Supplementary Online Content

Mozaffarian D, Maki KC, Bays HE, et al; TRILOGY (Study of CaPre in Lowering Very High Triglycerides) investigators. Effectiveness of a novel ω-3 krill oil agent in patients with severe hypertriglyceridemia: a randomized clinical trial. *JAMA Netw Open*. 2022;5(1):e2141898. doi:10.1001/jamanetworkopen.2021.41898

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Trial Operations, Inclusion and Exclusion Criteria, Laboratory Measurements, Assignment to Treatment Groups, and Statistical Analysis

Trial Operations

CRO:

IQVIA RDS Inc. (formerly known as Quintiles IMS), 4820 Emperor Blvd, Durham NC 27703

Central Laboratories:

Q2 Solutions, LLC, 27027 Tourney Road Suite 2E, Valencia CA USA 91355

Quest Diagnostics Nichols Institute, 33608 Orthega Hwy, San Juan Capistano CA 92675-2042

Central IRB:

Advarra (formerly Quorum), 1501 Fourth Avenue Suite 800, Seattle WA 98101

Independent Statistical Validation:

Peilin Shi, PhD, Senior Biostatistician, Tufts University, Boston, MA

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Subjects ≥18 years of age.
2. Isolated hypertriglyceridemia or mixed hyperlipidemia, with triglycerides ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) treated or not with a stable dose of statin, CAI, PCSK9I, fibrate, or a combination of these agents.

   If not contraindicated, fibrate treatment may be discontinued or dose reduced at the discretion of the investigator at time of screening.

   If not contraindicated, the investigator may prescribe new or different statin and/or CAI treatment to be initiated, or change current doses of statin and/or CAI at time of screening.
3. Willingness to aim to maintain current physical activity level and diet consistent with NCEP-TLC and to reduce added sugars intake throughout the study.
4. Be informed of the nature of the study and give written consent prior to any study procedure.

Exclusion Criteria:

1. Allergy or intolerance to OM3 fatty acids, OM3-acid ethyl esters, OM3 phospholipids, fish, shell fish, or any component of the study medication.
2. Subjects diagnosed with Familial Chylomicronemia Syndrome (FCS).
3. Subjects with lysosomal acid lipase deficiency.
4. Body mass index greater than 45 kg/m^2.
5. Subjects who are pregnant, lactating, and subjects of childbearing potential who are either planning to become pregnant or who are not using acceptable birth control methods during study participation. Subjects of childbearing potential are subjects who have experienced menarche and do not otherwise meet the criteria for subjects not of childbearing potential, defined as:
   - Subjects who have had surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation); or
   - Subjects who are postmenopausal, i.e., who have had a cessation of menses for at least 12 months without an alternative medical cause. A follicle stimulating hormone (FSH) test ≥40 mIU/mL may be used to confirm the post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

   Subjects of childbearing potential must test negative for pregnancy at the time of enrollment and agree to use an acceptable contraceptive method or remain abstinent during the study and for 8 weeks following the last dose of study medication.

6. Subjects taking tamoxifen, estrogens, or progestins, or other medications or nutritional supplements with mechanisms modifying estrogen or progestogen pathways, who have had dosage changes within 4 weeks prior to Visit 1.
7. Use of oral or injected corticosteroids or anabolic steroids within 6 weeks prior to randomization.
8. History of pancreatitis within the last 6 months prior to Visit 1.
9. History of symptomatic gallstone disease within the last 5 years, unless treated with cholecystectomy.
10. Diabetics requiring changes in glucose-lowering medication (other than short acting insulin dosage adjustments) within 6 weeks prior to Visit 1 or who have HbA1c greater than 9.5% at Visit 1.
11. Subjects with clinical evidence of hyperthyroidism or TSH level less than lower limit of normal (LLN) at Visit 1. Subjects diagnosed with hyperthyroidism must be treated with medication for at least 6 weeks prior to Visit 1.
12. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH) level more than 1.5 × upper limit of normal (ULN) within 6 weeks prior to Visit 1.
13. Thyroid hormone replacement therapy that has not been stable for more than 6 weeks prior to Visit 1.
14. History of cancer (other than basal cell carcinoma) within 2 years prior to Visit 1.
15. Cardiovascular event (i.e., myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, exacerbation of congestive heart failure requiring hospitalization or a change in treatment), life-threatening arrhythmia, or revascularization procedure within 6 months prior to Visit 1.
16. Use of other prohibited drugs: prescription or OTC medications specifically taken for weight loss such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, sibutramine, lorcaserin, topiramate+phentermine, bupropion+naltrexone, and bupropion+zonisamide; human immunodeficiency virus (HIV) protease inhibitors; cyclophosphamide; isotretinoin; routine or anticipated use of systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are permitted); or anabolic steroids. Stable use of anabolic steroids or testosterone for at least 6 weeks prior to V1 as a replacement therapy for hypogonadism are allowed.
17. Use of any lipid-altering agents other than statins, CAI, PCSK9I, or fibrate, including niacin at a dose greater than 200 mg/day, bile acid sequestrants, OM3 drugs (e.g., Lovaza or its generics,Vascepa, Epanova, Omtryg), OM3 supplements (e.g., fish oil, krill oil products), or any other herbal products or dietary supplements specifically taken for their lipid-altering effects. These agents must be discontinued 8 weeks prior to randomization.
18. Resection of an aortic aneurysm or endovascular aortic repair within 6 months prior to Visit 1.
19. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome or ≥3 gram proteinuria daily.

20. Poorly controlled hypertension (systolic blood pressure ≥170 mmHg and/or diastolic blood pressure ≥100 mmHg). Subjects with hypertension adequately controlled with medication are eligible provided that their antihypertensive therapy has been stable for at least 4 weeks prior to Visit 1.
21. Recent history (past 12 months) of drug abuse or alcohol abuse, or alcohol use greater than 2 units per day (a unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks).
22. Hepatobiliary disease or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN; if ALT/AST is >3× ULN, the levels must have been stable for 3 months prior to Visit 1.
23. Severe renal disease as defined by less than 30 mL/min serum creatinine clearance calculated using the Cockcroft-Gault formula.
24. Significant coagulopathy as defined by a known hereditary deficiency of coagulation factors or platelet function or an unexplained elevation of the prothrombin time (PT) international normalized ratio (INR) of ≥1.5. Subjects using warfarin [Coumadin®] or heparin are allowed. Subjects receiving other anticoagulants dabigatran, rivaroxaban, or apixaban are allowed. Subjects receiving acetylsalicylic acid (ASA) alone or in combination with other anti-platelet agents (e.g., clopidogrel, prasugrel, ticagrelor) are also allowed.
25. Unexplained creatine kinase concentration 3 × ULN.
26. Creatine kinase elevation owing to known hereditary or acquired muscle disease.
27. Exposure to any investigational product, within 4 weeks prior to Visit 1.
28. Presence of any other condition (such as severe pulmonary, gastrointestinal, or immunologic disease) the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.
29. Any life-threatening disease expected to result in death within 2 years, require frequent hospitalizations, extensive surgery or changes in medications or diet.

