P R O T O C O L T I T L E P A G E

A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia (STRENGTH)

Investigational Product: Epanova® (omega-3 carboxylic acids)

IND No.: 107,616
Phase: III

Protocol Number: D5881C00004

EudraCT Number: 2014-001069-28

Document Dates

Original Protocol v1.0:	March 2014
Amended Protocol v2.0	**July 2014**
Amended Protocol v3.0	**September 2014**
Administrative Change Number 1	**October 2014**
Amended Protocol v4.0	**May 2015**

Sponsor:
AstraZeneca AB
151 85 Södertälje, Sweden

Confidentiality Statement

PRINCIPAL INVESTIGATOR SIGNATURE SHEET

A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia (STRENGTH)

Protocol Number: D5881C00004

By my signature below, I attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol (including appendices). I will not initiate this study without approval from the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and I understand that any changes in the protocol must be approved in writing by AstraZeneca AB and the IRB/IEC before they can be implemented, except where necessary to eliminate immediate hazards to the patient.

Approval Signature

Principal Investigator: _____ Date _____
Signature

_____
Printed Name

_____
Name of Facility

_____
Address

_____
City, State, Zip Code

_____
Phone Number

_____
Fax Number

_____
Email Address

SPONSOR SIGNATURE SHEET

A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia (STRENGTH)

Protocol Number: D5881C00004

By my signature below, I approve this protocol (including appendices).

Sponsor: Redacted Date 4/6/2015

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Medical Science Director
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PROTOCOL SYNOPSIS

TITLE: A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia (STRENGTH)	
PROTOCOL NUMBER: D5881C00004	
INVESTIGATIONAL PRODUCT: Epanova® (omega-3 carboxylic acids)	**US IND No.** 107,616
PHASE: III	
INDICATION: Adjunct to statin therapy and diet in high cardiovascular risk adult patients with persistent hypertriglyceridemia **and low HDL-cholesterol (HDL-C)** for the prevention and reduction of major adverse cardiovascular events (MACE)	
PRIMARY OBJECTIVE and OUTCOME MEASURE: Primary Objective The primary objective is to evaluate the effectiveness of adding Epanova to statin therapy (with or without ezetimibe) for lowering MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina) in high cardiovascular risk patients with persistent hypertriglyceridemia and low HDL-cholesterol (HDL-C). Primary Outcome Measure The primary outcome measure is the time to the first occurrence of any component of the composite of MACE. Patients will remain in the study until the required number of patients with MACE has occurred. We anticipate that patients will be in the study for 3-5 years. Patients who discontinue investigational product (IP) will continue to be assessed as specified per the protocol.	
POPULATION: Eligible men or women considered at high risk for atherosclerotic cardiovascular events, with low-density lipoprotein cholesterol (LDL-C) <100 mg/dL (<2.59 mmol/L) while on statin therapy (with or without ezetimibe), or LDL-C ≥100 mg/dL (≥2.59 mmol/L) while on a high-intensity or maximum tolerated moderate- or low-intensity statin therapy, with or without ezetimibe,for at least 4 weeks, and who have triglycerides (TG) ≥180 and <500 mg/dL (≥2.03 and <5.65 mmol/L) and HDL-C <42 mg/dL (1.09 mmol/L) for men or HDL-C <47 mg/dL (1.22 mmol/L) for women.	
STUDY DESIGN AND DURATION: The study is a randomized, double-blind, placebo-controlled (corn oil), parallel group design that	

will enroll approximately 13,000 patients with hypertriglyceridemia and at high risk for CVD. Patients will be randomized to either Epanova or placebo (corn oil), administered once daily, for approximately 3-5 years as determined by the number of patients with MACE. There will be up to 3 screening/washout visits, depending on the need for a repeat lab for statin/ezetimibe adjustment, discontinuation of excluded lipid-modifying agent, or a borderline TG and/or high-density lipoprotein (HDL-C) value. During the screening period, patients will maintain a stable diet, and after randomization, patients must be willing to adhere to the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) or equivalent diet at the discretion of the investigator. During the screening period, and thereafter, patients will not be permitted to use any excluded therapies or products, and will continue or adjust their prescribed statin regimen as applicable. Patients who meet all Inclusion Criteria and no Exclusion Criteria will be randomized 1:1 (6,500/arm) to receive double-blinded Epanova (4 g daily) or a matching placebo (corn oil) (4 g daily) for the study duration. The randomization visit will be Month 0 and there will be 11 treatment visits at Months 3, 6 12, 18, 24, 30, 36, 42, 48, 54 and 60. There will be a 3-week follow-up visit after an early termination (ET) visit for those patients who undergo early permanent IP discontinuation due to a serious adverse event (SAE). All patients should be asked to continue the regular study visits thereafter.

INCLUSION CRITERIA

Patients who have provided written informed consent and an authorization for disclosure of protected health information must meet the following criteria:

1. Men or women, ≥18 years of age.
2. Patient must be on a stable diet and statin* therapy at least 4 weeks prior to randomization (Visit 2) and meet the following criteria, where the qualifying lipid parameters should be obtained from the same visit:
   a. LDL-C <100 mg/dL (<2.59 mmol/L). Patient will also qualify if LDL-C ≥100 mg/dL (≥2.59 mmol/L) and if on a high-intensity statin (atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg) or on maximum tolerated moderate- or low-intensity statin dose, with or without ezetimibe therapy, for at least 4 weeks (see Appendix D). The maximum tolerated dosage of a statin is defined as the approved dose per local label that the patient can tolerate without unacceptable adverse effects such as muscle aches/pain/weakness or elevations in liver enzymes or creatine kinase (CK) that are determined by the investigator to be clinically relevant and due to statin therapy.
   b. TG ≥180 and < 500 mg/dL (≥2.03 and < 5.65 mmol/L) and HDL-C <42 mg/dL (1.09 mmol/L) for men or HDL-C <47 mg/dL (1.22 mmol/L) for women

   *co-administration with ezetimibe or fixed-dose ezetimibe/simvastatin 10/10, 10/20, 10/40 mg (see restrictions regarding 80 mg simvastatin in Section 7.4) or fixed-dose ezetimibe/atorvastatin 10/10, 10/20, 10/40, or 10/80 mg is allowed.

3. Patient is at high risk for a future cardiovascular event if at least one of the following criteria (3a, 3b or 3c)* is present via patient history, physical exam, or medical records at the time of screening:

a. Any atherosclerotic CVD as defined by one or more of the following:

- previous clinical myocardial infarction (MI) ≥30 days prior to randomization
- percutaneous coronary intervention (PCI) including balloon angioplasty and coronary stenting ≥ 6 months prior to randomization
- coronary artery bypass grafting (CABG) ≥30 days prior to randomization
- coronary angiogram including computed tomography angiogram (CTA) showing ≥ 50% stenosis in at least one native or graft vessel
- anginal symptoms with a defect documented by stress testing with nuclear perfusion imaging or a wall motion abnormality determined by stress echocardiogram
- asymptomatic coronary ischemia documented by stress testing with nuclear perfusion imaging or by stress echocardiogram
- peripheral vascular disease with symptoms of claudication and ankle brachial index <0.9 performed by a vascular lab or angiogram (including CTA) showing ≥ 50% stenosis)
- history of peripheral arterial revascularization (surgical or percutaneous) ≥30 days prior to randomization
- carotid endarterectomy, carotid stenting or more than or equal to 50% stenosis in a carotid artery determined by carotid ultrasound or angiogram ≥30 days prior to randomization
- history of abdominal aortic aneurysm confirmed by imaging, diagnosed ≥30 days prior to randomization
- ischemic stroke ≥30 days prior to randomization

b. History of diabetes mellitus (type 1 or 2) and ≥40 years of age for men and ≥50 years of age for women, plus one of the following risk factors:

- chronic cigarette smoking at screening (at least 1 cigarette per day for > 1 month)
- history of hypertension (blood pressure >140/90 mm Hg) or taking antihypertensive medication
- high-sensitivity C-reactive protein (hs-CRP) > 2.0 mg/L (19.05 nmol/L) determined at Visit 1
- history of albuminuria (urinary albumin:creatinine ratio [ACR] >30 mg/g).

c. Male patients >50 years of age or females >60 years of age, with at least one of the following risk factors:

- family history (mother, father or sibling) of premature coronary heart disease (father or brother <55 years of age, mother or sister <65 years of age)
- chronic cigarette smoking at screening (at least 1 cigarette per day for > 1 month)
- hs-CRP >2.0 mg/L (19.05 nmol/L) determined at Visit 1
- impaired renal function as estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[81] for glomerular filtration rate (eGFR) <45 mL/min per 1.73 m^2 (patients on dialysis are excluded).
- coronary calcium score >300 Agatston units (AU) at any time in the past.

  *If patient will meet CVD secondary prevention criteria (3a) AND primary prevention criteria (3b and/or 3c) at the same time, then patient will be considered as meeting CVD secondary prevention criteria (3a) for the purpose of identifying the inclusion criteria for that patient.

4. Patient must have been on a stable diet prior to randomization and willing to follow the NCEP TLC diet, or equivalent diet, throughout the study.

Note a) A patient can, in specific circumstances, be re-screened. For details, see section 6.4.

Note b) If LDL-C and/or TG and/or HDL-C do not meet the inclusion criteria at Visit 1, the patient may return twice (Visit 1a and 1b) during the screening period to reassess lipids (LDL-C, TG, and HDL-C) for statin/ezetimibe adjustment, discontinuation of excluded lipid-modifying agent, or re-checking a borderline TG and/or HDL-C value (see footnote 2 of Table 6-1 for details on lipid reassessments and on statin/ezetimibe dose adjustments during the screening period). Repeated values at Visit 1a or 1b may be used directly to qualify if needed. At Visit 1b, if lab values do not satisfy all inclusion criteria, the patient will be screen failed.

Note c) Once the patient qualifies, they should be randomized within 14 days. At least 50% of randomized patients should satisfy 3a CVD secondary prevention criteria, and <50% of patients should satisfy 3b and 3c primary prevention criteria combined; the proportions will be monitored and controlled via an Interactive Web Response System (IWRS).

EXCLUSION CRITERIA

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. Allergy or intolerance to omega-3 carboxylic acids, omega-3 fatty acids, omega-3-acid ethyl esters, or corn oil.

2. Known hypersensitivity to fish and/or shellfish

3. Use of fibrates, bile acid sequestrants, or niacin or its analogues (>250 mg/day) within 4 weeks prior to Visit 2. Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued for 4 weeks or more prior to Visit 2. However, niacin or its analogues at a dose less than or equal to 250 mg/day is permissible.

