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Effects of MAT9001 containing eicosapentaenoic acid and docosapentaenoic acid, compared to eicosapentaenoic acid ethyl esters, on triglycerides, lipoprotein cholesterol, and related variables

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KEYWORDS:
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Proprotein convertase subtilisin kexin type 9

BACKGROUND: Long-chain omega-3 fatty acid concentrate pharmaceuticals are used in the United States for treatment of severe hypertriglyceridemia (≥500 mg/dL) and are under investigation as adjuncts to statins for lowering cardiovascular risk in patients with high triglycerides (TGs; 200–499 mg/dL).

OBJECTIVE: To evaluate MAT9001, an investigational prescription-only omega-3 fatty acid agent containing predominantly eicosapentaenoic acid (EPA) and docosapentaenoic acid, in 42 men and women with fasting TG 200 to 400 mg/dL.

METHODS: In this open-label, crossover trial, subjects received MAT9001 and EPA ethyl esters (EPA-EE) in random order. They were housed in a clinical research unit for 2 14-day treatment periods, separated by a ≥35-day washout. Lipoprotein lipids, apolipoproteins (Apos) and proprotein convertase subtilisin kexin type 9 levels were measured before and at the end of each treatment period.

RESULTS: MAT9001, compared with EPA-EE, resulted in significantly ($P < .05$) larger reductions from pretreatment levels for TG (−33.2% vs −10.5%), total cholesterol (−9.0% vs −6.2%), non–high-density lipoprotein cholesterol (−8.8% vs −4.6%), very low–density lipoprotein cholesterol (−32.5% vs −8.1%), Apo C3 (−25.5% vs −5.0%), and proprotein convertase subtilisin kexin type 9 (−12.3% vs +8.8%). MAT9001 also produced a significantly ($P = .003$) larger reduction in Apo A1 (−15.3% vs −10.2%), but responses for high-density lipoprotein cholesterol (−11.3% vs −11.1%), low-density lipoprotein cholesterol (−2.4% vs −4.3%), and Apo B (−3.8% vs −0.7%), respectively, were not significantly different relative to EPA-EE.

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CONCLUSIONS: MAT9001 produced significantly larger reductions than EPA-EE in several lipoprotein-related variables that would be expected to favorably alter cardiovascular disease risk in men and women with hypertriglyceridemia.

Introduction

Fasting and postprandial hypertriglyceridemia are associated with increased risk for cardiovascular disease and, when severe, pancreatitis.[1–5] Long-chain omega-3 fatty acid intake has been shown to lower triglyceride (TG) levels.[6–8] Currently in the United States, prescription forms of eicosapentaenoic acid (EPA) and EPA plus docosahexaenoic acid (DHA) concentrates have approved indications for the treatment of very high TG (≥500 mg/dL) to reduce the risk of pancreatitis. Although all lower TG levels, results from prior studies suggest that products with varying proportions and different chemical forms of these omega-3 fatty acids have differential effects on coronary artery disease and lipid responses.[9–14] This is likely due, at least in part, to the bioavailability of the omega-3 fatty acids in these products, for example, acid ethyl esters vs carboxylic acid forms.[11,15–17] In addition, some products, particularly those containing DHA, appear to raise low-density lipoprotein cholesterol (LDL-C) levels, whereas products with EPA alone do not.[9,10]

MAT9001 (Matinas BioPharma Holdings, Inc) is an omega-3 fatty acid formulation comprised of EPA and another long-chain omega-3 fatty acid with 5 double bonds, docosapentaenoic acid (DPA) but only trace amounts of DHA. In contrast to EPA and DHA, little is known about the effects of DPA on lipid levels in humans. In this clinical trial, MAT9001 was compared with icosapent ethyl, the ethyl ester of EPA (EPA-EE; Vascepa), a lipid-lowering agent approved by the Food and Drug Administration for use in adults with severe hypertriglyceridemia. The effects of MAT9001 and EPA-EE on lipoprotein lipids, apolipoproteins (Apos), and proprotein convertase subtilisin kexin type 9 (PCSK9) were evaluated and compared in men and women with hypertriglyceridemia while free of other lipid-altering drug therapy or while on stable-dose statin monotherapy.

