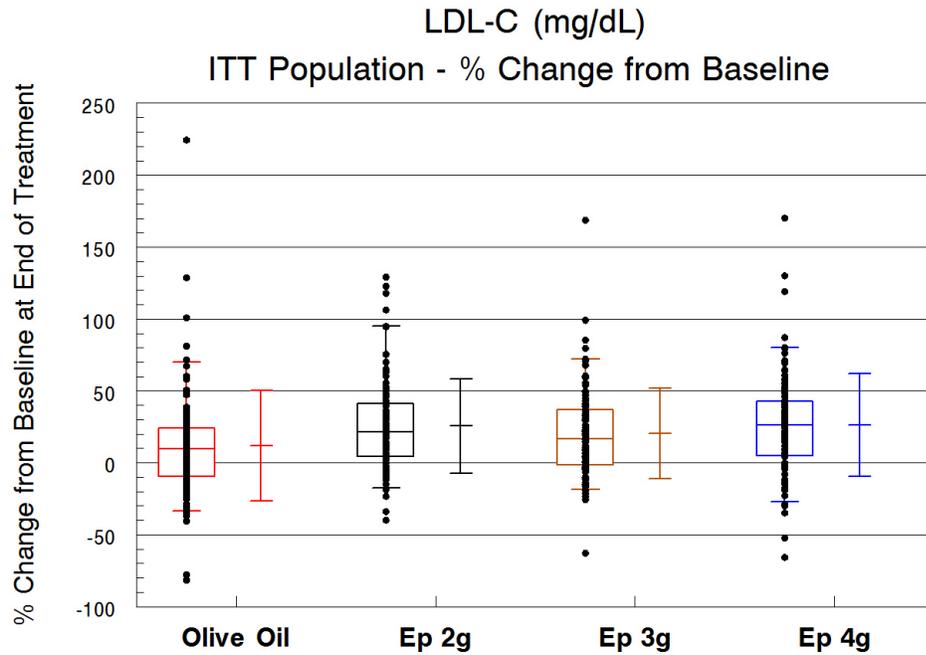
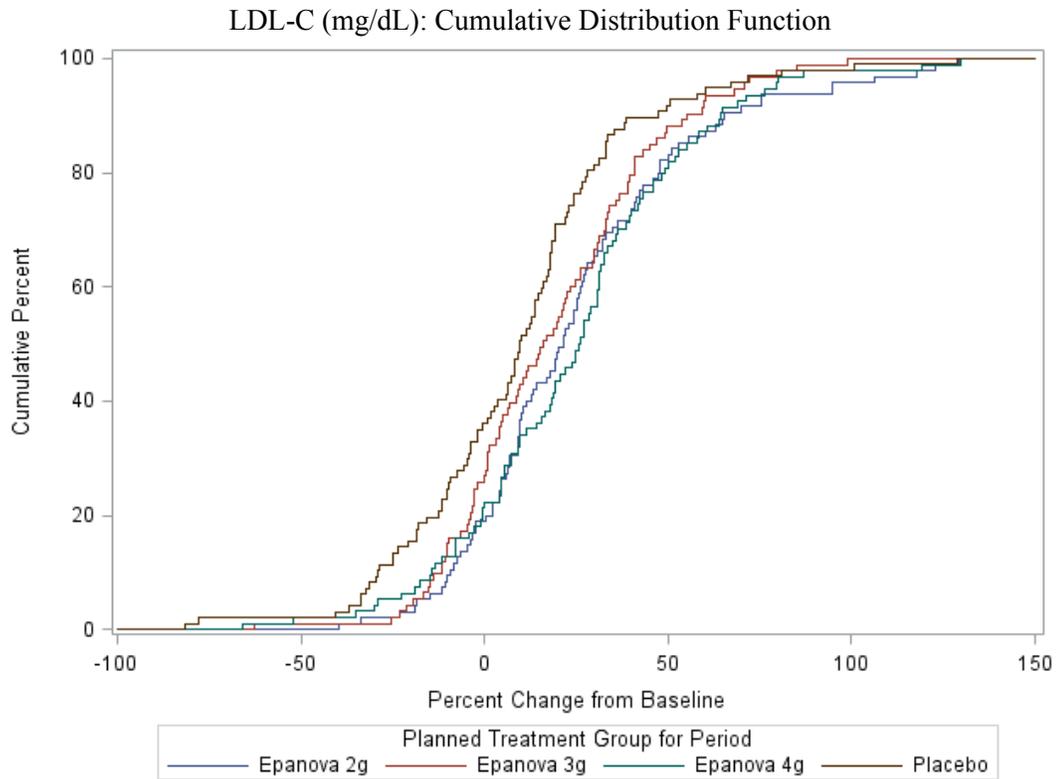


Figure 17



The box shows the range between the 25th and 75th percentiles with a horizontal line at the median value. The whiskers extend from the edge of the box to the 5th and 95th percentile of the data. Mean and SD are drawn next to the box.

Figure 18



Subjects with > 150% change were omitted from the graph.

Tertiary Efficacy Variable – Total Cholesterol (TC). The observed means and medians of TC over time for the 4 treatment groups are shown in Figures 19 and 20 below, respectively.

After 12 weeks of double-blind treatment period, all the Epanova dose groups showed a numerically greater mean percent decrease in TC from baseline when compared with the olive oil group. Since the Statistical Analysis Plan did not call for formal inferential testing with multiplicity adjustment for TC, I did not perform any statistical test for pairwise comparisons. The olive oil-adjusted treatment differences were -8.6%, -8.0%, and -10.6% for the Epanova 2 g, 3 g, and 4 g dose groups, respectively, based on the sponsor's natural-log-transformed data (Table 15). The Hodges-Lehmann median estimates were -5.8%, -5.2%, and -8.7% for the corresponding Epanova 2 g, 3 g, and 4 g dose relative to olive oil.