4. Statin naïve at Visit 1.

5. Use of simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg within 4 weeks prior to Visit 2. Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued and replaced with a protocol acceptable statin treatment that is stabilized for 4 weeks or more prior to Visit 2.

6. Use of any prescription medications containing eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), e.g. Lovaza® or Vascepa®, within 4 weeks prior to Visit 2. Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued for 4 weeks or more prior to Visit 2.

7. More than one capsule/day (any dose) of omega-3 dietary supplements. Patients taking >1 capsule/day of omega-3 supplements before Visit 1 DO NOT require a washout period but must agree to reduce the number of capsule per day to no more than 1 capsule of 1 g promptly after signing the informed consent. No new omega-3 supplements are permitted following initiation of screening procedures at Visit 1.

8. Use of prescription or over-the-counter (OTC) weight loss drugs at any time after Visit 1.

9. Chronic use of oral corticosteroids during screening (acute use for inflammation for example from poison ivy, or intranasal or inhaled steroids for allergies/asthma, or intraarticular injections are allowed).

10. Use of tamoxifen, estrogens, progestins, or testosterone, that has not been stable for >4 weeks at Visit 1, or is unstable prior to Visit 2.

11. Known lipoprotein lipase impairment or deficiency, or apolipoprotein C-II deficiency.

12. Hemoglobin A_{1c} (Hb A_{1c}) >12% at Visit 1.

13. Poorly controlled hypertension (resting blood pressure ≥180 mm Hg systolic and/or ≥100 mm Hg diastolic) at two consecutive visits prior to randomization at Visit 2.

14. Uncontrolled hypothyroidism, or thyroid stimulating hormone (TSH) >2.0 times upper limit of normal (ULN) at Visit 1. Patients who are clinically euthyroid, on stable thyroid replacement therapy for 2 months prior to Visit 1 are allowed.

15. History of cancer (except non-melanoma skin cancer, or carcinoma *in situ* of cervix) within the previous two years.

16. Patients on dialysis.

17. Females who are pregnant, planning to be pregnant during the study period, lactating, or women of childbearing potential who are not using an acceptable method of contraception. A woman is considered of childbearing potential if she is not surgically sterile or if her last menstrual period was <12 months prior to Visit 1. Acceptable methods of contraception for this study include use of double barrier contraception, intrauterine device, all oral, patch, etc. hormonal contraceptives as long as dose and type is stable for 3 months prior to Visit 1. In

addition, true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject.

18. Creatine kinase >5.0 times ULN; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0 times ULN; or total bilirubin (TBL) >2.0 times ULN (except with a confirmed diagnosis of Gilbert's disease), at Visit 1. A diagnosis of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) with stable elevations of AST and/or ALT (>3.0 times ULN) is eligible for participation in the study.

19. Excessive use of alcohol or other substance abuse that in the investigator's opinion would jeopardize the patient's participation in the study or interpretation of the data.

20. Exposure to any investigational agent within 4 weeks prior to Visit 1, including randomization in this study.

21. Previous clinical myocardial infarction (MI) <30 days prior to randomization

22. Percutaneous coronary intervention (PCI) including balloon angioplasty and coronary stenting<6 months prior to randomization

23. Coronary artery bypass grafting (CABG) <30 days prior to randomization

24. History of peripheral arterial revascularization (surgical or percutaneous) <30 days prior to randomization

25. Carotid endarterectomy or more than or equal to 50% stenosis in a carotid artery determined by carotid ultrasound or angiogram <30 days prior to randomization

26. History of abdominal aortic aneurysm diagnosed <30 days prior to randomization

27. Ischemic stroke <30 days prior to randomization

28. Any other condition the investigator believes would interfere with the patient's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the patient at undue risk.

29. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca or its representative and/or staff at the study site)

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

- Epanova (omega-3 carboxylic acids) capsules: 4 g (four 1-gram capsules) orally, once daily for the duration of the study.
- Placebo (corn oil) capsules: 4 g (four 1-gram capsules) orally, once daily for the duration of the study.
- Statins will be prescribed by the investigator or patient's health care provider.

OUTCOME VARIABLES:

The primary outcome measure is the time to event analysis using the first occurrence of any component of the composite of MACE: cardiovascular death, non-fatal MI, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina. Patients will remain in the study until the required number of patients with MACE has occurred.

Secondary outcome measures include:

KEY Secondary outcome measures include:

- The composite measure of CV events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal MI, and non-fatal stroke.
- The composite measure of coronary events that include the first occurrence of cardiovascular death, non-fatal MI, emergent/elective coronary revascularization, or hospitalization for unstable angina.
- Time to CV Death

Other Secondary outcome measures include:

a) Emergent/elective coronary revascularization

b) Hospitalization for unstable angina

c) Fatal or non-fatal MI

d) Non-fatal MI

e) Fatal or non-fatal stroke

f) Non-fatal stroke

g) All-cause death

Tertiary outcome measures will include:

- The first occurrence of new onset atrial fibrillation (AF)
- The composite measure of total thrombotic events that include the first occurrence of documented coronary stent thrombosis, any systemic thromboembolism including arterial stent (except coronary) thrombosis or venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) and/or pulmonary embolism (PE)
- First occurrence of a heart failure event.

Biomarker efficacy endpoints will evaluate differences between placebo (corn oil) and Epanova treatments for:

- non-HDL-C, TG and HDL-C;
- total cholesterol (TC), very low density lipoprotein (VLDL) cholesterol, TC:HDL-C ratio and calculated LDL-C (in patients with triglycerides >400mg/dl LDL-C will be directly

measured);

- apolipoprotein B-100 (Apo B-100) and apolipoprotein C-III (Apo C-III);
- plasma and red blood cell (RBC) EPA, DHA, docosapentaenoic acid (DPA) and arachidonic acid (AA); and hs-CRP.

A Clinical Events Committee (CEC) will adjudicate all components of the primary and secondary endpoints as well as the tertiary heart failure events endpoint.

SAFETY ASSESSMENTS:

Safety assessments will include adverse events, safety laboratory assessments, pregnancy tests, electrocardiogram (ECG), and physical examinations. A Data Monitoring Committee (DMC) will review data periodically throughout the study and will have the ability to recommend stopping the study for safety at any time. Details will be defined in the DMC charter.

SAMPLE SIZE ASSUMPTIONS and STATISTICAL ANALYSES:

Sample Size Assumptions

This event-driven study is designed to have 90% power to detect a 15% relative reduction in risk of primary efficacy MACE rate (hazard ratio=0.85) for patients treated with Epanova compared to placebo (corn oil) on top of a background of standard care (statin therapy). With an overall type I error rate (alpha level) of 5%, a total of 1,600 primary efficacy events are required to achieve approximately 90% power to detect the difference between Epanova and placebo (corn oil) (a constant hazard ratio of 0.85). The estimate of 4% annual event rate on placebo (corn oil) is based on previous studies investigating MACE, considering populations with documented cardiovascular disease and populations with cardiovascular risk factors only. **The enrollment of patients with documented CVD will be ≥50% of all randomized patients; the enrollment of patients with risk factors only (primary prevention) will be less than 50% of all randomized patients. These proportions will be monitored and controlled via IWRS.**

Assuming total study duration of 4.5 years and a placebo (corn oil) event rate of approximately 4% per year, a sample size of 13,000 patients (6,500 per treatment group) is required.

Statistical Analyses

The primary outcome measure is the time to first occurrence (TTE; time-to-event) of any component of the composite of MACE (cardiovascular death, non-fatal MI, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina).The primary outcome will be analyzed for the intent-to-treat (ITT) population using adjudicated events.

A Cox proportional hazards model for time to first MACE event will be assessed for comparing the two treatment groups, with treatment arm, established CV disease at baseline, multiple risk factors without established CV disease at baseline and geographic region as covariates. Event rates will be expressed as the percentage of events per follow-up year, taking into account censoring of follow-up data. The treatment effect will be assessed at a nominal 5% significance

level. Analysis results will be presented as hazard ratios, 95% confidence intervals and p-value.

For each TTE endpoint, a patient will be censored no later than the date of the last available information on that patient, from any source captured in the database. The specific rule(s) for each individual TTE will be explicitly specified in the SAP. Kaplan–Meier estimates will be used to quantify event rates during the course of the trial. Sensitivity analyses of the primary efficacy endpoint will also be performed to assess the robustness of the primary results. The sensitivity analyses will be performed for only on-treatment MACE events in the ITT population.

The secondary outcomes measures will be analyzed using the same model as outlined above for the primary outcomes measure, on the ITT population. The respective censoring rules will be defined explicitly in the SAP.

The evaluation will be carried out in a hierarchical fashion. Specifically, if the primary endpoint objective is met (2-sided p-value<0.05), the secondary outcomes will be evaluated hierarchically at an overall alpha of 0.05 for each comparison, sequentially. Once a key secondary endpoint is not met at alpha 0.05, all subsequent comparisons will be considered exploratory.

The hierarchy for sequential testing the following key secondary outcome measures will be defined as:

KEY SECONDARY (tested at α=0,05, conditional on success of the primary)

1. The composite measure of CV events that include the first occurrence of cardiovascular death, non-fatal MI and non-fatal stroke
2. The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal MI, emergent/elective coronary revascularization, or hospitalization for unstable angina.
3. Time to CV Death

Other SECONDARY (evaluated at α=0,05; NOT part of the hierarchical testing sequence; that is, exploratory)

Time to:

a) Emergent/elective coronary revascularization

b) Hospitalization for unstable angina

c) Fatal or non-fatal MI

d) Non-fatal MI

e) Fatal or non-fatal stroke

f) Non-fatal stroke

g) All-cause death

Further details will be provided in the SAP.

Tertiary outcome measures will include:

- The first occurrence of new onset AF.
- The composite measure of total thrombotic events that include the first occurrence of documented coronary stent thrombosis, any systemic thromboembolism including arterial stent thrombosis (except coronary) or venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) and/or pulmonary embolism (PE).
- First occurrence of a heart failure event.

The tertiary outcome measures will be analyzed using methods similar to those for the primary and secondary analyses. The analysis of the tertiary outcomes will be considered observational only. Further details will be provided in the SAP.

The analysis of biomarkers (e.g. lipids or other biomarkers) will be based on the differences in change from baseline (Month 0) to Month 12 (primary), between placebo (corn oil) and Epanova treatments. In addition, biomarker data after Month 12, will be presented in a descriptive manner. The biomarker variables include:

- non-HDL-C, TG and HDL-C;
- TC, VLDL cholesterol, TC:HDL-C ratio and calculated LDL-C; in patients with triglycerides > 400mg/dl LDL-C will be directly measured
- Apo B-100 and Apo C-III;
- EPA, DHA, DPA and AA in plasma and RBC; andhs-CRP.