Methods

Study design and treatments

This was a randomized, open-label, crossover trial with 2 14-day treatment periods, separated by at least a 35-day washout period (Fig. 1). Each treatment period had its own baseline. A sample of 42 subjects (31 men and 11 women) was randomized to 2 treatment sequences with 4 g/d MAT9001 or EPA-EE first, and crossover to the opposite treatment for the second period. MAT9001 is a long-chain omega-3 free fatty acid concentrate in a delayed release 1 g capsule, containing a proprietary and patented mixture of EPA and DPA predominantly, with trace levels of DHA and certain other omega-3 fatty acids (Matinas BioPharma, Inc, Bedminster, NJ).[18] The EPA-EE comparator was formulated and administered as 1 g capsules (Vascepa, icosapent ethyl, Amarin Pharma, Inc, Bedminster, NJ).[19] Four 1-g capsules were administered once daily, 30 minutes after consumption of a standard low-fat breakfast meal, along with 240 mL of water. The breakfast consisted of corn flakes, skim milk, honeydew melon, raisins, and toast, and provided 502 kcal (4% of energy from fat, 82% from carbohydrates, and 14% from protein).

Subjects were housed in a clinical research unit (Pharma Medica Research, Inc, Mississauga, Ontario, Canada) for the duration of each treatment period. Treatment compliance was ensured by the presence of study staff during study drug

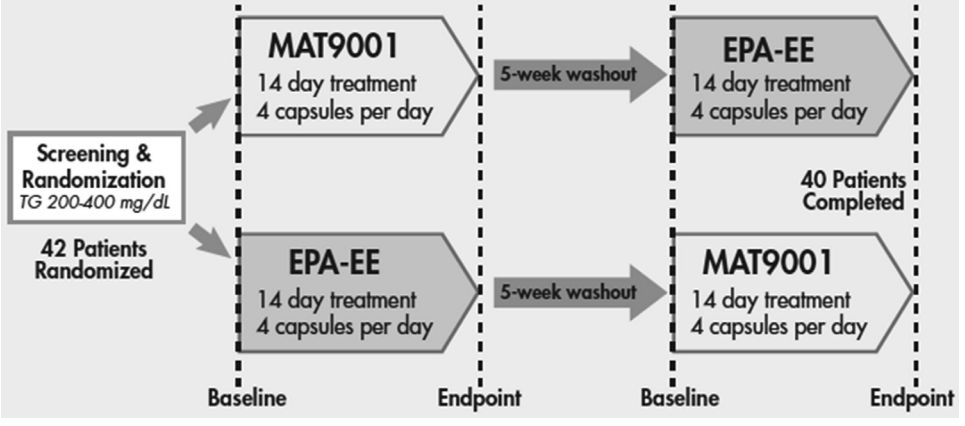

Figure 1 Study flow diagram. EPA-EE, eicosapentaenoic acid ethyl esters; TG, triglycerides.

administration. Subjects did not engage in any strenuous activity throughout the housing period. Standardized meals were void of omega-3 fatty acids and provided throughout the treatment periods. The meals and administration of the meals were identical between treatment periods.

The study was conducted in accordance with current Food and Drug Administration guidance documents, Good Clinical Practices as established by the International Conference on Harmonization,[20] the basic principles defined in the US Code of Federal Regulations,[21] and the principles of the World Medical Association Declaration of Helsinki (Fortaleza, Brazil, 2013). The protocol was approved by an appropriately constituted ethics review board (Optimum Clinical Research, Inc, Oshawa, Ontario, Canada) and subjects completed informed consent forms before their enrollment in the study (ClinicalTrials.gov identifier: NCT02310022).