Laboratory Methods

All laboratory measurements were performed centrally by accredited central laboratories (Q Squared Solutions, Valencia, CA; Quest Diagnostics Nichols Institute, San Juan Capistrano, California) obtained from fasting (minimum of 9 hours) blood samples at all study visits. TG, HDL-C and total cholesterol were measured using enzymatic colorimetric tests on (Roche COBAS 6000/8000) under certification of performance by the Centers for Disease Control and Prevention Lipid Standardization Program. Non-HDL-C was calculated by subtracting HDL-C from Total Cholesterol. LDL-C was obtained by lipoprotein ultracentrifugation. VLDL-C was calculated as Total Cholesterol minus HDL-minus LDL-C from ultracentrifugation values. Direct LDL-C measured by homogeneous enzymatic colorimetric assay was also obtained at all study visits. Apolipoprotein (apo)-A1, Apo-B and Apo-C3 were measured by turbidimetric assay. Apo-A5 was measured by a validated ELISA assay [Kamiya

Biomedical, Seattle, Washington). High sensitive C-Reactive Protein (hsCRP) was measured by chemistry autoanalyser [Roche COBAS 6000/8000]. Lipoprotein particle number and sizes were obtained by Ion Mobility (11). Relative concentrations of OM3 and Omega-6 fatty acids were measured in plasma phospholipids by LC/MS-MS using single ion monitoring and selected reaction monitoring under Atmospheric Pressure Chemical Ionization negative mode. Oxidised LDL was measured in plasma by a validated ELISA assay (Mercodia AB, Uppsala, Sweden). Lp-PLA2 was measured by a validated enzymatic assay (Quest Diagnostics). Investigators were kept blind to the fasting serum lipid assessments made during the course of the study after randomization. Any TG value greater than 1500 mg/dL initiated a blinded alert to the site, and required clinical and laboratory follow-up within a one week.

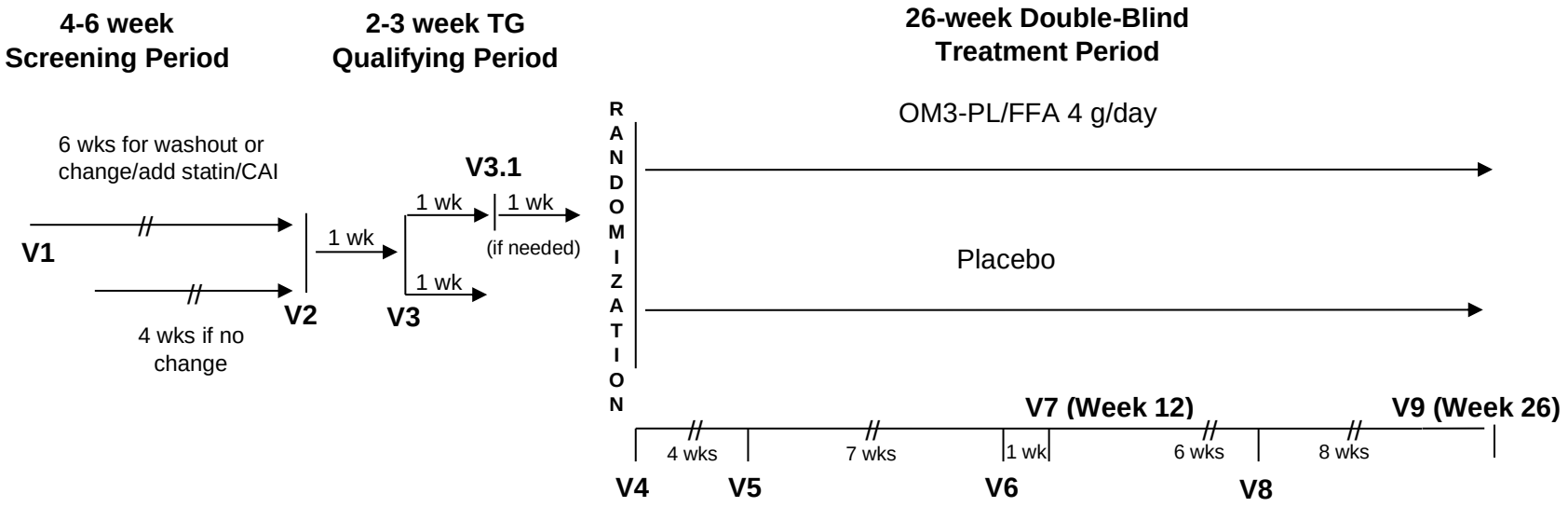
Method of Assigning Subjects to Treatment Groups

After completing the informed consent process, subjects were assigned an identification number by interactive response technology (IRT) at screening (Visit 1). At Visit 4, once the subject satisfied inclusion and exclusion criteria at the end of the TG qualifying period, the study center requested a subject to be randomly assigned to a treatment group following a 2.5:1 treatment allocation ratio (CaPre : placebo) using IRT. Once randomized, the study center was provided by the IRT with details of the corresponding study medication kit to be dispensed to the subject at Visit 4. Similarly, details of the corresponding study medication kit dispensed to the subject at subsequent study visits was provided to the study center through the IRT.The randomization code for treatment assignment was held by the IRT vendor.

Statistical Analysis – Multiple Imputation

Missing endpoint values were imputed using multiple imputation. First, partial imputation assuming a missing-at-random mechanism was carried out to impute intermittent (non-monotone) missing data based on multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method, with a separate model for each treatment group and including the randomization-stratifying covariates as fixed covariates and observed TG values at baseline, Week 4, Week 11, Week 12, Week 18 and Week 26. The MCMC method in the MI procedure in SAS was used with multiple chains, 200 burn-in iterations, and a non-informative prior. Then, the remaining monotone missing data were imputed using sequential regression multiple imputation.