Table 15 – Efficacy Results for TC (mg/dL) (extracted from sponsor's table)

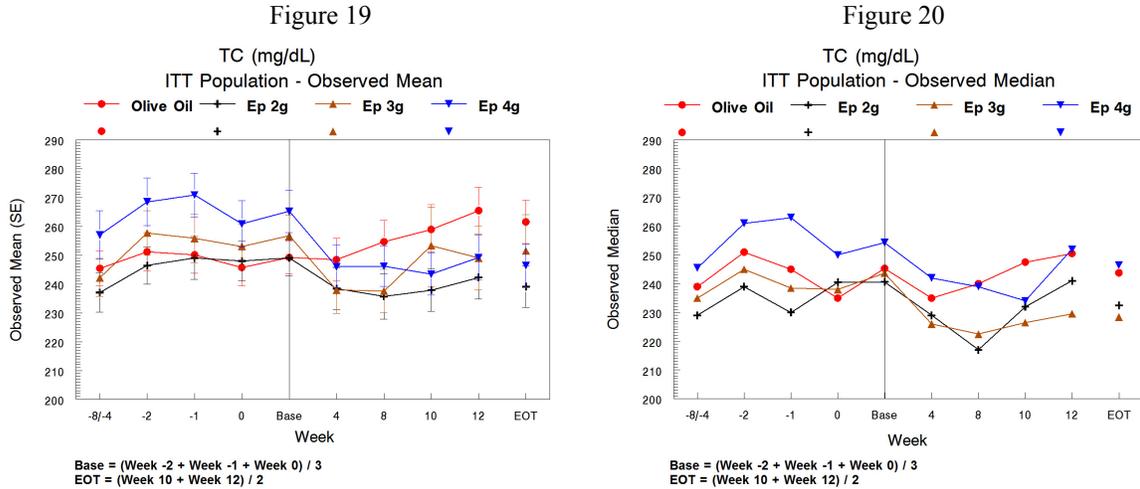
| Lipid Parameter | Olive Oil (N=99) | Epanova | | |
|-------------------------------|---------------------|----------------|----------------|---------------|
| | | 2 g (N=100) | 3 g (N=101) | 4 g (N=99) |
| Total Cholesterol | | | | |
| Baseline (mg/dL) [1] | | | | |
| N | 98 | 99 | 97 | 99 |
| Mean (SD) | 249.4 (56.82) | 249.0 (62.98) | 257.4 (73.80) | 265.3 (73.14) |
| Median | 245.5 | 240.7 | 243.7 | 254.3 |
| Min, Max | 135.0, 409.0 | 131.0, 542.3 | 150.7, 641.3 | 119.3, 564.0 |
| % Change from Baseline [2] | | | | |
| N | 98 | 95 | 94 | 95 |
| Mean (SD) | 7.0 (32.21) | -3.6 (16.81) | -2.6 (24.85) | -6.3 (17.43) |
| Median | -0.3 | -6.4 | -2.9 | -6.2 |
| Min, Max | -44.1, 178.3 | -47.1, 70.9 | -64.5, 188.6 | -45.8, 51.7 |
| LSM [3] | 3.17 | -5.44 | -4.85 | -7.46 |
| LSM Difference from Olive Oil | | -8.61 | -8.02 | -10.63 |

[1] Baseline = Average of Weeks -2, -1 and 0.

[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

Source: Extracted from Table 11.4.4 in sponsor's clinical study report



Tertiary Efficacy Variable – Very Low-Density Lipoprotein Cholesterol (VLDL-C). The observed means and medians of VLDL-C over time for the 4 treatment groups are shown in Figures 21 and 22 below, respectively.

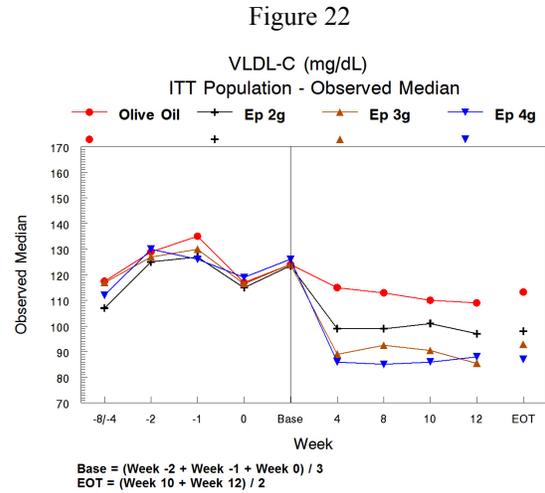
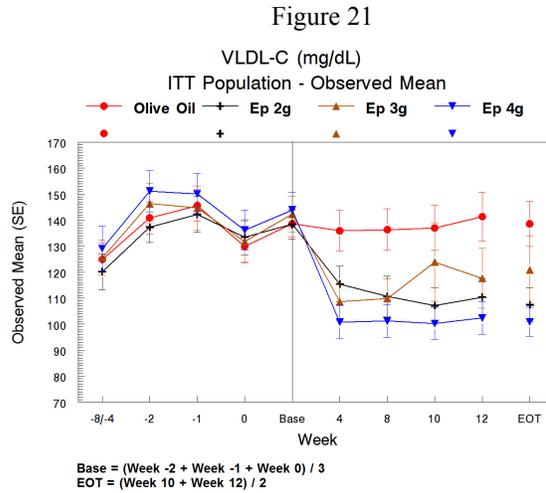
After 12 weeks of double-blind treatment period, all the Epanova dose groups showed a numerically greater mean percent decrease in VLDL-C from baseline when compared with the olive oil group. Since the Statistical Analysis Plan did not call for formal inferential testing with multiplicity adjustment for TC, I did not perform any statistical test for pairwise comparisons. The olive oil-adjusted treatment differences were -18.0%, -17.9%, and -24.5% for the Epanova 2 g, 3 g, and 4 g dose groups, respectively, based on the sponsor’s natural-log transformed data (Table 16). The Hodges-Lehmann median estimates and the associated 95% CIs were -14.1% (-23.7%, -5.0%), -14.3% (-23.8%, -5.1%), and -20.8% (-29.9%, -11.8%) for the corresponding Epanova 2 g, 3 g, and 4 g dose relative to olive oil.