Subjects

Eligible subjects included men and women 18 to 70 years of age with a body mass index of 19.0 to 40.0 kg/m^2 who were light smokers (≤10 cigarettes/d) or nonsmokers and had fasting TG levels of 200 to 400 mg/dL without the use of lipid-altering therapy or 200 to 350 mg/dL with the use of stable-dose statin monotherapy. The use of cigars, pipes, vapor inhalers, or any other tobacco-containing product (other than cigarettes) was prohibited within 6 months before drug administration. Irregular use of statin therapy within 8 weeks before study drug administration; use of the highest recommended dose of any statin medication; and use of TG-targeted drugs, beta blockers, estrogen products, hormone therapy, weight loss agents, thiazides, nonsteroidal antiinflammatory drugs, or drugs affecting coagulation within 30 days before study drug administration were also excluded. Additional major exclusion criteria were total cholesterol (TC) levels >300 mg/dL; hemoglobin levels <13.5 g/dL for males or <12.0 g/dL for females; abnormal or clinically significant vital signs; known or suspected carcinoma; known history or presence of angioedema, pancreatitis, hypothyroidism, or diabetes; known history or presence of cardiovascular disease or impaired cardiovascular function; presence of hepatic or renal dysfunction; and the presence of clinically significant gastrointestinal disease or history of malabsorption within the last year. Subjects who regularly consumed more than one meal containing fish or shellfish per week for 6 months before drug administration were not enrolled, nor were those who had been following a special diet within 30 days of study start. Females of childbearing potential were required to use a method of contraception during the study.

Laboratory measurements

Blood samples were collected at the beginning and end of each treatment period by venipuncture or from an indwelling cannula that had been placed in the arm vein of the subject. With day 0 defined as the initiation of treatment, for the lipid analyses, fasting (at least 12 hours) blood samples were collected at 4 time points: twice just before and twice at the end of each treatment period (day 12 and day 14). The 2 values from the beginning and the 2 values from the end of each treatment period were averaged for the baseline and endpoint values, respectively. For the Apo and PCSK9 analyses, samples were collected at 2 time points in each treatment period (day −1 and on day 14). Whole blood was centrifuged at 3000 rpm, and serum samples were stored at either 5 ± 3°C for measuring lipoprotein lipids or −80 ± 15°C for measuring Apo A1, Apo B, Apo C3, and PCSK9. Lipoprotein lipid and Apo analyses were conducted by Alpha Laboratories, Inc (Toronto, Ontario, Canada). TC, high-density lipoprotein cholesterol (HDL-C), and TG concentrations were measured using a Cobas 6000 analyzer series module c501 (Roche Diagnostics, Indianapolis, IN).[22] LDL-C and VLDL-C concentrations were calculated using the Friedewald equation.[23] Non-HDL-C was determined by subtracting HDL-C from TC values. Apo A1 and Apo B concentrations were determined using a BN ProSpec nephelometer (Siemens, Munich, Bavaria), and Apo C3 concentrations were measured using a human enzyme-linked immunosorbent assay kit (Abcam, Cambridge, UK; catalog number: ab154131). PCSK9 concentrations were analyzed by Charles River Laboratories (Senneville, Quebec, Canada) using a Quantikine human enzyme-linked immunosorbent assay kit (R&D Systems, Inc, Minneapolis, MN).

Statistical analyses

SAS version 9.3 (SAS, Cary, NC) was used for statistical analyses. Safety analyses were performed for all enrolled subjects, and the efficacy analyses data set included the subjects that completed both treatment periods. All tests for significance were performed at alpha = 0.05, 2 sided. The primary efficacy endpoint was the difference between MAT9001 and EPA-EE in the change (or percent change) from pretreatment (baseline for each condition) to endpoint TG levels. Repeated-measures analysis of covariance with subject in sequence as a random variable, and terms for baseline value, sequence and treatment by sequence interaction were performed for variables with normal response distributions. For variables with nonnormal response distributions, determined using the Shapiro-Wilk test at an alpha level of 0.01, the same procedure was used after rank transformation.[24] LDL-C, Apo A1, and PCSK9 responses were nonnormally distributed. The difference between MAT9001 and EPA-EE in the percentage of subjects with reductions from pretreatment in TG of ≥5% and ≥10% were assessed with McNemar's test.

