Effects of MAT9001, an Omega-3 Fatty Acid Drug, Compared with Eicosapentaenoic Acid Ethyl Esters, on Triglycerides, Lipoprotein Cholesterol and Related Variables in Hypertriglyceridemic Subjects

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Background

- Elevated triglycerides (TG), defined as a fasting TG concentration ≥150 mg/dL, affects approximately 31% of the US adult population (1).
  - Borderline high TG: 150–199 mg/dL
  - High TG: 200–499 mg/dL
  - Very high TG: ≥500 mg/dL
- A growing body of evidence suggests that elevated levels of TG and TG-rich lipoproteins are independently and causally associated with increased risk for cardiovascular disease (CVD) events (2).
- Several omega-3 fatty acid (OM3) concentrate pharmaceutical agents have been approved for the treatment of very high TG levels in the United States, and are under investigation as an adjunct to statins for lowering CVD event risk in patients with high TG.
- MAT9001 (Matinas Biopharma Inc., Bedminster, NJ), is a novel investigational OM3 drug containing predominantly docosapentaenoic acid (DPA) and eicosapentaenoic acid (EPA).

Objective

- This open-label, randomized, crossover trial compared the bioavailability and the effects of MAT9001 and an approved OM3 agent comprised predominantly of EPA ethyl esters (EPA-EE; Vascepa; Amarin Pharmaceuticals, Bedminster, NJ) (3) on lipoprotein lipids, apolipoproteins (apo), and proprotein convertase subtilisin/kexin type 9 (PCSK9) levels in men and women with hypertriglyceridemia with or without stable statin therapy.

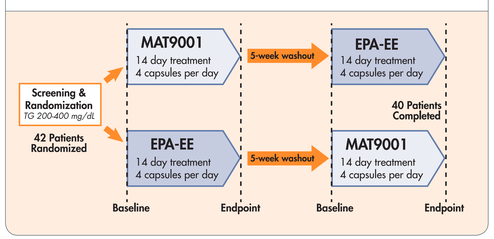
Subjects

- Eligible subjects were men and women 18-70 years of age with a body mass index (BMI) of 19.0-40.0 kg/m^2, who were light smokers (≤10 cigarettes/day) or non-smokers, with fasting TG 200-400 mg/dL without lipid-altering therapy, or fasting TG 200-350 mg/dL if on stable-dose statin monotherapy.
- Exclusion criteria included
  - total cholesterol (TC) levels >300 mg/dL;
  - hemoglobin <13.5 g/dL for males or <12.0 g/dL for females;
  - known or suspected carcinoma;
  - known history or presence of hypersensitivity or idiosyncratic reaction to fish, shellfish, gelatin, or OM3 products;
  - known history or presence of angioedema, pancreatitis, hypothyroidism, or diabetes;
  - known history or presence of CVD or impaired cardiovascular function;
  - presence of hepatic or renal dysfunction;
  - presence of clinically significant gastrointestinal disease or history of malabsorption within the last year;
  - history of drug or alcohol addiction requiring treatment;
  - positive urine test result for illicit drugs;
  - regular consumption of greater than one meal containing fish or shellfish per week for 6 months prior to drug administration;
  - adherence to a special diet within 30 days of study start;
  - abnormal or clinically significant vital signs measurements;
  - irregular use of statin therapy within 8 weeks prior to study drug administration;
  - use of the highest recommended dose of any statin medication;
  - use of TG-lowering drugs, beta-blockers, estrogen products, hormone therapy, weight loss agents, thiazides, non-steroidal anti-inflammatory drugs, or drugs affecting coagulation within 30 days prior to drug administration;
  - known history or presence of any clinically significant medical condition that, in the opinion of the investigator, would compromise the subject's safety or the integrity of the study results.

Methods

- ClinicalTrials.gov identifier: NCT02310022.
- This was an open-label, randomized, crossover trial. A sample of 42 men and women received 4 g/d MAT9001 and EPA-EE in random order, for 14-day treatment periods, separated by ≥35 days of wash-out (refer to Figure 1 for study design).
- Subjects were housed in a clinical research unit (Pharma Medica Research Inc., Mississauga, Ontario, Canada) for the duration of each treatment period.
- The dose (four 1 g capsules) was given daily, 30 minutes after consumption of a breakfast meal. On day 13 of each treatment, subjects consumed a low-fat breakfast (502 kcal; 4/82/14% kcal from fat, carbohydrate and protein, respectively) and samples were collected over a 24-hour period for pharmacokinetic analyses.
- Baseline values for lipoprotein lipids, apolipoproteins, and PCSK9 were determined from 1 or 2 fasting samples drawn on days -1 and 0 of treatment, and on-treatment values were from 1 or 2 fasting samples drawn on days 12 and 14 of treatment.
- TC, HDL-C, and TG concentrations were measured using a Cobas® 6000 analyzer series module c501 (Roche Diagnostics, Indianapolis, IN) (4). LDL-C and VLDL-C concentrations were calculated using the Friedewald equation (5). Non-HDL-C was determined by subtracting HDL-C from TC values.
- Apo B and apo AI concentrations were determined using a BN ProSpec® nephelometer (Siemens, Munich, Bavaria; catalog numbers: 10446287 and 10446438 for apo B and apo AI, respectively). Apo CIII concentration was measured using a human enzyme-linked immunosorbent assay (ELISA) kit (Abcam®, Cambridge, UK; catalog number: ab154131).
- PCSK9 concentrations were quantitatively determined using a Quantikine® human ELISA kit (R&D Systems, Inc., Minneapolis, MN; catalog number: DPC900).
- Repeated measures analysis of covariance (ANCOVA) with subject in sequence as a random variable, and terms for baseline value, sequence and treatment by sequence interaction was performed for variables with normal response distribution. For those variables with non-normal response distributions (Shapiro-Wilk $p < 0.01$), the same procedure was used after rank transformation.