Table 16 – Efficacy Results for VLDL-C (mg/dL) (extracted from sponsor’s table)

| Lipid Parameter | Olive Oil (N=99) | Epanova | | |
|-------------------------------|---------------------|----------------|----------------|---------------|
| | | 2 g (N=100) | 3 g (N=101) | 4 g (N=99) |
| VLDL Cholesterol | | | | |
| Baseline (mg/dL) [1] | | | | |
| N | 98 | 99 | 97 | 99 |
| Mean (SD) | 139.0 (51.52) | 137.9 (56.45) | 143.6 (71.46) | 143.9 (66.92) |
| Median | 124.5 | 123.3 | 124.0 | 126.0 |
| Min, Max | 60.7, 295.7 | 34.7, 419.7 | 47.7, 440.0 | 64.0, 457.7 |
| % Change from Baseline [2] | | | | |
| N | 98 | 95 | 94 | 95 |
| Mean (SD) | 2.7 (63.74) | -20.7 (31.58) | -19.6 (39.60) | -27.3 (30.67) |
| Median | -11.3 | -24.7 | -21.6 | -34.7 |
| Min, Max | -67.4, 305.5 | -91.1, 117.1 | -86.1, 239.8 | -86.8, 65.3 |
| LSM [3] | -8.52 | -26.55 | -26.44 | -32.98 |
| LSM Difference from Olive Oil | | -18.03 | -17.92 | -24.46 |

- [1] Baseline = Average of Weeks -2, -1 and 0.
- [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
- [3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

Source: Extracted from Table 11.4.4 in sponsor’s clinical study report



3.2 Evaluation of Safety

In consultation with the reviewing medical officers, there were no aspects of safety that required review by a statistician. See Dr. Giovanni Cizza’s report for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

As shown in Table 17, treatment effects on mean percent change from baseline in TG at endpoint for the subgroups of patients defined as age < 65 years, males, and White were similar to the effects observed based on the overall population. Due to the small sample size, the point estimates of the treatment differences for the subgroups of patients defined as age ≥ 65 years, females, and non-White were not close to the ones observed in the overall population. There were no significant interactions of treatment-by-subgroup observed (all p > 0.10).

4.2 Other Special/Subgroup Populations

As shown in Table 17, treatment effects on mean percent change from baseline in TG at endpoint for the subgroups of patients defined by country (USA, non-USA), baseline TG (< 750 mg/dL, ≥ 750 mg/dL), and statin/CAI use (yes vs. no) were similar to the effects observed based on the overall population. There were no significant interactions of treatment-by-subgroup observed (all p > 0.10).

Table 17 – LS Mean Percent Change from Baseline in TG for Subgroups

| | N | Olive Oil | EP 2 g | EP 3 g | EP 4g | EP 2 g vs. Olive Oil | EP 3 g vs. Olive Oil | EP 4 g vs. Olive Oil |
|-------------------------|-----|-----------|--------|--------|-------|----------------------|----------------------|----------------------|
| Age < 65 years | 345 | -2.0 | -25.0 | -25.8 | -30.3 | -23.0 | -23.9 | -28.4 |
| Age ≥ 65 years | 37 | -18.5 | -37.4 | -21.4 | -31.7 | -18.9 | -2.9 | -13.2 |
| Males | 292 | 2.2 | -25.4 | -24.8 | -30.4 | -27.6 | -27.0 | -32.6 |
| Females | 90 | -23.8 | -28.6 | -27.2 | -31.6 | -4.8 | -3.4 | -7.8 |
| White | 353 | -4.1 | -26.7 | -24.4 | -32.0 | -22.6 | -20.4 | -27.9 |
| Non-White | 29 | -7.4 | -4.5 | -26.0 | -19.5 | 2.8 | -18.6 | -12.1 |
| USA | 102 | -4.1 | -19.6 | -17.5 | -35.8 | -15.4 | -13.4 | -31.7 |
| Non-USA | 280 | -4.3 | -28.7 | -28.1 | -29.3 | -24.3 | -23.8 | -24.9 |
| Baseline TG ≥ 750 mg/dL | 161 | 2.1 | -31.0 | -24.5 | -33.6 | -33.1 | -26.6 | -35.7 |
| Baseline TG < 750 mg/dL | 221 | -9.0 | -22.6 | -26.6 | -28.6 | -13.6 | -17.6 | -19.6 |
| Statin/CAI Users | 131 | 7.8 | -24.2 | -25.2 | -24.9 | -32.0 | -33.0 | -32.7 |
| Statin/CAI Non-users | 251 | -13.0 | -28.8 | -27.7 | -35.1 | -15.9 | -14.8 | -22.1 |

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Table 18 below summarizes median baseline, median % change, and least-squares mean (LSM) % change at end of treatment for each study group. As one can see, the decreases in TG, non-HDL-C, TC, and VLDL-C in the olive oil group were all numerically much less than that in each of the 3 Epanova dose groups. Among the 3 Epanova dose groups, the decreases in these parameters were also numerically less in the 3 g dose group than in the 2 g and 4 g dose groups. The dose-response in TG lowering apparently was not in a linear fashion. In fact, the Jonckheere-Terpstra non-parametric test showed that there was no marked association between the percent change data of TG and Epanova doses (nominal two-sided $p = 0.20$). Note that the study was not powered for evaluation of dose-response or between-Epanova-group comparisons.

