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ORIGINAL RESEARCH

A Head-to-Head Comparison of a Free Fatty Acid Formulation of Omega-3 Pentaenoic Acids Versus Icosapent Ethyl in Adults With Hypertriglyceridemia: The ENHANCE-IT Study

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BACKGROUND: MAT9001 is an omega-3 free fatty acid (FFA) formulation containing mainly eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA). Compared with icosapent ethyl (EPA-ethyl esters [EE]), EPA+DPA-FFA previously showed enhanced triglyceride lowering and higher plasma EPA when both were administered once daily with a very–low fat diet. This trial compared pharmacodynamic responses and plasma omega-3 levels following twice daily dosing, with meals, of EPA+DPA-FFA and EPA-EE in hypertriglyceridemic subjects consuming a Therapeutic Lifestyle Changes diet.

METHODS AND RESULTS: This open-label, randomized, 2-way crossover trial, with 28-day treatment periods separated by ≥28-day washout, was conducted at 8 US centers and included 100 subjects with fasting triglycerides 1.70 to 5.64 mmol/L (150–499 mg/dL) (median 2.31 mmol/L [204 mg/dL]; 57% women, average age 60.3 years). The primary end point was least squares geometric mean percent change from baseline plasma triglycerides. In the 94 subjects with analyzable data for both treatment periods, EPA+DPA-FFA and EPA-EE reduced least squares geometric mean triglycerides from baseline: 20.9% and 18.3%, respectively (*P*=not significant). EPA+DPA-FFA reduced least squares geometric mean high-sensitivity C-reactive protein by 5.8%; EPA-EE increased high-sensitivity C-reactive protein by 8.5% (*P*=0.034). EPA+DPA-FFA increased least squares geometric mean plasma EPA, DPA, and total omega-3 (EPA+docosahexaenoic acid+DPA) concentrations by 848%, 177%, and 205%, respectively, compared with corresponding changes with EPA-EE of 692%, 140%, and 165% (all *P*<0.001). EPA+DPA-FFA increased docosahexaenoic acid by 1.7%; EPA-EE decreased docosahexaenoic acid by 3.3% (*P*=0.011). Lipoprotein cholesterol and apolipoprotein responses did not differ between treatments.

CONCLUSIONS: EPA+DPA-FFA raised plasma EPA, DPA, and total omega-3 significantly more than did EPA-EE. EPA+DPA-FFA also reduced triglycerides and high-sensitivity C-reactive protein without increasing low-density lipoprotein cholesterol.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04177680.

Key Words: docosapentaenoic acid ■ eicosapentaenoic acid ■ hypertriglyceridemia ■ omega-3 fatty acids ■ triglycerides

Fasting and postprandial hypertriglyceridemia are associated with increased risk for cardiovascular disease and, when severe, pancreatitis.[1,2] Long-chain omega-3 fatty acids, when consumed in sufficient quantities, have been shown to lower triglyceride levels and to have antiatherosclerotic properties.[3,4]

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CLINICAL PERSPECTIVE

What Is New?

- Twice daily dosing with meals of a free fatty acid formulation of eicosapentaenoic acid (EPA) plus docosapentaenoic acid (DPA) was compared with an EPA ethyl ester formulation in hypertriglyceridemic subjects consuming a Therapeutic Lifestyle Changes diet.
- EPA+DPA-free fatty acid raised plasma EPA, DPA, and total omega-3 fatty acid concentrations significantly more than did EPA-ethyl ester.
- Both formulations reduced triglycerides and lipoprotein lipid, apolipoprotein, and proprotein convertase subtilisin kexin type 9 concentrations; EPA+DPA-free fatty acid reduced high-sensitivity C-reactive protein concentration compared with EPA-ethyl ester.

What Are the Clinical Implications?

- These data support the potential for atherosclerotic cardiovascular disease risk reduction with a highly bioavailable free fatty acid formulation of EPA+DPA.

Nonstandard Abbreviations and Acronyms

DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EE	ethyl esters
EPA	eicosapentaenoic acid
FFA	free fatty acid
LSGM	least squares geometric mean
PCSK9	proprotein convertase subtilisin kexin type 9
TC	total cholesterol
TLC	Therapeutic Lifestyle Changes

Both ethyl ester (EE) and carboxylic acid (also referred to as free fatty acid [FFA]) formulations of long-chain omega-3 fatty acid concentrates have been authorized by the Food and Drug Administration in the United States for the management of severe hypertriglyceridemia (fasting triglycerides ≥5.65 mmol/L [500 mg/dL]).[3] In REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial), 4 g/d of icosapent ethyl, an EE formulation of eicosapentaenoic acid (EPA), lowered the incidence of major adverse cardiovascular events by 25% in high- and very–high-risk patients on statin therapy with persistent triglyceride elevation (1.53–5.64 mmol/L [135–499 mg/dL]),[5] leading to Food and Drug Administration authorization of icosapent ethyl for an indication for reducing cardiovascular risk among patients with elevated triglycerides as an add-on to maximally tolerated statin therapy.

FFA formulations of long-chain omega-3 fatty acids have been shown to have less dependence than EE formulations on coadministration with a fat-containing meal for bioavailability.[6–8] MAT9001 (Matinas BioPharma, Bedminster, NJ), an investigational product that delivers a mixture of long-chain omega-3 FFA, including EPA and docosapentaenoic acid (DPA), resulted in a significantly higher plasma EPA area under the concentration curve as well as significantly larger reductions in triglycerides and other lipoprotein-related variables (including total cholesterol [TC], non–high-density lipoprotein cholesterol [non–HDL-C], very–low-density lipoprotein cholesterol [VLDL-C], and PCSK9 [proprotein convertase subtilisin kexin type 9]) compared with EPA-EE when administered with a very–low-fat meal to subjects with triglycerides 2.26 to 4.52 mmol/L (200–400 mg/dL) without use of stable-dose statin, or 2.26 to 3.96 mmol/L (200–350 mg/dL) with use of stable-dose statin.[8,9] However, there have been no head-to-head comparisons of the pharmacodynamic effects of EPA+DPA-FFA versus EPA-EE when both are consumed with a diet containing a more moderate level of fat. In this randomized, open-label, crossover trial, 4 g/d of EPA+DPA-FFA and EPA-EE were studied to assess and compare their effects on triglycerides and other lipoprotein lipids, apolipoproteins, PCSK9, hs-CRP (high-sensitivity C-reactive protein) , and plasma long-chain omega-3 fatty acid levels in men and women with elevated triglycerides (1.70–5.64 mmol/L [150–499 mg/dL]) on a Therapeutic Lifestyle Changes (TLC) diet.[10]

METHODS

Study Design and Treatments

This open label, randomized, crossover study was conducted at 8 clinical research sites in the United States from June 2020 to November 2020 in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki (2000), and the US 21 Code of Federal Regulations. A list of the investigators is available in the Appendix. The trial was registered at ClinicalTrials.gov with the identifier NCT04177680. The data that support the findings of this study are available from the corresponding author upon reasonable request. The protocol was approved by Advarra (Columbia, MD), an appropriately constituted institutional review board. All subjects provided informed consent before their enrollment in the study.

The trial included a 4-week TLC diet[10] lead-in period, followed by two 28-day treatment periods, which were separated by a washout period of ≥28 days. Subjects

visited the clinic for assessments during screening (days –28, –14, and –7, where day 1 is the first day of treatment), on the first day of each treatment period (day 1), on days 22 and 29 of each treatment period, and when 1 week remained of the washout period between treatments (day –7 of the second treatment period). At the first visit (day –28), subjects completed the Meats, Eggs, Dairy, Fried Foods, In Baked Goods, Convenience Foods, Table Fats, Snacks (MEDFICTS) dietary assessment questionnaire,[11] and those who scored <40, indicating compliance with the TLC diet, proceeded directly to the visit 2 (day –14) procedures. On day 1 of the first treatment period, eligible subjects were randomly assigned to 1 of 2 treatment sequences: EPA-EE during the first treatment period and EPA+DPA-FFA during the second treatment period, or vice versa, using a computer-generated randomization scheme. The clinical research site used an interactive web response system to randomize the subjects. The EPA+DPA-FFA product (known experimentally as MAT9001 and commercially as Lypdiso) was manufactured by Matinas BioPharma, Inc. (Bedminster, NJ). It is a long-chain omega-3 FFA concentrate in a 1-g capsule that contains a proprietary and patented mixture of predominantly EPA, with meaningful amounts of DPA, with trace levels of docosahexaenoic acid (DHA) and other omega-3 fatty acids. The EPA-EE comparator (Vascepa) was manufactured by Amarin Pharma, Inc. (Bedminster, NJ). It is a 1-g capsule containing icosapent ethyl, the EE form of EPA, and 0 g DPA. Subjects were instructed to take 2 capsules twice daily with meals each day during the 28-day treatment periods. The first doses in each treatment period were administered at the clinic along with a TLC-compliant meal replacement bar.