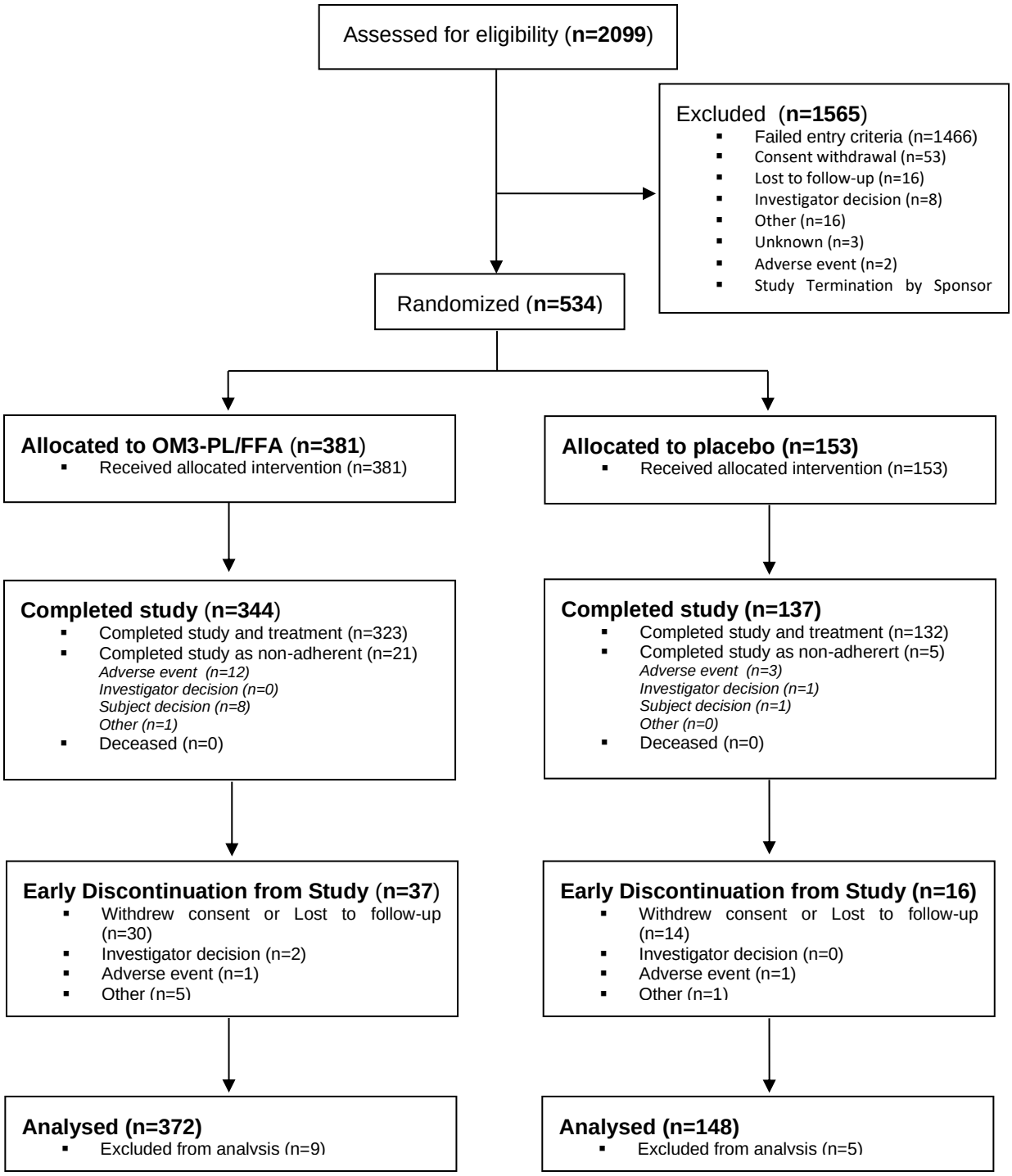
eFigure 1. Design of the TRILOGY Trials



At the screening visit (V) 1, patients entered a diet, lifestyle and medication stabilization period which lasted 4 weeks for patients not currently taking or receiving a stable dose of statin, PCSK9I, CAI, fibrate, or a combination of these agents, and 6 weeks for patients who i) required to discontinue prohibited lipid-altering agents or ii) initiated or changed dose of a statin and/or CAI treatment. At V2, patients entered the TG qualifying period during which an average fasting TG level ≥500 mg/dL and ≤1500 mg/dL based on the average (arithmetic mean) of V2 and V3 was required prior to enter the 26-week double-blind treatment period. If a patient's average TG level from V2 to V3 fell outside the required range, an additional TG measurement could be made one week later at V3.1 and entry into the study was to be based on the average of V3 and V3.1. Qualifying patients were randomized at V4 and entered the 26-week double-blind safety and efficacy measurement phase. The baseline value was defined as the average of the 3 measurements corresponding to V2, V3, and V4 or V3, V3.1 and V4 in case an additional TG measurement was necessary during qualification. The Week 12 endpoint was defined as the average of the 2 measurements obtained at the end of 12-weeks of double-blind treatment, approximately 1 week apart that is V6 (Week 11) and V7 (Week 12).

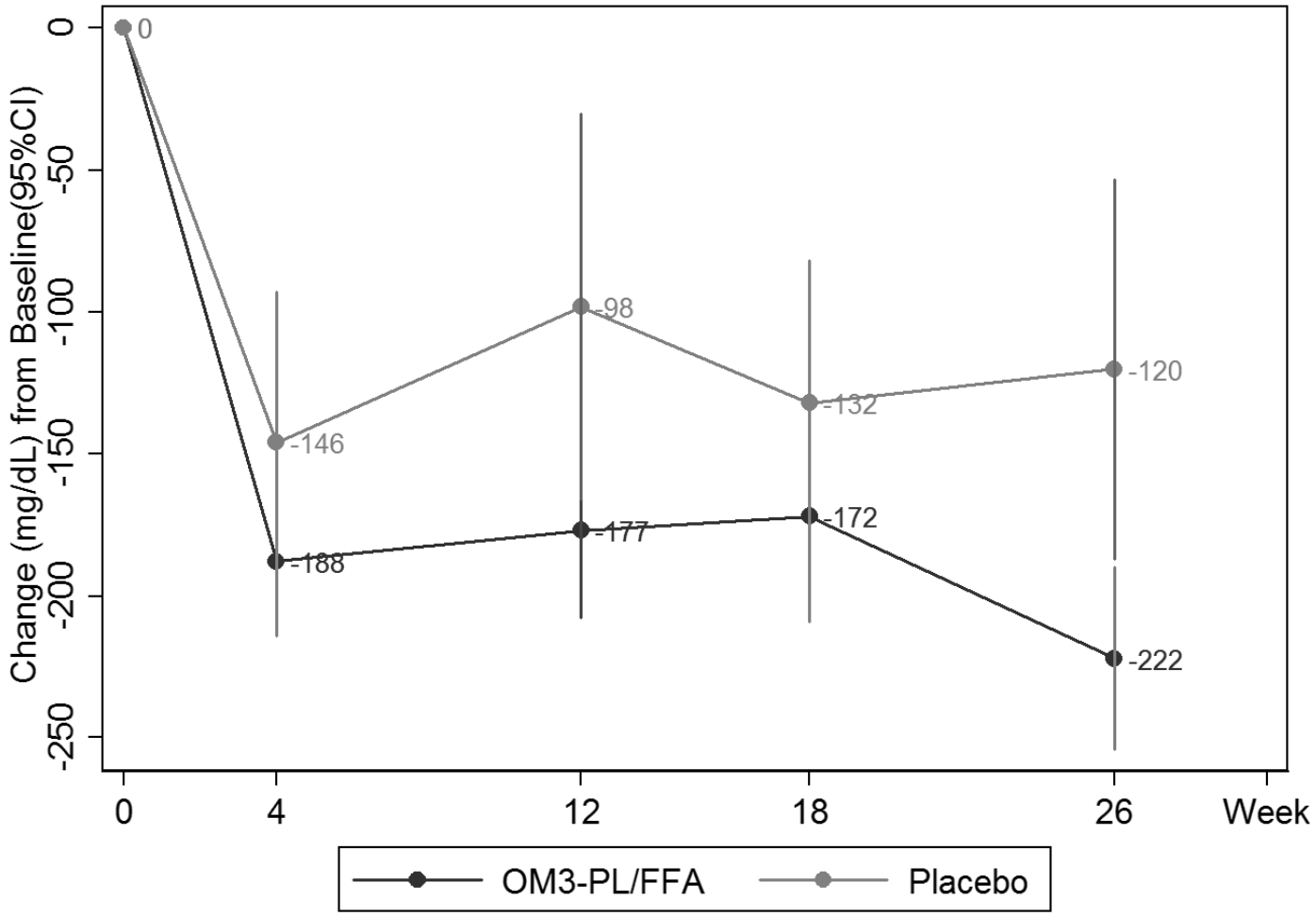
PCSK9I: proprotein convertase subtilisin/kexin type 9 serine protease inhibitors, TG: Triglycerides.

eFigure 2. Flow Diagram of Participants
One site (14 subjects) was excluded prior to analysis due to inability to confirm the fidelity of data from this site.

