



A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Assess the Efficacy and Safety of Ethyl-Ester Omega-3 Fatty Acid in Taiwanese Hypertriglyceridemic Patients

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Aim: Information regarding the effects of omega-3 fatty acid on hypertriglyceridemic patients in Chinese is still limited. This study aimed to investigate the efficacy and safety of Omacor[®], a prescription ethyl-ester omega-3 fatty acid for the treatment of hypertriglyceridemia, administered at doses of 2 g/day and 4 g/day to Taiwanese hypertriglyceridemic patients.

Methods: A multicenter, randomized, double-blind, placebo-controlled, parallel study in adults with hypertriglyceridemia was conducted. After a five-week diet lead in period patients with triglycerides = 200–1000 mg/dL were randomized to receive Omacor[®], a concentrated preparation of omega-3 eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) in a dose of 1 g twice daily (2 g Omacor[®]), 2 g twice daily (4 g Omacor[®]) or placebo, for eight weeks. The primary endpoint was the percentage change in triglyceride serum levels from baseline to the end of treatment.

Results: A total of 253 Taiwanese patients were randomized, of which 65.6% (166) were men. At the end of the treatment, the percentage change in triglyceride serum levels in both the Omacor[®] 4 g/day (−32.1%) and 2 g/day (−29.7%) groups was larger than in the placebo group (−5.4%) ($p < 0.001$). The incidence of drug-related adverse events was as follows: 0.0%, 1.2%, and 0.0% in Omacor[®] 4 g/day, Omacor[®] 2 g/day, and placebo groups, respectively. No drug-related serious adverse events were reported during the study.

Conclusions: Omacor[®] may be a feasible option to treat hypertriglyceridemia in Taiwanese patients.

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Key words: Hypertriglyceridemia, Omega-3 fatty acids, Omacor, Docosahexaenoic acid, Eicosapentaenoic acid, Ethnic chinese

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Introduction

Hypertriglyceridemia, together with low levels of high-density lipoprotein cholesterol (HDL-C), is an independent risk factor for coronary heart disease, according to the guidelines for the management of triglycerides (TG) and cardiovascular disease^{1, 2}. High TG levels are often concomitant with insulin resis-

tance, obesity, and acute pancreatitis, and low levels of high-density lipoprotein cholesterol (HDL-C) are present in patients with metabolic syndrome.

The standard recommendations for hypertriglyceridemic patients comprise measures to modify the root causes, such as weight loss, increased regular exercise, reduced intake of refined carbohydrates, as well as thyroid hormone replacement in patients with hypothyroidism, or alcohol cessation. At present, there are limited drugs specially indicated for the treatment of moderately elevated triglycerides; only omega-3 fatty acids, fibrates, and niacin³⁾. The American Heart Association states that doses of fatty acids of 2–4 g/day of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) can be used under a physician's care to lower elevated triglycerides⁴⁾.

Omacor[®] (Pronova BioPharma), a capsule formed of 90% omega-3-acid ethyl esters, is the first US Food and Drug Administration (FDA) and EU-approved omega-3-acid drug. Omacor[®] is prepared from fish using various patented procedures; each capsule contains 460 mg of EPA and 380 mg of DHA⁵⁾. The drug's effects include lowering plasma triglyceride levels⁶⁾, increasing conversion of very low-density lipoprotein cholesterol (VLDL-C) to low-density lipoprotein cholesterol (LDL-C), depressing triglyceride synthesis⁶⁾, and reducing postprandial lipemia⁷⁾.

Several placebo-controlled studies have reported the efficacy of omega-3 fatty acids concentrates in lowering triglyceride in patients with moderately-elevated triglycerides. In addition, it has been observed that the degree of lowering depends on the dose and on baseline triglyceride levels³⁾. The indicated doses of prescription omega-3 fatty acids range from 2 to 4g/day, with an efficacy on reduction of triglyceride levels of a 20%–45%³⁾. Such a reduction is also consistent with that observed when it was combined with a statin⁸⁾, such as simvastatin⁹⁾. Additionally, baseline TG levels may be affected by ethnicity-related factors associated with different lifestyles and the frequency of fish intake. Indeed, the Eastern diet and lifestyle differs substantially from other countries where Omacor[®] is currently authorized.

Therefore, this study aimed to demonstrate the efficacy and safety of Omacor[®], administered at doses of 2 g/day and 4 g/day on hypertriglyceridemic patients in Taiwanese patients.

Materials and Methods

This was a randomized, double-blind, placebo-controlled, parallel study with two active dosage levels (1:1:1), conducted at four medical centers in Taiwan. The study consisted in five clinic visits: one screening

visit (leading period), one randomization visit, and two biweekly visits with one monthly visit during the double-blind/treatment period. The study was supported and coordinated by Excelsior Pharmatech Labs. The registration number in ClinicalTrial.gov is NCT01725646. This study was conducted in accordance with the Investigational New Drug (IND), Informed Consent and IRB Regulations from the Taiwan Food and Drug Administration (TFDA), and Good Clinical Practice as outlined in the International Conference on Harmonization (ICH), E6 Good Clinical Practice (GCP). The study was approved by all appropriate national regulatory authorities and ethics committees of the participating hospitals. All patients participated voluntarily in the study after signing the informed consent.

Ethics

The study was approved by National Taiwan University Hospital (NTUH) Research Ethics Committee on May 13, 2011, by Institutional Review Board of the Taichung Veterans General Hospital (TCVGH) on July 27, 2011, by Institutional Review Board, Taipei Veterans General Hospital (TPVGH) on Sep 16, 2011, and by National Cheng Kung University Hospital (NCKUH) Institutional Review Board on July 26, 2011. The first patient was recruited on July 8, 2011 in NTUH, on Aug 25, 2011 in TCVGH, on Nov 24, 2011 in TPVGH, and on Sep 29, 2011 in NCKUH, and the last patient was recruited on Feb 20, 2013 and completed the follow-up on May 24, 2013.

The study was registered in the Center of Drug Evaluation (CDE) Taiwan and assigned a registration number, 1001401529, before recruiting the first patient, according to Taiwan's regulations. It was then assigned a delayed registration number of NCT01725646 on ClinicalTrial.gov, because the sponsor did not originally plan to publish the study internationally. It was thus registered in Taiwan's CDE but not on ClinicalTrial.gov before recruiting the first patient. The authors confirm that all ongoing and related trials for this drug/intervention are registered.