During screening and throughout the study, subjects were instructed to follow the TLC diet[10] along with balanced energy intake and expenditure to maintain desirable body weight and prevent weight gain. They were also instructed to consume not >1 meal per week containing fish or seafood, and to avoid fish or seafood consumption at least 48 hours before each clinic visit. Compliance with the TLC diet was assessed verbally during screening and periodically throughout the study using the MEDFICTS dietary assessment questionnaire.[11] A score of <40 was considered compliant with the TLC diet. Compliance with study product consumption was assessed verbally and by collection of excess study product returned to the clinic on days 22 and 29 of each treatment period. Compliance was calculated as the number of capsules consumed, divided by the number of capsules prescribed, multiplied by 100. If calculated compliance was <80%, subjects received additional instructions about the treatment regimens to increase compliance.

Subjects

Eligible subjects included generally healthy men and women at least 18 years of age, each with a body mass index of ≥20.0 kg/m^2, and fasting plasma triglyceride levels of ≥1.70 to ≤5.64 mmol/L (150–499 mg/dL). Fasting (at least 9 hours, water only) blood samples collected on days –14 and –7 of the screening period were used to determine triglyceride eligibility for entry into the study. If the subject's average triglyceride level from these 2 visits fell outside of the required range, an additional measurement was obtained with a minimum window of 3 days before the randomization visit (day 1). If a third sample was collected, entry into the study was based on the average of the triglyceride values from all 3 samples. Individuals taking a statin (with or without ezetimibe), oral diabetes medication, antihypertensive medication, or hormone therapy were still eligible if the dose had been stable for at least 4 weeks before the first triglyceride qualification measurement (day –14). Use of other lipid-altering medications, including bile acid sequestrants, fibrates, drug forms of niacin, bempedoic acid, and omega-3 EE drugs within 4 weeks of the first triglyceride qualification measurement or during the study, and PCSK9 inhibitor agents within 12 weeks of the first triglyceride qualification measurement or during the study, was not allowed. Likewise, use of high-dose fish oil or omega-3 supplements containing >1 g of EPA and DHA within 4 weeks, use of supplements containing ≤1 g EPA and DHA within 2 weeks, or use of any other dietary supplement known to alter the lipid profile or triglycerides within 2 weeks of the first triglyceride qualification measurement or during the study was not allowed.

Pharmacodynamic and Safety Assessments

For the examination of the treatment effects on plasma lipoprotein lipids and hs-CRP, the average of the values from analyses of the 2 fasting blood samples collected at the beginning of each treatment period (days –7 and 1) and the 2 samples from the end of each treatment period (days 22 and 29) were averaged for baseline and end of treatment, respectively. For the apolipoprotein, PCSK9, and omega-3 fatty acid analyses, baseline and end of treatment were the values from the analyses of samples collected on day 1 and day 29, respectively. Lipoprotein lipid, apolipoprotein, PCSK9, and hs-CRP analyses were performed by a central laboratory, Medpace Reference Laboratory (Cincinnati, OH), using validated assays. TC was assessed using a photometric assay, HDL-C by precipitation, and triglycerides by colorimetry. Low-density lipoprotein cholesterol (LDL-C) and VLDL-C were calculated using the Martin/Hopkins method,[12] and non–HDL-C was calculated as TC minus HDL-C. Plasma apo (apolipoprotein) A1, apo

B, and hs-CRP were assessed by nephelometery, apo C3 by a turbidimetric assay, and PCSK9 by an enzyme immunoassay. Plasma concentrations of total EPA, DHA, and DPA were measured by the Bioanalytical Laboratory of Pharma Medica Research (Mississauga, Ontario, Canada) using Analyst Software version 1.6.3 according to an achiral, liquid chromatographic, tandem mass spectrometric detection method.

Chemistry and hematology panels were completed at the beginning and end of each treatment period (also by Medpace Reference Laboratory), and treatment-emergent adverse events were assessed by asking open-ended questions at all clinic visits or through spontaneous reporting by the subject. Blood pressure, heart rate, body weight, and waist circumference were assessed at all visits; height was measured at the first screening visit only.

Statistical Analysis

Based on results from prior research, a sample size of 85 evaluable subjects was needed to detect a difference of 10% in the triglyceride response between treatment conditions, based on an α of 0.05, β of 0.10 (90% power), and an SD of 28% for the difference between treatments in the change from baseline triglyceride concentration.[9] A sample of 100 subjects was randomized to allow for subject attrition. A minimum of 50% of the study sample (as controlled through randomization stratification) was required to have a qualifying triglyceride value in the range of 2.26 to 5.64 mmol/L (200–499 mg/dL; ie, no more than 49.9% of subjects could have triglycerides 1.70–2.25 mmol/L [150–199 mg/dL]).

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Tests for significance were performed at α=0.05 and were 2-sided. The pharmacodynamic analyses, including the primary and secondary end points, were conducted in subjects for whom the estimation of the pharmacodynamic parameters was possible for both treatment periods (defined as the pharmacodynamic population). Because the half-life of EPA from EPA-EE is ≈89 hours, and that for EPA from EPA+DPA-FFA is ≈27 hours, samples from subjects who had been off the study drug for at least 3 days were not included in the pharmacodynamic analyses. Analyses were also completed in a per protocol population, which included all subjects in the pharmacodynamic population for whom compliance with the study drug for both study periods was at least 80%, and no clinically important protocol violations or deviations occurred during the trial, and in an intent-to-treat population, which included all subjects who were randomized to a treatment sequence. Because no material differences were observed between results for the intent-to-treat (ie, all randomized subjects) and the pharmacodynamic analyses, the results for the pharmacodynamic analyses are emphasized herein, and selected results for the per protocol analyses (for groups of variables that contained differences from the pharmacodynamic population results) are also presented in the body of the article. Complete per protocol results are provided in the Supplemental Material. Safety analyses were performed for all subjects who were randomized and received at least 1 dose of any study treatment.

Results for the primary and secondary outcomes were summarized using geometric means (GM) for baseline values and least squares GM (LSGM) for end of treatment and percent change from baseline values. Table S1 for the pharmacodynamic population and Table S2 for the per protocol population are provided showing median and interquartile limits for values at baseline, end of treatment, and percent change from baseline to facilitate comparisons with results from other studies. Variability in the GM and LSGM were reported as 95% CIs. LSGM and 95% CI for end of treatment were computed as the back-transformed LS means and 95% CI obtained from a mixed-effects model using the natural log (ln)-transformed end of treatment values as the dependent variable in the model with terms for the ln-transformed baseline as a covariate, and period, sequence, treatment, and triglycerides group as fixed effects and subject nested within sequence as a random effect. The treatments were compared using a mixed-effects model using the ln-transformed values of percent change from baseline in triglycerides + scaling factor of 100 (scaling factor used to account for possible negative values) as the dependent variable in the model with terms for the ln-transformed baseline as a covariate, and period, sequence, treatment, and triglycerides group as fixed effects and subject nested within sequence as a random effect. LSGM and 95% CIs for percent change from baseline were computed as the back-transformed, scaled down least squares means and 95% CI for each treatment. Treatment difference as measured by least squares mean differences and 95% CI were constructed for the ln-scale values, back-transformed, and expressed as the ratio of LSGMs. There was no adjustment for multiplicity (ie, multiple testing of secondary outcomes), because the trial had a single, prespecified primary outcome variable (percent change from baseline for plasma triglycerides). All other outcome variables were considered secondary or exploratory. Assumptions of normality of residuals were examined for substantial departures from normality. No substantial departures from normality were noted after ln-transformation. *P* values for sequence were not statistically significant for any of the primary and secondary end points. Also, no clinically relevant differences were apparent in responses according to treatment sequence, so only pooled data by treatment are presented.

Differences between treatments in the changes from baseline in vital signs and anthropometric values were

compared using a paired *t*- test or Wilcoxon signed rank test, depending on the distribution of the data.