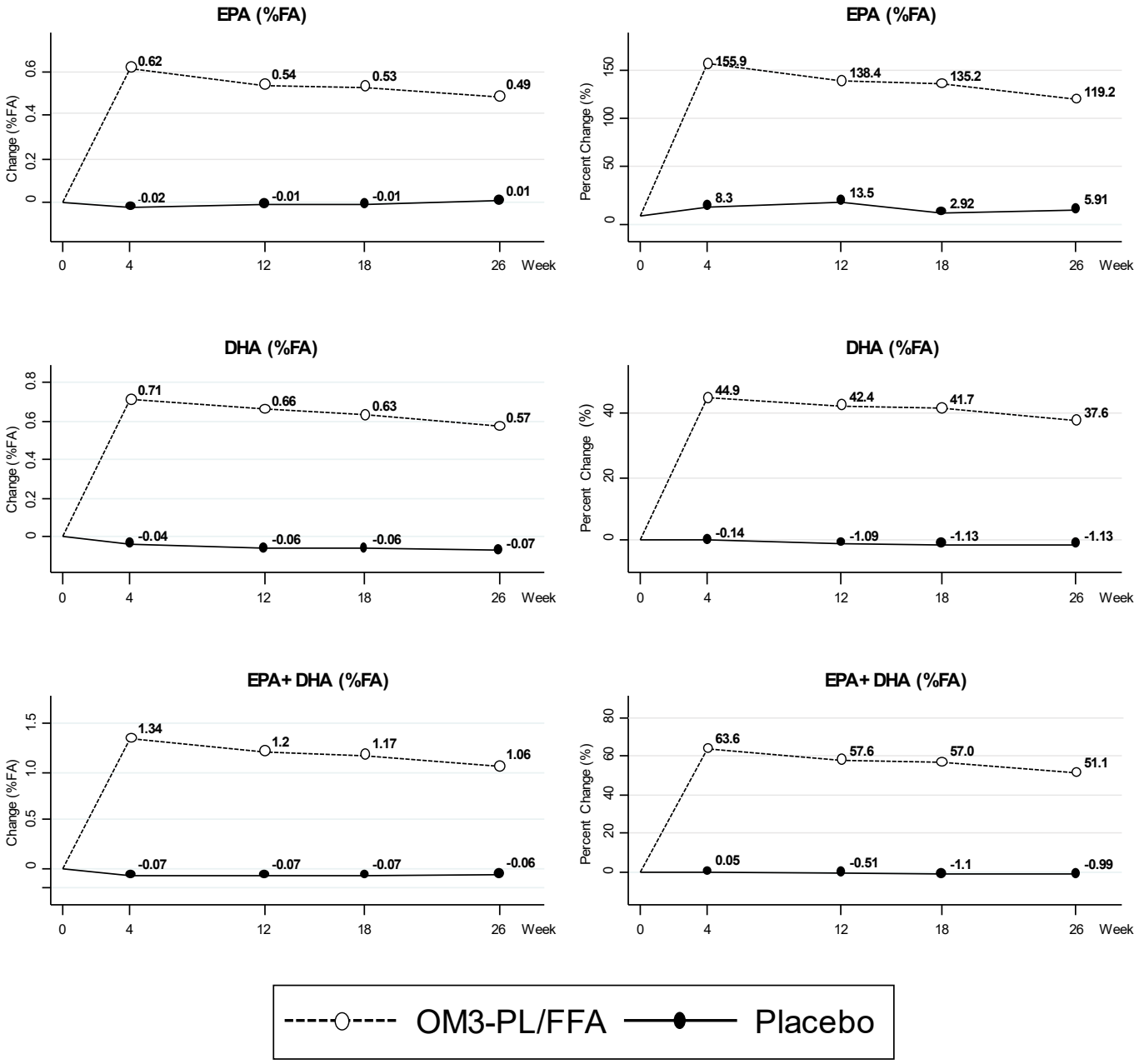


eFigure 3. Changes in Fasting Triglyceride (TG) Levels in the 4-g/d ω-3–PL/FFA and Placebo Groups Between Baseline and Week 26 (n = 520)

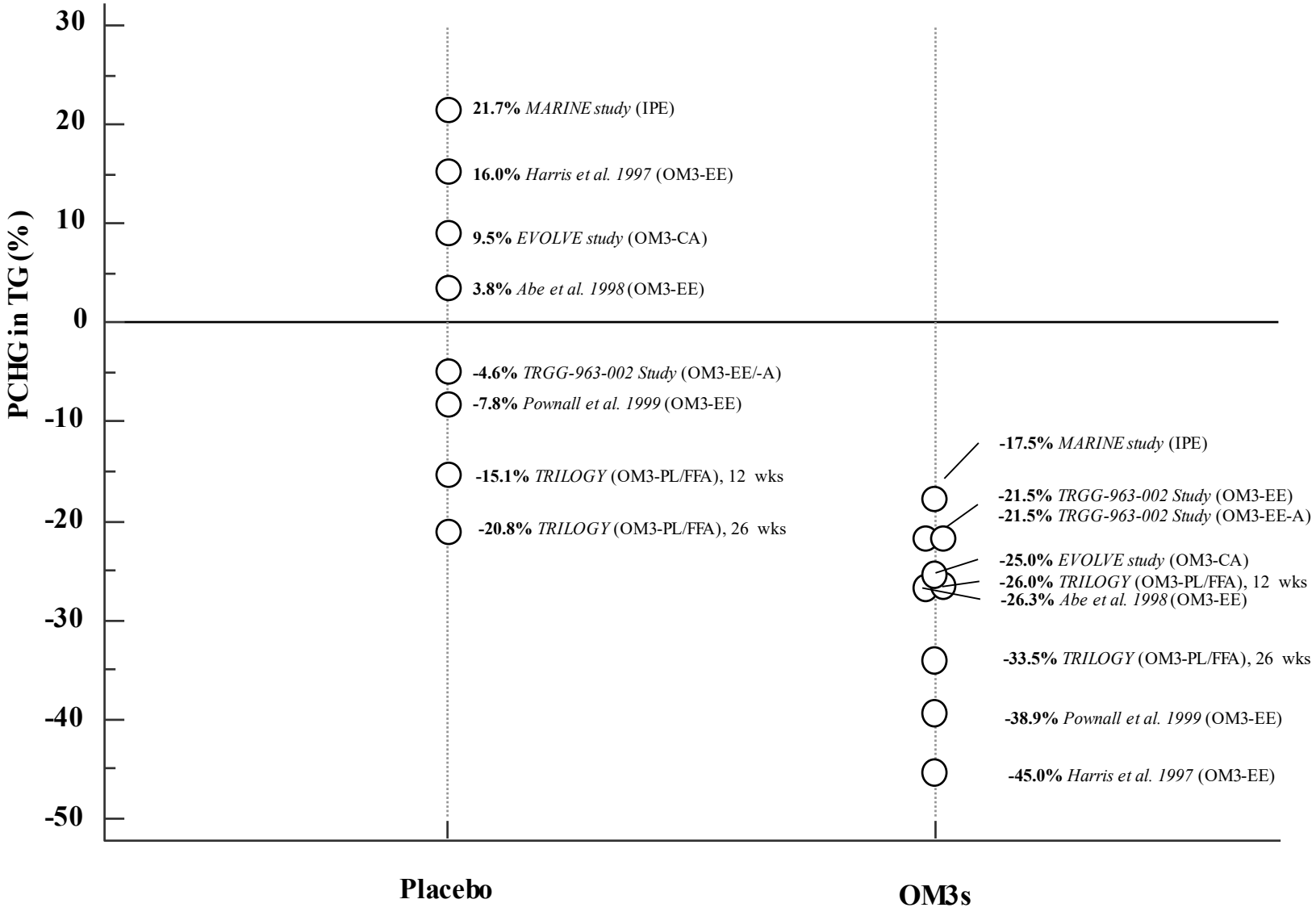
Values are least-square mean differences from baseline, with 95% CIs (error bars) from ANCOVA including main effects of treatment, qualifying TG category (≤750 vs. >750 mg/dl), use of statin, CAI and/or PCKSK9 (yes/no), and baseline TG value as a covariate.