Study Participants

Patient eligibility criteria were: 1) age between 20 and 79 years; 2) fasting serum TG level between 200 and 1000 mg/dL at screening and also at randomization; 3) having discontinued the following lipid-altering agents: rosuvastatin, bile acid sequestrants, nicotinic acid, probucol, cholesterol absorption inhibitors, gemfibrozil or fibric acid derivatives, for at least one month; 4) if a current smoker, having no plan to change smoking habits during the study; and 5) at the

randomization visit, either to have discontinued 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, or to have been on a stable dose and schedule of HMG-CoA reductase inhibitors for at least eight weeks. The main reasons for exclusion were: 1) LDL-C control levels above the Bureau of National Health Insurance (BNHI) treatment goal at screening and randomization; 2) to be taking drugs such as non-study related omega-3, red yeast rice, weight loss drugs, immunomodulatory therapy, rosuvastatin, bile acid sequestrants, fibrates, niacin, probucol or cholesterol absorption inhibitors; 3) high consumption of fatty fish (>two servings of 150 g of fatty fish per week during the leading period); 4) severe diseases, such as uncontrolled diabetes mellitus, thyroid dysfunction, obstructive liver disease, chronic kidney disease, nephrotic syndrome or any serious renal, pulmonary, hepatic, biliary, gastrointestinal diseases or cancer within 6 months prior to randomization; and 5) a history of alcoholism (taking at least three glasses of wine or equivalent per day) during the previous three months. After the screening visit, patients who either had hypolipidemia with total cholesterol (TC) <120 mg/dL and LDL-C <50 mg/dL at any visit or had TG >1,000 mg/dL with a 30% elevation or more compared to baseline were requested to be withdrawn from study.

Procedures

For this intervention study, eligible patients entered a five-week leading period and were counseled on low fat diets throughout the study. After this leading phase, patients needed serum triglycerides levels of 200 mg/dL or more and to meet the selection criteria to be randomized. Patients were equally stratified by their lipid-altering agents/statin (with or without) and by the baseline triglyceride level (200–499 mg/dL or 500–1,000 mg/dL) prior to being randomized. The randomization schedules were generated using a validated SAS system that automates the random assignment of treatment groups to randomized numbers and were prepared with a 1:1:1 randomization ratio in block numbers as 6. Thus, patients were randomized to receive 1 g of Omacor[®] twice a day (2 g Omacor[®]/day), 2 g of Omacor[®] twice a day (4 g Omacor[®]/day) or placebo (i.e., olive oil in identical capsules) twice a day for a total of eight weeks. The Omacor[®] 2 g/day arm received one bottle with Omacor[®] capsules and one bottle with placebo capsules; the Omacor[®] 4 g/day arm received two bottles with Omacor[®] capsules; and the placebo arm received two bottles with placebo capsules. Every study medication bottle had the same appearance. The investigator kept individual blind-breaker envelopes containing the drug assignments.

Including the leading period, the total follow up lasted for 13 weeks. After the five-week leading period, the double blind period covered two biweekly visits and one monthly visit. At each visit, a 12-hour fasting blood sample was obtained to determine the efficacy measurements: serum TG, TC, HDL-C, and LDL-C. The listed items were assessed locally. The TG, TC, HDL-C, and LDL-C were analyzed using a homogeneous enzymatic method by Bayer-Siemens AVDIA 1800 Chemistry System with the corresponding reagent kits (AVDIA[®] Chemistry, Siemens).

Other additional information collected included: medical history review at screening and randomization, ECG at screening and at completion, dietary compliance (patient's dietary history review), vital signs (blood pressure, pulse), safety hematology (white blood cell count, red blood cell count, platelet count, and hemoglobin), safety biochemistry test (fasting glucose, total protein, total bilirubin, aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), alkaline phosphatase, total bilirubin, lactate dehydrogenase, γ -gamma-glutamyl transpeptidase, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride and high-sensitivity C-reactive protein). Blood samples were analyzed locally. Adverse events were reported spontaneously by the patient or elicited by open (non-leading) questioning.

The diet control is also an important part. A registered dietitian interviewed the enrolled patients monthly to evaluate their diet compliance. The patients had to record their diet in a diary card for three days before the interview with the dietitian. The dietitian reviewed the diary card in the interview and used a questionnaire to evaluate low fat diet compliance. In addition to the low fat diet, dietitians also evaluated fish consumption.

Study Endpoints

The primary efficacy endpoint was the effect of Omacor[®] for lowering serum TG, measured by the percent change from baseline to week 8 of the given treatment. Secondary endpoints included the percentage change in serum TG levels from baseline to week 4 of study treatment, the percentage change from baseline to weeks 4 and 8 in non-HDL-C concentration, TC, HDL-C, and TC: HDL-C ratio. The safety endpoint included information on adverse events (AEs), vital signs, and clinical laboratory tests.

Statistical Analysis

Sample size calculation was performed using a superiority test based on the percentage change of TG levels. From a similar study with Omacor[®] in Japanese

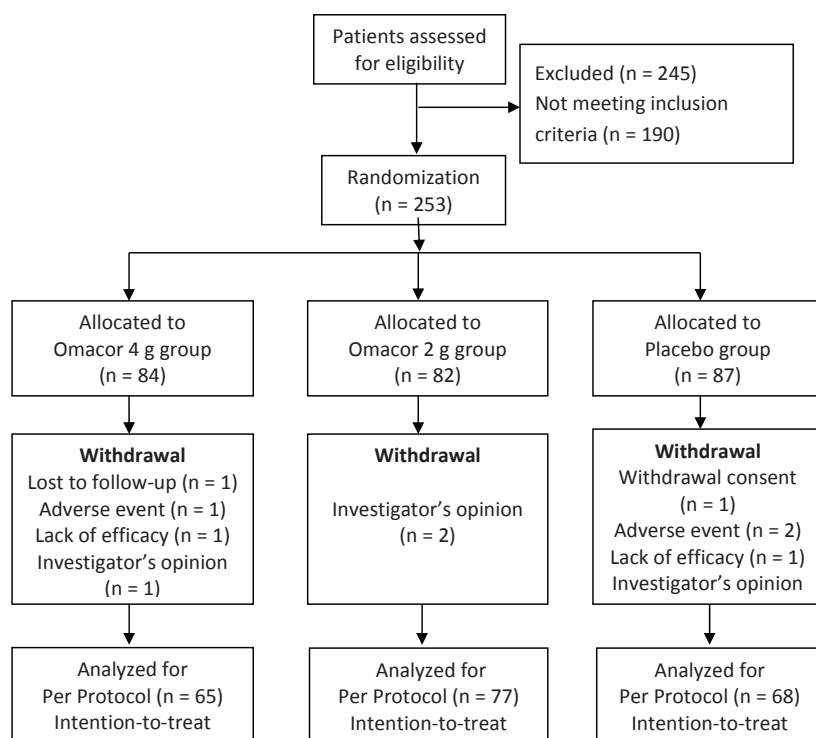


Fig. 1. Flowchart of Subject Disposition in Trial

cohorts¹⁰), a standard deviation (SD) of approximately 30% may be expected. Similarly, in the cited study, a reduction in serum TG of 12% and 26.6% was observed for patients with plasma TG above 200 mg/dL treated with Omacor[®] 2 g/day and Omacor[®] 4 g/day at eight weeks.