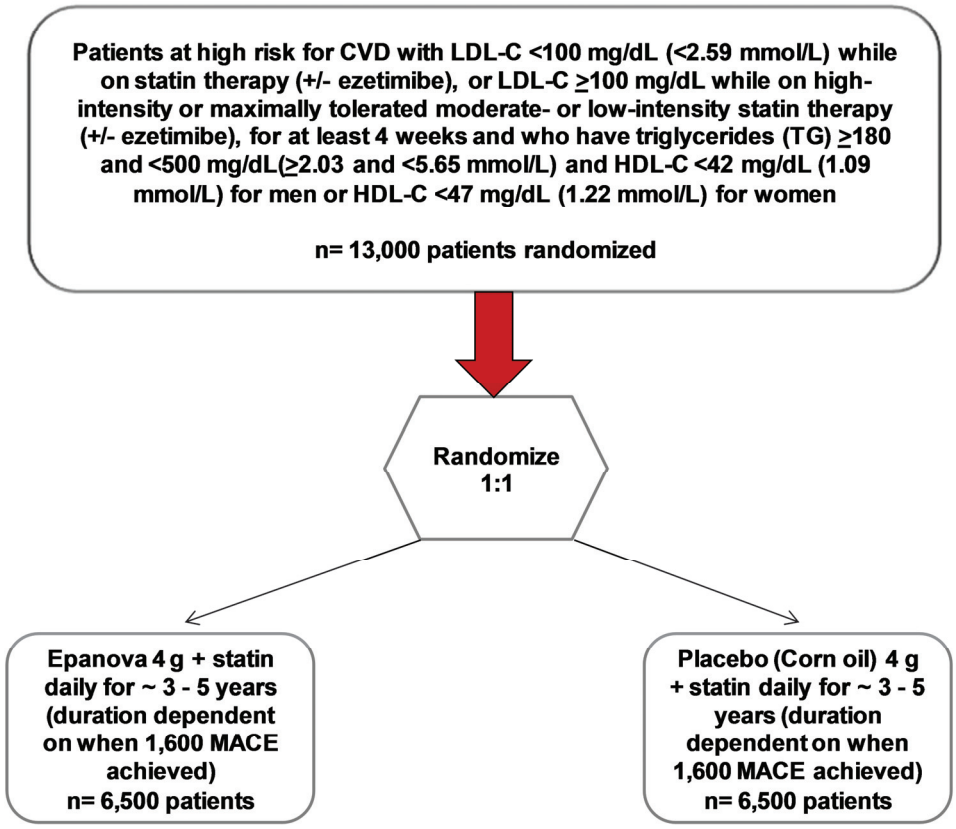
A repeated measures mixed model will be used for each biomarker endpoint with patient fitted as a random effect and terms included for treatment, visit, baseline value, treatment by visit and baseline by visit interactions using log-transformations where appropriate. A point estimate, 95% confidence interval and p-value for the mean difference between Epanova and placebo (corn oil) patients from Month 0 to Month 12 (primary) will be produced based on this repeated measures model. Further details in the SAP will specify how each biomarker variable will be analyzed, i.e. whether as mean change or as percent change.

The CEC will adjudicate all components of the primary and secondary endpoints as well as the tertiary heart failure events endpoint.

Safety analyses will include, where appropriate, descriptive statistics, counts and percentages. At each DMC meeting, the committee will review all individual cases of LDL-C increases, AST/ALT increases or other increases in liver-related chemistries, new onset diabetes mellitus type II, or bleeding related events, in addition to other safety and laboratory data (i.e. fasting

glucose, hemoglobin A_{1c} and hematocrit).
SITES: The study will be conducted globally in approximately 600 sites.
SPONSOR: AstraZeneca AB

STUDY FLOW DIAGRAM



SCHEDULE OF PROCEDURES

Study Period	**Screening[2]**			**Randomization and treatment**					**EOT/ET**	**EOT/ET Follow-up for SAE**
Visit[1]	**1**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6 – 12**	**13**	**14**
Month (±2 weeks)				**0**	**3**	**6**	**12**	**18, 24, 30, 36, 42, 48 and 54**	**60[15]**	**3 weeks after EOT/ET for SAE[17]**
Informed Consent	X									
Medical History	X	X	X	X						
Prior Medications	X	X	X	X						
Physical Exam	X						X		X	
Clinical Assessments[3]	X	X	X	X	X	X	X	X	X	
Fasting Lipid Panel[4,5]	X	X	X	X			X[13]	X[13]	X[13]	
Hemoglobin A_{1c}	X			X			X[13]	X[13]	X[13]	
Eligibility Review	X	X	X	X						
hs-CRP	X			X					X	
Serum Chemistry[6]	X			X			X	X[7]	X[7]	
TSH	X									
Urine Pregnancy Test[8]	X									
Fasting Plasma Glucose				X			X[13]	X[13]	X[13]	
Hematocrit							X[13]	X[13]	X[13]	
ECG				X						
Fasting Special Lipid Markers[4,9]				X			X		X	
Plasma and RBC Fatty Acids[4,10]				X			X		X[9]	
Fasting CV Risk Markers[4,11]				X	X					
Genetic sample[14]				X						
Counseling on TLC or Equivalent Diet	X									
AEs, Concomitant Medications and Endpoint Assessments[12]					X	X	X	X	X[16]	X[18]
Telephone Calls[12]							→			
Randomization				X						
Dispense IP				X	X	X	X	X		
Assess IP Compliance					X	X	X	X	X	

AE = adverse event;
EOT = End of treatment; EOT is defined for patients who 1) permanently discontinue IP before the study has ended but agree for further follow-up assessments (on-site visits or telephone or via third party) until end of study 2) complete Visit 12 (Month 60) and have not discontinued IP early;
ET = Early Termination. ET is defined for patients who permanently discontinue IP before the study has ended and decide **not** to participate with any follow-up assessments (on-site visits or telephone or via third party);
TSH = thyroid stimulating hormone;
hs-CRP = high-sensitivity C-reactive protein;
ECG = electrocardiogram;
CV = cardiovascular;
TLC = Therapeutic Lifestyle Changes;
IP = Investigational Product.
RBC= red blood cells

1. If fasting is not normal routine clinical practice, informed consent should be obtained prior to request for fasting for the Screening visit. If this is the case, the Screening visit should be split into 2 separate visits with informed consent obtained and IWRS accessed to obtain the patient number at the initial visit; and all other procedures obtained at the subsequent visit. In the event that the Screening visit is split into 2 separate visits, the screening visit lab draw must be completed within 3 days. At any subsequent visit, if the patient did not fast for the recommended 9-14 hours, the fasted lab may be drawn the next day.
2. If at Visit 1 the patient's TG, LDL-C, and HDL-C meet the inclusion criteria and the patient has been on a stable diet and has met all other inclusion criteria and none of the exclusion criteria the patient should return within 2 weeks for randomization at Visit 2.

   If at Visit 1 the patient requires an adjustment to their statin regimen and/or a washout of other excluded lipid medications, the patient should return 4-6 weeks later to have their lipids re-drawn at Visit 1a.

   If at Visit 1 the patient does not require an adjustment to their statin regimen and/or a washout of other excluded lipid medications and either the patient's TG and/or HDL-C are borderline: TG ≥160 - 179 mg/dL (>1.81 – 2.02 mmol/L) or TG ≥500 and <575 mg/dL (>5.65 and <6.49 mmol/L) and/or HDL-C ≤45 mg/dL (1.17 mmol/L) for men and ≤50 mg/dL (1.30 mmol/L) for women, the patient can return within 2 weeks later to have all lipids re-drawn at Visit 1a.

   If at Visit 1 the patient does not require an adjustment to their statin regimen and/or a washout of other excluded lipid medications, and TG and HDL-C values are outside of borderline boundaries, the patient is considered screen failed.

The TG, LDL-C and HDL-C results from Visit 1a will be used to determine eligibility in the same way as for Visit 1. If re-drawn TG and HDL-C values are again borderline (as above), lipids can be repeated once more at Visit 1b to determine eligibility. Note that all lipid parameters qualifying for randomization should be obtained from the same visit.

If the TG, LDL-C and HDL-C criteria are not met after Visit 1b, the patient should be screen failed.

Please note the possibility to rescreen in the some situations, please see section 6.4.

3. Includes height (Visit 1 only), waist circumference and weight (Visit 1, 5, 7, 9, 11, 13 only), blood pressure, and heart rate.
4. Fasting blood samples should be drawn after the recommended 9-14 hour fast.
5. Lipid panel includes serum TG, TC, calculated LDL-C (in patients with triglycerides > 400 mg/dl LDL-C will be directly measured), HDL-C, calculated non-HDL-C, VLDL-C and TC: HDL-C ratio.
6. Serum chemistry includes creatine kinase, ALT, AST, total and direct bilirubin, and creatinine. Glomerular Filtration Rate (GFR) will be calculated only at Visits 1 and 5
7. Only ALT, AST and bilirubin will be analysed, and only at Visits 7, 9, 11 and 13.
8. Females of childbearing potential only (see Exclusion No. 17).
9. Special lipid markers include serum apolipoprotein B-100 (Apo B-100), and apolipoprotein C-III (Apo C-III).
10. Plasma and RBC fatty acids (EPA, DHA, DPA and AA) will be measured from the recommended 9-14 hour fasting samples. Note: Plasma and RBC assessments are performed only at Visits 2 and 5, or ET before Visit 5.
11. Blood samples will be collected for future analyses on a subset of patients located in the US, of lipid fractions, inflammatory markers and other CV markers that may be identified during the course of the study.
12. In addition to these scheduled procedures, a well-being phone call will be made every 6 months (±2 weeks) starting after Visit 4 that will occur at Months 9, 15, 21, 27, 33, 39, 45, 51, and 57, except at scheduled visits, to question about adverse events, endpoint assessment, changes in medications and any major issues with the IP (losses or noncompliance). For further assessment of any identified potential or confirmed AE, a physical examination should be carried out if clinically appropriate.
13. Fasting lipid panel, Hb A_{1c}, fasting plasma glucose and hematocrit will be measured annually at Visits 5, 7, 9, 11 and 13.