eFigure 4. Absolute and Percentage Changes in Plasma Phospholipid EPA, DHA, and EPA Plus DHA (% Fatty Acids) During the 26-Week Double-Blind Period



eFigure 5. Comparison of Triglyceride Lowering Between Placebo and ω-3 Drugs in Severe Hypertriglyceridemia



Values expressed as mean percent change from baseline, except Harris et al. 1997 (median). PCHG. Percent change from baseline (%). IPE: Icosapent ethyl, OM3-CA: omega-3-carboxyl acids, OM-3-EE: omega-3 ethyl esters. Drugs given in a dose of 4 g/d. Severe Hypertriglyceridemia = TG ≥500 mg/dL. References: (1) Harris et al. 1997 (Lovaza [OM3-

EE]), (2) Abe et al. 1998 (Lovaza [OM3-EE]); (3) Pownall et al. 1999 (Lovaza [OM3-EE]). (4) NDA 202057. Statistical Review(s) (MARINE Study, Icosapent ethyl [IPE], Vascepa); (5) NDA 205060. Statistical Review(s) (EVOLVE Study, omega-3-carboxyl acids [OM3-CA], Epanova); (6) NDA 204977. Statistical Review(s) (TRGG-963-002 Study, Omtryg [OM3-EE-A], Lovaza [OM3-EE]).

eTable 1. Percentage Changes in Primary**, Key Secondary, and Other Secondary End Points in Intention-to-Treat Analysis for TRILOGY 1 and 2**

	Percent Change in Placebo (N=148) (95% CI)	Percent Change in OM3-PL/FFA (N=372) (95% CI)	Treatment Difference (95% CI)	P-value
TG, mg/dL				
Trilogy 1, week 12	-21.54 (-32.72, -10.36)	-28.06 (-35.62, 20.51)	-6.52 (-19.51, 6.47)	0.325
Trilogy 1, week 26	-23.06 (-34.22, -11.89)	-36.57 (-43.95, -29.19)	-13.52 (-26.24, -0.80)	0.037
Trilogy 2, week 12	-6.98 (-18.21, 4.25)	-22.25 (-29.25, -15.24)	-15.27 (-27.66, -2.88)	0.016
Trilogy 2, week 26	-16.94 (-29.15, -4.72)	-29.05 (-36.97, -21.13)	-12.11 (-25.85, 1.64)	0.084
Non-HDL-C, mg/dL				
Trilogy 1, week 12	-6.66 (-13.05, -0.27)	-9.53 (-13.74, -5.31)	-2.87 (-10.25, 4.52)	0.447
Trilogy 1, week 26	-6.51 (-12.47, -0.55)	-11.83 (-16.01, -7.64)	-5.32 (-12.35, 1.72)	0.138
Trilogy 2, week 12	-2.87 (-8.23, 2.49)	-6.38 (-9.80, -2.95)	-3.51 (-9.64, 2.63)	0.263
Trilogy 2, week 26	-1.11 (-8.04, 5.83)	-7.30 (-11.95, -2.65)	-6.2 (-14.18, 1.78)	0.128
VLDL-C, mg/dL				
Trilogy 1, week 12	-17.94 (-28.20, -7.68)	-20.49 (-27.00, -13.99)	-2.55 (-14.04, 8.94)	0.663
Trilogy 1, week 26	-16.23 (-30.26, -2.21)	-24.83 (-33.17, -16.48)	-8.60 (-23.20, 6.01)	0.248
Trilogy 2, week 12	-2.76 (-13.05,7.53)	-7.17 (-13.96, -0.39)	-4.41 (-16.34, 7.51)	0.468
Trilogy 2, week 26	-6.42 (-20.95,8.12)	-16.12 (-27.07, -5.18)	-9.71 (-26.64, 7.23)	0.261
HDL-C, mg/dL				
Trilogy 1, week 12	10.71 (5.34, 16.07)	10.00 (6.48, 13.51)	-0.71 (-6.90, 5.49)	0.823
Trilogy 1, week 26	9.48 (3.58, 15.39)	12.53 (8.51, 16.55)	3.05 (-3.89, 9.99)	0.389
Trilogy 2, week 12	7.01 (1.56, 12.46)	8.94 (5.49, 12.38)	1.93 (-4.28, 8.13)	0.543
Trilogy 2, week 26	11.77 (2.55, 21.00)	12.78 (6.68, 18.89)	1.01 (-9.68, 11.70)	0.853
LDL-C, mg/dL				
Trilogy 1, week 12	6.69 (-12.91, 26.30)	8.65 (1.58, 15.72)	1.96 (-17.15, 1.07)	0.84
Trilogy 1, week 26	25.14 (-14.54,64.81)	17.98 (3.83,32.13)	-7.16 (-45.17, 0.86)	0.711
Trilogy 2, week 12	9.00 (-0.28, 18.28)	15.96 (10.01, 21.90)	6.96 (-3.71, 17.63)	0.201
Trilogy 2, week 26	6.86 (-5.63, 19.36)	24.53 (14.95, 34.10)	17.66 (3.68, 31.65)	0.013

*The primary endpoint was the treatment difference in TG levels at 12 weeks; and the key secondary endpoint, the treatment difference in TG levels at 26 weeks. Values are least-square mean percentage point differences from baseline, with p-value from ANCOVA including main effects of treatment, qualifying TG category (≤750 vs. >750 mg/dl), use of statin, CAI and/or PCKSK9 (yes/no), and baseline TG value as a covariate.