With a SD of 30% and estimated 80% power, a sample size of 74 patients in each treatment group was required to detect a difference in TG reduction of 14% at the 5% significance level (two-sided). To adjust for an expected 10% drop-out or non-compliance rate, 83 patients were included in each treatment group.

The intent-to-treat (ITT) population comprised all patients who were randomized to the study treatment and who had taken at least one dose of study medication and have at least one follow-up efficacy endpoint evaluation. The primary efficacy analysis was based on the ITT population used a last observation carried forward (LOCF) method of imputation for missing response variable due to patient early termination or incomplete assessment. The primary endpoint was also analyzed in the per protocol (PP) population, which included all patients who underwent any study treatment and had no major protocol violations affecting their efficacy assessments; and in the created strata based on statin usage or hypertriglyceridemia levels.

For the analysis of TG levels, the geometric mean and 95% confidence interval (CI) were computed by taking the exponent of the mean and of the lower and upper limits of the 95% CI of the natural-log-transformed sizes. The change from baseline to the end-of-treatment in natural-log-transformed TG level was evaluated by an analysis of covariance (ANCOVA) model with terms for baseline natural-log-transformed TG value, baseline fatty fish consumption (i.e., none, ≤ 150 g or > 150 g), stratification factors and treatment group. The test drug (Omacor[®]) was concluded to be superior to the control (placebo) on average if the null hypothesis was rejected. The test was performed separately for each dose versus placebo. The comparison between 2 g/day Omacor[®] and placebo could only be concluded if 4 g/day Omacor[®] was superior to placebo at the significant level of 0.05 (two-sided). For the secondary efficacy endpoints, hypothesis tests (all two-sided) were performed individually at the 5% significance level and there was no adjustment for multiple tests or for adjustment for multiplicity of endpoints. All data were analyzed using the SAS system.

The safety profile of Omacor[®] was analyzed according to adverse events reported during the study, vital signs measurements, serum chemistry and hematology results, and ECG reports. This analysis was

Table 1. Baseline characteristics of participants by treatment groups

Characteristics	Omacor [®] 4 g/day N=84	Omacor [®] 2 g/day N=82	Placebo N=87
Male	55 (65.5%)	47 (57.3%)	64 (73.6%)
Age (years)	53.7 (11.0)	54.7 (9.2)	54.4 (10.7)
Body Mass Index (kg/m ²)	26.63(3.73)	26.61(4.19)	26.66(3.86)
With Statin Treatment	29 (34.5%)	29 (35.4%)	31 (35.6%)
Triglycerides level			
≥ 200 and < 500 mg/dL	70 (83.3%)	70 (85.4%)	73 (83.9%)
≥ 500 and ≤ 1,000 mg/dL	14 (16.7%)	12 (14.6%)	14 (16.1%)
Any Cardiovascular Disease	4 (4.8%)	3 (3.7%)	4 (4.6%)
Cerebral Vascular Disease	1 (1.2%)	1 (1.2%)	1 (1.1%)
Coronary Artery Disease	3 (3.6%)	2 (2.4%)	4 (4.6%)
Hypertension	55 (65.5%)	51 (62.2%)	50 (57.5%)
Diabetes mellitus	21 (25.0%)	19 (23.2%)	17 (19.5%)
Smoking habit	14 (16.7%)	13 (15.9%)	22 (25.3%)

Data was presented as mean (SD) if continuous variables and n (%) if binary variables

conducted on the “Safety Population,” which included all randomized patients. The Medical Dictionary for Regulatory Activities (MedDRA, version 15.0) adverse event dictionary was used to map verbatim adverse events to preferred terms and system organ class.

Results

An overview of patient disposition from screening to study termination is provided in **Fig. 1**. This study was conducted from July 08, 2011 (first patient first visit) to May 24, 2013 (last patient last visit). A total of 498 patients were screened and 253 were randomized: 84 patients to Omacor[®] 4 g/day, 82 patients to Omacor[®] 2 g/day, and 87 patients to placebo. Of all randomized patients, 240 patients completed the study. The baseline characteristics of each group are shown in **Table 1**. A total of 166 (65.6%) patients were males and the mean age was 54 years old. At baseline, the mean (SD) TG levels were 375.1 (151.7) mg/dL, 363.5 (157.0) mg/dL, and 359.0 (138.8) mg/dL in Omacor[®] 4 g/day, Omacor[®] 2 g/day, and placebo groups, respectively.

Compliance

Median (interquartile range, IQR) compliance during the double-blind treatment phase was 96.6% (50.0%–117.0%), 97.1% (70.7%–110.2%) and 95.8% (59.3%–123.6%) in the Omacor[®] 4 g/day, Omacor[®] 2 g/day and placebo groups, respectively (**Supplementary Table 1**). About 85%–95% of patients in each treatment groups achieved a good compliance with treatment percentage above 85%. The low fat diet compliance is shown in **Supplemen-**

tary Table 2. From baseline to the end of the study, at least about 80% of patients achieved low fat diet compliance in each treatment group, without statistically significant differences between treatment with Omacor[®] 4 g/day and Omacor[®] 2 g/day groups during the study follow-up. Regarding weekly fish consumption, the proportion of patients who consumed none or less than 150 g of fish per week reached at least 90% from the leading period to the end of eight weeks of treatment (**Supplementary Table 3**).

Efficacy Analysis

Statistically significant reductions in TG levels were observed between Omacor[®] arms and placebo as early as week 2 and up to the end of the study (**Fig. 2**). At week 8, the percent of change in both Omacor[®] 4 g/day (–32.1%) and 2 g/day (–29.7%) groups was significantly larger than in the placebo group (–5.4%), Omacor[®] 4 g/day vs. placebo, $p < 0.0001$; Omacor[®] 2 g/day vs. placebo, $p < 0.0001$. When the PP population was analyzed at week 8, the percent of change was –32.4%, –31.1%, and –10.0% in Omacor[®] 4 g/day, Omacor[®] 2 g/day and placebo groups, respectively, with statistically significant differences between groups (Omacor[®] 4 g/day vs placebo, $p = 0.0001$; Omacor[®] 2 g/day vs placebo, $p = 0.0002$). Similar results were obtained at week 4, with percent changes of –27.8%, –28.7%, and –6.8% in Omacor[®] 4 g/day, Omacor[®] 2 g/day and placebo groups, respectively, with statistical differences between groups (Omacor[®] 4 g/day vs placebo, $p < 0.0001$; Omacor[®] 2 g/day vs placebo, $p < 0.0001$).