14. Genetic samples will be collected for future analysis on approximately 2000 patients in the US, see Appendix F for details.The sample should be taken at Visit 2.
15. Patients who permanently discontinue taking IP for any reason will be asked to continue the regular study visits after the scheduled ET visit and (for permanent discontinuation of IP due to SAE) the 3-week Follow-up visit unless they withdraw consent for further participation and the use of their data. In this case, patient will be asked to provide written documentation (when possible) of withdrawal of consent and complete the ET Visit procedures only. If the patient is permanently discontinued from study medication and agrees to continue in the protocol, then the patient, if possible, should have regularly scheduled study visits.
16. Patients who have early permanent discontinuation of IP due to an SAE and have an ET visit, will be required to schedule a 3-week Follow-up (Visit 14) to assess the SAE and concomitant medications. The patients should be asked to continue the regular study visits as described above thereafter.
17. Visit window is ±1 week for Visit 14 (ET/EOT Follow-up for SAE).
18. At Follow-up Visit 14, other assessments from the procedures table may be performed upon investigator discretion to further evaluate the SAE causing ET or for SAE identified at EOT.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
AA	Arachidonic acid
ACCF	American College of Cardiology Foundation
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACR	Albumin:creatinine ratio
AE	Adverse event
AF	Atrial fibrillation
AHA	American Heart Association
ALT	Alanine aminotransferase
Apo B-100	Apolipoprotein B-100
Apo C-III	Apolipoprotein C-III
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AU	Agatston units
AUC	Area Under the Curve
BIP	Bezafibrate Infarction Prevention
C5Research	Cleveland Clinic Cardiovascular Coordinating Center for Clinical Research
CABG	Coronary Artery Bypass Grafting
CD	Compact disc
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CHD	Coronary heart disease
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COMBOS	COMBination of prescription Omega-3 with Simvastatin
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTA	Computed tomography angiogram
CTT	Cholesterol Treatment Trialists'
CVD	Cardiovascular disease
CV	Cardiovascular

Abbreviation/Term	Definition
d	Day
dL	Deciliter
DHA	Docosahexaenoic acid
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DPA	Docosapentaenoic acid
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EPA	Eicosapentaenoic Acid
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FFA	Free fatty acids
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb A_{1c}	Hemoglobin A_{1c}
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
hs-CRP	high-sensitivity C-reactive protein
IC	Informed consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational product
IRB	Institutional Review Board or Independent Review Board
ITT	Intent-to-Treat
IWRS	Interactive web response system

Abbreviation/Term	Definition
JELIS	Japan EPA Lipid Intervention Study
JUPITER	Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, emergent/elective coronary revascularization or hospitalization for unstable angina)
MAR	Missing At Random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	Milligrams
MI	Myocardial infarction
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCEP	National Cholesterol Education Program
NEPTUNE	National Cholesterol Education Program Evaluation ProjecT Utilizing Novel E-Technology
OTC	Over-the-counter
PDF	Portable Document Format
PE	Pulmonary embolism
PI	Principal Investigator
PCI	Percutaneous coronary intervention
PHL	Potential Hy´s Law
PUFA	Polyunsaturated fatty acids
RBC	Red blood cells
RCT	Randomized control trial
RR	Risk reduction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SFA	Saturated fatty acids
SOC	System Organ Class
STRENGTH	A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event

Abbreviation/Term	Definition
TSH	Thyroid stimulating hormone
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
TLC	Therapeutic Lifestyle Changes
TTE	Time-to –event
ULN	Upper Limit of Normal
USP	United States Pharmacopeia
VLDL	Very low-density lipoprotein
VLDL-C	Very low-density lipoprotein cholesterol
VTE	Venous thromboembolism
WOSCOPS	West Of Scotland Coronary Prevention Study

1 BACKGROUND AND RATIONALE

1.1 Background

In patients with hypertriglyceridemia (≥200 mg/dL), the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP) recommended that non-high-density lipoprotein cholesterol (non-HDL-C) should be considered as secondary target of treatment once low-density lipoprotein cholesterol (LDL-C) goals are achieved.[1] Non-HDL-C is routinely calculated as total cholesterol minus HDL-C but is mainly the sum of LDL-C and very-low-density lipoprotein (VLDL) and includes cholesterol carried by all lipoproteins that contain apolipoprotein B (Apo B-100). When triglycerides (TG) are >200 mg/dL most cholesterol in the VLDL fraction is contained in smaller (atherogenic remnant) VLDL.[1] Therefore, when serum triglycerides are high, VLDL cholesterol can reasonably be combined with LDL-C to use non-HDL-C as a secondary target of treatment and a means to enhance risk prediction.[1]

In patients with hypertriglyceridemia, non-HDL-C goals are frequently not achieved. In the NEPTUNE II study (National Cholesterol Education Program Evaluation ProjecT Utilizing Novel E-Technology), only 4% of patients with TG >200 mg/dL and at very high risk were at the optimal non-HDL-C goal of < 100 mg/dL.[2] In order to reduce non-HDL-C in patients with hypertriglyceridemia, combination therapy with statins is frequently necessary to maximize goal achievement. The NCEP panel recognized that statins are not powerful TG-lowering drugs, and therefore recommended the use of specific add-on therapies to lower TG levels in patients with hypertriglyceridemia (fish oils to replace some long-chain TG levels in diet, as well as fibrates or nicotinic acid).[1]

During the last 30 years, epidemiological studies reported a relationship between lower serum TG concentrations and the consumption of omega-3 fatty acids-rich fish.[3,4] Further, clinical studies have shown that consumption of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been associated with lower serum TG concentrations and reduced risk for cardiovascular disease.[5,6,7,8] Marine-based omega-3 fatty acids (EPA and DHA) were shown to be more effective than the plant-based alpha-linoleic acid products, with the former lowering serum TG levels 25-50% after consuming 3-8 g/day EPA+DHA compared to controls.[9,10] Therefore, marine omega-3 fatty acids represent a class of compounds with demonstrated efficacy in reducing severe elevation of TG levels.

A fatty fish diet provides only modest doses of the polyunsaturated omega-3 fatty acids (EPA and DHA) needed to treat severe hypertriglyceridemi a.[11] Therefore, omega-3

concentrates are more suitable for this purpose. Unprocessed marine oil products contain only approximately 30% omega-3 fatty acids while the concentrates, after ethanol extraction and distillation, contain approximately 80% omega-3 in the form of ethyl esters.[10,12] In 2004, a concentrate of omega-3-acid ethyl esters (Lovaza®) was approved by the Food and Drug Administration (FDA) as an adjunct to diet for the reduction of very high TG (≥500 mg/dL) levels in adult patients.[10] This product provides 84% content of EPA+ DHA ethyl esters. Epanova® is a newer formulation that has undergone an additional manufacturing step to hydrolyze and distill the ethyl esters into omega-3 free fatty acids (FFAs) with a final concentration of 75% EPA + DHA (omega-3 carboxylic acids).[12] Therefore, intestinal absorption of the omega-3 FFAs in Epanova will not require the hydrolysis with pancreatic lipase as is required for the ethyl ester form (Lovaza®) in the small intestine. It is also important to note that the molecular weight of the free fatty acid EPA and DHA in Epanova is less than the molecular weight of ethyl ester EPA and DHA in Lovaza®. Accounting for this difference, 465 mg of ethyl-EPA is equivalent to 426 mg of EPA in the free fatty acid form and 375 mg of ethyl-DHA is equivalent to 346 mg of DHA in the free fatty acid form. Therefore, the 84% EPA + DHA ethyl esters in Lovaza® are comparable to the 75% EPA + DHA in Epanova.

Previous studies have demonstrated that the TG form of marine omega-3 fatty acids, EPA and DHA are more resistant to pancreatic lipase hydrolysis compared to other polyunsaturated fatty acids.[13,14,15] Furthermore, ethyl ester omega-3 fatty acids are up to 50 times more resistant than the natural TG form to pancreatic lipase hydrolysis.[16,17,18,19,20] Several studies have compared human intestinal absorption of fish oil fatty acids in the form of TG, ethyl ester and FFA and found that FFAs have up to 5 times more bioavailability as determined by the plasma area under the curve (AUC) than the ethyl ester form.[17,18,19] In addition, pancreatic lipases are secreted into the intestines in response to fat intake. Patients with hypertriglyceridemia are often advised to restrict fat intake and therefore pancreatic lipase secretion may be lower with severe hypertriglyceridemia which could lead to EPA and DHA malabsorption from the ethyl ester formulations.[21] Absorption of the FFA form of omega-3 EPA and DHA would not be compromised by a fat intake restriction and would therefore offer a therapeutic advantage over the ethyl ester to the patient with severe hypertriglyceridemia. Therefore, Epanova, a FFA formulation, will have significantly greater bioavailability than the ethyl esters form, and would have little dependence on meal fat content.[15,16,17,18,19]

1.1.1 Clinical Pharmacology and Efficacy of Epanova

In a Phase IIb, open-label, clinical study of Epanova in which patients were taking 4 g per day for 52 weeks without regard to meal timing, trough plasma levels of EPA had reached a steady-state level by Week 16 at which EPA levels increased 351% from baseline.[22] This is in contrast to a Lovaza® study in which 16 weeks of 4 g per day dosing increased trough EPA levels only 163% from baseline.[23] In the Epanova study, red blood cell membrane EPA also stabilized at Week 16.[22] In a bioavailability study that compared single 4-gram doses of Epanova and Lovaza® administered under low-fat diet conditions in healthy subjects, Epanova showed a 4-fold increase in area under the curve to the last time point (AUC_t) for plasma EPA and DHA relative to Lovaza®.[24] The C_{max} for EPA and DHA during Epanova dosing was 3.7-fold greater than Lovaza® dosing under the low-fat diet conditions.[24] This improved bioavailability under low-fat meal conditions provides Epanova a potential therapeutic advantage over Lovaza® because the NCEP ATP III guidelines recommend that patients with severe TG elevations adhere to the lower fat Therapeutic Lifestyle Changes (TLC) diet. In addition, on the low-fat diet, 30 of 51 (58.82%) subjects on Epanova versus 3 of 50 (6.00%) subjects on Lovaza® maintained an AUC_t that was > 50% of the respective high fat diet AUC_t.[24] These data suggest that Epanova will have superior absorption on either a low-fat or high-fat diet.

The enhanced bioavailability of Epanova and the effectiveness in improving lipid parameters were demonstrated in two phase III trials: OM-EPA-003 (EVOLVE) and OM-EPA-004 (ESPRIT).[25,26]

EVOLVE was a phase III, 12-week, multicenter, multinational, placebo–controlled (olive oil), randomized, double-blind study evaluating 399 subjects with fasting TG levels ≥500 and <2000 mg/dL (with or without statin therapy), who were randomized to Epanova 2 g/day, 3 g/day, 4 g/day, or olive oil control. Subjects were permitted to administer Epanova without regard to meal timing. Lipids were measured at all in-clinic visits, plasma EPA and DHA were measured pre-treatment for baseline (Week 0) and at end of treatment (Week 12). Administration of 2 g, 3 g and 4 g Epanova daily for 12 weeks demonstrated large dose-dependent increases (least squares mean; LSM) in plasma EPA levels from baseline to end of treatment: approximately 267%, 332 % and 406%, respectively. Plasma trough DHA levels also showed a dose-response to Epanova treatment. Mean percent changes in plasma DHA levels were approximately 57%, 64% and 72%, respectively, for the 2 g, 3 g and 4 g/day doses. Furthermore, the dose dependent increases in plasma EPA and DHA were associated with dose dependent

decreases in plasma arachidonic acid (AA) concentrations of -15%, -16% and -23% from baseline with the 2 g, 3 g and 4 g/day doses respectively.