Nevertheless, as shown in Table 19, the percent reductions in TG and non-HDL-C in the 3 Epanova dose groups after 12 weeks of treatment were all statistically significantly greater than that in the olive oil group (all adjusted $p < 0.05$). The treatment differences in mean percent change between each of the Epanova 2 g, 3 g, and 4 g dose groups and olive oil were -21.7%, -21.2%, and -26.6%, respectively for TG, and -10.1%, -9.4%, and -12.2%, respectively, for non-HDL-C based on the natural-log-transformed data. No statistical inferential testing was performed for TC and VLDL-C according to the SAP. The olive oil-adjusted mean percent changes after 12 weeks of treatment were -8.6%, -8.0%, and -10.6% for TC, and -18.0%, -17.9%, and -24.5% for VLDL-C for the corresponding Epanova 2 g, 3

g, and 4 g dose groups. The Hodges-Lehmann median estimates showed similar response patterns in these parameters, but in a slightly less degree of reduction.

Both olive oil and Epanova increased HDL-C and LDL-C after 12-weeks of treatment. The increases in the 3 Epanova dose groups were all numerically greater than that in the olive oil group in either parameter. The treatment differences in mean percent change in HDL-C between each of the Epanova 2 g, 3 g, and 4 g dose groups and olive oil were 5.4%, 1.9%, and 3.8%, respectively, which were not statistically significant. The treatment differences in mean percent change in LDL-C between each of the Epanova 2 g, 3 g, and 4 g dose groups and olive oil were 16.2%, 11.2%, and 16.3%, respectively (no statistical inferential testing performed according to the SAP). As depicted in Figures 23 – 26, each of the 4 treatment groups showed that there was a negative correlation between the percent change data of LDL-C and TG; i.e., greater increases in LDL-C were associated with greater reductions in TG.

Table 18 – Summary of Efficacy Results for Each Study Group

| MITT | | Olive Oil | Epanova 2 g | Epanova 3 g | Epanova 4 g |
|--|-------------------------|-----------|-------------|-------------|-------------|
| TG | Median Baseline (mg/dL) | 682.3 | 717.0 | 728.0 | 655.0 |
| | Median % Change | -10.4 | -24.5 | -23.4 | -30.7 |
| | LSM % Change | -4.3 | -25.9 | -25.5 | -30.9 |
| Non-HDL-C | Median Baseline (mg/dL) | 214.5 | 205.3 | 215.3 | 225.0 |
| | Median % Change | -0.9 | -7.7 | -3.6 | -7.7 |
| | LSM % Change | 2.5 | -7.6 | -6.9 | -9.6 |
| HDL-C | Median Baseline (mg/dL) | 28.7 | 27.3 | 28.0 | 28.7 |
| | Median % Change | 2.2 | 7.0 | 6.9 | 5.0 |
| | LSM % Change | 1.9 | 7.3 | 3.8 | 5.8 |
| LDL-C | Median Baseline (mg/dL) | 78.2 | 77.3 | 81.0 | 90.3 |
| | Median % Change | 9.8 | 21.4 | 16.6 | 26.2 |
| | LSM % Change | 3.0 | 19.2 | 14.2 | 19.3 |
| TC | Median Baseline (mg/dL) | 245.5 | 240.7 | 243.7 | 254.3 |
| | Median % Change | -0.3 | -6.4 | -2.9 | -6.2 |
| | LSM % Change | 3.2 | -5.4 | -4.8 | -7.5 |
| VLDL-C | Median Baseline (mg/dL) | 124.5 | 123.3 | 124.0 | 126.0 |
| | Median % Change | -11.3 | -24.7 | -21.6 | -34.7 |
| | LSM % Change | -8.5 | -26.5 | -26.4 | -33.0 |
| N for baseline: 98, 99, 97, and 99 for olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. | | | | | |
| N for % Change: 98, 95, 94, and 95 for olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. | | | | | |
| LSM % change from baseline was obtained from an ANCOVA model using natural-log-transformed data. | | | | | |
| Source: Summarized from Table 11.4.1 – Table 11.4.4 in sponsor's clinical study report. | | | | | |

Table 19 – Summary of Efficacy Results for Between-Group Comparison

| MITT | Treatment Difference | Ep 2 g vs. Olive Oil | Ep 3 g vs. Olive Oil | Ep 4 g vs. Olive Oil |
|-----------|-----------------------------|----------------------|----------------------|----------------------|
| TG | LSM difference | -21.7 ** | -21.2 ** | -26.6 *** |
| | 95% CI Bonferroni-corrected | (-40.7, -2.9) | (-40.3, -2.3) | (-45.1, -8.4) |
| | Hodges-Lehmann median | -15.5 | -15.4 | -20.8 |
| | 95% CI, unadjusted | (-25.5, -5.7) | (-26.0, -5.2) | (-31.2, -11.1) |
| Non-HDL-C | LSM difference | -10.1 * | -9.4 * | -12.2 ** |
| | 95% CI Bonferroni-corrected | (-21.0, 0.7) | (-20.3, 1.5) | (-22.9, -1.4) |
| | Hodges-Lehmann median | -7.2 | -6.5 | -10.3 |
| | 95% CI, unadjusted | (-12.6, -2.1) | (-12.7, -1.0) | (-16.1, -4.7) |
| HDL-C | LSM difference | 5.4 NS | 1.9 NS | 3.8 NS |
| | 95% CI Bonferroni-corrected | (-4.0, 14.9) | (-7.4, 11.1) | (-5.5, 13.2) |
| | Hodges-Lehmann median | 5.1 | 4.4 | 3.6 |
| | 95% CI, unadjusted | (0.4, 10.3) | (-0.2, 8.6) | (-0.6, 7.8) |
| LDL-C | LSM difference | 16.2 | 11.2 | 16.3 |
| | Hodges-Lehmann median | 13.1 | 8.8 | 15.3 |
| TC | LSM difference | -8.6 | -8.0 | -10.6 |
| | Hodges-Lehmann median | -5.8 | -5.2 | -8.7 |
| VLDL-C | LSM difference | -18.0 | -17.9 | -24.5 |
| | Hodges-Lehmann median | -14.1 | -14.3 | -20.8 |