Results

A total of 42 subjects were enrolled in the study and received at least one dose of at least one treatment, but 40

subjects completed both the MAT9001 and 42 EPA-EE treatment periods. The reasons for the 2 discontinuations were a positive urine drug test plus noncompliance (n = 1) and withdrawal by the subject (n = 1). Baseline demographic and anthropometric data are shown in Table 1. Subjects had a mean (standard deviation) age of 50.0 [8.0] years and body mass index of 29.5 [3.5] kg/m^2 and were predominantly male (73.8%) and of white (78.6%)/not Hispanic or Latino (73.8%) race/ethnicity.

Median pretreatment (baseline) concentrations of lipoprotein lipids, Apos, and PCSK9 for each treatment condition are shown in Table 2. Median percent changes from baseline for lipoprotein lipids, Apos, and PCSK9 according to treatment condition are shown in Figures 2 and 3. Data shown are for the percent changes from baseline for all subjects who completed each treatment and had sufficient sample volume available for analysis. Sample sizes ranged from 37 to 41 for the standard lipid profiles. Median TG concentration was significantly reduced from pretreatment with MAT9001 (−88.1 mg/dL [−33.2%], $P < .001$ for percent change) and to a significantly larger extent than with EPA-EE treatment (−19.5 mg/dL [−10.5%], $P = .171$; $P < .001$ between treatments for percent change). Significantly ($P < .001$) higher percentages of subjects had a TG reduction of ≥5% and ≥10% when treated with MAT9001 (92.5% and 90.0%, respectively) compared with EPA-EE (61.0% and 53.7%, respectively; Fig. 4). Compared with pretreatment levels, both MAT9001 and EPA-EE significantly ($P < .05$) reduced TC (−24.1 mg/dL [−9.0%] and −13.7 mg/dL [−6.2%], respectively), non-HDL-C (−16.4 mg/dL [−8.8%] and −7.9 mg/dL [−4.6%], respectively), HDL-C (−4.4 mg/dL [−11.3%] and −4.3 mg/dL [−11.1%], respectively), and Apo A1 (−22.0 mg/dL [−15.3%] and −14.0 mg/dL [−10.2%], respectively). These reductions in all cases were significantly larger with MAT9001 vs EPA-EE (all $P < .05$ for the percent change). MAT9001, but not EPA-EE, also significantly ($P < .001$ for percent change) reduced VLDL-C (−16.5 mg/dL [−32.5%] vs −3.5 mg/dL [−8.1%], $P < .001$ between treatments), Apo C3 (−4.9 mg/dL [−25.5%] and −0.4 mg/dL [−5.0%]) ($P = .006$ between treatments), and PCSK9 (−12.3% and +8.8%) ($P = .001$

Table 1 Subject demographic data (N = 42)

Parameter	Mean (SD) or n (%)
Age, y	50.0 (8.0)
Weight, kg	88.4 (14.9)
Body mass index, kg/m^2	29.5 (3.5)
Sex	
Male	31 (73.8)
Female	11 (26.2)
Ethnicity, %	
Hispanic or Latino	11 (26.2)
Not Hispanic or Latino	31 (73.8)
Race, %	
White	33 (78.6)
Asian	7 (16.7)
Black or African American	2 (4.8)

SD, standard deviation.