In addition to triglycerides, only LDL-C levels reached statistical significance when Omacor[®] and

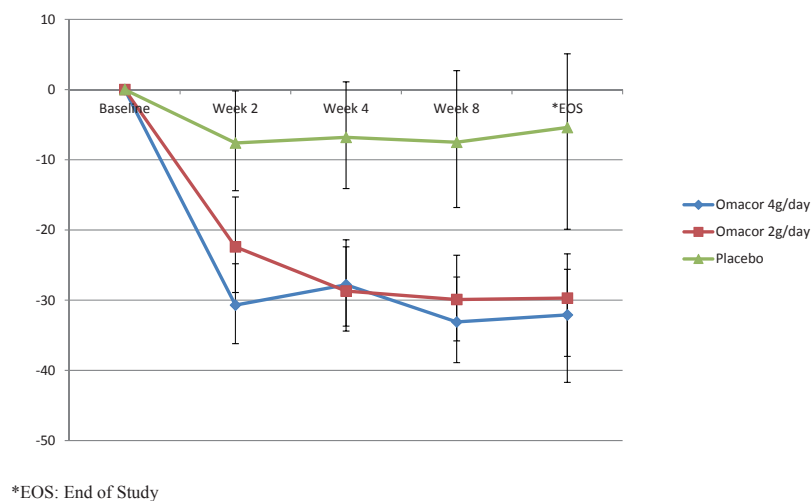


Fig. 2. Time-course of percent change in triglyceride levels (ITT population)

placebo groups were compared (Table 2). With regard to LDL-C levels, significant changes from baseline were reported at week 4 with Omacor[®] 2 g/day (7.2%, $p=0.0036$) and Omacor[®] 4 g/day (6.3%, $p=0.0096$) and sustained until the end of the study (9.9%, $p=0.0136$ and 7.2%, $p=0.0010$, respectively). Additionally, the mean LDL-C levels remained within normal ranges in all patients among the three groups during the whole study duration.

In the subgroup analysis of the primary endpoint, when the stratification was for statin or no lipid-altering medication use, the percentage change in TG levels was larger in the group that did not receive lipid-altering agents (Table 3). Similarly, the severe hypertriglyceridemia group experienced a larger change in TG levels than the group with moderate hypertriglyceridemia, although it was not statistically significant owing to the small patient numbers in the severe hypertriglyceridemia stratum (Table 4).

Safety Analysis

The incidence of drug-related AEs was 0.0%, 1.2% (one case of nausea), and 0.0% in Omacor[®] 4 g/day, Omacor[®] 2 g/day, and placebo groups, respectively. Only one patient (1.2%) treated with Omacor[®] 4 g/day group had an AE with conjunctival hemorrhage, which was unlikely related to the study drug. The incidence of serious AEs in Omacor[®] 2 g/day group was 1.2% (one case of coronary artery disease), and in placebo group was 1.1% (one case of sick sinus syndrome), both of them were unlikely related to the study drug. The incidence of AEs that led to the study drug discontinuation was 1.2% in the Omacor[®] 4 g/day group and 2.3% in placebo group. There was only

one patient treated with Omacor 4 g/day, who had an AE of mild myalgia, and then recovered without further treatment during the study, and the investigator thought it unlikely related to the study drug. The serum creatinine level also did not show significant elevation during the study in the three study groups (Supplementary Table 4). No drug-related severe AEs were observed during the study.

Discussion

The goal of the present study was to demonstrate the efficacy and safety of the doses of Omacor[®] 2 g/day and 4 g/day in the Taiwanese population. Based on the results obtained, the primary hypothesis was confirmed; significant improvements in triglyceride levels in both Omacor[®] arms versus placebo were achieved. Furthermore, it was confirmed in both the ITT and the PP population, which demonstrates the robustness of the outcome. These improvements are in agreement with the previous clinical evidence¹⁰. In fact, a review by Skulas *et al.*³ indicated an average triglyceride reduction for patients at the higher end of moderate hypertriglyceridemia of approximately 30% for Omacor[®] in studies with treatment duration between eight weeks and six months. Additionally, two randomized, double-blind, placebo-controlled studies assessing the effect of Omacor[®] 4 g/day reported a reduction of -38.9% after six weeks of treatment¹¹ and -45% in TG levels after 16 weeks of treatment¹², in patients with TG levels within the range of 500–2,000 mg/dL.

A reference study performed in the United States, the COMBOS trial⁷, which used a dose of 4 g/day in

Table 2. Treatment effects after lipid-lowering therapy from baseline to end of study