LSM difference was obtained from an ANCOVA model using natural-log-transformed data.
 * for p < 0.05; ** for p < 0.01; *** for p < 0.001; NS for p not significant at 0.05 level
 No statistical inferential testing was performed for LDL-C, TC, and VLDL-C since they were tertiary endpoints.
 Source: Summarized from Table 11.4.1 – Table 11.4.4 in sponsor’s clinical study report.

Figure 23

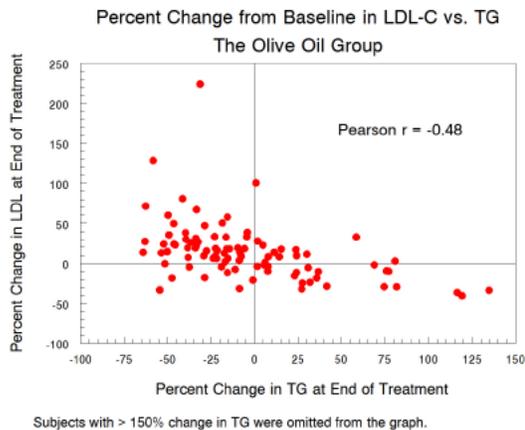
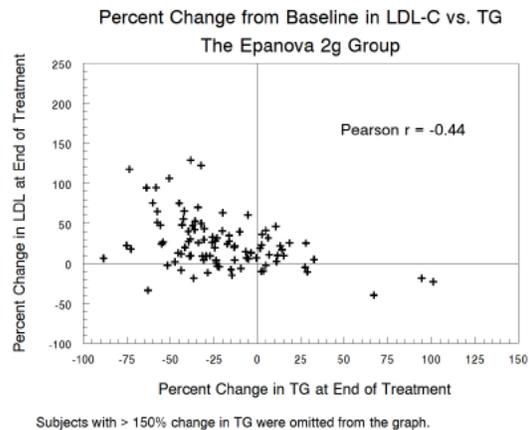
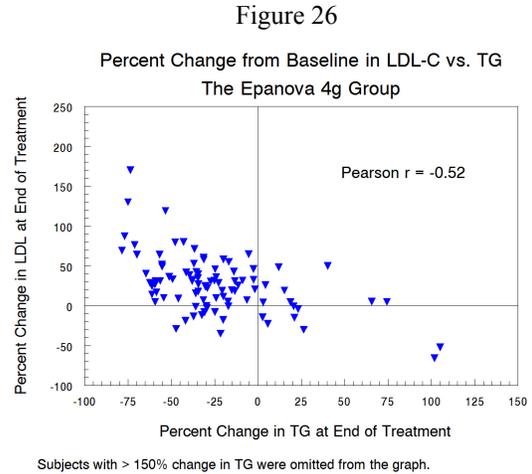
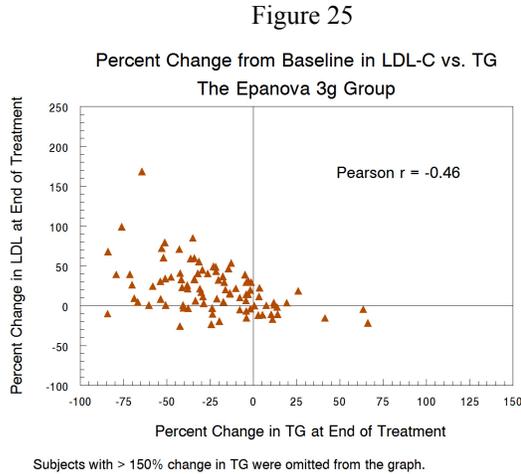


Figure 24





The percentages of patients with an improved response for TG, non-HDL-C, HDL-C, and LDL-C at end of treatment are shown in Table 20. Except for LDL-C, all the percentages were numerically higher in the Epanova groups than in the olive oil group. The percentages of Epanova-treated patients with an improved TG or non-HDL-C (% change < 0) were increased as the doses increased. However, the study was not designed to test for any significant dose-response based on a binary variable. Similar findings were also observed for percentage of patients achieving TG < 500 mg/dL at Week 12.

Table 20 – Percentage of Patients with an Improved Response at End of Treatment

| MITT Population | Olive Oil (N = 98) | Epanova 2 g (N = 95) | Epanova 3 g (N = 94) | Epanova 4 g (N = 95) |
|--|-----------------------|-------------------------|-------------------------|-------------------------|
| Percentage of Patients with an Improved Response at End of Treatment | | | | |
| TG | 59% | 76% | 80% | 83% |
| Non-HDL-C | 53% | 61% | 62% | 73% |
| HDL-C | 55% | 65% | 68% | 64% |
| LDL-C | 36% | 19% | 26% | 22% |
| Percentage of Patients Achieving TG < 500 mg/dL at Week 12 | | | | |
| | 37% | 39% | 45% | 52% |

The missing data rates on the lipid endpoints (average of Weeks 10 and 12) evaluated in this review were 5%, 6%, 13%, and 7% in the olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. All the statistical analyses discussed above were based on the MITT population (i.e., consisting of all randomized subjects who had received at least one dose of investigational product and had at least one post-randomization efficacy assessment) with the LOCF for missing data. Sensitivity analyses using multiple imputation method and MMRM

approach to assess the impact of missing data on the analysis results of TG, non-HDL-C, and HDL-C were performed by the sponsor and similar findings were observed (see Tables 6, 7, 9, 10, 12, and 13 above).