ESPRIT was a phase III, 6-week, U.S. multicenter, placebo–controlled (olive oil), randomized, double-blind study evaluating 647 patients with fasting TG levels ≥200 mg/dL and <500 mg/dL and at high risk for a future cardiovascular disease (CVD) event, who were randomized 1:1:1 to olive oil control, 2 g or 4 g/day Epanova. Subjects were permitted to administer Epanova without regard to meal timing. At in-clinic visits, plasma EPA and DHA were measured pre-treatment for baseline (Week 0) and at end of treatment (Week 6). Administration of 2 g and 4 g Epanova, daily for 6 weeks, demonstrated large dose-dependent increases from baseline in plasma trough EPA levels at the end of treatment. Plasma EPA increased (LSM) approximately 188% and 348% from baseline, respectively, with 2 and 4 g/day doses. Plasma DHA also showed a dose-dependent increase, with LSM percent changes from baseline to end of treatment of approximately 50% for the 2 g/day group and 71% for the 4 g/day group. Plasma AA decreased in a dose-dependent manner, approximately -11% for the 2 g/day group and -20% for the Epanova 4 g group.

There was a consistent dose-dependent TG-lowering response with Epanova treatment in both trials. The difference in TG reductions between the 2 g and 4 g/day doses in both trials was similar: approximately -5% in EVOLVE (from -26% to -31%) and -6% in ESPRIT (from -15% to -21%). These data also demonstrated that the 2-3 fold greater TG levels in EVOLVE yielded an approximate 10% additional decrease in TG levels for each Epanova dose: 2 g/day dose produced a median -25% and -15% TG reduction in the EVOLVE and ESPRIT trials, respectively, while the 4 g/day dose lowered TG by approximately -31% and -21%, respectively, in the trials. A clinically important result is that as the baseline TG increases there is nearly a direct increase in the 2 g dose efficacy: -15% in ESPRIT and -26% in EVOLVE. The 4 g dose showed a less direct increase in efficacy (about 50% increase in TG lowering between the trials; - 21% to -31%).

Non-HDL cholesterol was the primary endpoint in ESPRIT and the secondary endpoint in EVOLVE. Baseline levels were about 1.5 fold greater in EVOLVE than ESPRIT. The difference in non-HDL-C reductions between the 2 g and 4 g/day doses was also similar in EVOLVE and ESPRIT: approximately -2% in EVOLVE (from LSM -7.6% to -9.6%) and -3% in ESPRIT (from 3.9% to -6.9%). Again, the direct relationship between baseline lipid levels and 2 g efficacy was apparent: with an approximate 1.5 increase in baseline non-HDL-C levels from ESPRIT to EVOLVE, there was an approximate 2-fold

increase in efficacy (-4% in ESPRIT and 8% in EVOLVE). The 4 g dose showed closer to a 50% increase in non-HDL-C lowering efficacy between the trials (-6.9% to -9.6%).

In summary, both the 2 g/day and 4 g/day Epanova doses had clinically meaningful efficacy in lowering plasma TG and non-HDL-C levels in subjects with severe hypertriglyceridemia in the EVOLVE trial and in subjects with high triglyceride levels in the ESPRIT trial. Further, the Epanova treatments demonstrated lipid lowering in other parameters (TC, TC/HDL cholesterol ratio, VLDL cholesterol and Apo C-III). The results suggest that both Epanova doses may offer a clinical therapeutic option to start therapy at 2 g/day or 4 g/day, or start therapy at 2 g/day and increase to a maximum 4 g/day, as needed to effectively treat patients with severe hypertriglyceridemia (TG ≥500 mg/dL) or high risk patients with persistent hypertriglyceridemia (TG ≥200 mg/dL and <500 mg/dL) despite receiving statin therapy.

1.1.2 Clinical Safety of Epanova

Epanova capsules are coated with a polyacrylate material that is intended to facilitate release of the omega-3 fatty acids in the gut leading to a significant reduction of the unpleasant gastrointestinal (GI) side-effects often observed with other omega-3 products.[22,24,25,26,27,28,29,30,31,32,33,34] The safety of Epanova was collectively summarized and included 1343 subjects treated with Epanova in 10 clinical studies.[22,24,25,26,27,28,29,30,31,32] The clinical studies included 2 studies in subjects with hypertriglyceridemia (EVOLVE and ESPRIT; N = 731) who received Epanova 2 to 4 g daily for 6 to 12 weeks, 4 studies in subjects with Crohn's disease (N = 432) who received Epanova 4 g daily ≥ 52 weeks, and 4 studies in healthy subjects who received Epanova in clinical pharmacology/pharmacokinetic studies (N = 180).

The integrated safety analysis demonstrated that Epanova was safe and well tolerated for up to 12 weeks in subjects with hypertriglyceridemia and 3 years in subjects with Crohn's disease. Most treatment-emergent adverse events (TEAEs) were considered by the investigator to be mild or moderate in severity. The most common system organ class (SOC) of TEAEs was gastrointestinal disorders, with higher incidences of diarrhea, nausea, and eructation reported in the Epanova dose groups (2 g, 3 g, or 4 g daily) compared with olive oil (placebo). There was no clear dose-related trend among the gastrointestinal preferred terms; however, a higher incidence of diarrhea occurred in the 4 g group. Most GI TEAEs, including diarrhea, were mild or moderate in severity and few (≤1.1% for each individual GI TEAE) resulted in discontinuation of study drug. This lack of a dose-response relationship with the severity and incidence of GI effects following

exposure to Epanova is consistent with the published literature reports of adverse events following EPA and DHA exposure.[34,35,36]

1.2 Rationale

Few prospective studies have explicitly examined the predictive CVD risk of non-HDL-C levels versus LDL-C levels in persons with hypertriglyceridemia, however, several lines of evidence favor use of non-HDL-C over LDL-C in clinical evaluation of risk.1 This hypothesis is supported by reports from the follow-up of the Lipid Research Clinic cohort which showed a stronger correlation with coronary mortality for non-HDL-C than for LDL-C, as well as other studies that showed non-HDL-C is a better predictor of coronary heart disease (CHD) risk than LDL-C alone.1[,37,38,39] This clinical evidence is consistent with metabolic evidence that shows non-HDL-C to be highly correlated with total Apo B-100, the major apolipoprotein of all atherogenic lipoproteins. Serum Apo B-100 has also been shown to have a strong predictive power for severity of coronary atherosclerosis and CHD events.1 Therefore, because of the high correlation between non-HDL-C and Apo B-100 levels, non-HDL-C represents an acceptable surrogate marker for total Apo B-100 in routine clinical practice. Standardized measures of Apo B-100 are not widely available for routine measurement.

The use of statins to lower cholesterol has been established as an effective method of reducing death and myocardial infarction (MI) among patients with CHD. However, a significant fraction of individuals who receive statin therapy continue to have high residual CHD risk.2[,40,41,42] A meta-analysis of 14 statin trials suggests that for every 1% reduction in non–HDL-C the relative CHD risk is reduced by approximately 1%.[36] Unfortunately, a substantial proportion of patients with elevated non–HDL-C and triglyceride levels do not achieve non-HDL-C level goals despite the use of statins.2[,41,42] In the NEPTUNE II study, 61% of patients with hypertriglyceridemia (triglyceride level ≥200 mg/dL) achieved their LDL-C treatment goal, whereas only 39% achieved their non–HDL-C goal. Among the subset with hypertriglyceridemia and CHD or CHD-risk equivalents, 52% achieved their LDL-C goal, whereas 27% achieved their non–HDL-C goal.2 Part of the challenge in achieving the non–HDL-C goal is that statins have less robust effects on triglyceride levels relative to their reductions in LDL-C levels and thus may not optimally reduce the cholesterol carried by triglyceride-rich lipoproteins, such as VLDLs, intermediate-density lipoproteins, and chylomicrons.

Combination therapy appears most appropriate for patients with risk for a high rate of CHD events despite being on optimal statin therapy. In addition to lifestyle modification,

the use of combination therapy in CHD is an acknowledged strategy in optimal management to prevent or delay the morbidity and mortality associated with high-risk patients including those with combined hyperlipidemia and diabetic dyslipidemia.[43] In patients with hypertriglyceridemia (≥200 mg/dL), non-HDL-C (VLDL + LDL cholesterol) can serve as a secondary target of therapy. A "normal" VLDL-C can be defined as that present when triglycerides are <150 mg/dL; this value typically is ≤30 mg/dL. Conversely, when triglyceride levels are >150 mg/dL, VLDL-C usually is >30 mg/dL. Thus, a reasonable goal for non-HDL-C is one that is 30 mg/dL higher than the LDL-C goal. Because increasing the statin dose to achieve non-HDL-C and triglyceride levels has limited efficacy as well as safety concerns, adding other lipid altering therapies to statins is a valuable alternative.

CVD risk increases with triglyceride levels over 100 mg/dL, and at triglycerides ≥200 mg/dL the CVD risk is increased approximately 2-fold.1 The inclusion criterion of fasting TG for this protocol was based on recommendations from the NCEP ATP III and 2004 Update.1,[43] In the high-risk patient, the 2004 Update recommends that when triglycerides are ≥200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.[43] For persons with borderline high triglycerides (150-199 mg/dL), according the guidelines, the VLDL cholesterol is not elevated enough to evoke non-HDL cholesterol as a secondary target. In addition, the Secondary Prevention 2010 Guidelines from the American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) also recommend the addition of second drug to statin therapy for non-HDL-C reduction when the triglycerides exceed 200 mg/dL.[44] In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, the primary endpoint CV outcomes benefit for the entire cohort was not significant -11% (0.16), however, for the subgroup with TG ≥ 204 mg/dL and HDL-C < 42 mg/dL the benefit was significant (-27%; 0.005).[45] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial that also investigated fenofibrate, the primary end point was not significant yet the subgroup with TG ≥ 204 mg/dL and HDL-C < 34 mg/dL the benefit was nearly significant (-31%; 0.06).[46,47] In the Japan EPA Lipid Intervention Study (JELIS) that investigated the effectiveness of ethyl-EPA, the primary CV endpoint was significant -19% (0.011) for the entire cohort but demonstrated a dramatically larger significant benefit in the subgroup with TG ≥ 150 mg/dL and HDL-C < 40 mg/dL (-53%; 0.043).[48,49] Omega-3s lower non-HDL-C, primarily by lowering VLDL-C and the greater the baseline triglyceride level the more non-HDL-C reduction. Therefore, a baseline TG of approximately ≥200 mg/dL with HDL-C approximately <40 mg/dL in men or <45 mg/dL in women will result in a greater non-HDL-C reduction with Epanova which is

more likely to result in a clinically significant CV benefit. Due to the well known variability of these lipids, a variability for the inclusion criteria of 10% at the lower end of the TG interval and of 5% at the upper end of the HDL interval is reasonable based on reports of high TG/low HDL subgroups in this range from previous outcomes trials[46-49]. Thus, the resulting range for inclusion are those stipulated in the inclusion criteria of this protocol: TG ≥180 and < 500 mg/dL (≥2.03 and < 5.65 mmol/L) and HDL-C <42 mg/dL (1.09 mmol/L) for men or HDL-C <47 mg/dL (1.22 mmol/L) for women. These criteria are considered adequate to define a CV high-risk population likely to benefit from an intervention with Epanova.