RESULTS

A description of the number of subjects screened, randomized, completed, and included in the pharmacodynamic, intent-to-treat/safety, and per protocol populations is shown in the Figure. The pharmacodynamic population was the primary population used for the pharmacodynamic analyses, but supportive analyses of pharmacodynamic parameters were also performed in the per protocol and intent-to-treat populations. Differences from the pharmacodynamic population for key outcomes are mentioned herein. A total of 100 subjects were enrolled in the study, and 95 completed both treatment periods with at least 1 post-baseline efficacy sample available for both. A summary of the demographic and other baseline characteristics of subjects in the pharmacodynamic population is shown in Table 1. Mean percent compliance (SD) with EPA+DPA-FFA was 95.5 (9.9) and with EPA-EE was 96.1 (5.4); 92.6% of subjects were at least 80% compliant with EPA+DPA-FFA and 96.8% with EPA-EE.

GM and LSGM baseline, end of treatment, and percent change from baseline for lipoprotein lipids in the pharmacodynamic population are shown in Table 2 and in the per protocol population in Table 3. The LSGM percent change from baseline triglycerides in the pharmacodynamic population was –20.9% with EPA+DPA-FFA and –18.3% with EPA-EE (P=0.270). Although the difference between treatments was not statistically significant in the pharmacodynamic population, in the per protocol population, the LSGM percent changes from baseline of –20.0% and –15.1%, for EPA+DPA-FFA and EPA-EE, respectively, were significantly different (P=0.041). Both EPA+DPA-FFA and EPA-EE reduced TC, LDL-C, HDL-C, VLDL-C, and non–HDL-C concentrations, but there were no statistically significant differences between treatments in their effects on these parameters in the pharmacodynamic population. However, in the per protocol population, EPA+DPA-FFA compared with EPA-EE produced significantly larger reductions in TC (5.7% versus 3.5%, P=0.043) and VLDL-C (15.0% versus 10.9%, P=0.033).

GM and LSGM baseline, end of treatment, and percent change from baseline values for apolipoproteins, PCSK9, and hs-CRP for the pharmacodynamic population are shown in Table 4. Both EPA+DPA-FFA and EPA-EE reduced apo A1, apo B, apo C3, and PCSK9, but there were no significant differences between treatments in their effects on these parameters. Hs-CRP was reduced by 5.8% with EPA+DPA-FFA but increased by 8.5% with EPA-EE (P=0.034).

GM and LSGM baseline, end of treatment, and percent change from baseline values for plasma omega-3 fatty acid concentrations are shown in Table 5. Plasma EPA, DPA, and EPA+DHA+DPA concentrations increased substantially with both treatments, but to a significantly larger extent with EPA+DPA-FFA than with EPA-EE (P<0.001 for all). DHA increased by 1.7% with EPA+DPA-FFA and decreased by 3.3% with EPA-EE (P=0.011).

Median (first quartile, third quartile) values at baseline, end of treatment, and percent change from baseline for plasma lipoprotein lipids, apolipoproteins, PCSK9, hs-CRP, and omega-3 fatty acids in the pharmacodynamic population and in the per protocol population are provided as Table S1 and Table S2, respectively. GM and LSGM baseline, end of treatment, and percent change from baseline values for apolipoproteins, PCSK9, hs-CRP, and plasma omega-3 fatty acid concentrations for the per protocol population are provided in Table S3. Waterfall plots for subjects in the pharmacodynamic population for the change from baseline to end of treatment triglycerides and EPA concentrations are presented in Figure S1 and Figure S2, respectively.

Forty-three subjects (44.3%) who received EPA+DPA-FFA and 28 subjects (28.0%) who received EPA-EE reported at least 1 adverse event. The adverse events that occurred in at least 2 subjects in either treatment condition in the safety population are presented in Table 6. The most common events among subjects who received EPA+DPA-FFA were nausea,

Table 1. Demographic and Baseline Characteristics of Subjects in the Intent-to-Treat/Safety Population (n=100)

Parameter	Mean (SD) or n (%)
Age, y	60.3 (10.9)
Sex	
Men	43 (43.0%)
Women	57 (57.0%)
Race	
White	97 (97.0%)
Black	2 (2.0%)
American Indian or Alaska Native	1 (1.0%)
Ethnicity	
Hispanic or Latino	7 (7.0%)
Not Hispanic or Latino	91 (91.0%)
Not reported	2 (2.0%)
Body mass index, kg/m^2	32.1 (6.6)
Lipid drug	
Neither statin nor ezetimibe	53 (53.0%)
Statin only	46 (46.0%)
Both statin and ezetimibe	1 (1.0%)
Triglyceride stratification factor	
<2.26 mmol/L, 200 mg/dL	41 (41.0%)
≥2.26–5.64 mmol/L, 200–499 mg/dL	59 (59.0%)

Table 2. Baseline, End of Treatment, and Percent Changes From Baseline Lipoprotein Lipid Concentrations in the Pharmacodynamic Population (n=94)

Lipid*	Baseline†	End of treatment‡	% Δ‡	*P* value§
Triglycerides, mmol/L				0.270
EPA+DPA-FFA	2.41 (2.28 to 2.54)	1.89 (1.81 to 1.99)	−20.9 (−24.6 to −17.1)	
EPA-EE	2.37 (2.23 to 2.54)	1.95 (1.86 to 2.05)	−18.3 (−22.1 to −14.3)	
TC, mmol/L				0.166
EPA+DPA-FFA	5.05 (4.77 to 5.34)	4.74 (4.66 to 4.84)	−5.6 (−7.3 to −3.8)	
EPA-EE	5.02 (4.74 to 5.31)	4.82 (4.74 to 4.92)	−4.1 (−5.9 to −2.3)	
LDL-C, mmol/L				0.237
EPA+DPA-FFA	3.00 (2.77 to 3.26)	2.85 (2.77 to 2.93)	−4.8 (−7.2 to −2.4)	
EPA-EE	2.98 (2.75 to 3.24)	2.90 (2.82 to 2.98)	−3.1 (−5.6 to −0.6)	
HDL-C, mmol/L				0.689
EPA+DPA-FFA	1.05 (0.99 to 1.10)	1.03 (1.00 to 1.05)	−1.7 (−4.0 to 0.6)	
EPA-EE	1.05 (1.00 to 1.10)	1.04 (1.01to 1.06)	−1.1 (−3.3 to 1.2)	
VLDL-C, mmol/L				0.264
EPA+DPA-FFA	0.88 (0.84 to 0.91)	0.87 (0.83 to 0.91)	−15.5 (−18.3 to −12.5)	
EPA-EE	0.74 (0.71 to 0.76)	0.76 (0.73 to 0.78)	−13.3 (−16.2 to −10.3)	
Non–HDL-C, mmol/L				0.188
EPA+DPA-FFA	3.94 (3.68 to 4.20)	3.65 (3.55 to 3.73)	−7.0 (−9.1 to −4.8)	
EPA-EE	3.91 (3.65 to 4.17)	3.70 (3.63 to 3.81)	−5.2 (−7.4 to −3.0)	

DPA indicates docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non–HDL-C, non–high-density lipoprotein cholesterol; TC, total cholesterol; and VLDL-C, very–low-density lipoprotein cholesterol.

*To convert millimoles per liter to milligrams per deciliter values for triglycerides, multiply by 88.5 and for cholesterol multiply by 38.6.

†Values are geometric mean (95% CI). Baseline was defined as the average of the final 2 pretreatment visits for each treatment period.

‡Values are least squares geometric mean (95% CI). End of treatment was defined as the average of values collected at the treatment visits on days 22 and 29; % Δ is the percent change from baseline to end of treatment.

§*P* value is for the difference between treatments in the percent change from baseline.

diarrhea, eructation, and arthralgia. Among subjects who received EPA-EE, the most common events were diarrhea, arthralgia, and constipation. All but 1 adverse event was rated mild or moderate in severity. No subject who received EPA+DPA-FFA experienced an adverse event that resulted in discontinuation from the study. Two subjects who received EPA-EE discontinued the study because of adverse events: one experienced moderate arthralgia and jaw pain, and severe tinnitus while on treatment; the other experienced moderate arthralgia while off treatment. None of these was considered to be related to the study treatment, and each of the events subsequently resolved. No serious adverse events or deaths were reported during the study. There were no clinically meaningful serum chemistry or hematology changes during the study, and no statistically significant differences between treatment conditions in changes from baseline systolic blood pressure, diastolic blood pressure, pulse rate, or body weight.