eTable 2. Changes in Exploratory End Points in Intention-to-Treat Analysis

	Change in Placebo (N=148) (95% CI)	Change in OM3-PL/FFA (N=372) (95% CI)	Treatment Difference (95% CI)	P-value
Subjects with Achieved Fasting TG < 500 mg/dl, n (%)				
Week 12	68 (46.0%)	210 (56.5%)	10.5% (1.0%, 20.1%)	0.021
Week 26	76 (51.4%)	234 (62.9%)	11.5% (2.1%, 21.0%)	0.012
Total Cholesterol, mg/dl				
Week 12	-3.00% (-6.43, 0.43)	-5.67% (-7.90, -3.44)	-2.67% (-6.61, 1.27)	0.184
Week 26	-2.11% (-6.08, 1.85)	-6.38% (-9.16, -3.61)	-4.27% (-8.86, 0.32)	0.068
ApoB, mg/dL				
Week 12	0.64% (-3.21, 4.49)	-1.43% (-3.98, 1.12)	-2.07% (-6.39, 2.24)	0.347
Week 26	1.72% (-2.15, 5.60)	0.83% (-1.63, 3.29)	-0.89% (-5.30, 3.51)	0.690
ApoC3, mg/dL				
Week 12	-1.69% (-17.46, 14.08)	2.08% (-5.39, 9.54)	3.77% (-10.89, 18.43)	0.613
Week 26	18.77% (-0.42, 37.97)	-3.11% (-13.75, 7.52)	-21.89% (-42.01, -1.77)	0.033
ApoA5, µg/dL				
Week 12	-1.27% (-47.24, 44.69)	0.35% (-33.39, 34.08)	1.62% (-52.30, 55.54)	0.953
Week 26	-10.96% (-43.85, 21.93)	-14.38% (-29.76, 0.99)	-3.42% (-37.33, 30.49)	0.843
LDL Particle Conc., nmol/L)				
Week 12	5.57% (0.75, 10.40)	2.91% (-0.20, 6.02)	-2.66% (-8.18, 2.85)	0.344
Week 26	5.23% (0.00, 10.47)	4.36% (0.89, 7.83)	-0.87% (-6.82, 5.07)	0.774
hs-CRP, mg/dL				
Week 12	109.0% (13.4, 204.7)	29.3% (-49.0, 107.6)	-79.7% (-194.8, 35.4)	0.175
Week 26	51.9% (-67.7,171.6)	75.0% (-35.6, 185.6)	23.1% (-125.4, 171.5)	0.761
Log hs-CRP				
Week 12	27.3% (-72.5, 127.1)	-32.4% (-106.4, 41.7)	-59.6% (-177.5, 58.2)	0.321
Week 26	12.3 (-86.2, 110.8)	-35.1 (-110.9, 40.6)	-47.4 (-165.1, 70.3)	0.430
Fasting Glucose, mg/dL †				
All patients				
Week 12	9.91% (-28.22, 9.49)	3.71% (-12.72, 20.15)	-6.19% (-45.98, 33.59)	0.759
Week 26	8.64% (-29.57, 46.85)	13.00% (-9.81, 35.81)	4.36% (-39.38, 48.09)	0.845
Patients with Diabetes				
Week 12	6.39% (-24.26, 37.04)	4.16% (-17.58, 25.90)	-2.23% (-35.17, 30.71)	0.894

Week 26	1.82% (-29.82, 33.45)	12.96% (-14.67, 40.59)	11.14% (-29.13, 51.42)	0,587
HbA1c, % †				
All patients				
Week 12	2.18% (-0.11, 4.47)	2.09% (0.75, 3.44)	-0.09% (-2.56, 2.38)	0.944
Week 26	0.54% (-2.24, 3.32)	1.44% (-0.40, 3.28)	0.9% (-2.24, 4.04)	0.575
Patients with Diabetes				
Week 12	2.28% (-0.69, 5.24)	2.09% (0.08, 4.10)	-0.19% (-3.57, 3.19)	0.914
Week 26	0.14% (-3.48, 3.76)	1.61% (-0.88, 4.09)	1.47% (-2.74, 5.69)	0.493

*The proportion of subjects with achieved fasting TG <500 mg/dl was assessed using a Cochran-Mantel-Haenszel test for the main effect of treatment, controlling for qualifying TG category (≤750 vs. >750 mg/dl) and use of statin, CAI, or PCSK9I (yes/no). Other values are least-square mean differences from baseline, with p-value from ANCOVA including main effects of treatment, qualifying TG category (≤750 vs. >750 mg/dl), use of statin, CAI and/or PCKSK9 (yes/no), and baseline value as a covariate.
†Among subjects with diabetes at baseline

eTable 3. Changes in Primary, Key Secondary, and Other Secondary End Points After 12 and 26 Weeks in Intention-to-Treat Analysis, Subgroup—Use of Statin, CAI and/or PCSK9

	Placebo (N=148)	OM3-PL/FFA (N=372)	Treatment difference (95% CI)	P-value*
Use of statin, CAI and/or PCSK9 (Yes)				
TG (mg/dL)				
Week 12	-9.0% (-23.4, 5.4)	-28.5% (-37.7, -19.3)	-19.5% (-34.5, -4.6)	0.010
Week 26	-15.1% (-29.0, -1.2)	-37.4% (-46.2, -28.6)	-22.3% (-36.7, -7.8)	0.003
Non-HDL-C (mg/dL)				
Week 12	-2.4% (-9.1, 4.4)	-9.3% (-13.7, -4.8)	-6.9% (-14.5, 0.7)	0.074
Week 26	1.9% (-5.8, 9.6)	-11.2% (-16.4, -6.0)	-13.1% (-21.6, -4.6)	0.003
VLDL-C (mg/dL)				
Week 12	-5.3% (-18.5, 8.0)	-14.5% (-22.5, -6.6)	-9.3% (-23.2, 4.7)	0.193
Week 26	0.4% (-19.0, 19.8)	-19.6% (-30.5, -8.6)	-20.0% (-38.7, -1.3)	0.036
HDL-C (mg/dL)				
Week 12	7.6% (1.1, 14.0)	11.1% (6.9, 15.3)	3.6% (-3.7, 10.8)	0.337
Week 26	9.2% (-1.1, 19.5)	14.8% (7.8, 21.7)	5.6% (-6.0, 17.2)	0.347
LDL-C (mg/dL)				
Week 12	3.6% (-16.5, 23.8)	10.1% (1.6, 18.6)	6.5% (-12.6, 25.6)	0.504
Week 26	18.0%[1] (-22.8, 58.8)	18.2%[1] (0.6, 35.7)	0.1% (-36.3, 36.5)	0.995
Use of statin, CAI and/or PCSK9 (No)				
TG (mg/dL)				
Week 12	-20.1% (-29.8, -10.4)	-23.1% (-30.0, -16.3)	-3.0% (-14.6, 8.5)	0.606
Week 26	-25.1% (-37.0, -13.2)	-29.1% (-37.5, -20.8)	-4.1% (-17.9, 9.8)	0.565
Non-HDL-C (mg/dL)				
Week 12	-5.5% (-10.5, -0.5)	-5.8% (-9.1, -2.5)	-0.2% (-6.1, 5.6)	0.935
Week 26	-7.6% (-13.0, -2.1)	-7.2% (-11.2, -3.2)	0.4% (-6.2, 7.0)	0.910
VLDL-C (mg/dL)				
Week 12	-10.4% (-18.9, -2.0)	-10.5% (-16.5, -4.5)	-0.1% (-10.4, 10.2)	0.988
Week 26	-16.8% (-28.8, -4.8)	-18.6% (-28.6, -8.5)	-1.8% (-16.7, 13.1)	0.814
HDL-C (mg/dL)				
Week 12	9.2% (4.7, 13.7)	7.5% (4.6, 10.5)	-1.7% (-7.0, 3.6)	0.533
Week 26	9.7% (4.1, 15.3)	9.5% (5.5, 13.5)	-0.2% (-6.8, 6.5)	0.955
LDL-C (mg/dL)				
Week 12	12.2% (4.5, 19.8)	14.7% (9.7, 19.7)	2.5% (-6.5, 11.5)	0.585
Week 26	13.3% (2.5, 24.1)	25.1% (17.8, 32.5)	11.9% (-0.8, 24.6)	0.067

* p-value and LSM estimates from primary analysis on MI data with analysis of covariance model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCKSK9, alone or in combination, and baseline value as a covariate. Treatment difference (difference in LSM between CaPre and placebo) with associated two-sided 95% CI Rubin's combination rule.