	Omacor® 4 g (n = 82)		Omacor® 2 g (n = 82)		Placebo (n = 87)		<i>p</i> -value [#]	
	Geometric Mean	95%CI	Geometric Mean	95%CI	Geometric Mean	95%CI	Omacor 4 g/day ^a	Omacor 2 g/day ^b
Total cholesterol								
Baseline, mg/dL	184.0	177.5 – 190.8	186.9	179.9 – 194.0	185.7	178.9 – 192.8	0.732	0.812
Week 2, mg/dL	176.9	169.4 – 184.7	184.2	176.7 – 192.0	184.1	177.1 – 191.2	0.035	0.747
Change from baseline, %	-3.9%	-6.0 – -1.8%	-1.4%	-4.0 – 1.3%	-0.9%	-3.0 – 1.3%		
Week 4, mg/dL	180.0	172.3 – 188.1	179.9	172.0 – 188.2	182.0	173.8 – 190.5	0.997	0.309
Change from baseline, %	-1.8%	-4.3 – 0.8%	-3.7%	-6.7 – -0.7%	-1.9%	-4.5 – 0.7%		
Week 8, mg/dL	178.3	170.3 – 186.7	181.3	173.2 – 189.7	186.8	178.9 – 195.1	0.068	0.092
Change from baseline, %	-3.1%	-5.9 – -0.3%	-3.0%	-6.1 – 0.3%	0.6%	-2.2 – 3.5%		
Triglycerides								
Baseline, mg/dL	351.2	325.2 – 379.3	338.6	313.0 – 366.4	336.9	312.8 – 362.9	0.442	0.923
Week 2, mg/dL	243.2	219.5 – 269.5	262.8	238.8 – 289.1	311.3	282.8 – 342.6	<.001	0.003
Change from baseline, %	-30.7%	-36.2 – -24.8%	-22.4%	-28.9 – -15.3%	-7.6%	-14.4 – -0.2%		
Week 4, mg/dL	251.9	229.7 – 276.2	241.6	221.2 – 263.9	311.9	282.1 – 344.8	<.001	<.001
Change from baseline, %	-27.8%	-33.7 – -21.4%	-28.7%	-34.4 – -22.4%	-6.8%	-14.1 – 1.1%		
Week 8, mg/dL	238.5	216.1 – 263.1	238.2	218.8 – 259.4	318.7	283.6 – 358.2	<.001	<.001
Change from baseline, %	-32.1%	-38.0 – -25.6%	-29.7%	-35.4 – -23.4%	-5.4%	-14.8 – 5.1%		
HDL-C								
Baseline, mg/dL	37.1	35.8 – 38.5	39.3	37.7 – 40.9	37.4	35.9 – 39.1	0.757	0.094
Week 2, mg/dL	38.0	36.6 – 39.4	39.8	38.3 – 41.4	37.9	36.4 – 39.5	0.617	0.348
Change from baseline, %	2.3%	-0.5 – 5.2%	1.5%	-1.6 – 4.6%	1.2%	-1.2 – 3.6%		
Week 4, mg/dL	37.9	36.5 – 39.4	39.4	37.6 – 41.3	37.8	36.3 – 39.4	0.662	0.587
Change from baseline, %	1.9%	-1.9 – 5.9%	0.4%	-2.6 – 3.6%	0.8%	-1.9 – 3.5%		
Week 8, mg/dL	38.0	36.4 – 39.7	39.9	38.1 – 41.8	38.6	37.0 – 40.3	0.690	0.967
Change from baseline, %	2.4%	-1.3 – 6.4%	1.6%	-1.5 – 4.8%	3.2%	0.1 – 6.3%		
Non-HDL-C								
Baseline, mg/dL	146.1	139.9 – 152.5	146.6	140.1 – 153.4	147.4	141.3 – 153.8	0.765	0.858
Week 2, mg/dL	137.9	131.0 – 145.3	143.4	136.6 – 150.7	145.3	139.0 – 151.9	0.018	0.609
Change from baseline, %	-5.6%	-8.3 – -2.8%	-2.2%	-5.4 – 1.2%	-1.4%	-4.0 – 1.2%		
Week 4, mg/dL	141.4	134.3 – 148.8	139.5	132.4 – 147.0	143.3	136.0 – 151.0	0.891	0.257
Change from baseline, %	-2.7%	-5.7 – -0.4%	-4.9%	-8.3 – -1.3%	-2.6%	-5.7 – 0.5%		
Week 8, mg/dL	139.1	131.7 – 146.9	140.4	133.2 – 148.0	147.2	140.0 – 154.7	0.059	0.101
Change from baseline, %	-4.8%	-8.0 – -1.4%	-4.2%	-8.1 – -0.2%	-0.1%	-3.6 – 3.4%		
LDL-C								
Baseline, mg/dL	80.4	75.3 – 85.9	80.8	75.2 – 86.8	83.4	77.6 – 89.7	0.457	0.524
Week 2, mg/dL	87.4	81.7 – 93.6	89.0	82.6 – 96.0	83.2	76.6 – 90.4	0.010	0.001
Change from baseline, %	8.7%	4.1 – 13.6%	10.1%	4.9 – 15.7%	-0.3%	-4.8 – 4.4%		
Week 4, mg/dL	85.5	78.8 – 92.7	86.6	79.3 – 94.6	81.0	74.3 – 88.3	0.010	0.004
Change from baseline, %	6.3%	0.9 – 12.1%	7.2%	1.0 – 13.6%	-3.6%	-8.0 – 0.9%		
Week 8, mg/dL	86.2	79.7 – 93.2	88.8	81.5 – 96.9	80.5	73.5 – 88.2	0.014	0.001
Change from baseline, %	7.2%	1.0 – 13.7%	9.9%	3.9 – 16.3%	-3.5%	-8.9 – 2.2%		

Abbreviations: HDL-C and LDL-C, High-density and Low-density lipoprotein cholesterol

[#]*p*-value: Omacor 4 g/day^a indicates the differences between Omacor 4 g/day and placebo after treatmentOmacor 2 g/day^b indicates the differences between Omacor 2 g/day and placebo after treatment

Table 3. Subgroup analyses by usage of statins and triglyceride-lowering effects at end of study (ITT population)

Subgroups	Treatment Group	N	Baseline TG level (Geometric Mean with 95% CI), mg/dL	Percent Change from Baseline (Intra <i>p</i> -value)	Omacor [®] vs Placebo (Group Difference)	<i>p</i> -value	
Statin usage	Omacor [®] 4 g	28	339.8 (292.8 – 394.5)	–28.7% (<.001)	–29.7% (–43.4 – –12.5%)	0.002	
	Stable statins	Omacor [®] 2 g	29	309.1 (273.9 – 348.9)	–27.5% (<.001)	–31.3% (–44.7 – –14.6%)	<.001
		Placebo	31	325.0 (281.1 – 375.7)	4.3% (0.678)	--	--
	No lipid- altering Agent	Omacor [®] 4 g	54	357.3 (326.2 – 391.4)	–33.8% (<.001)	–25.0% (–36.0 – –12.0%)	<.001
		Omacor [®] 2 g	53	356.0 (321.3 – 394.4)	–30.8% (<.001)	–22.0% (–33.5 – –8.4%)	0.003
		Placebo	56	343.7 (315.2 – 374.6)	–10.4% (0.072)	--	--
Baseline TG level	Omacor [®] 4 g	68	311.3 (294.3 – 329.3)	–28.4% (<.001)	–25.3% (–34.5 – –14.9%)	<.001	
	Moderate hypertrigly ceridemia	Omacor [®] 2 g	70	302.3 (286.2 – 319.4)	–25.2% (<.001)	–22.7% (–32.1 – –12.0%)	<.001
		Placebo	73	301.3 (284.4 – 319.2)	–3.0% (0.588)	--	--
	Severe hypertrigly ceridemia	Omacor [®] 4 g	14	631.4 (562.6 – 708.6)	–47.7% (0.001)	–35.6% (–57.9 – –1.5%)	0.043
		Omacor [®] 2 g	12	656.4 (565.9 – 761.4)	–50.7% (<.001)	–38.3% (–60.9 – –2.6%)	0.039
		Placebo	14	603.0 (546.7 – 665.1)	–16.8% (0.231)	--	--

p-value: Paired *t*-test for intragroup comparison; *t*-test per ANCOVA model for intergroup comparison.

Table 4. Comparison of triglyceride levels change between the subgroup of severe and moderate hypertriglyceridemia after treatment

Subgroup	200 mg/dL ≤ TG < 500 mg/dL		TG ≥ 500 mg/dL		<i>p</i> -value
	<i>n</i>	Change	<i>n</i>	Change	
Omacor [®] 4 g	68	–28.4%	14	–47.7%	0.6095
Omacor [®] 2 g	70	–25.2%	12	–50.7%	0.6654

combination with simvastatin for eight weeks versus placebo, reported a median of percent change of –29.5% in the Omacor[®] + simvastatin arm and –6.3% in the placebo simvastatin arm. Another reference study performed in UK¹³ reported a mean of percent change of –22.4%. More specific to the Asian area is a Japanese phase III study¹⁰, similar to ours in both the population of patients and doses used which

reported lower TG reduction in comparison with our study (–10.8% in the Omacor[®] 2 g group and –22.9% in the Omacor[®] 4 g group). A comparison among Taiwan, Japan, and UK studies at dose 4 g was showed in **Supplementary Table 5**.