DISCUSSION

In this study of subjects with triglycerides 1.70 to 5.64 mmol/L (150–499 mg/dL), 28-day treatment with EPA+DPA-FFA or EPA-EE administered twice daily with meals, on a background TLC diet, reduced triglycerides 20.9% and 18.3%, respectively. Among the 94 subjects in the a priori defined primary pharmacodynamic population, this difference did not reach statistical significance. However, among the 82 subjects in the per protocol population without material protocol violations or deviations, whose overall compliance in both treatment periods was at least 80%, EPA+DPA-FFA and EPA-EE reduced triglycerides 20.0% and 15.1% (*P*=0.041). The greater reduction in triglyceride concentration in the per protocol population was consistent with the result from a prior study comparing these agents in a group with fasting triglycerides of 2.26 to 4.52 mmol/L (200–400 mg/dL) (median reductions of 33.0% and 10.5% with EPA+DPA-EE and EPA-EE, respectively).[9] In that trial, subjects were housed in a clinical research unit where they consumed the treatments (four 1-g capsules) 30 minutes after consumption of a standard low-fat breakfast meal for 14 days.[9] Similarly, reductions from baseline for TC and VLDL-C in the present study were not significantly different between treatments in the pharmacodynamic analyses but were significantly larger for EPA+DPA-FFA than EPA-EE in

Table 3. Baseline, End of Treatment, and Percent Changes From Baseline Lipoprotein Lipid Concentrations in the Per Protocol Population (n=82)

Lipid*	Baseline†	End of treatment‡	% Δ‡	*P* value§
Triglycerides, mmol/L				0.041
EPA+DPA-FFA	2.41 (2.27 to 2.55)	1.91 (1.82 to 2.00)	–20.0 (–23.7 to –16.2)	
EPA-EE	2.37 (2.21 to 2.54)	2.03 (1.93 to 2.12)	–15.1 (–19.0 to –11.0)	
TC, mmol/L				0.043
EPA+DPA-FFA	5.00 (4.71 to 5.31)	4.71 (4.61 to 4.79)	–5.7 (–7.4 to –3.9)	
EPA-EE	4.97 (4.69 to 5.28)	4.82 (4.71 to 4.90)	–3.5 (–5.2 to –1.7)	
LDL-C, mmol/L				0.169
EPA+DPA-FFA	2.95 (2.69to 3.24)	2.80 (2.75 to 2.87)	–4.8 (–7.3 to –2.3)	
EPA-EE	2.93 (2.67 to 3.21)	2.87 (2.80 to 2.95)	–2.8 (–5.3 to –0.2)	
HDL-C, mmol/L				0.524
EPA+DPA-FFA	1.05 (0.99 to 1.11)	1.03 (1.00 to 1.05)	–2.4 (–4.8 to 0.0)	
EPA-EE	1.05 (0.99 to 1.10)	1.04 (1.01 to 1.06)	–1.3 (–3.7 to 1.1)	
VLDL-C, mmol/L				0.033
EPA+DPA-FFA	0.87 (0.83 to 0.91)	0.74 (0.71 to 0.76)	–15.0 (–17.8 to –12.1)	
EPA-EE	0.86 (0.82 to 0.91)	0.77 (0.75 to 0.80)	–10.9 (–13.8 to –7.8)	
Non–HDL-C, mmol/L				0.074
EPA+DPA-FFA	3.89 (3.60 to 4.17)	3.60 (3.52 to 3.68)	–6.9 (–9.0 to –4.7)	
EPA-EE	3.86 (3.57 to 4.14)	3.70 (3.60 to 3.78)	–4.4 (–6.6 to –2.2)	

DPA indicates docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non–HDL-C, non–high-density lipoprotein cholesterol; TC, total cholesterol; and VLDL-C, very–low-density lipoprotein cholesterol.

*To convert millimoles per liter to milligrams per deciliter values for triglycerides multiply by 88.5 and for cholesterol multiply by 38.6.

†Values are geometric mean (95% CI). Baseline was defined as the average of the final 2 pretreatment visits for each treatment period.

‡Values are least squares geometric mean (95% CI). End of treatment was defined as the average of values collected at the treatment visits on days 22 and 29; % Δ is the percent change from baseline to end of treatment.

§*P* value is for the difference between treatments in the percent change from baseline.

the per protocol analysis, also in line with the previous study results that showed larger effects with EPA+DPA-FFA.[9] Both EPA+DPA-FFA and EPA-EE modestly reduced LDL-C from baseline (–4.8% and –3.1%, respectively, in the present study; –2.4% and –4.3%, respectively, in the prior study). Both EPA+DPA-FFA and EPA-EE reduced HDL-C and apo A1. These effects were also observed in a prior study and are of uncertain clinical relevance.[9]

EE forms of long-chain omega-3 fatty acids are not well absorbed if consumed with little or no fat, because intestinal lipase from bile that is produced upon ingestion of lipid is necessary to hydrolyze the bond between the fatty acid and the ester.[6,7,13] Results of a pharmacokinetic study showed that EPA+DPA-FFA exhibited significantly increased bioavailability in plasma compared with EPA-EE after both single- and multiple-dose administrations when administered with a breakfast meal providing 4% of energy from fat.[8] The results of the present trial, where EPA+DPA-FFA and EPA-EE were consumed with meals as part of a diet targeting <7% of calories from saturated fat, up to 10% of calories from polyunsaturated fat, and up to 20% of calories from monounsaturated fat,[10] confirm the increased bioavailability of the FFA formulation compared with the EE formulation when consumed with meals that have moderate fat content and when the daily dosage is split between 2 administrations.

A recent analysis examining EPA levels and cardiovascular outcomes in REDUCE-IT demonstrated that higher on-treatment EPA levels correlated strongly with reduced cardiovascular events.[14] However, an examination of the top tertiles of achieved EPA (>116 µg/mL) and DHA (>105 µg/mL) in the STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia) study, which examined a different FFA formulation of omega-3, showed neither benefit nor harm, suggesting a neutral effect of omega-3 fatty acids in that study, even at the highest achieved levels.[15] A required threshold of achieved EPA level (≈100 µg/mL) has been suggested to be necessary to achieve a clinical cardiovascular benefit.[16] However, the results from the STRENGTH study suggest that either a higher EPA threshold may be necessary, or perhaps that the combination of EPA with DHA may be less effective. In the present trial, plasma EPA levels increased significantly by 848% with EPA+DPA-FFA and by 692% with EPA-EE (LSGM percent changes from baseline), resulting in

Table 4. Baseline, End of Treatment, and Percent Changes From Baseline Apolipoprotein, PCSK9, and hs-CRP Concentrations in the Pharmacodynamic Population (n=94)

Parameter	Baseline*	End of treatment†	% Δ†	*P* value‡
apo A1, g/L				0.457
EPA+DPA-FFA	1.46 (1.41 to 1.51)	1.40 (1.38 to 1.42)	−4.0 (−5.6 to −2.3)	
EPA-EE	1.45 (1.41 to 1.50)	1.41 (1.39 to 1.44)	−3.1 (−4.7 to −1.5)	
apo B, g/L				0.538
EPA+DPA-FFA	1.01 (0.95 to 1.07)	0.97 (0.95 to 0.99)	−3.5 (−5.9 to −1.1)	
EPA-EE	1.00 (0.94 to 1.06)	0.98 (0.96 to 1.00)	−2.5 (−4.9 to −0.2)	
apo C3, g/L				0.529
EPA+DPA-FFA	0.13 (0.13 to 0.14)	0.12 (0.11 to 0.12)	−12.4 (−15.8 to −9.0)	
EPA-EE	0.13 (0.13 to 0.14)	0.12 (0.11 to 0.12)	−11.1 (−14.4 to −7.7)	
PCSK9, ng/mL				0.800
EPA+DPA-FFA	353 (332 to 376)	331 (316 to 347)	−6.6 (−10.9 to −2.1)	
EPA-EE	355 (336 to 376)	329 (314 to 344)	−7.3 (−11.5 to −2.9)	
hs-CRP, mg/L				0.034
EPA+DPA-FFA	2.3 (1.9 to 2.9)	2.1 (1.9 to 2.4)	−5.8 (−15.3 to 4.7)	
EPA-EE	2.2 (1.7 to 2.7)	2.4 (2.2 to 2.7)	8.5 (−2.4 to 20.7)	

apo indicates apolipoprotein; DPA, docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids; hs-CRP, high-sensitivity C-reactive protein; and PCSK9, proprotein convertase subtilisin kexin type 9.