In a study assessing combination therapy with simvastatin 40 mg and omega-3-acid ethyl esters 4 g daily (COMBination of prescription Omega-3 with Simvastatin [COMBOS]), median percent decreases in non-HDL-C were significantly greater with combination therapy compared to placebo (vegetable oil) plus simvastatin (9.0% vs. 2.2% respectively, p<0.001).[50] In addition, combination therapy significantly lowered TG (29.5%) and VLDL-C (27.5%) raised HDL-C (3.4%) and lowered total cholesterol:HDL-C ratio (9.6%; p ≤ 0.001 vs. placebo for all), although LDL-C increased by 3.5%. In a post hoc analysis of the COMBOS study, the baseline LDL-C predicted the LDL-C response.[51] The median LDL-C responses among the baseline LDL-C levels were +9.5% (first tertile, <80.4 mg/dL), -0.9% (second tertile), and -6.4% (third tertile, ≥99.0 mg/dL). Non-HDL-C, VLDL-C, HDL-C, and triglyceride responses did not vary significantly by baseline LDL-C tertile. The reductions in VLDL-C concentrations were greater than the increases in LDL-C, where present, resulting in a net decrease in the concentration of cholesterol carried by atherogenic particles associated with non-HDL-C, in all baseline LDL-C tertiles. In conclusion, these results suggest that the increase in LDL-C that occurred with the addition of omega-3-acid ethyl esters therapy to simvastatin therapy in subjects with mixed dyslipidemia was confined predominantly to those with low baseline LDL-C levels. In addition, LDL-particle number and Apo B-100 were reduced with the combination therapy suggesting that the increase in LDL-C was associated with an increase in LDL particle size rather than particle number.

A recent simulation study assessed the risk of CV events in 5000 individuals with severe hypertriglyceridemia (>500 mg/dL) and normal LDL-C levels (<100 mg/dL) using the Archimedes Model.[52] At 10 years and 20 years respectively, the rate per individual at baseline of total MIs was estimated to be 14.6% and 32.5%, the rate of ischemic stroke was 3.5% and 7.9%, CHD death was 5% and 11.8%, CVD death was 7.1% and 16.7%, and the cumulative fraction of people with composite major adverse cardiovascular event

(MACE) were 16.2% and 31.5%. Individuals with severe hypertriglyceridemia are more than twice as likely to suffer an adverse cardiac outcome as compared with individuals with normal TG levels; the corresponding incidence rates for CHD mortality are 0.20% per year for the general US adult population and 0.45% for individuals with severe hypertriglyceridemia.

There are no long-term CV outcomes studies that specifically assess the impact of adding omega-3 fatty acids to statins in reducing the risk of cardiovascular events associated with persistent hypertriglyceridemia. The current protocol will investigate the effectiveness of adding Epanova to statin, with or without ezetimibe, as needed, for lowering MACE (cardiovascular death, non-fatal MI, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina) in patients with persistent hypertriglyceridemia and high risk for CVD. The primary outcome measure is the time to the first occurrence of any component of the composite of MACE.

In the STRENGTH trial, all patients will be on statin therapy, with or without ezetimibe therapy, in order to achieve LDL-C <100 mg/dL (<2.59 mmol/L). If a patient is not at this LDL-C goal at Visit 1 and not at the maximum tolerated statin dose, the statin must be titrated to the maximum tolerable dose. Another option is to treat with a high intensity statin such as either atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg, based on current 2013 ACC/AHA Guidelines.[53] Rather than LDL-C or non-HDL-C targets, this guideline used the intensity of statin therapy as the goal of treatment (Appendix D). Through a rigorous process, 4 groups of individuals were identified for whom an extensive body of randomized control trial (RCT) evidence demonstrated a reduction in atherosclerotic cardiovascular disease (ASCVD) events with a good margin of safety from moderate- or high-intensity statin therapy:

1. Individuals with clinical ASCVD
2. Individuals with primary elevations of LDL-C ≥190 mg/dL
3. Individuals 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL without clinical ASCVD
4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70 to 189 mg/dL and have an estimated 10-year ASCVD risk of 7.5% or higher.

For patients who do not tolerate statins in doses needed to reach 100 mg/dL or the high intensity doses of atorvastatin and rosuvastatin described in the ACC/AHA 2013 guidelines, the maximum tolerable dose of any statin should be used.

If the patient is already at the maximum tolerated statin dose, then ezetimibe 10 mg may be added (if available in the country). Bile acid sequestrants are contraindicated in these patients due to elevated triglyceride levels. Fibrates do not lower LDL-C in patients with hypertriglyceridemia and they carry cautions for use in combination with the maximum doses of statins. Niacin requires doses of 2000 mg to significantly lower LDL-C and it carries cautions for use in combination with the maximum doses of certain statins and has not been proven to provide cardiovascular benefits. Therefore, no additional therapy is either available or safe to combine with high dose statins in patients with hypertriglyceridemia.

In the STRENGTH protocol, male patients >50 years of age with HDL-C <40 mg/dL or females >60 years of age with HDL-C <45 mg/dL, with at least one risk factor (family history of premature CHD, cigarette smoking, elevated high-sensitivity C-reactive protein [hs-CRP] or impaired renal function), have high risk for CHD and are therefore good candidates for the present study. Further, the West Of Scotland Coronary Prevention Study (WOSCOPS) demonstrated that patients with multiple risk factors treated with statin therapy continued to have a high rate of CHD events (10.2%).[53] In the Cholesterol Treatment Trialists' (CTT) metanalysis,[55] the elderly, defined as greater than 65 years of age, had a 30% greater risk of CHD events on statin therapy compared to those less than age 65. In the CTT analysis, the subgroup of subjects in the highest tertile (TG >177 mg/dL), which is comparable to the population for STRENGTH, had a significantly higher risk of CHD events on statin therapy. Therefore, hypertriglyceridemic patients greater than 65 years of age with two or more major risk factors have a significantly elevated risk of incidence of CHD events and will be an important subpopulation in the STRENGTH trial to evaluate the potential cardiovascular benefits of Epanova.

2 OBJECTIVES AND OUTCOMES

2.1 Primary Objective and Outcome Measure

The primary objective is to evaluate the effectiveness of adding Epanova to statin therapy (with or without ezetimibe) for lowering MACE (cardiovascular death, non-fatal MI, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina) in high cardiovascular risk patients with persistent hypertriglyceridemia and low HDL-C.

The primary outcome measure is the time to the first occurrence of any component of the composite of MACE. Patients will remain in the study until the required number of patients with MACE has occurred. We anticipate that patients will be in the study for 3-5 years. Patients who discontinue investigational product (IP) will continue to be assessed as specified per the protocol.

2.2 Secondary Outcome Measures

2.2.1 Key Secondary Outcome Measures

- The composite measure of CV events that include the first occurrence of cardiovascular death, non-fatal MI, and non-fatal stroke.
- The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal MI, emergent/elective coronary revascularization, or hospitalization for unstable angina.
- Time to CV Death

2.2.2 Other Secondary Outcome Measures

Other secondary outcome measure will include:

a) Emergent/elective coronary revascularization
b) Hospitalization for unstable angina
c) Fatal or non-fatal MI
d) Non-fatal MI
e) Fatal or non-fatal stroke
f) Non-fatal stroke
g) All-cause death

2.3 Tertiary Outcome Measures

Tertiary endpoints will include:

- The first occurrence of new onset atrial fibrillation (AF).
- The composite measure of total thrombotic events that include the first occurrence documented coronary stent thrombosis, any systemic thromboembolism including arterial stent (except coronary) thrombosis or venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) and/or pulmonary embolism (PE).
- First occurrence of a heart failure event.

2.4 Clinical Events Adjudication

An independent Clinical Events Committee (CEC) will systematically identify and adjudicate all components of the primary and secondary endpoints as well as the tertiary heart failure events endpoint. The CEC will be comprised of qualified adjudicators from a pre-established group at the Cleveland Clinic Cardiovascular Coordinating Center for Clinical Research (C5Research) located at the Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, U.S. Members of the CEC will be blinded to treatment assignment. The CEC-adjudicated data will be used in the final analysis.

Events will be analyzed per pre-specified definitions provided in a separate CEC charter and will be agreed upon by the CEC and the Executive Committee. Standardized definitions for endpoint events are provided by the Standardized Data Collection for Cardiovascular Trials Initiative (Appendix C: Standardized Definitions for Endpoint Events in Cardiovascular Trials). For the purposes of this protocol, MACE are defined as cardiovascular death, non-fatal MI, non-fatal stroke, emergent/elective coronary revascularization, and hospitalization for unstable angina. Non-fatal MI will NOT include silent MI. Unstable angina will require evidence of myocardial ischemia.

2.5 Efficacy Endpoints

Biomarker efficacy endpoints will evaluate the differences in change from baseline (Month 0) to Month 12 (primary), between placebo (corn oil) and Epanova treatments. In addition, biomarker data after Month 12, will be presented in a descriptive manner. Biomarker variables include non-HDL-C, TG, HDL-C, total cholesterol (TC), VLDL-C, TC:HDL-C ratio and calculated LDL-C (in patients with triglycerides > 400 mg/dl LDL-C will be directly measured);apolipoprotein B-100 (Apo B-100) and apolipoprotein C-III

(Apo C-III); EPA, DHA, docosapentaenoic acid (DPA) and AA in plasma and red blood cells (RBC), hs-CRP.