[1] Values artefactually inflated due to MI.; Observed cases (no MI) values are 8.7% and 14.8%, respectively, for placebo and OM3-PL/FFA for comparison.

eTable 4. Changes in Primary, Key Secondary, and Other Secondary End Points After 12 and 26 Weeks in Intention-to-Treat Analysis, Subgroup—Baseline Phospholipid EPA Plus DHA

	Placebo (N=148)	OM3-PL/FFA (N=372)	Treatment difference (95% CI)	*P* value*
Baseline phospholipid EPA+DHA ≤ median (n=253)				
TG (mg/dL)				
Week 12	-5.3% (-18.3, 7.6)	-24.8% (-33.0, -16.7)	-19.5% (-33.8, -5.3)	0.007
Week 26	-24.5% (-36.8, -12.2)	-31.9% (-40.0, -23.7)	-7.4% (-21.1, 6.4)	0.294
Non-HDL-C (mg/dL)				
Week 12	-4.3% (-10.4, 1.9)	-8.1% (-11.9, -4.3)	-3.8% (-10.8, 3.2)	0.283
Week 26	-7.0% (-13.3, -0.6)	-9.1% (-13.3, -4.9)	-2.1% (-9.4, 5.1)	0.565
VLDL-C (mg/dL)				
Week 12	-3.9% (-15.0, 7.2)	-11.9% (-18.9, -4.9)	-8.0% (-20.5, 4.6)	0.213
Week 26	-13.4% (-26.1, -0.8)	-18.8% (-28.0, -9.7)	-5.4% (-20.2, 9.4)	0.473
HDL-C (mg/dL)				
Week 12	3.4% (-1.7, 8.6)	6.9% (3.7, 10.1)	3.5% (-2.3, 9.3)	0.239
Week 26	11.2% (1.7, 20.6)	11.6% (5.4, 17.7)	0.4% (-10.3, 11.1)	0.941
LDL-C (mg/dL)				
Week 12	4.6% (-5.4, 14.5)	13.8% (7.6, 19.9)	9.2% (-2.0, 20.4)	0.106
Week 26	9.4% (-3.1, 21.8)	23.1% (13.3, 32.8)	13.7% (-0.4, 27.8)	0.057
Baseline phospholipid EPA+DHA > median (n=236)				
TG (mg/dL)				
Week 12	-24.4% (-35.7, -13,0)	-26.9% (-34.9, -18.9)	-2.5% (-15.4, 10.3)	0.698
Week 26	-19.7% (-33.1, -6.4)	-34.2% (-43.8, -24.7)	-14.5% (-29.5, 0.5)	0.058
Non-HDL-C (mg/dL)				
Week 12	-6.6% (-12.3, -0.9)	-8.1% (-12.0, -4.2)	-1.5% (-8.2, 5.1)	0.657
Week 26	-3.2% (-10.2, 3.8)	-9.3% (-14.3, -4.2)	-6.0% (-14.3, 2.2)	0.152
VLDL-C (mg/dL)				
Week 12	-16.7% (-27.2, -6.2)	-14.0% (-21.0, -7.0)	2.8% (-9.2, 14.7)	0.651
Week 26	-10.8% (-27.5, 6.0)	-20.4% (-32.2, -8.4)	-9.6% (-27.4, 8.2)	0.292
HDL-C (mg/dL)				
Week 12	11.3% (5.6, 17.0)	11.3% (7.4, 15.2)	-0.0% (-6.7, 6.6)	0.992
Week 26	10.0% (3.3, 16.7)	13.1% (8.5, 17.7)	3.1% (-4.8, 10.9)	0.439
LDL-C (mg/dL)				
Week 12	10.0% (2.7, 17.2)	9.9% (4.8, 15.0)	-0.1% (-8.7, 8.5)	0.982
Week 26	8.3% (-3.3, 19.9)	18.2% (10.7, 25.8)	10.0% (-2.9, 22.8)	0.128

* p-value and LSM estimates from primary analysis on MI data with analysis of covariance model with main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCKSK9, alone or in combination, and baseline value as a covariate. Treatment difference (difference in LSM between CaPre and placebo) with associated two-sided 95% CI Rubin's combination rule.

eTable 5. Changes in Triglycerides After 12 and 26 Weeks in Intention-to-Treat Analysis (Sensitivity Analyses)

	TG Values (mg/dL)	Placebo (N=148)	OM3-PL/FFA (N=372)	Treatment Difference
Baseline	Mean (SD)	706 (219)	699 (223)	
	Median	644	637	
Week 12	Mean (SD)	609 (477)	521 (346)	
	Median	517	444	
	Mean percent change (SD)	-15.9% (52.0)	-26.9% (37.3)	
	LSM percent change (95% CI) †	-15.1% (-23.5, -6.6)	-26.0% (-31.5, -20.4)	-10.9% (-20.4, -1.5)
	p-value			0.023
	Median percent change ‡	-22.4%	-33.4%	-9.8% (-19.2, -0.4)
	p-value	-	-	0.301
Week 26	Mean (SD)	585 (464)	476 (320)	
	Median	493	419	
	Mean percent change (SD)	-19.2% (48.3)	-32.1% (37.2)	
	LSM percent change (95% CI) †	-20.8% (-30.1, -11.5)	-33.5% (-39.8, -27.2)	-12.7% (-23.1, -2.4)
	p-value			0.016
	Median percent change ‡	-26.9%	-37.0%	-10.1% (-21.4, 1.2)
	p-value	-	-	0.112

*Baseline values are the average of the last 3 measurements obtained up to the time of randomization. Week 12 is the average of Week 11 and Week 12 measurements obtained approximately 1 week apart.

†Primary analysis, based on least-square mean (LSM) differences from baseline, with p-value from ANCOVA including main effects of treatment, qualifying TG category (≤750 vs. >750 mg/dl), use of statin, CAI and/or PCKSK9 (yes/no), and baseline TG value as a covariate.

‡Adjusted median estimate from sensitivity analysis based on parametric rank-based ANCOVA including main effects of treatment, qualifying TG category (≤750 mg/dL vs. >750 mg/dL), use of statin, CAI or PCKSK9 (yes/no), and baseline TG value as a covariate. For the treatment difference, quantile regression is used to obtain the adjusted estimate of the median treatment difference.

eTable 6. Summary of Adverse Events

System Organ Class Preferred term	**Placebo (N=148)**	**OM3-PL/FFA (N=372)**	**Total (N=520)**
Subjects with at least one AE	88 (59.5%)	215 (57.8%)	303 (58.3%)
Subjects with at least one severe AE	6 (4.1%)	17 (4.6%)	23 (4.4%)
Subjects with at least one treatment-related AE	11 (7.4%)	49 (13.2%)	60 (11.5%)
Subjects with at least one serious AE	7 (4.7%)	15 (4.0%)	22 (4.2%)
Subjects with at least one AE leading to treatment or study withdrawal	5 (3.4%)	15 (4.0%)	20 (3.8%)
Gastrointestinal Disorders			
Diarrhea	9 (6.1%)	8 (2.2%)	17 (3.3%)
Nausea	4 (2.7%)	11 (3.0%)	15 (2.9%)
Infections and Infestations			
Bronchitis	5 (3.4%)	10 (2.7%)	15 (2.9%)
Nasopharyngitis	6 (4.1%)	20 (5.4%)	26 (5.0%)
Urinary Tract Infection	3 (2.0%)	16 (4.3%)	19 (3.7%)
Metabolism and Nutrition Disorders			
Diabetes Mellitus	12 (8.1%)	20 (5.4%)	32 (6.2%)
Nervous System Disorders			
Dizziness	5 (3.4%)	6 (1.6%)	11 (2.1%)
Headache	9 (6.1%)	27 (7.3%)	36 (6.9%)
Respiratory, thoracic and mediastinal disorders			
Cough	5 (3.4%)	9 (2.4%)	14 (2.7%)
Vascular disorders			
Hypertension	5 (3.4%)	14 (3.8%)	19 (3.7%)

Values are N (%).