*Values are geometric mean (95% CI). For apolipoproteins and PCSK9, baseline was the value obtained on day 1; for hs-CRP, baseline was defined as the average of the values obtained on the final 2 pretreatment visits for each treatment period.

†Values are least squares geometric mean (95% CI). For apolipoproteins and PCSK9, end of treatment was the value obtained on day 29; for hs-CRP, end of treatment was defined as the average of values collected at the treatment visits on days 22 and 29; % Δ is the percent change from baseline to end of treatment.

‡*P* value is for the difference between treatments in the percent change from baseline.

end-of-treatment LSGM plasma EPA concentrations of 138 and 115 µg/mL, respectively.

In the omega-3 polyunsaturated fatty acid pathway, alpha linolenic acid is converted to DHA through several steps producing multiple intermediary fatty acids, including EPA and DPA. The ≈140% increase in plasma DPA level with EPA-EE, compared with the ≈170% increase with EPA+DPA-EE was somewhat surprising, considering EPA-EE contained no DPA, and suggests there was substantial conversion of EPA to DPA with EPA-EE. Changes in plasma DHA levels were relatively small with both treatments,

Table 5. Baseline, End of Treatment, and Percent Changes From Baseline Plasma Omega-3 Fatty Acid Concentrations in the Pharmacodynamic Population (n=94)

Plasma fatty acid	Baseline*	End of treatment†	% Δ†	*P* value‡
EPA, µg/mL				<0.001
EPA+DPA-FFA	14.4 (13.1–15.8)	138 (124–153)	848 (754–952)	
EPA-EE	14.8 (13.5–16.2)	115 (104–128)	692 (614–778)	
DHA, µg/mL				0.011
EPA+DPA-FFA	48.1 (45.5–50.9)	49.0 (47.2–50.8)	1.7 (−2.0 to 5.5)	
EPA-EE	48.2 (45.4–51.3)	46.6 (44.9–48.3)	−3.3 (−6.8 to 0.2)	
DPA, µg/mL				<0.001
EPA+DPA-FFA	20.2 (19.0–21.5)	56.1 (52.8–59.6)	177 (160–194)	
EPA-EE	20.3 (19.2–21.6)	48.6 (45.8–51.7)	140 (126–155)	
EPA+DHA+DPA, nmol/mL				<0.001
EPA+DPA-FFA	260 (246–274)	797 (748–849)	205 (187–225)	
EPA-EE	262 (249–276)	692 (650–737)	165 (149–182)	

DHA indicates docosahexaenoic acid; DPA, docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; and FFA, free fatty acids.

*Values are geometric mean (95% CI). Baseline was the value obtained at day 1.

†Values are least squares geometric mean (95% CI). End of treatment was value obtained at day 29; % Δ is the percent change from baseline to end of treatment.

‡*P* value is for the difference between treatments in the percent change from baseline.

Table 6. Adverse Events Occurring in at Least 2 Subjects in Either Treatment Condition

System organ class Preferred term	EPA+DPA-FFA, n (%), n=97	EPA-EE, n (%), n=100
Eye disorders	0 (0.0)	2 (2.0)
Cataracts	0 (0.0)	2 (2.0)
Gastrointestinal disorders	25 (25.8)	11 (11.0)
Abdominal distension	1 (1.0)	2 (2.0)
Constipation	0 (0.0)	3 (3.0)
Diarrhea	10 (10.3)	4 (4.0)
Dyspepsia	2 (2.1)	0 (0.0)
Eructation	6 (6.2)	0 (0.0)
Flatulence	2 (2.1)	1 (1.0)
Nausea	11 (11.3)	0 (0.0)
Infections and infestations	4 (4.1)	2 (2.0)
Urinary tract infection	2 (2.1)	0 (0.0)
Injury, poisoning and procedural complications	5 (5.2)	3 (3.0)
Muscle strain	2 (2.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	7 (7.2)	7 (7.0)
Arthralgia	3 (3.1)	4 (4.0)
Nervous system disorders	2 (2.1)	3 (3.0)
Dizziness	2 (2.1)	0 (0.0)

DPA indicates docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; and FFA, free fatty acids.

a 1.7% LSGM increase with EPA+DPA-FFA and a 3.3% LSGM decrease with EPA-EE, which is consistent with evidence indicating that EPA supplementation does not substantially increase plasma DHA concentrations, and that DPA can be converted to DHA.[17,18]

Although elevated triglycerides have been linked with residual cardiovascular disease risk among patients on statins with well-controlled LDL-C levels, results from the REDUCE-IT and STRENGTH studies have brought the relationships of triglyceride elevation and triglyceride lowering to cardiovascular risk into question.[16] In REDUCE-IT, cardiovascular events with EPA-EE were reduced to a greater extent than would have been expected from the 17% reduction in triglyceride concentration, and STRENGTH was prematurely stopped because of a low probability of demonstrating a clinical benefit, despite a similar triglyceride reduction of 19%.[15,16] These results suggest that omega-3 fatty acids may act to reduce cardiovascular risk through other non–triglyceride-lowering related mechanisms, such as anti-inflammatory and antithrombotic effects.[16,19] In this trial, EPA+DPA-FFA significantly lowered LSGM hs-CRP (–5.8%) compared with EPA-EE (+8.5%). This is notable, because evidence is building that demonstrates reducing inflammatory markers is associated with a lower risk of recurrent cardiovascular events.[20–22]

In contrast to EPA and DHA, less is known about the lipid and cardiovascular effects of DPA, which contains 2 more carbon chain units than EPA and was originally regarded simply as a biosynthetic intermediate in the formation of DHA from EPA. However, results from recent studies indicate that DPA also has substantial triglyceride-lowering effects, and improves other cardiovascular and metabolic disease risk markers, such as platelet aggregation, insulin sensitivity, and cellular plasticity.[23] Hydroxy metabolites from DPA are also involved in promoting resolution of inflammation.[23,24] A pooled analysis from 17 prospective studies demonstrated that risk for all-cause mortality was significantly lower (15%–18%) in the highest versus the lowest quintiles for EPA, DHA, and DPA individually; similar relationships were reported for cardiovascular mortality.[25]

In general, both treatments were well tolerated in this study. All adverse events were mild or moderate in nature, there were no serious adverse events, and there were no laboratory results of clinical concern. However, as in the previous 2-week examination of EPA+DPA-FFA,[9] in this 4-week trial, more subjects reported adverse events when taking EPA+DPA-FFA (44.3%) than when taking EPA-EE (28.0%). More subjects reported nausea and diarrhea when taking EPA+DPA-FFA (11.3% and 10.3%, respectively, compared with 0.0% and 4.0% with EPA-EE). These events did not lead to subject discontinuation but could impact the clinical acceptability of EPA+DPA-FFA for some patients, which might affect adherence. A longer study is needed to better assess the long-term tolerability of EPA+DPA-FFA.

Strengths of the present investigation include its crossover design with a relatively large sample size for a head-to-head comparison trial and the use of a more clinically relevant design (ie, twice daily dosing while following a TLC diet containing a more moderate amount of fat), compared with a previous investigation in which subjects consumed the study products with a very–low-fat meal and took all 4 capsules at once. A limitation of this trial is the predominantly White, non-Hispanic/Latino study sample, which was surprising, because prior collaborations with these research sites had typically yielded more diverse populations. Future research may need to use a stratified randomization scheme to ensure greater representation of racial and ethnic minorities.

In conclusion, these results are consistent with higher bioavailability of EPA from EPA+DPA-FFA, compared with EPA-EE, and support its efficacy for reducing triglycerides and hs-CRP, without significant increases in LDL-C, suggesting potential for beneficial effects of this FFA formulation for atherosclerotic cardiovascular disease risk reduction.