Table 2 Median pretreatment values for each condition*

Parameter	Median (interquartile range) MAT9001	EPA-EE
TG, mg/dL	253 (180–289)	230 (180–296)
VLDL-C†, mg/dL	49 (36–57)	46 (36–53)
Non-HDL-C, mg/dL	189 (166–208)	181 (163–207)
HDL-C, mg/dL	41 (35–54)	42 (34–53)
LDL-C†, mg/dL	142 (113–164)	139 (106–157)
TC, mg/dL	237 (201–257)	226 (198–252)
Apo B, mg/dL	121 (111–128)	119 (107–129)
Apo A1, mg/dL	144 (125–168)	137 (120–164)
Apo C3, mg/dL	21 (15–24)	22 (15–29)
PCSK9, ng/dL	333 (272–368)	328 (285–360)

Apo, apolipoprotein; EPA-EE, eicosapentaenoic acid ethyl esters; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non–high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin type 9; TC, total cholesterol; TG, triglycerides; VLDL-C, very low–density lipoprotein cholesterol.

*Approximately half of the subjects received MAT9001 first and half received EPA-EE first. Two separate sets of baseline measurements were collected, one before each treatment, and the data shown here are for the pretreatment baseline for each condition. Sample sizes for these measurements ranged from N = 35 to N = 42.

†Some values were not calculated because the TG concentration was >400 mg/dL.

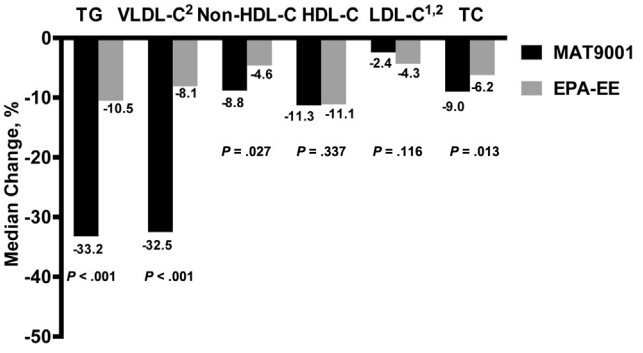

Figure 2 Median percent changes from pretreatment values for lipids in response to MAT9001 and EPA-EE. Samples sizes ranged from 37 to 41 subjects. Between treatment P values derived from ANCOVA models with baseline value, treatment, period, sequence, and subject within sequence as factors in the model (SAS PROC GLM). [1]Some values were not calculated because the TG concentration pretreatment or posttreatment was >400 mg/dL. [2]Response variable was not normally distributed determined using the Shapiro-Wilk test at an alpha level of .01. Analysis was completed using ANCOVA after rank transformation for between treatment comparisons. ANCOVA, analysis of covariance; EPA-EE, eicosapentaenoic acid ethyl esters; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

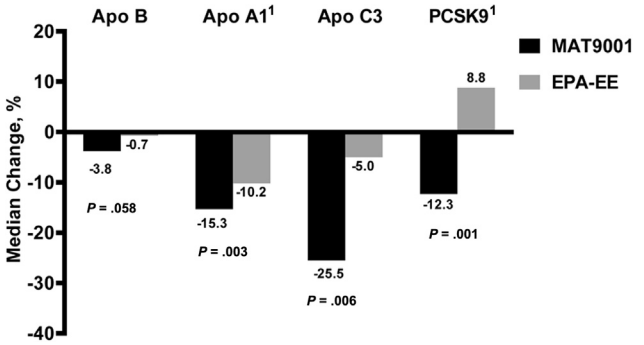

Figure 3 Median percent changes from pretreatment values for apolipoproteins and PCSK9 in response to MAT9001 and EPA-EE. Sample sizes ranged from 33 to 40 subjects. Between treatment *P* values derived from ANCOVA models with baseline value, treatment, period, sequence and subject within sequence as factors in the model (SAS PROC GLM). [1]Response variable was not normally distributed determined using the Shapiro-Wilk test at an alpha level of .01. Analysis was completed using ANCOVA after rank transformation for between treatment comparisons. ANCOVA, analysis of covariance; Apo, apolipoprotein; EPA-EE, eicosapentaenoic acid ethyl esters; PCSK9, proprotein convertase subtilisin kexin type 9.

between treatments). The changes (and percent changes) from pretreatment levels for MAT9001 and EPA-EE in LDL-C (−4.1 mg/dL [−2.4%] vs −6.4 mg/dL [−4.3%]) and Apo B (−4.0 mg/dL [−3.8%] vs −1.0 mg/dL [−0.7%]) were not statistically significant, and there were no significant differences between treatment responses.