Surprisingly, the two doses used in our study, 4 g/day and 2 g/day, achieved a very similar percentage of TG reduction. Based on the clinical evidence, it is

widely accepted that the effect of this drug is dose-dependent^{14, 15}). In addition, the Japanese study demonstrated the expected differences between both active groups. In the investigators' opinion, one explanation could be moderation of Chinese foods with a large amount of carbohydrates may attenuate the additional dose of omega-3 fatty acids on triglyceride-lowering effects¹⁶). Besides, the low fat diet compliances for Omacor[®] 4 g and Omacor[®] 2 g groups were 81.0% and 91.5%, respectively. Although the difference was not statistically significant; however, it was close to statistical significance ($p=0.067$). The trend of better compliance of maintaining low fat diet may contribute to the triglyceride-lowering effects for Omacor[®] 2 g group, thus attenuate the dose-dependent response of higher dose of Omacor[®] 4 g/day.

After treatment with Omacor[®] 2 g, a higher omega-3/omega-6 ratio also significantly improved insulin resistance and subsequently decreased the levels of triglycerides of study participants^{17, 18}). Another explanation is the high percentage of overweight in our study patients, which had been demonstrated to have a higher risk of severe hypertriglyceridemia (TG ≥ 500 mg/dL) while concurrent with genetic polymorphism in apolipoprotein A5 in Chinese¹⁹). An interaction between omega-3 fatty acids supplement and genetic variants in APOA5 and/or APOE4 may modify the response to omega-3 fatty acids treatment significantly independent of dose-response pattern in these patients. Not only the insulin resistance, but also the arterial stiffness, can be improved by a higher EPA/AA ratio²⁰).

In addition, our study demonstrated an even larger reduction in triglyceride levels in Taiwanese compared to Japanese participants. The difference in triglyceride-lowering effects between the Taiwanese and Japanese might be mediated by the difference in eating habits: more fish and seaweeds are consumed by the Japanese (rich in omega-3 fatty acids), which may attenuate the additional lipid-lowering effects of fish oil in Omacor[®]²¹).

It is worth mentioning that the significant improvement with Omacor[®] was achieved at week two and maintained until the end of our study. According to Rupp *et al.*⁵), when Omacor[®] 1 g/day is administered for 30 days, the bioavailability of the drug remains constant and optimal during the treatment period, reaching plateau levels from the tenth day. In our literature review, most studies also support such a reduction after week 4^{13, 22-24}), but no data is available for the preceding period and it therefore cannot be appropriately contextualized.

The effectiveness of Omacor[®] is influenced by baseline TG levels³). Indeed, in our study, patients in

the severe hypertriglyceridemia stratum experienced a larger change in TG levels than those in the moderate hypertriglyceridemia stratum, although it was not statistically significant. In all cases, treatment groups versus placebo were statistically significant in both the Omacor[®] 4 g/day and 2 g/day arms.

On the other hand, LDL-C levels slightly increased after four to eight weeks with both doses of Omacor[®], comparing with placebo, although the mean levels of LDL-C remained within the normal ranges throughout the study in all groups. In this context, Maki *et al.* in a *post hoc* analysis of the COMBOS trial²⁵) showed that Omacor[®] treatment also increased the levels of LDL-C but only in patients in the lowest tertile (<80.4 mg/dL) level at the beginning of the study. In the present study, mean (SD) baseline LDL-C levels were 83.9 (24.3) mg/dL, 84.9 (25.8) mg/dL, and 88.1 (28.1) mg/dL in Omacor[®] 4 g/day, Omacor[®] 2 g/day, and placebo groups, respectively, which were close to the report of Maki *et al.* Another example is the TAK-085 study in Japan²⁶), in which the mean (SD) baseline LDL-C levels were 129.0 (30.3) mg/dL, 133.2 (29.9) mg/dL, and 129.3 (33.0) mg/dL in Omacor[®] (TAK-085) 4 g/day, Omacor[®] (TAK-085) 2 g/day, and EPA-E groups, respectively, resulting in a slight increase or even decrease at the end of study ($2.38 \pm 20.5\%$, $-0.42 \pm 17.3\%$, and $-1.49 \pm 16.8\%$ in Omacor[®] 4 g/day, Omacor[®] 2 g/day, and EPA-E groups, respectively). However, it seems that the increment of LDL-C level was larger in Omacor[®] 2 g/day than that in Omacor[®] 4 g/day in the present study, but this was not statistically significant ($p=0.391$). Further studies are needed to clarify the mechanism.

Additionally, a subgroup analysis of the COMBOS trial focusing on lipoprotein sizes and concentrations revealed that Omacor[®] 4 g/day produced significant reductions in intermediate density lipoprotein cholesterol (IDL-C) ($p<0.0001$ vs. baseline) and small LDL-C ($p=0.0035$ vs. baseline)²⁷). The TAK-085 study in Japan also showed a shift from small dense LDL-C to large buoyant LDL-C and increased LDL-C/Apo B ratios, as well as a decrement of Apo C-III after treatment with Omacor[®]²⁸). Higher levels of IDL-C and small dense LDL-C usually presenting in hypertriglyceridemic patients are considered more harmful than other lipid particles because they can more easily penetrate the arterial wall²⁹). Our recent study also demonstrated that small dense LDL-C particles might potentiate postchallenge hyperglycemia on the risk of arterial stiffness in middle-aged healthy adults³⁰). The safety profile of both Omacor[®] arms was as expected, with a rate of adverse event reactions comparable to the 3% reported in the Summary of

Product Characteristics. Indeed, no significant safety concerns arose during the course of the trial.

In the COMBOS trial, with a treatment period of eight weeks, the short treatment duration has been noted as a study limitation. However, a 24-month extension of the COMBOS study confirmed the results about efficacy and safety³¹). In this case, the goal of the study was to confirm the efficacy of Omacor[®] and the duration was not considered a weakness for this purpose, but the authors admit that longer trials might better characterize clinical efficacy and safety. Additionally, the specificity of the population, all of which was Asian, offers valuable information regarding these patients, though it makes it difficult to extrapolate the results to other patient populations.

EPA also showed the effects on inflammatory markers, including high sensitivity CRP³²). However, in the present study, there was no significant change in all of three treatment groups (**Supplementary Table 6**). This may have been due to the shorter period and the different remedies and doses, or different patient cohorts.