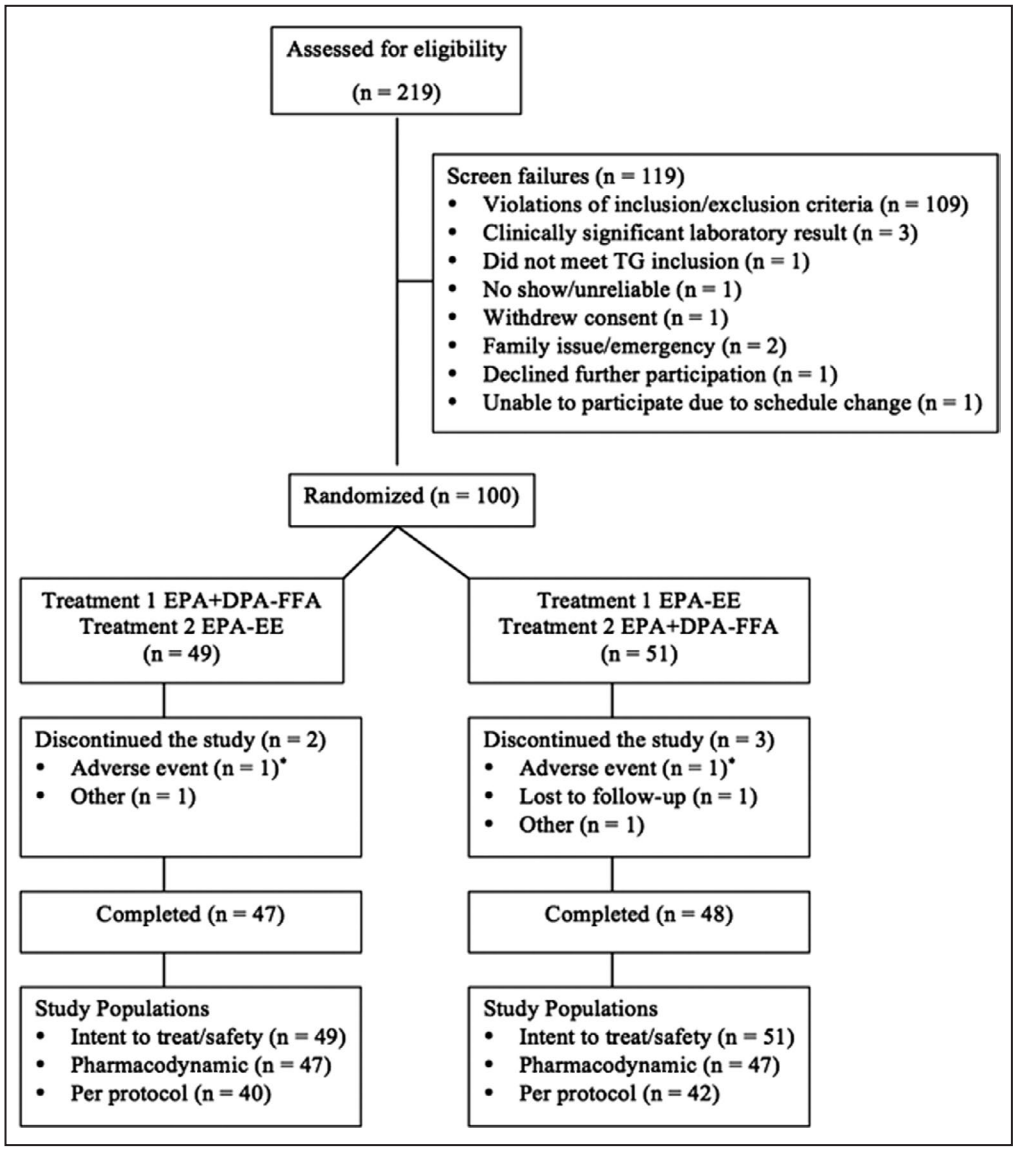

Figure. Flow diagram of subjects assessed for eligibility, randomized, and included in the populations analyzed for the study.
The intent-to-treat population included all subjects who were randomly assigned to a treatment sequence. The safety population included all subjects who were randomly assigned and received at least 1 dose of any study treatment. The pharmacodynamic (PD) population included subjects with PD parameters for both treatment periods. The per protocol population included all subjects in the PD population for whom compliance for both treatment periods was at least 80%, and for whom no clinically important protocol violations or deviations occurred during the trial. DPA indicates docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids; and TG, triglycerides. *Both discontinuations because of adverse events during the study were in subjects receiving EPA-EE.

APPENDIX

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Dr Maki has received research grants from Matinas BioPharma, Inc. and Pharmavite, and served as a consultant for Matinas BioPharma, Inc., Acasti Pharma Inc., New Amsterdam Pharma, Pharmavite, and 89bio. Dr Bays has received research grants from Matinas BioPharma, Inc. and Amarin and served as a consultant for Matinas BioPharma, Inc., Acasti Pharma Inc., and Amarin. Dr Ballantyne has received research grants from Abbott Diagnostics, Akcea, Amgen, Arrowhead, Esperion, Ionis, Novartis, Regeneron, Roche Diagnostic, National Institutes of Health, American Heart Association, and American Diabetes Association, and has served as a consultant for Matinas BioPharma, Inc., Amarin, Abbott Diagnostics, Althera, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Merck, New Amsterdam Pharma, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo. Dr Underberg has served as a consultant for Matinas BioPharma, Inc. and Amgen, and is on the speaker's bureaus for Amgen, Regeneron, Amryt, Alexion, and Esperion. Dr Kastelein served as a consultant for Matinas BioPharma, Inc. and AstraZeneca, and has ownership in New Amsterdam Pharma. J. B. Johnson is a former employee of Matinas BioPharma, Inc., and current employee of New Amsterdam Pharma. Dr Ferguson is an employee of Matinas BioPharma, Inc.

Supplemental Material

Tables S1–S3
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline, end of treatment, and percent change from baseline median (first quartile, third quartile) values for plasma lipoprotein lipids, apolipoproteins, proprotein convertase subtilisin kexin type 9, high-sensitivity C-reactive protein, and omega-3 fatty acids in the pharmacodynamic population (n = 94)

	Baseline* Median (Q1, Q3)		End-of Treatment† Median (Q1, Q3)		Percent Change from Baseline Median (Q1, Q3)	
Parameter‡	**MAT9001**	**Vascepa**	**MAT9001**	**Vascepa**	**MAT9001**	**Vascepa**
TG (mmol/L)	2.31 (2.01, 2.97)	2.32 (2.02, 2.95)	1.85 (1.50, 2.42)	1.97 (1.53, 2.45)	-21.9 (-30.9, -7.62)	-15.7 (-27.4, -3.59)
TC (mmol/L)	5.08 (4.17, 6.06)	4.90 (4.14, 6.16)	4.74 (3.76, 5.93)	4.82 (3.96, 5.88)	-5.17 (-9.66, 0.00)	-2.91 (-9.33, 0.73)
LDL-C (mmol/L)	3.19 (2.25, 4.12)	2.98 (2.20, 4.17)	2.98 (2.12, 3.99)	2.98 (2.15, 3.96)	-5.40 (-13.0, 5.56)	-2.52 (-9.41, 2.81)
VLDL-C (mmol/L)	0.84 (0.75, 1.04)	0.85 (0.73, 1.01)	0.73 (0.62, 0.88)	0.73 (0.62, 0.88)	-16.3 (-23.3, -5.41)	-12.9 (-22.5, -3.64)
HDL-C (mmol/L)	1.06 (0.88, 1.24)	1.05 (0.88, 1.24)	0.99 (0.91, 1.17)	1.00 (0.91, 1.24)	-1.26 (-8.20, 4.48)	-1.51 (-8.45, 7.00)
Non-HDL-C (mmol/L)	3.91 (3.03, 5.02)	3.86 (3.11, 5.02)	3.70 (2.80, 4.84)	3.68 (2.93, 4.90)	-7.53 (-12.3, 0.36)	-3.82 (-11.6, 0.96)
Apo A1 (g/L)	1.45 (1.32, 1.57)	1.45 (1.32, 1.63)	1.42 (1.28, 1.52)	1.39 (1.29, 1.56)	-5.03 (-9.26, 0.81)	-3.51 (-7.93, 2.31)
Apo B (g/L)	1.01 (0.83, 1.25)	0.99 (0.81, 1.29)	0.95 (0.77, 1.28)	0.97 (0.79, 1.20)	-4.66 (-11.1, 4.05)	-1.85 (-9.09, 3.26)
Apo C3 (g/L)	0.13 (0.11, 0.16)	0.14 (0.11, 0.15)	0.12 (0.10, 0.14)	0.12 (0.10, 0.14)	-12.5 (-22.2, 0.00)	-10.5 (-22.2, 0.00)
PCSK9 (ng/mL)	352 (297, 431)	358 (294, 421)	325 (282, 397)	332 (283, 387)	-7.65 (-19.8, 9.77)	-6.07 (-17.0, 8.31)
hs-CRP (mg/L)	2.60 (1.1, 5.0)	2.30 (1.0, 4.6)	2.25 (1.1, 5.2)	2.23 (1.2, 5.4)	-5.71 (-20.3, 14.4)	9.36 (-16.9, 33.3)
EPA (µg/mL)	13.8 (10.9, 19.5)	15.5 (10.9, 19.9)	143 (119, 190)	115 (94.8, 160)	1009 (694, 1208)	690 (481, 963)
DPA (µg/mL)	20.3 (16.7, 24.3)	20.7 (17.3, 24.6)	57.8 (47.3, 72.3)	50.3 (39.5, 58.8)	183 (151, 246)	145 (97.3, 188)
DHA (µg/mL)	48.6 (41.1, 57.4)	50.2 (40.2, 60.1)	49.7 (43.4, 59.1)	48.1 (39.3, 56.3)	4.49 (-9.87, 18.1)	-1.36 (-11.2, 8.31)