*All reported adverse events (AEs) occurring on or after the first dose of study medication and with an incidence of >3% in either treatment group, irrespective of causality. Subjects with multiple AEs within any single AE category are only counted once under each category.

e**Table 7.** Detailed Summary of Severe Adverse Events

System Organ Class Preferred term	**Placebo (N=148)**	**OM3-PL/FFA (N=372)**	**Total (N=520)**
Subjects with at least one serious AE	7 (4.7%)	15 (4.0%)	22 (4.2%)
Blood and lymphatic system disorders	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Normocytic anaemia	0 (0.0%)	1 (0.3%)	1 (0.2%)
Cardiac disorders	**0 (0.0%)**	**4 (1.1%)**	**4 (0.8%)**
Acute myocardial infarction	0 (0.0%)	1 (0.3%)	1 (0.2%)
Angina unstable	0 (0.0%)	1 (0.3%)	1 (0.2%)
Atrial fibrillation	0 (0.0%)	1 (0.3%)	1 (0.2%)
Coronary artery disease	0 (0.0%)	1 (0.3%)	1 (0.2%)
Gastrointestinal disorders	**1 (0.7%)**	**3 (0.8%)**	**4 (0.8%)**
Gastrointestinal haemorrhage	0 (0.0%)	1 (0.3%)	1 (0.2%)
Pancreatitis	0 (0.0%)	1 (0.3%)	1 (0.2%)
Pancreatitis acute	1 (0.7%)	1 (0.3%)	2 (0.4%)
General disorders and administration site conditions	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Non-cardiac chest pain	0 (0.0%)	1 (0.3%)	1 (0.2%)
Infections and infestations	**1 (0.7%)**	**1 (0.3%)**	**2 (0.4%)**
Influenza	1 (0.7%)	0 (0.0%)	1 (0.2%)
Sepsis	1 (0.7%)	0 (0.0%)	1 (0.2%)
Urinary tract infection	0 (0.0%)	1 (0.3%)	1 (0.2%)
Injury, poisoning and procedural complications	**1 (0.7%)**	**2 (0.5%)**	**3 (0.6%)**
Cervical vertebral fracture	1 (0.7%)	0 (0.0%)	1 (0.2%)
Fall	0 (0.0%)	1 (0.3%)	1 (0.2%)
Intentional product use issue	0 (0.0%)	1 (0.3%)	1 (0.2%)
Wrist fracture	0 (0.0%)	1 (0.3%)	1 (0.2%)
Metabolism and nutrition disorders	**1 (0.7%)**	**0 (0.0%)**	**1 (0.2%)**
Diabetes mellitus inadequate control	1 (0.7%)	0 (0.0%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	**1 (0.7%)**	**0 (0.0%)**	**1 (0.2%)**
Osteoarthritis	1 (0.7%)	0 (0.0%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Meningioma	1 (0.7%)	0 (0.0%)	1 (0.2%)
Nervous system disorders	**0 (0.0%)**	**2 (0.5%)**	**2 (0.4%)**
Epilepsy	0 (0.0%)	1 (0.3%)	1 (0.2%)
Subarachnoid haemorrhage	0 (0.0%)	1 (0.3%)	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Abortion spontaneous	0 (0.0%)	1 (0.3%)	1 (0.2%)
Renal and urinary disorders	**0 (0.0%)**	**2 (0.5%)**	**2 (0.4%)**
Acute kidney injury	0 (0.0%)	2 (0.5%)	2 (0.4%)
Respiratory, thoracic and mediastinal disorders	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Chronic obstructive pulmonary disease	0 (0.0%)	1 (0.3%)	1 (0.2%)
Vascular disorders	**1 (0.7%)**	**0 (0.0%)**	**1 (0.2%)**
Peripheral arterial occlusive disease	1 (0.7%)	0 (0.0%)	1 (0.2%)

Values are N (%).

*All reported serious adverse events (SAEs) occurring on or after the first dose of study medication in either treatment group, irrespective of causality. Subjects with multiple SAEs within any single SAE category are only counted once under each category and system organ class.

eTable 8. Comparison of TG-Lowering Effect of ω-3 Drugs at 4 g/d in Severe Hypertriglyceridemia

Study (OM3 drug)	Year	EPA+DHA	Treatment Duration (weeks)	Statistic	Placebo	OM3	Treatment Difference[a] (95% CI)	Citation
Harris et al. 1997 (OM-3-EE)	1997	3.1 g[1]	16	N Baseline TG End TG Mean Change (%) Median Change (%) P value	20 877 1007 16% NR	22 919 505 -45% NR	 NR NR p < 0.0001	(1)
Abe et al. 1998 (OM3-3-EE)	1998	3.1 g[1]	6	N Baseline TG End TG Mean Change (%) Median Change (%) P value	20 875 859 +4% NR	19 948 632 -26% NR	 NR NR p = 0.03	(2)
Pownall al. 1999 (OM3-3-EE)	1999	3.1 g[1]	6	N Baseline TG End TG Mean Change (%) Median Change (%) P value	21 786† – NR -7.8%	19 801† 512† NR -39%	 NR NR p = 0.001	(3)
MARINE (IPE, EPA-EE)	2011	3.5 g[2]	12	N Baseline TG End TG Mean Change (%) Median Change(%) P value	75 703† 746† 21.7% +10%	76 680† 502† -17.5% -27%	 -39% (-56%, -10%) -33% (-47%, -22%) p < 0.001	(7,8)
EVOLVE (OM3-CA)	2014	3.0 g[3]	12	N Baseline TG End TG Mean Change (%) Median Change(%) P value	99 788 NR 10% -10%	99 655 NR -25% -31%	 NR -21% (-31%, -11%) p < 0.001	(9,10)
TRGG-963-002 (OM3-EE)	2013	3.1 g[1]	12	N Baseline TG End TG Mean Change (%) Median Change (%) P value	43 751 NR -4.6% -17.4%	103 732 NR -21.5% -26.8%	 NR -14% (NR, NR) p < 0.05	(11)
TRGG-963-002 (OM3-EE-A)	2013	3.1 g[1]	12	N Baseline TG End TG Mean Change (%) Median Change(%) P value	43 751 NR -4.6% -17.4%	104 789 NR -21.5% -24.7%	 NR -12% (NR, NR) p < 0.05	(11)

Abbreviations: NR: Not Reported, IPE: Icosapent ethyl (EPA-EE), OM3-CA: omega-3-carboxyl acids, OM-3-EE: omega-3 ethyl esters. OM-3-EE-A. omega-3 ethyl esters-A, FFA eq.: Free fatty acid equivalent.

All baseline and endpoint values (in mg/dL) are mean unless otherwise noted († denotes median).

EPA+DHA content expressed as FFA eq. per daily dose (12).

[1] Contains 465 mg and 375 mg of EPA and DHA as EE per g (or capsule for OM3-EE-A). Multiply by 0.915 and 0.921, respectively, to convert to their FFA eq.

[2] Contains 960 mg of EPA only as EE per g. Multiply by 0.915 to convert to FFA eq.

[3] Contains 550 mg and 200 mg of EPA and DHA as FFA per g.

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