2.6 Safety Assessments

The study will provide long-term safety assessments of Epanova administration, including adverse events, safety laboratory assessments, pregnancy tests and physical examinations.

An independent Data Monitoring Committee (DMC) will review safety data periodically and may recommend stopping the study for safety concerns at any time.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

The study is a randomized, double-blind, placebo-controlled (corn oil), parallel group design that will enroll approximately 13,000 patients with hypertriglyceridemia and high risk for CVD to be randomized 1:1 to either placebo (corn oil) + statin or Epanova + statin, once daily, for approximately 3-5 years as determined when the number of patients with MACE outcomes is reached. There will be up to 15 scheduled clinic visits (1, 1a and 1b screening visits, one randomization [Visit 2], and 11 treatment visits [3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months]), and a 3-week follow-up visit (Visit 14) for those patients who undergo early permanent IP discontinuation due to an SAE. Patients will remain in the study until the required number of patients with MACE have occurred; see Table 6-1 Schedule of Procedures and Study Flow Diagram Figure 3.1. Patients with potential, per investigator opinion, to achieve a fasting TG level of approximately ≥180 and <500 mg/dL (≥2.03 and <5.65 mmol/L) will undergo an initial screening period during which they will discontinue use of any excluded therapies or products and continue or adjust their current statin regimen (statin adjustments may be permitted per investigator discretion, see Section 7.5). There will be up to 3 screening visits, depending on the need for repeated laboratory sample assessments or statin/ezetimibe adjustment. During the screening period, patients will maintain a stable diet, and after randomization, be willing to adhere to the NCEP TLC or equivalent diet. Patients who meet all Inclusion Criteria and no Exclusion Criteria will be randomized 1:1 (6,500/arm) to receive double-blinded Epanova (4 g daily) or a matching placebo (corn oil; 4 g daily) for the study duration.

The selection of the study population, i.e. patients with persistent hypertriglyceridemia despite statin therapy and a high risk for CVD, is in agreement with NCEP ATP III guidelines,1 as well as with more recent evidence-based reports.[44,56,57,58,59,60] Adding a 'low HDL criterion' increases the chance of showing benefit with triglyceride lowering therapy[46-49]. The study population is not restricted to a Framingham 10-year risk >20% for cardiovascular events and allows for both primary and secondary prevention populations. The study has inclusion criteria for patients with confirmed medical history of CVD as well as for patients with risk for CVD based on other conditions: type 1 or 2 diabetes mellitus, elevated coronary calcium score, impaired renal function and advanced age. 1,[53 55,56,57,58,59,60,61] In addition, the study may include patients based on hs-CRP levels which is associated with significant risk for CVD.[57,58,59] The Justification for the

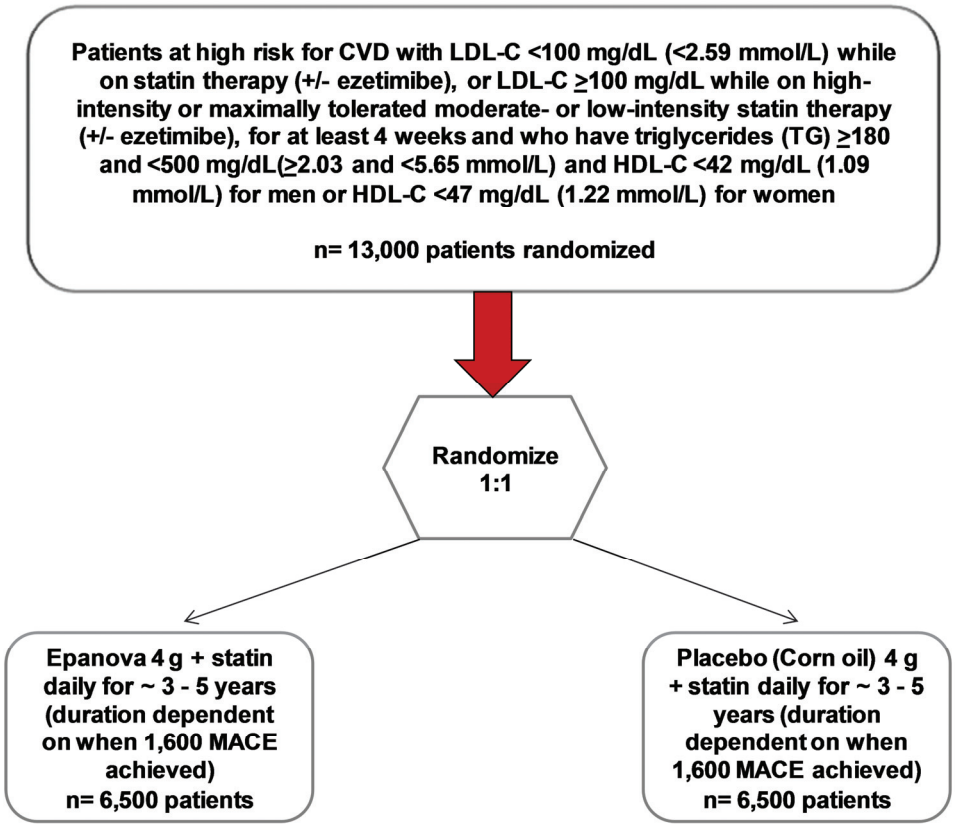
Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial demonstrated that the absolute risk of major vascular events increased with increasing hs-CRP, and that the absolute risk reduction associated with rosuvastatin was also greatest among those with the highest baseline hs-CRP levels.[57]

Patients will be allowed entry into the study if they are at the NCEP ATP III LDL cholesterol goal of <100 mg/dL (2.59 mol/L), if they are on treatment with a high intensity statin (atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg) based on the 2013 ACC/AHA lipid guidelines, or if they have an LDL-C ≥100 mg/dL and on the highest tolerated, moderate- or low-intensity statin therapy (with or without ezetimibe). The maximum tolerated dosage of a statin is defined as the maximum approved dose per local label or the maximal dose that the patient can tolerate without unacceptable adverse effects such as muscle pain or elevations in liver enzymes or creatine kinase (CK) felt by the investigator to be clinically relevant and due to statin therapy.

The study allows for intra-patient variability of lipid measurements. For example, borderline values of TG ≥ 160-179 mg/dL (≥1.81-2.02 mmol/L) or TG ≥500 and <575 mg/dL (>5.65 and <6.49 mmol/L) and/or borderline values of HDL-C ≤ 45 mg/dL (1.17 mmol/L) for men and ≤50 mg/dL (1.30 mmol/L) for women, may require a repeat test. Repeated lab values may be used to qualify if needed. Day-to-day variability of lipid measurements with different statin treatments as well as the variability between statins in achieving LDL cholesterol goals despite optimal dosing is well known.[62,63,64]

A total of 13,000 patients will be randomized into the 2 treatment arms according to the Study Flow Diagram (Figure 3.1).

Figure 3.1 STUDY FLOW DIAGRAM



The CEC will adjudicate all MACE components of the primary endpoint, all MACE components and composite of the secondary endpoints, and the tertiary heart failure endpoint (Table 3-1). The MACE primary endpoint is based on the 2008 FDA guidance[63] "Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes", the published JUPITER outcomes trial,[66] and the draft guidance on the standardized definitions for endpoint events provided by the Standardized Data Collection for Cardiovascular Trials Initiative (Appendix C: Standardized Definitions for Endpoint Events in Cardiovascular Trials).

In JUPITER, the primary objective investigated whether treatment with rosuvastatin, 20 mg daily, as compared with placebo, would decrease the rate of first major cardiovascular events.[66] The primary outcome was the occurrence of a first major cardiovascular event, defined as non-fatal MI, non-fatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes.

The JUPITER results showed that healthy men and women with elevated levels of hs-CRP who were treated with rosuvastatin had a significantly reduced incidence of major cardiovascular events. The decrease in events occurred despite the fact that nearly all study participants had lipid levels at baseline that were well below the threshold for treatment according to current prevention guidelines. Rosuvastatin also significantly reduced the incidence of death from any cause. These effects were consistent in all subgroups evaluated with elevated levels of hs-CRP, including subgroups customarily considered to be at low risk, such as people with Framingham risk scores of 10% or less, those with LDL cholesterol levels of 100 mg/dL or less, those without the metabolic syndrome, but no other major risk factor. The trial also showed robust reductions in cardiovascular events with statin therapy in women and black and Hispanic populations for which data on primary prevention are limited. Therefore, the JUPITER design for MACE proved to be adequate for an outcomes study.

Table 3-1. COMPONENTS OF PRIMARY, SECONDARY AND TERTIARY OUTCOME ENDPOINTS

	Primary Endpoint	KEY Secondary Endpoint			Other Secondary Endpoint	Tertiary Endpoint	
Component:	**TTE; First occurrence (composite) of any component of**	**Composite of**	**Composite of**	**Time to**	**Time to**	**Time to**	**Composite of**
CV Death	X	X		X			
Cardiac Death[3]			X				
Non-fatal MI[1]	X	X	X		X		
Non-fatal Stroke	X	X			X		
Emergent/ elective coronary revascularization	X		X		X		
Hospitalization for unstable angina[2]	X		X		X		
Fatal or non-fatal MI					X		
Fatal or non-fatal Stroke					X		
All-cause death					X		

New onset AF						X	
Coronary stent thrombosis							X
Systemic stent thrombosis							X
VTE/PE							X
HF						X	

[1] Note: Excludes silent myocardial infarction (MI); AF = atrial fibrillation; VTE = venous thromboembolism. PE = pulmonary embolism; HF = heart failure.

[2] Note: Unstable angina must be confirmed by evidence of myocardial ischemia.
[3] Note: Cardiac death includes death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures

3.2 Discussion of Study Design

Despite the widespread use of statin therapy, a considerable residual risk of cardiovascular events remains.[67] While statins reduce the relative risk of cardiovascular events by approximately 20% to 50%, depending on the degree of LDL-C reduction, there remains considerable risk of future events in some subgroups of patients.[55,68] One of the strongest predictors of residual risk is hypertriglyceridemia associated with low levels of HDL-C.[67,69,70] In the ACCORD Lipid trial, patients with diabetes on simvastatin monotherapy in the upper tertile of triglycerides (TG ≥204 mg/dL) and the lower tertile of HDL-C (≤34 mg/dL) had a cardiovascular event frequency of 17.3% compared with 10.1% in all other patients receiving simvastatin monotherapy.[69] This subgroup of patients with high TG and low HDL-C represented approximately 17% of the study population receiving statin monotherapy, but accounted for 25% of the cardiovascular events. The high TG and low HDL-C subgroup in the ACCORD Lipid trial had not only a greater cardiovascular event rate, but also a 29% relative risk reduction on fenofibrate combination therapy with simvastatin, compared with simvastatin monotherapy (12.4% vs. 17.3% events; p=0.057). However, the patients outside of this dyslipidemic subgroup did not benefit from the addition of fenofibrate to simvastatin therapy (10.1% vs. 10.1% events, p=0.06 for the treatment-by-subgroup interaction). These results are consistent with those from the five other cardiovascular outcome trials that evaluated the benefits of a TG-lowering therapy in the subgroup of patients with significant hypertriglyceridemia.[45,71,72,73,74]

The benefits of triglyceride lowering agent such as Epanova is significantly more likely to occur in patients with a fasting triglyceride level greater than approximately 180 mg/dL. A combination of higher triglycerides and low HDL-C is also a stronger predictor of both residual CV risk on a statin as well as outcome benefits in randomized clinical trials in the subgroup of patients that received a triglyceride lowering therapy. Therefore, the clinical study inclusion criteria were adopted to maximize the potential CV outcome benefits of Epanova, which is predominately a treatment to lower triglycerides, VLDL-C and non-HDL-C in patients with elevated CV risk due to residual hypertriglyceridemia on a statin.