	Baseline* Median (Q1, Q3)		End-of Treatment† Median (Q1, Q3)		Percent Change from Baseline Median (Q1, Q3)	
Parameter‡	**MAT9001**	**Vascepa**	**MAT9001**	**Vascepa**	**MAT9001**	**Vascepa**
EPA+DPA+DHA (nmol/mL)	254 (215, 312)	263 (229, 315)	789 (682, 993)	696 (575, 863)	221 (163, 276)	160 (119, 224)

Abbreviations: Apo, apolipoprotein; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin type 9; Q1, first quartile; Q3, third quartile; TG, triglycerides; TC, total cholesterol; VLDL-C, very low-density lipoprotein cholesterol

*Baseline for lipids and hs-CRP was the average of the values obtained during the 2 pre-treatment visits in each period, and for apolipoproteins, PCSK9, and plasma omega-3 fatty acids it was the last value before the first dose.

†End of treatment was the average of the day 22 and 29 values for lipids and hs-CRP, and the day 29 value for apolipoproteins, PCSK9, and plasma omega-3 fatty acids.

‡To convert mmol/L to mg/dL values for TG multiply by 88.5 and for cholesterol multiply by 38.6.

Table S2. Baseline, end of treatment, and percent change from baseline median (first quartile, third quartile) values for plasma lipoprotein lipids, apolipoproteins, proprotein convertase subtilisin kexin type 9, high-sensitivity C-reactive protein, and omega-3 fatty acids in the per protocol population (n = 82)

	Baseline* Median (Q1, Q3)		End-of Treatment† Median (Q1, Q3)		Percent Change from Baseline Median (Q1, Q3)	
Parameter‡	**MAT9001**	**Vascepa**	**MAT9001**	**Vascepa**	**MAT9001**	**Vascepa**
TG (mmol/L)	2.32 (2.01, 2.92)	2.28 (2.02, 2.89)	1.84 (1.54, 2.42)	1.99 (1.57, 2.53)	-20.9 (-28.7, -7.62)	-13.8 (-24.5, -2.76)
TC (mmol/L)	5.08 (4.09, 6.03)	4.90 (4.09, 6.14)	4.69 (3.73, 5.85)	4.77 (3.91, 5.88)	-5.54 (-9.66, 0.00)	-2.34 (-7.21, 1.06)
LDL-C (mmol/L)	3.06 (2.25, 3.91)	2.87 (2.15, 4.01)	2.95 (2.10, 3.91)	2.93 (2.10, 3.96)	-5.61 (-13.0, 5.56)	-2.15 (-7.57, 3.01)
VLDL-C (mmol/L)	0.84 (0.75, 1.04)	0.85 (0.73, 1.01)	0.73 (0.62, 0.85)	0.75 (0.65, 0.88)	-16.0 (-22.9, -6.45)	-10.9 (-18.6, -2.86)
HDL-C (mmol/L)	1.06 (0.88, 1.24)	1.05 (0.88, 1.24)	0.99 (0.88, 1.17)	0.98 (0.91, 1.24)	-1.64 (-8.22, 4.23)	-2.01 (-8.43, 6.00)
Non-HDL-C (mmol/L)	3.81 (3.00, 4.90)	3.73 (3.08, 4.87)	3.63 (2.75, 4.77)	3.65 (2.90, 4.90)	-7.61 (-12.3, 0.56)	-3.17 (-9.52, 1.43)
Apo A1 (g/L)	1.46 (1.32, 1.58)	1.44 (1.32, 1.63)	1.43 (1.28, 1.52)	1.41 (1.29, 1.59)	-5.03 (-8.50, 0.81)	-2.94 (-7.69, 3.11)
Apo B (g/L)	0.99 (0.82, 1.24)	0.96 (0.80, 1.31)	0.94 (0.76, 1.28)	0.96 (0.78, 1.20)	-4.08 (-10.8, 4.05)	-1.76 (-9.17, 3.23)
Apo C3 (g/L)	0.13 (0.11, 0.16)	0.14 (0.11, 0.15)	0.12 (0.10, 0.14)	0.12 (0.10, 0.15)	-11.1 (-22.2, 0.00)	-8.71 (-20.0, 4.76)
PCSK9 (ng/mL)	351 (297, 425)	356 (295, 416)	323 (282, 390)	328 (283, 387)	-6.72 (-19.0, 11.1)	-5.48 (-14.9, 10.7)
hs-CRP (mg/L)	2.83 (1.2, 5.3)	2.45 (1.0, 5.0)	2.43 (1.3, 5.2)	2.38 (1.2, 5.6)	-6.06 (-20.6, 13.0)	9.92 (-15.4, 33.3)
EPA (µg/mL)	13.9 (11.0, 19.5)	15.5 (10.9, 19.9)	143 (121, 191)	115 (96.0, 162)	950 (694, 1208)	713 (481, 963)
DPA (µg/mL)	20.4 (17.0, 24.3)	20.7 (17.3, 25.1)	57.8 (47.3, 72.6)	52.4 (39.8, 58.8)	178 (151, 242)	149 (99.2, 188)
DHA (µg/mL)	48.2 (41.1, 57.5)	50.4 (40.7, 59.9)	49.7 (43.9, 58.6)	48.8 (40.2, 56.9)	4.49 (-9.87, 17.4)	-0.60 (-10.2, 8.39)

	Baseline* Median (Q1, Q3)		End-of Treatment† Median (Q1, Q3)		Percent Change from Baseline Median (Q1, Q3)	
Parameter‡	**MAT9001**	**Vascepa**	**MAT9001**	**Vascepa**	**MAT9001**	**Vascepa**
EPA+DPA+DHA (nmol/mL)	260 (218, 313)	264 (231, 317)	789 (687, 997)	698 (579, 877)	219 (163, 269)	164 (119, 224)

Abbreviations: Apo, apolipoprotein; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin type 9; Q1, first quartile; Q3, third quartile; TG, triglycerides; TC, total cholesterol; VLDL-C, very low-density lipoprotein cholesterol

*Baseline for lipids and hs-CRP was the average of the values obtained during the 2 pre-treatment visits in each period, and for apolipoproteins, PCSK9, and plasma omega-3 fatty acids it was the last value before the first dose.

†End of treatment was the average of the day 22 and 29 values for lipids and hs-CRP, and the day 29 value for apolipoproteins, PCSK9, and plasma omega-3 fatty acids.

‡To convert mmol/L to mg/dL values for TG multiply by 88.5 and for cholesterol multiply by 38.6.