There were no significant findings related to vital signs, electrocardiograms, or physical examinations. Overall, 282 adverse events (166 in the MAT9001 period and 96 in the EPA-EE period) were reported by the subjects. Of these, 149 adverse events (95 in the MAT9001 period and 54 in the EPA-EE period) were classified as possibly related to the study drugs. Table 3 shows the incidence of adverse events judged as possibly related to treatment that occurred in at least 5.0% of subjects during either treatment. The most commonly reported adverse events were dry skin (MAT9001, 4 [10.0%] of subjects and EPA-EE, 2 [4.8%] of subjects) and rhinorrhea (MAT9001, 3 [7.5%] of subjects and EPA-EE, 0 [0%] of subjects). All the adverse events reported in the study were mild or moderate in nature, and no serious events were reported.

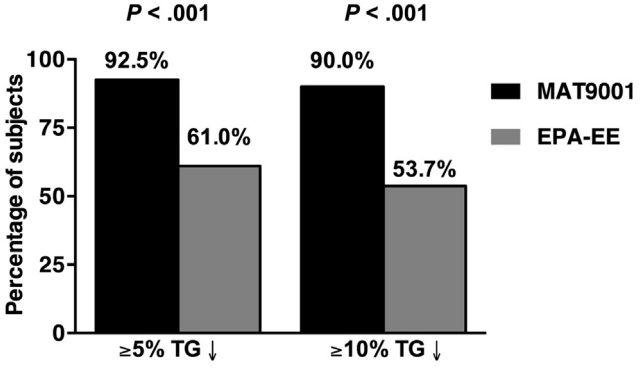

Figure 4 Percentage of subjects with reductions from pretreatment levels in TG of ≥5% and ≥10% during MAT9001 or EPA-EE treatment. Between treatment *P* value derived from McNemar's test. EPA-EE, eicosapentaenoic acid ethyl esters; TG, triglycerides.

Discussion

The results of this study demonstrated that, in men and women with high TG, MAT9001, an investigational omega-3 fatty acid drug containing primarily EPA and DPA, produced significantly larger reductions in TG (−33.2% vs −10.5%), TC (−9.0% vs −6.2%), VLDL-C (−32.5% vs −8.1%), non-HDL-C (−8.8% vs −4.6%), Apo C3 (−25.5% vs −5.0%), and PCSK9 (−12.3% vs +8.8%), compared to EPA-EE. Overall, MAT9001 was well tolerated by the study participants. All the adverse events reported in this study were mild in nature; the most commonly reported were dry skin and rhinorrhea.

In a placebo-controlled study of EPA-EE administered to subjects with TG ≥200 mg/dL and <500 mg/dL while on statin therapy, 4 g/d EPA-EE reduced TG by 17.5%,[25] which is somewhat larger than the 10.5% reduction observed in the present trial. The smaller response in the present study may be attributable to the use of a low-fat background diet. Currently, EPA-EE and other prescription omega-3 products are approved for the treatment of very high TG levels to reduce the risk of pancreatitis. For such patients, a low-fat diet is recommended to minimize chylomicron formation. Therefore, a low-fat diet was used in the present study. Given the low prevalence of very high TG levels in the population (<2%),[26] it was not felt to be feasible to study a sample of subjects with very high TG, thus, a sample with high TG was recruited instead.