In conclusion, the use of Omacor[®] 4 g/day or Omacor[®] 2 g/day in Taiwanese patients significantly reduced TG levels compared to placebo in the present study. Although extrapolation of data from clinical trials to routine clinical practice is not always straightforward, owing to the heterogeneous patient population, the presence of comorbidities, and the unstructured follow-up characteristics of daily practice, Omacor[®] appears a valid option for treating hypertriglyceridemia in Taiwanese patients. Furthermore, differences in diet and behavior in the Chinese population reinforce the need to conduct confirmatory studies on the efficacy of Omacor[®] in this specific population of patients.

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Supplementary Table 1. Summary of study drug compliance

	Omcor 4 g/day	Omacor 2 g/day	Placebo	Group difference			
				Omacor 4 g/day vs Placebo	Omacor 2 g/day vs Placebo	Omacor 4 g/day vs Omacor 2 g/day	Omacor vs Placebo
<i>N</i>	82	82	87				
Mean (SD), %	94.9 (10.6)	96.0 (6.4)	93.5 (10.3)				
Median, %	96.6	97.1	95.8				
(Min, Max), %	(50.0, 117.0)	(70.7, 110.2)	(59.3, 123.6)				
Mean, %				1.40	2.56	-1.16	1.98
95% CI, %				-1.43 - 4.22	-0.26 - 5.38	-4.03 - 1.70	-0.46 - 4.41
<i>p</i> -value (a)				0.3314	0.0755	0.4246	
<i>p</i> -value (b)				0.3051	0.0891	0.5039	0.1108

p-value(a): *t*-test for intergroup comparison

p-value(b): Rank transformation ANOVA for intergroup comparison

Supplementary Table 2. Summary of low fat diet compliance

	Omacor 4 g/day		Omacor 2 g/day		Placebo		<i>p</i> -value (Overall)
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	
Baseline							0.262
Compliance	62	75.6%	69	84.1%	74	85.1%	
Not Compliance	20	24.4%	13	15.9%	13	14.9%	
<i>p</i> -value (Group Comparison)	0.242 (4 g vs 2 g)		1.000 (2 g vs Placebo)		0.174 (4 g vs Placebo)		
First Month							1.000
Compliance	64	79.0%	63	77.8%	67	78.8%	
Not Compliance	17	21.0%	18	22.2%	18	21.2%	
<i>p</i> -value (Group Comparison)	1.000 (4 g vs 2 g)		1.000 (2 g vs Placebo)		1.000 (4 g vs Placebo)		
Second Month							0.129
Compliance	64	81.0%	75	91.5%	69	83.1%	
Not Compliance	15	19.0%	7	8.5%	14	16.9%	
<i>p</i> -value (Group Comparison)	0.067 (4 g vs 2 g)		0.160 (2 g vs Placebo)		0.838 (4 g vs Placebo)		

p-value: Fisher's exact test

Supplementary Table 3. Summary of fish consumption

	Omacor 4 g/day		Omacor 2 g/day		Placebo		<i>p</i> -value (overall)
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	
Baseline							0.4452
None per week	27	32.9%	36	43.9%	28	32.2%	
≤ 150g per week	50	61.0%	40	48.8%	54	62.1%	
> 150g per week	5	6.1%	6	7.3%	5	5.7%	
<i>p</i> -value (Group comparison)	0.299 (4 g vs 2 g)		0.211 (2 g vs Placebo)		1.000 (4 g vs Placebo)		
First Month							0.070
None per week	40	79.0%	34	42.0%	26	30.6%	
≤ 150g per week	36	21.0%	45	55.6%	52	61.2%	
> 150g per week	5		2	2.5%	7	8.2%	
<i>p</i> -value (Group comparison)	0.263 (4 g vs 2 g)		0.125 (2 g vs Placebo)		0.051 (4 g vs Placebo)		
Second Month							0.695
None per week	30	38.0%	35	42.7%	27	32.5%	
≤ 150g per week	47	59.5%	44	53.7%	52	62.7%	
> 150g per week	2	2.5%	3	3.7%	4	4.8%	
<i>p</i> -value (Group comparison)	0.695 (4 g vs 2 g)		0.378 (2 g vs Placebo)		0.631 (4 g vs Placebo)		

p-value: Fisher's exact test**Supplementary Table 4.** Changes of serum creatinine level during the study period by treatment groups

Creatinine level (mg/dL)	Omacor® 4 g/day (<i>n</i> =84)		Omacor® 2 g/day (<i>n</i> =82)		Placebo (<i>n</i> =87)		<i>p</i> -value	
	Mean (SD)	Min – Max	Mean (SD)	Min – Max	Mean (SD)	Min – Max	Omacor 4 g/day	Omacor 2 g/day
Baseline	0.88 (0.24)	0.42 – 2.18	0.86 (0.24)	0.47 – 1.72	0.87 (0.25)	0.46 – 1.71	0.811	0.630
Week 2	0.87 (0.24)	0.43 – 2.31	0.86 (0.25)	0.43 – 1.81	0.88 (0.25)	0.49 – 1.88	0.380	0.396
Change from baseline	–0.01	–0.04 – 0.02 (95%CI)	–0.01	–0.03 – 0.01 (95%CI)	0.00	–0.02 – 0.02 (95%CI)		
Week 4	0.87 (0.24)	0.51 – 2.22	0.87 (0.27)	0.43 – 1.87	0.87 (0.26)	0.45 – 1.87	0.571	0.407
Change from baseline	–0.01	–0.04 – 0.02 (95%CI)	0.01	–0.01 – 0.03 (95%CI)	–0.00	–0.02 – 0.02 (95%CI)		
Week 8	0.86 (0.20)	0.48 – 1.47	0.88 (0.27)	0.42 – 1.94	0.88 (0.24)	0.48 – 1.70	0.735	0.252
Change from baseline	0.00	–0.03 – 0.03 (95%CI)	0.03	0.00 – 0.06 (95%CI)	0.01	–0.02 – 0.03 (95%CI)		
End of Study	0.89 (0.25)	0.48 – 2.22	0.89 (0.28)	0.42 – 1.94	0.88 (0.24)	0.48 – 1.70	0.918	0.960
Change from baseline	0.00	–0.03 – 0.03 (95%CI)	0.03	0.00 – 0.06 (95%CI)	0.01	–0.02 – 0.03 (95%CI)		

Supplementary Table 5. Comparisons of lipid-lowering effects among the trials in Taiwan, Japan, and UK at the dose of 4 g/day