Table S3. Baseline, end of treatment, and percent changes from baseline apolipoprotein, proprotein convertase subtilisin kexin type 9, high-sensitivity C-reactive protein, and plasma omega-3 concentrations in the per protocol population (n = 82)

Parameter	Baseline*	End of treatment†	% Δ†	p-value‡
Apo A1, g/L				0.440
EPA+DPA-FFA	1.46 (1.42, 1.52)	1.40 (1.38, 1.43)	-3.9 (-5.6, -2.1)	
EPA-EE	1.46 (1.41, 1.50)	1.42 (1.39, 1.44)	-2.9 (-4.7, -1.2)	
Apo B, g/L				0.602
EPA+DPA-FFA	1.00 (0.94, 1.07)	0.97 (0.94, 0.99)	-3.3 (-5.6, -1.0)	
EPA-EE	1.00 (0.93, 1.06)	0.97 (0.95, 1.00)	-2.5 (-4.9, -0.2)	
Apo C3, g/L				0.099
EPA+DPA-FFA	0.13 (0.13, 0.14)	0.12 (0.11, 0.12)	-13.0 (-16.2, -9.6)	
EPA-EE	0.14 (0.13, 0.14)	0.12 (0.12, 0.13)	-9.6, (-13.0, -6.1)	
PCSK9, ng/mL				0.678
EPA+DPA-FFA	348 (326, 372)	331 (315, 348)	-5.4 (-10.0, -0.6)	
EPA-EE	351 (331, 372)	326 (310, 343)	-6.8 (-11.3, -2.0)	
hs-CRP, mg/L				0.008
EPA+DPA-FFA	2.5 (2.0, 3.1)	2.2 (2.0, 2.4)	-7.6 (-17.4, 3.4)	
EPA-EE	2.3 (1.8, 2.9)	2.6 (2.3, 2.9)	11.0 (-0.8, 24.2)	
EPA, µg/mL				0.001
EPA+DPA-FFA	14.6 (13.2, 16.1)	138 (124, 155)	845 (743, 958)	
EPA-EE	14.7 (13.4, 16.3)	115 (102, 128)	682 (599, 776)	
DHA, µg/mL				0.036
EPA+DPA-FFA	48.6 (45.9, 51.6)	49.6 (47.8, 51.5)	1.5 (-2.2, 5.4)	
EPA-EE	49.0 (46.1, 52.2)	47.5 (45.8, 49.4)	-2.6 (-6.2, 1.1)	
DPA, µg/mL				<0.0001
EPA+DPA-FFA	20.3 (19.1, 21.7)	55.8 (52.3, 59.5)	174 (156, 192)	
EPA-EE	20.4 (19.1, 21.8)	48.7 (45.7, 52.0)	139 (124, 155)	
EPA+DHA+DPA, nmol/mL				<0.0001
EPA+DPA-FFA	262 (248, 278)	801 (749, 857)	204 (184, 225)	

EPA-EE	265 (251, 280)	694 (649, 743)	163 (146, 182)

Abbreviations: Apo, apolipoprotein; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids; hs-CRP, high-sensitivity C-reactive protein; PCSK9, proprotein convertase subtilisin kexin type 9

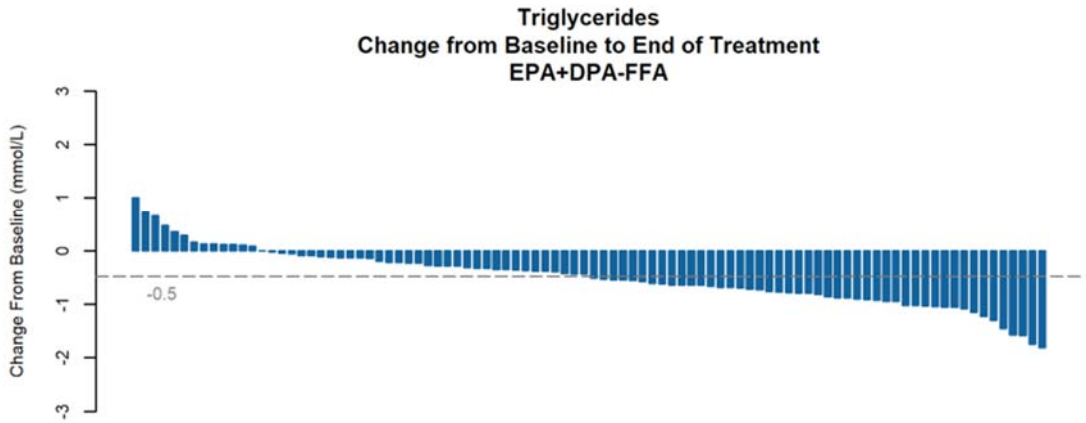
*Values are geometric mean (95% confidence interval); for apolipoproteins, PCSK9, and omega-3 fatty acids, baseline was the value obtained at day 1; for hs-CRP, baseline was defined as the average of the values obtained on the final two pre-treatment visits for each treatment period.

†Values are least squares geometric mean (95% confidence interval); for apolipoproteins, PCSK9, and omega-3 fatty acids, end of treatment was defined as the value obtained at day 29; for hs-CRP, end of treatment was defined as the average of values collected at treatment visits on days 22 and 29; the treatment % Δ is the percent change from baseline to end of treatment.

‡p-value is for the difference between treatments in the percent change from baseline.

Figure S1. Waterfall plots (n = 94) for the change from baseline to end of treatment triglyceride concentrations for EPA+DPA-FFA (Panel A) and EPA-EE (Panel B). Baseline is the average of the final two pre-treatment values and end of treatment is the average of the day 22 and day 29 values in each treatment period. Dashed line represents the median value. Abbreviations: DPA, docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids

A



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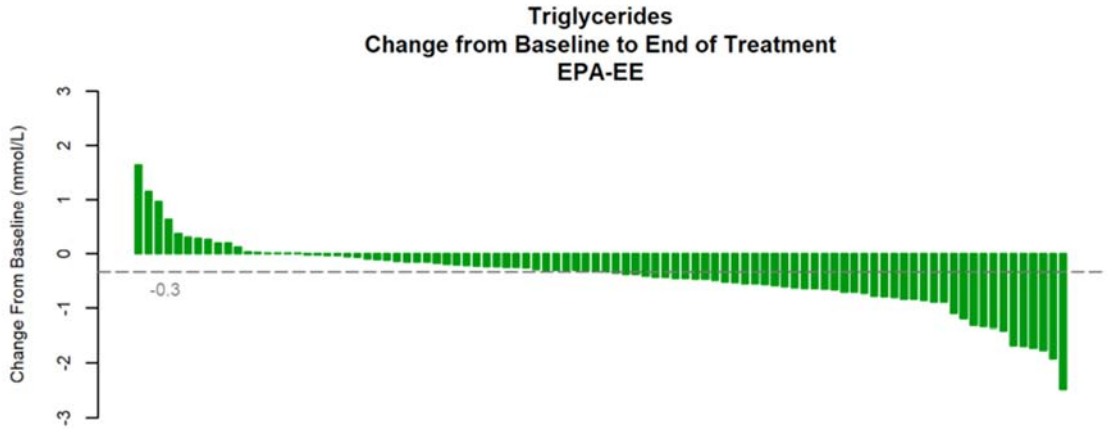
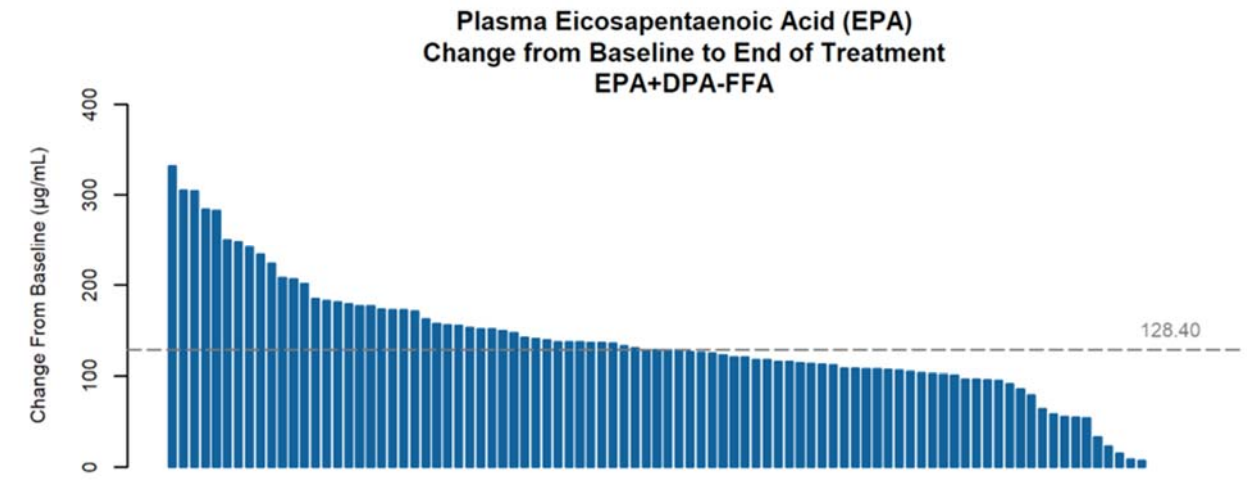


Figure S2. Waterfall plots (n = 94) for the change from baseline to end of treatment EPA concentration for EPA+DPA-FFA (Panel A) and EPA-EE (Panel B). Baseline is the value obtained at day 1 and end of treatment is the value obtained at day 29 in each treatment period. Dashed line represents the median value. Abbreviations: DPA, docosapentaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; FFA, free fatty acids

A



B