Table 3 Adverse events judged as possibly related to treatment that occurred in ≥5.0% of subjects during either treatment

Variable	No. (%) of patients	
	MAT9001 (N = 40)	EPA-EE (N = 42)
Total	20 (50.0)	12 (28.6)
Eructation	2 (5.0)	0 (0.0)
Feeling cold	2 (5.0)	0 (0.0)
Local swelling	2 (5.0)	0 (0.0)
Vessel puncture site reaction	2 (5.0)	0 (0.0)
Excoriation	2 (5.0)	1 (2.4)
Rhinorrhea	3 (7.5)	0 (0.0)
Dry skin	4 (10.0)	2 (4.8)
Petechiae	2 (5.0)	2 (4.8)

EPA-EE, eicosapentaenoic acid ethyl esters.

A key factor to explain the improved lipid-lowering effects of MAT9001, vs EPA-EE, is its DPA content.[27] The currently available prescription omega-3 fatty acid products contain predominantly EPA, or EPA plus DHA, but there are many other long-chain omega-3 fatty acids present in nature, albeit at substantially lower levels. One of these, DPA, is structurally similar to EPA, but with 2 more carbon chain units. Results of research in animal models suggest that DPA may be more effective than EPA for inhibiting platelet aggregation and inducing endothelial cell migration.[28] Research focused on understanding the effects of DPA on TG levels, particularly pure or isolated DPA, is in its early stages.[27–29] However, seal oil, which is a relatively rich source of DPA has been shown to significantly reduce TG in hypertriglyceridemic adults.[30] A double-blind crossover study in healthy women also found that plasma chylomicronemia was substantially reduced after a meal containing DPA, compared with a meal containing EPA only, or olive oil only,[27] supporting a likely role of DPA in the TG response to MAT9001.

Results from previous studies suggest that ethyl ester forms of long-chain omega-3 fatty acids are not well absorbed when consumed on an empty stomach because intestinal lipase from pancreatic secretions that enter the gut via the common bile duct is needed to hydrolyze the bond between the fatty acid and the ester.[16,31] Therefore, another potential mechanism for the greater lipid-lowering effects demonstrated for MAT9001 compared to EPA-EE is the increased bioavailability of omega-3 fatty acids within MAT9001, based on studies of other products containing acid ethyl ester vs carboxylic acid forms of omega-3 fatty acids.[11,15–17] Bioavailability results reported previously from the present trial,[32] showed that after single-dose administration of MAT9001, EPA, DPA, and total omega-3 fatty acids had approximately 8-fold higher areas under the curve and maximal concentrations, compared to those associated with EPA-EE administration. Similar results were reported after multiple-dose administration.[32] Areas under the curve and maximal concentrations of DHA were not significantly different between MAT9001 and EPA-EE treatments (unpublished data, Matinas BioPharma, Inc). Additional work will be needed to fully characterize the pharmacokinetic and pharmacodynamic profiles of MAT9001 relative to those for other prescription omega-3 formulations.

Evidence suggests that omega-3 fatty acids reduce TG by decreasing hepatic VLDL-TG production and secretion through a variety of mechanisms including (1) decreasing enzymatic conversion of acetyl CoA to fatty acids, (2) increasing beta oxidation of fatty acids, (3) inhibiting phosphatidic acid phosphatase/phosphohydrolase, the enzyme that catalyzes the conversion of phosphatidic acid to diacylglycerol, and (4) inhibiting diacylglycerol acyltransferase, the enzyme that catalyzes a critical step in TG synthesis.[33] Omega-3 fatty acids have also been shown to affect the expression of genes involved in lipogenesis (eg, genes for hepatic cholesterol, fatty acid, and TG-synthesis enzymes).[34,35] Results from studies of DPA in vitro in rat liver cells indicate that it downregulates the genes for sterol regulatory element binding protein-1c, acetyl coenzyme A carboxylase, carbohydrate-responsive element-binding protein, and fatty acid synthase.[28] DPA has also been shown to reduce messenger RNA expression for 3-hydroxy-3-methylglutaryl coenzyme A reductase and PCSK9.[28] In contrast, statin therapy may upregulate certain lipogenic genes in an attempt to compensate for lower LDL-C concentrations. Therefore, omega-3 fatty acids (and in particular, DPA) may mitigate some of these compensatory effects of statins, when administered in combination with a statin. Additional research will be needed to explore this relationship.