5.2 Conclusions and Recommendations

Data from the EVOLVE trial have demonstrated that Epanova, either 2 g, 3 g, or 4 g dose, were able to significantly reduce TG and non-HDL-C after 12 weeks of treatment when compared with olive oil (placebo) in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. Although not statistically significant, numerically greater mean percent increases in HDL from baseline after 12 weeks of treatment were also observed in all the Epanova dose groups when compared with the olive oil group. For the other efficacy variables such as TC and VLDL-C, all 3 doses of Epanova consistently exhibited greater mean percent reductions from baseline to end of treatment when compared with olive oil. However, Epanova had an unfavorable effect on LDL-C since the mean percent increases in LDL-C in the 3 dose groups were all greater than that in the olive oil group.

Although the 3 doses of Epanova were all effective in reducing TG and non-HDL-C, the dose-response was modest. In fact, the observed treatment effects from the 3 g dose on TG and non-HDL-C lowering were numerically slightly smaller than that from the 2 g dose. Therefore, whether to approve higher doses or not will need to take safety into consideration. In addition, as Figures 4 and 8 depict, the TG and non-HDL-C levels in the Epanova groups seem to turn back up after Week 10. Evaluation of data after Week 12 may be important since the long-term treatment effect of Epanova on these parameters remains to be seen.

5.3 Labeling Comments

The sponsor presents the results of [REDACTED] (b) (4). [REDACTED] [REDACTED] [REDACTED], I recommend removing these results from the proposed labeling. Similarly, results of [REDACTED] (b) (4); therefore, they should not be presented in the labeling unless there is a clinical reason to. In addition, [REDACTED] (b) (4) of the proposed labeling presents median for baseline [REDACTED] (b) (4). To be consistent with the previous fish oil labels, median is suggested for both baseline and percent change data, and Hodges-Lehmann estimate for treatment difference. The following table is recommended to replace the current Table 3 of the proposed labeling.

| Table 2. Median Baseline (BL) and Median Percent (%) Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥ 500 mg/dL) | | | | | | | | |
|---|------------------------|-------------|-----------------------|-------------|-------------------|-------------|----------------------------|----------------------------|
| Parameter | EPANOVA 2 g N = 100 | | EPANOVA 4 g N = 99 | | Placebo N = 99 | | EPANOVA 2 g vs. Placebo | EPANOVA 4 g vs. Placebo |
| | BL | % Change | BL | % Change | BL | % Change | Treatment Difference | |
| TG | 717 | -25 | 655 | -31 | 682 | -10 | -15 ** | -21 *** |
| Non-HDL-C | 205 | -8 | 225 | -8 | 215 | -1 | -7 * | -10 ** |
| VLDL-C | 123 | -25 | 126 | -35 | 125 | -11 | -14 | -21 |
| TC | 241 | -6 | 254 | -6 | 246 | -0 | -6 | -9 |
| HDL-C | 27 | +7 | 29 | +5 | 29 | +2 | +5 | +4 |
| LDL-C | 77 | +21 | 90 | +26 | 78 | +10 | +13 | +15 |

Placebo = Olive Oil
Difference = Median of [EPANOVA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
* for $p < 0.05$; ** for $p < 0.01$; *** for $p < 0.001$ for primary and secondary efficacy endpoints with multiplicity adjustment (p-value obtained from an ANCOVA model on rank-transformed data that included terms for treatment and use of lipid-altering drugs as factors and baseline as a covariate)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CYNTHIA Y LIU
04/15/2014

MARK D ROTHMANN
04/16/2014
I concur

THOMAS J PERMUTT
04/16/2014
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

| | | |
|--|---|--|
| NDA No.: 205,060 (SN 0000, SDN 0) | Applicant: Omthera Pharmaceuticals, Inc. | Stamp Date: 07/05/2013 |
| Drug Name: Epanova™ (omefas) Capsules | Indication: Treatment of severe hypertriglyceridemia | NDA Type: Standard |
| Filing Meeting Date: 08/29/2013 | PDUFA goal date: 05/01/2014 | Statistical Reviewer: Cynthia Liu |
| Link to location of original submission in EDR \\CDSESUB1\EVSPROD\NDA205060\0000 | | |

Background

Epanova is a lipid-altering agent containing a complex mixture of polyunsaturated free fatty acids derived from fish oils. The sponsor is submitting an original NDA seeking approval of Epanova™ (omefas) capsules for treatment as an adjunct to diet to reduce triglyceride (TG), (b) (4) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. The efficacy of Epanova for the proposed indication is determined primarily based on the results from a SPA agreed (issued on 10/22/2010, under IND 107,616) Phase 3 study OM-EPA-003 (EVOLVE). Supportive efficacy is provided by the OM-EPA-004 (ESPRIT) trial where Epanova was studied as an adjunct to diet and statin therapy in high-risk patients with persistent high TG levels (≥ 200 and < 500 mg/dL).