Figure 1. Study Flow Diagram



Results

- Subject demographic data are shown in Table 1.
- MAT9001 was superior to EPA-EE for bioavailability of EPA, with baseline-adjusted area under the curve (AUC) and maximal concentration (C_{max}) approximately 4 to 6-fold higher with MAT9001 on day 14 (Figure 2).
- Pharmacodynamic variables with non-normal response distributions included low-density lipoprotein cholesterol (LDL-C), apo AI, and PCSK9.
- Median pre-treatment values for each condition are shown in Table 2.
- Median changes from pre-treatment values are shown for each treatment condition in Figures 3 and 4. Compared with EPA-EE, MAT9001 produced significantly ($p < 0.05$) larger reductions in PCSK9, as well as all lipoprotein lipid and apolipoprotein variables except high-density lipoprotein cholesterol (HDL-C), LDL-C, and apo B.

Table 1. Subject Demographic Data

Parameter	Mean (SD) or %
Age, years	50.0 (8.0)
Weight, kg	88.4 (14.9)
BMI, kg/m^2	29.5 (3.5)
Gender, %	
Male	74
Female	26
Ethnicity, %	
Hispanic or Latino	26
Not Hispanic or Latino	74
Race, %	
Asian	17
Black or African American	5
White	78

Table 2. Median Pre-treatment Values for Each Treatment

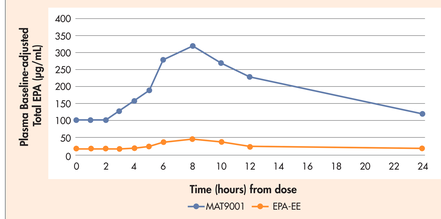
	Median (IQR) pre-treatment values	
	MAT9001	EPA-EE
TG, mg/dL	253 (180, 289)	230 (180, 296)
VLDL-C[1], mg/dL	49 (36, 57)	46 (36, 53)
Non-HDL-C, mg/dL	189 (166, 208)	181 (163, 207)
HDL-C, mg/dL	41 (35, 54)	42 (34, 53)
LDL-C[1,2], mg/dL	142 (113, 164)	139 (106, 157)
TC, mg/dL	237 (201, 257)	226 (198, 252)
Apo B, mg/dL	121 (111, 128)	119 (107, 129)
Apo AI[2], mg/dL	144 (125, 168)	137 (120, 164)
Apo CIII, mg/dL	21 (15, 24)	22 (15, 29)
PCSK9[2], ng/dL	333 (272, 368)	328 (285, 360)

Sample sizes ranged from 35-42.

[1]Some values were not calculated because the TG concentration pre- or post-treatment was >400 mg/dL.

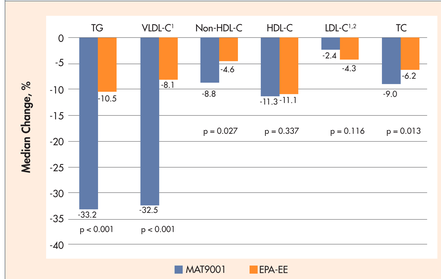
[2]Non-normal response distribution

Figure 2. Mean Plasma Baseline-adjusted Total EPA Concentration-Time Profiles on Final Day of Treatment[1]



[1]T = 0 is drug administration on final day of treatment

Figure 3. Median % Changes from Pre-Treatment Values for Lipids



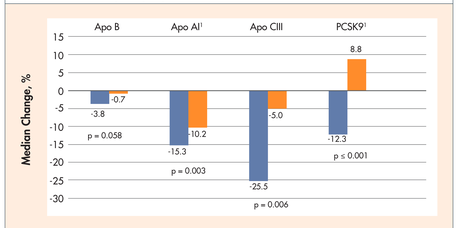
Sample sizes ranged from 37-41.

[1]Some values were not calculated because the TG concentration pre- or post-treatment was >400 mg/dL.

[2]Response variable was not normally distributed (Shapiro-Wilk $p < 0.01$), analysis was completed using ANCOVA after rank transformation for between treatment comparisons

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).

Figure 4. Median % Changes from Pre-Treatment Values for Apolipoproteins and PCSK9



Sample sizes ranged from 33-40.

[1]Response variable was not normally distributed (Shapiro-Wilk $p < 0.01$), analysis was completed using ANCOVA after rank transformation for between treatment comparisons

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).

Conclusions

- **Compared to EPA-EE, MAT9001 significantly reduced TG,VLDL-C, non-HDL-C, TC, apo CIII, and PCSK9.**

Abbreviations

ANCOVA = analysis of covariance
Apo = apolipoprotein
AUC = area under the curve
BMI = body mass index
C_{max} = maximal concentration
CVD = cardiovascular disease
CI = confidence interval
DPA = docosapentaenoic acid
EE = ethyl esters
ELISA = enzyme-linked immunosorbent assay
EPA = eicosapentaenoic acid
HDL-C = high-density lipoprotein cholesterol
IQR = interquartile range
kcal = kilocalorie
LDL-C = low-density lipoprotein cholesterol
Non-HDL-C = non-high-density cholesterol
OM3 = omega-3 fatty acids
PCSK9 = proprotein convertase subtilsin/kexin type 9
SD = standard deviation
TC = total cholesterol
TG = triglycerides
VLDL-C = very low-density lipoprotein cholesterol

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