Omega-3 fatty acids also lower circulating TG levels, especially postprandially, by increasing lipoprotein lipase (LPL) activity.[33] Apo C3 is a protein component of VLDL that has been shown to inhibit the activity of LPL in humans.[36] Therefore, when Apo C3 is decreased, as was the case for both MAT9001 and EPA-EE in the present study, there should be less inhibition of LPL, although it is not certain that LPL activity was increased in this study, as LPL activity was not measured. An increase in LPL activity would also increase the conversion of VLDL to LDL particles. In some studies of omega-3 fatty acids, particularly those that administered DHA, the increased conversion of VLDL to LDL has been implicated as a cause for increased LDL-C concentrations sometimes observed with omega-3 treatment. In the present trial, LDL-C was slightly reduced by both MAT9001 (−2.4%) and EPA-EE (−4.3%), supporting the hypothesis that the increase in LDL-C sometimes reported with omega-3 fatty acid consumption is related to DHA content, whereas EPA and DPA do not increase LDL-C.[9,10] Even in studies where LDL-C has been increased with omega-3 fatty acids, VLDL-C reductions have generally been larger than the increase in LDL-C, which results in a net reduction in non-HDL-C.[37–39] The Apo B concentration is generally modestly reduced or unchanged.[37–39] In the present trial, non-HDL-C and Apo B levels were reduced with both the MAT9001 and EPA-EE treatments. However, VLDL particle concentration was not measured, so it is not clear to what degree a reduction in VLDL-C and total TG may have been attributable to a reduction in VLDL particle concentration vs reduction in the average cholesterol and TG contents of circulating VLDL particles.

PCSK9 inhibitors, which act by inhibiting the degradation of the LDL receptor, were recently approved for lowering LDL-C in severe forms of hypercholesterolemia.[40] Several lines of research also indicate that PCSK9 influences the metabolism of TG-rich lipoproteins.[41] There is a positive correlation between plasma PCSK9 and TG levels in the general population and in some disease states,[41] and it has been shown to predominantly relate to levels of intermediate density lipoprotein (VLDL remnants). A recent study in which 2.2 g of marine omega-3 fatty acids were administered to 92 healthy women,

PCSK9 levels were significantly reduced (−16.1% for premenopausal women and −13.1% for postmenopausal women).[42] Another double-blind, controlled feeding study reported that canola oil enriched with DHA significantly reduced plasma PCSK9 and TG levels.[43] Further research is needed to clarify the link between TG-lowering therapies and PCSK9 changes.

A limitation of this trial is the relatively short treatment period of 2 weeks. The 2-week treatment period was selected because previous studies with omega-3 fatty acids have shown that the effect on the TG concentration is maximal or near maximal by this time point.[16,44] However, longer studies are needed to more fully characterize the response to MAT9001.

In conclusion, compared to EPA-EE, MAT9001 significantly reduced concentrations of TG, TC, VLDL-C, non-HDL-C, Apo C3, and PCSK9. All these changes would be expected to reduce cardiovascular disease risk. Studies evaluating cardiovascular disease outcomes of omega-3 fatty acids in subjects with hypertriglyceridemia are underway.[45,46]

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Authors' contributions: Drs. Maki, Bobotas, and Keane designed the study. Drs. Maki, Bobotas, Dicklin, and Keane, and Ms. Huebner analyzed and interpreted the data and contributed in drafting, critical revision, and approval of the article.

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