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|--------------------------|----------------------------------|--------------------------|--|---|--|--------------------|--|-----------------------|------------------------------|
| Phase III Efficacy PK/PD | Study OM-EPA-003 | 5.3.5.1 | To evaluate the efficacy and safety of Epanova™ in severe hypertriglyceridemic subjects | Randomized, double blind, olive oil-controlled, parallel group design | Epanova™ 2g QD arm (n=100) Epanova™ 3g QD arm (101) Epanova™ 4g QD arm (n=99) Olive oil (placebo) QD arm (n=99) | 399 | M or F, age ≥ 18 years, with serum TG values at screening in the range ≥ 500 mg/dL and < 2000 mg/dL | 12 weeks | Completed CSR |
| Phase III Efficacy PK/PD | Study OM-EPA-004 | 5.3.5.1 | To evaluate efficacy and safety of adding Epanova™ to statin therapy for lowering non-HDL cholesterol in subjects with persistent hypertriglyceridemia and high-risk for cardiovascular disease. | Randomized, double-blind, olive oil-controlled, parallel group design | Epanova™ 2g QD (n=215); Epanova™ 4g QD (n=216) Olive oil (placebo) QD arm (n=216) | 647 | Subjects at high risk for a future cardiovascular event (with high serum TG ≥ 200 and < 500 mg/dL despite being on a statin for at least 4 weeks prior to screening | 6 weeks | Completed CSR |

The pivotal study, EVOLVE, was a 12-week, randomized (1:1:1:1), double-blind, placebo (olive oil)-controlled, 4-parallel-group, multicenter (74), multinational trial. A total of 399 subjects were enrolled. The overall dropout rate was about 9%. The ITT population included 399 subjects; the modified ITT included 393 subjects.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

The primary efficacy endpoint was the % change in TG levels from baseline (average of Weeks -2, -1, and 0) to the end of treatment (average of Weeks 10 and 12). The secondary efficacy endpoint included the % change from baseline (average of Weeks -2, -1, and 0) to end of treatment (average of Weeks 10 and 12) in serum non-HDL-C and HDL-C. The other lipid and lipoprotein variables were under tertiary efficacy endpoints.

The primary, secondary, and tertiary continuous efficacy endpoints were analyzed using an ANCOVA model with treatment and use of lipid-altering drugs (yes or no) as factors and baseline as a covariate. If the data were not normally distributed, they were ranked prior to the final analysis. Pairwise comparisons of each Epanova group to olive oil were performed using the Dunnett's procedure for the primary efficacy endpoint and the Hommel's procedure for the secondary efficacy endpoints to control the type 1 error rate. No multiplicity adjustment was planned for the tertiary endpoints (however, the sponsor used the Dunnett's procedure to adjust p-values for the pairwise comparisons).

Comments for Internal Discussion:

The indication the sponsor is seeking includes TG, (b) (4) variables. TG is the (b) (4)

. In addition, in the proposed labeling, (b) (4) . Therefore, how to present the results may be a labeling issue.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

File-ability Checklist

| Content Parameter | Yes | No | NA | Comments |
|---|-----|----|----|--|
| Index is sufficient to locate necessary reports, tables, data, etc. | X | | | |
| ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | X | | | No ISE is required and submitted. |
| Data sets in EDR are accessible and include adequate files for describing the data (e.g., define.pdf files). | X | | | Datasets with both SDTM and ADaM formats were submitted. |
| Data listings and intermediate analysis tables were sufficient to permit a statistical review. | X | | | |
| Safety and efficacy were investigated for subgroups based on gender, race, and age (including a subgroup for 65 and older) (if applicable). | X | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans and followed in the study reports. | X | | | |
| Designs utilized are appropriate for the indications requested. | X | | | |
| Intention-to-treat analysis was performed. | X | | | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | X | | | Datasets for ISS were submitted. |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | No interim analysis was planned or conducted. |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | |
| Effects of dropouts on primary analyses were investigated. | X | | | LOCF; Multiple Imputation; MMRM |

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? **YES**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Identify and list any potential review issues.
None at this moment except labeling.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Table 3.1.1 Summary of TG Primary Endpoint Analysis — MITT Population

| Triglycerides (mg/dL) | Olive Oil (N=99) | Epanova | | |
|-----------------------------------|---------------------|------------------|------------------|------------------|
| | | 2 g (N=100) | 3 g (N=101) | 4 g (N=99) |
| Baseline [1] | | | | |
| N | 98 | 99 | 97 | 98 |
| Mean (SD) | 788.5 (305.11) | 790.1 (269.01) | 820.4 (353.15) | 783.6 (335.21) |
| Median | 682.3 | 717.0 | 728.0 | 655.0 |
| % Change from Baseline [2] | | | | |
| N | 98 | 95 | 94 | 95 |
| Mean (SD) | 9.5 (76.32) | -20.7 (32.37) | -15.5 (65.89) | -25.0 (34.72) |
| Median | -10.4 | -24.5 | -23.4 | -30.7 |
| LSM [3] | -4.26 | -25.94 | -25.46 | -30.86 |
| 95% CI | (-13.07, 5.44) | (-32.84, -18.33) | (-32.44, -17.75) | (-37.32, -23.74) |
| LSM Difference from Olive Oil | | -21.68 | -21.19 | -26.60 |
| 95% CI Bonferroni-corrected | | (-40.70, -2.89) | (-40.32, -2.29) | (-45.12, -8.38) |
| P-value [4] | | 0.005 [r] | 0.007 [r] | < 0.001 [r] |

[1] Baseline = Average of Weeks -2, -1 and 0.

[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed data. LSM, LSM differences and 95% CIs were back-transformed for tabulation.

[4] P-value for treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil. [r] indicates data were ranked prior to performing ANCOVA.