	Taiwan		Japan		UK	
	Geometric Mean	95%CI	Mean (SD)	95%CI	Mean (SD)	Min – Max
Triglycerides						
Baseline, mg/dL	351.2	325.2 – 379.3	277.5 (97.3)	—	284.3 (92.1)	177.1 – 554.5
Week 2, mg/dL	243.2	219.5 – 269.5	—	—	—	—
Change from baseline, %	-30.7%	-36.2 – -24.8%	—	—	—	—
Week 4, mg/dL	251.9	229.7 – 276.2	200 (87.9)	—	222.3 (93.0)	103.6 – 524.4
Change from baseline, %	-27.8%	-33.7 – -21.4%	-26.9%	-29.8 – -24.1%	-21.8%	—
Week 8, mg/dL	238.5	216.1 – 263.1	212.5 (107.4)	—	217.0 (83.3)	92.1 – 430.5
Change from baseline, %	-32.1%	-38.0 – -25.6%	-22.5%	-26.6 – -18.4%	-23.7%	—
Week 10, mg/dL	—	—	205.9 (99.3)	—	—	—
Change from baseline, %	—	—	-23.4%	-27.8 – -19.0%	—	—
Week 12, mg/dL	—	—	208.8 (86.0)	—	220.5 (98.3)	68.2 – 544.7
Change from baseline, %	—	—	-22.9%	-26.0 – -19.7%	-22.4%	—
Total cholesterol						
Baseline, mg/dL	184.0	177.5 – 190.8	212.0 (30.2)	—	288.5 (43.7)	205.0 – 380.9
Week 2, mg/dL	176.9	169.4 – 184.7	—	—	—	—
Change from baseline, %	-3.9%	-6.0 – -1.8%	—	—	—	—
Week 4, mg/dL	180.0	172.3 – 188.1	206.2 (32.5)	—	287.7 (50.3)	193.4 – 406.0
Change from baseline, %	-1.8%	-4.3 – 0.8%	-2.7%	-4.0 – -1.5%	-0.3%	—
Week 8, mg/dL	178.3	170.3 – 186.7	206.1 (32.9)	—	282.3 (60.7)	166.3 – 464.0
Change from baseline, %	-3.1%	-5.9 – -0.3%	-2.9%	-4.2 – -1.5%	-0.3%	—
Week 10, mg/dL	—	—	203.5 (31.6)	—	—	—
Change from baseline, %	—	—	-3.9%	-5.4 – -2.5%	—	—
Week 12, mg/dL	—	—	203.9 (31.5)	—	291.2 (54.9)	177.9 – 444.7
Change from baseline, %	—	—	-3.7%	-5.0 – -2.4	0.9%	—
HDL-C						
Baseline, mg/dL	37.1	35.8 – 38.5	45.7 (10.0)	—	41.0 (10.4)	35.9 – 39.1
Week 2, mg/dL	38.0	36.6 – 39.4	—	—	—	—
Change from baseline, %	2.3%	-0.5 – 5.2%	—	—	—	—
Week 4, mg/dL	37.9	36.5 – 39.4	47.6 (11.2)	—	42.9 (12.4)	15.5 – 77.3
Change from baseline, %	1.9%	-1.9 – 5.9%	4.1%	2.6 – 5.6%	4.7%	—
Week 8, mg/dL	38.0	36.4 – 39.7	47.5 (11.6)	—	41.0 (10.8)	19.3 – 69.6
Change from baseline, %	2.4%	-1.3 – 6.4%	3.9%	2.2 – 5.6%	0.0%	—
Week 10, mg/dL	—	—	47.4 (11.3)	—	—	—
Change from baseline, %	—	—	4.2%	2.5 – 5.9%	—	—
Week 12, mg/dL	—	—	47.6 (11.0)	—	42.5 (11.2)	19.3 – 65.7
Change from baseline, %	—	—	4.3%	2.8 – 5.8%	3.8%	—
LDL-C						
Baseline, mg/dL	80.4	75.3 – 85.9	125.7 (28.5)	—	174.0 (42.5)	99.8 – 245.9
Week 2, mg/dL	87.4	81.7 – 93.6	—	—0	—	—
Change from baseline, %	8.7%	4.1 – 13.6%	—	—	—	—
Week 4, mg/dL	85.5	78.8 – 92.7	127.9 (30.3)	—	191.4 (51.8)	75.8 – 309.4
Change from baseline, %	6.3%	0.9 – 12.1%	2.3%	0.1 – 4.39%	10.0%	—
Week 8, mg/dL	86.2	79.7 – 93.2	125.2 (31.9)	—	184.5 (45.6)	83.5 – 304.7
Change from baseline, %	7.2%	1.0 – 13.7%	-0.4%	-2.9 – 2.0%	6.0%	—
Week 10, mg/dL	—	—	124.2 (29.7)	—	—	—
Change from baseline, %	—	—	-0.9%	-3.4 – 1.6%	—	—
Week 12, mg/dL	—	—	123.6 (29.0)	—	183.3 (56.1)	84.7 – 290.4
Change from baseline, %	—	—	-1.1%	-3.35 – 1.2%	5.3%	—

Abbreviations: HDL-C and LDL-C, High-density and Low-density lipoprotein cholesterol

Supplementary Table 6. Summary of mean high-sensitivity CRP level before and after Omacor treatment

Unit: %	Omacor 4 g/day	Omacor 2 g/day	Placebo	Group difference			
				Omacor 4 g/day vs Placebo	Omacor 2 g/day vs Placebo	Omacor 4 g/day vs Omacor 2 g/day	Omacor vs Placebo
Baseline							
<i>N</i>	84	82	87				
Mean (SD)	0.2272 (0.2820)	0.1631 (0.1676)	0.1652 (0.2475)	0.0620	-0.0020	0.0640	0.0300
Median	0.1130	0.1070	0.0810				
(Min, Max)	(0.0120, 1.1830)	(0.0120, 0.8700)	(0.0120, 1.5390)				
95% CI				-0.0097 - 0.1336	-0.0741 - 0.0701	-0.0087 - 0.1367	-0.0320 - 0.0920
<i>p</i> -value (a)				0.0897	0.9556	0.0842	0.3420
End of Study							
<i>N</i>	79	82	86				
Mean (SD)	0.2438 (0.4548)	0.2182 (0.4560)	0.1508 (0.2525)				
Median	0.1030	0.0830	0.0520				
(Min, Max)	(0.0120, 3.6870)	(0.0120, 3.1250)	(0.0120, 1.4410)				
Change	0.0162	0.0550	-0.0151	0.0617	0.0688	-0.0072	0.0652
95% CI	-0.0873 - 0.1197	0.0399 - 0.1500	-0.0737 - 0.0435	-0.0551 - 0.1784	-0.0462 - 0.1838	-0.1253 - 0.1110	-0.0345 - 0.1649
<i>p</i> -value (a)	0.7562	0.2522	0.6093	0.2994	0.2397	0.9051	0.1987
<i>p</i> -value (b)	0.9939	0.5316	0.1599	0.1331	0.8708	0.1845	0.3298

p-value (a): t-test for intergroup comparison*p*-value (b): Rank transformation ANOVA for intergroup comparison