Table 3.1.2 Non-HDL and HDL Cholesterol Secondary Endpoint Analyses — MITT Population

| Lipid (mg/dL) | Olive Oil (N=99) | Epanova | | |
|-----------------------------------|---------------------|-----------------|-----------------|-----------------|
| | | 2 g (N=100) | 2 g (N=100) | 2 g (N=100) |
| Non-HDL Cholesterol | | | | |
| Baseline [1] | | | | |
| N | 98 | 99 | 97 | 99 |
| Mean (SD) | 220.2 (54.37) | 221.0 (62.30) | 228.3 (74.10) | 235.3 (72.77) |
| Median | 214.5 | 205.3 | 215.3 | 225.0 |
| % Change from Baseline [2] | | | | |
| Mean (SD) | 7.5 (37.43) | -5.2 (19.62) | -3.9 (28.10) | -7.9 (19.63) |
| Median | -0.9 | -7.7 | -3.6 | -7.7 |
| LSM [3] | 2.53 | -7.61 | -6.89 | -9.63 |
| 95% CI | (-2.31, 7.61) | (-12.02, -2.97) | (-11.35, -2.21) | (-13.95, -5.09) |
| LSM Difference from Olive Oil | | -10.14 | -9.42 | -12.16 |
| 95% CI Bonferroni-corrected | | (-21.01, 0.71) | (-20.34, 1.48) | (-22.92, -1.43) |
| P-value [4] | | 0.017 [r] | 0.019 [r] | 0.001 [r] |
| HDL Cholesterol | | | | |
| Baseline [1] | | | | |
| N | 98 | 99 | 97 | 99 |
| Mean (SD) | 29.2 (7.93) | 28.0 (6.87) | 29.0 (7.93) | 29.9 (9.22) |
| Median | 28.7 | 27.3 | 28.0 | 28.7 |
| % Change from Baseline [2] | | | | |
| Mean (SD) | 5.1 (29.94) | 9.8 (22.22) | 6.0 (19.69) | 7.3 (17.88) |
| Median | 2.2 | 7.0 | 6.9 | 5.0 |
| LSM [3] | 1.92 | 7.35 | 3.78 | 5.77 |
| 95% CI | (-1.98, 5.98) | (3.18, 11.68) | (-0.27, 7.99) | (1.65, 10.06) |
| LSM Difference from Olive Oil | | 5.42 | 1.86 | 3.85 |
| 95% CI Bonferroni-corrected | | (-4.00, 14.86) | (-7.42, 11.14) | (-5.51, 13.23) |

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

P-value [4] 0.076 [r] 0.091 [r] 0.091 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.

[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed percent change. LSM, LSM differences and 95% CIs were back-transformed for tabulation.

[4] Adjusted p-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Hommel's procedure for multiple comparisons of each Epanova vs. olive oil. [r] indicates data were ranked prior to performing ANCOVA.

Table 3.1.3 Tertiary Lipid Analyses for the MITT Population

| Lipid (mg/dL) | Baseline [1] LSM % Change [2] P-value [3] | Olive Oil (N=99) | Epanova 2 g (N=100) | Epanova 3 g (N=101) | Epanova 4 g (N=99) |
|--------------------|---|---------------------|---------------------------|---------------------------|--------------------------|
| TC | Baseline | 249.4 | 249.0 | 257.4 | 265.3 |
| | LSM % Change | 3.17 | -5.44 | -4.85 | -7.46 |
| | P-value | | 0.037 [r] | 0.083 [r] | 0.003 [r] |
| TC/HDL-C | Baseline | 9.1 | 9.5 | 9.7 | 9.6 |
| | LSM % Change | -0.15 | -11.82 | -8.62 | -13.13 |
| | P-value | | 0.024 [r] | 0.049 [r] | 0.002 [r] |
| LDL-C | Baseline | 81.5 | 83.0 | 84.7 | 90.3 |
| | LSM % Change | 3.00 | 19.20 | 14.25 | 19.35 |
| | P-value | | 0.003 [r] | 0.072 [r] | < 0.001 [r] |
| VLDL-C | Baseline | 139.0 | 137.9 | 143.6 | 143.9 |
| | LSM % Change | -8.52 | -26.55 | -26.44 | -32.98 |
| | P-value | | 0.007 [r] | 0.006 [r] | < 0.001 [r] |
| Apo A-I | Baseline | 131.9 | 130.2 | 131.1 | 135.9 |
| | LSM % Change | 5.94 | 0.02 | 1.91 | -0.91 |
| | P-value | | 0.004 [r] | 0.256 [r] | 0.002 [r] |
| Apo B | Baseline | 112.2 | 115.6 | 114.5 | 119.3 |
| | LSM % Change | 0.86 | 3.84 | 2.28 | 3.78 |
| | P-value | | 0.322 [r] | 0.798 [r] | 0.422 [r] |
| Apo C-III | Baseline | 26.0 | 26.7 | 27.5 | 26.6 |
| | LSM % Change | 1.57 | -10.87 | -12.16 | -14.39 |
| | P-value | | 0.020 [r] | 0.005 [r] | < 0.001 [r] |
| Lp-PLA2 (ng/mL) | Baseline | 269.9 | 270.6 | 271.2 | 266.9 |
| | LSM % Change | -1.93 | -14.93 | -11.06 | -17.17 |
| | P-value | | < 0.001 [r] | 0.004 [r] | < 0.001 [r] |
| RLP-C | Baseline | 59.5 | 55.5 | 62.7 | 58.1 |
| | LSM % Change | 3.41 | -20.67 | -22.63 | -27.52 |
| | P-value | | 0.025 [r] | 0.035 [r] | < 0.001 [r] |

[1] Mean Baseline = Average of Weeks -2, -1 and 0 for lipids; = Average of Weeks -1 and 0 for lipoproteins.

[2] % Change at End of Treatment (Average of Weeks 10 and 12) for lipids; = Week 12 for lipoproteins. LSM % change from the ANCOVA model using natural log transformed percent change.

[3] Adjusted p-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil. [r] Indicates the values were ranked prior to performing ANCOVA.

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/s/

CYNTHIA Y LIU
08/30/2013

MARK D ROTHMANN
08/30/2013
I concur