The inclusion criterion of fasting TG level ≥180 and <500 mg/dL is also based on recommendations from the NCEP ATP III and 2004 Update. 1,[43] Although CVD risk increases with TG levels over 100 mg/dL, only at TG ≥200 mg/dL does the CVD risk increase by 2-fold. 1 Further, in the high-risk patient, the 2004 Update concurs that when triglycerides are ≥200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal

30 mg/dL higher than the identified LDL-C goal. In clinical trials with fenofibrate or bezafibrate, the CV benefit of these TG lowering drugs are not achieved unless the triglyceride level is >200 mg/dL (FIELD, ACCORD, Bezafibrate Infarction Prevention [BIP] trials).[75] Omega-3s lower non-HDL-C primarily by lowering VLDL-C and the greater the baseline TG level the more non-HDL-C reduction. Therefore, a baseline TG of approximately ≥200 mg/dL will result in a greater non-HDL-C reduction with Epanova, which is more likely to result in a clinical benefit. Due to the well known variability of these lipids, a variability for the inclusion criteria of 10% at the lower end of the TG interval and of 5% at the upper end of the HDL interval is reasonable based on reports of the results for high TG/low HDL subgroups in this range from previous outcomes trials[46-49]. Thus, the resulting range for inclusion are those stipulated in the inclusion criteria of this protocol: TG ≥180 and < 500 mg/dL (≥2.03 and < 5.65 mmol/L) and HDL-C <42 mg/dL (1.09 mmol/L) for men or HDL-C <47 mg/dL (1.22 mmol/L) for women. These criteria are considered adequate to define a CV high-risk population likely to benefit from an intervention with Epanova.

Regarding the choice of statin as the standard of care in this study, the NCEP guidelines recommend statins as a first-line treatment for targeting LDL-C goals.1 If the patient at LDL-C goal has persistent hypertriglyceridemia while on an optimal or maximum tolerated statin dose, the recommendation is to add a second lipid-lowering therapy to target non-HDL-C.

The current study is referred to as a 'superiority' trial in which the effects of Epanova will be compared to placebo (corn oil). The choice of corn oil, rich in omega-6 polyunsaturated fatty acids (n-6 PUFA) as the control is based on both epidemiologic and interventional studies that suggest that although substituting n-6 PUFA-rich foods for saturated fatty acid (SFA)-rich foods in the diet can potentially lower total plasma cholesterol concentrations, this substitution provides only a modest reduction in cardiovascular events.[76] In a meta-analysis of randomized clinical trials of replacing SFA with n-6 PUFA, the overall pooled risk reduction was 19% (RR = 0.81, 95% confidence interval [CI] 0.70-0.95, p = 0.008), corresponding to 10% reduced CHD risk (RR = 0.90, 95% CI = 0.83-0.97) for each 5% energy of increased PUFA.[77] Therefore a 4 gram dose or approximately 1% of energy from of corn oil would be expected to achieve approximately a 2% reduction in CHD risk. Extra virgin olive oil has been demonstrated in an interventional trial to reduce CV events by approximately 30 % over 4.8 years of median follow up.[77] In recent literature, it was shown that olive oil (or more likely oleic acid) has an impact on overall and CVD mortality in that there was a reduction in CVD

mortality of 13% for each 10 g of olive oil intake.[78] Extrapolating this result to a 4 g dose would result in a 5.2% reduction. Therefore, based on the published literature, either common olive oil or extra virgin olive oil would provide a greater CV risk reduction than corn oil.

Liquid paraffin or mineral oil has also been used in a few clinical trials as a control for evaluating the effects of omega-3's but has been associated with increased gastrointestinal side effects, adverse lipid effects and potentially may interfere with the absorption of certain drugs.[79] Mineral oil also does not provide caloric control which may result in an imbalance in the consumption of other nutrients such as carbohydrates that may lead to an exacerbation of hypertriglyceridemia. Other oils such a medium chain triglycerides or miglyol have been used as a control for short-term omega-3 lipid and have potential lipid changes that may affect CV outcomes. In addition, there is a lack of data regarding the long-term health effects of these oils. Therefore, the preferred option for the control selected for this study is corn oil (United States Pharmacopeia [USP] standard) even though modest changes in lipid parameters are expected as well as a slight reduction in CV risk. Further, the sample size assumptions for this study have taken into account the potential beneficial health effects of corn oil.

4 SELECTION AND WITHDRAWAL OF PATIENTS

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all of the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Quintiles Medical Monitor study physician immediately, and a discussion should occur between the Quintiles Medical Monitor and the investigator regarding whether to continue or discontinue the patient from treatment. A patient who does not meet all of the eligibility criteria, is subsequently discontinued from treatment but has received at least 1 dose of randomized IP must be followed-up until End of the study in order to collect safety information and vital status (see Section 6.13). The Quintiles Medical Monitor must ensure all decisions are appropriately documented.

4.1 Inclusion Criteria

Patients who have provided written informed consent and authorization for disclosure of protected health information must meet the following criteria:

1. Men or women, ≥18 years of age.
2. Patient must be on a stable diet and statin* therapy at least 4 weeks prior to randomization (Visit 2) and meet the following criteria,where the qualifying lipid parameters should be obtained from the same visit:
   a. LDL-C <100 mg/dL (<2.59 mmol/L). Patient will also qualify if LDL-C ≥100 mg/dL (≥2.59 mmol/L) and if on a high-intensity statin (atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg) or on highest tolerated moderate- or low-intensity statin dose, with or without ezetimibe therapy, for at least 4 weeks (see Appendix D). The maximum tolerated dosage of a statin is defined as the approved dose per local label that the patient can tolerate without unacceptable adverse effects such as muscle aches/pain/weakness or elevations in liver enzymes or creatine kinase (CK) that are determined by the investigator to be clinically relevant and due to statin therapy.
   b. TG ≥180 and < 500 mg/dL (≥2.03 and < 5.65 mmol/L) and HDL-C <42 mg/dL (1.09 mmol/L) for men or HDL-C <47 mg/dL (1.22 mmol/L) for women.

*co-administration with ezetimibe or fixed-dose ezetimibe/simvastatin 10/10, 10/20, 10/40 mg (see restrictions regarding 80 mg simvastatin in Section 7.4) or fixed-dose ezetimibe/atorvastatin 10/10, 10/20, 10/40, or 10/80 mg is allowed.

3. Patient is at high risk for a future cardiovascular event if at least one of the following criteria (3a, 3b or 3c)* is present via patient history, physical exam, or medical records at the time of screening:

a. Any atherosclerotic CVD as defined by one or more of the following:

- previous clinical myocardial infarction (MI) ≥30 days prior to randomization
- percutaneous coronary intervention (PCI) including balloon angioplasty and coronary stenting ≥ 6 months prior to randomization
- coronary artery bypass grafting (CABG) ≥30 days prior to randomization
- coronary angiogram including computed tomography angiogram (CTA) showing ≥ 50% stenosis in at least one native or graft vessel
- anginal symptoms with a defect documented by stress testing with nuclear perfusion imaging or a wall motion abnormality determined by stress echocardiogram
- asymptomatic coronary ischemia documented by stress testing with nuclear perfusion imaging or by stress echocardiogram
- peripheral vascular disease with symptoms of claudication and ankle brachial index <0.9 performed by a vascular lab or angiogram (including CTA) showing ≥ 50% stenosis)
- history of peripheral arterial revascularization (surgical or percutaneous) ≥30 days prior to randomization
- carotid endarterectomy, carotid stenting or more than or equal to 50% stenosis in a carotid artery determined by carotid ultrasound or angiogram ≥30 days prior to randomization
- history of abdominal aortic aneurysm confirmed by imaging, diagnosed ≥30 days prior to randomization
- ischemic stroke ≥30 days prior to randomization

b. History of diabetes mellitus (type 1 or 2) and ≥40 years of age for men and ≥50 years of age for women, plus one of the following risk factors:

- chronic cigarette smoking at screening (at least 1 cigarette per day for > 1 month)
- history of hypertension (blood pressure >140/90 mm Hg) or taking antihypertensive medication
- high-sensitivity C-reactive protein (hs-CRP) > 2.0 mg/L (19.05 nmol/L) determined at Visit 1
- history of albuminuria (urinary albumin:creatinine ratio [ACR] >30 mg/g).

c. Male patients >50 years of age or females >60 years of age, with at least one of the following risk factors:

- family history (mother, father or sibling) of premature coronary heart disease (father or brother <55 years of age, mother or sister <65 years of age)
- chronic cigarette smoking at screening (at least 1 cigarette per day for > 1 month)
- hs-CRP >2.0 mg/L (19.05 nmol/L) determined at Visit 1
- impaired renal function as estimated using the Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI)[81] formula for glomerular filtration rate (eGFR) <45 mL/min per 1.73 m^2 (patients on dialysis are excluded).
- coronary calcium score >300 Agatston units (AU) at any time in the past.

*If patient will meet CVD secondary prevention criteria (3a) AND primary prevention criteria (3b and/or 3c) at the same time then patient will be considered as meeting CVD secondary prevention criteria (3a) for the purpose of identifying the inclusion criteria for that patient.

4. Patient must have been on a stable diet prior to randomization and willing to follow the NCEP TLC diet, or equivalent diet, throughout the study.

Note a) A patient can, in specific circumstances, be re-screened. For details, see section 6.4.

Note b): If LDL-C and/or TG and/or HDL-C do not meet the inclusion criteria at Visit 1, the patient may return twice (Visit 1a and 1b) during the screening period to reassess lipids for statin/ezetimibe adjustment, discontinuation of excluded lipid-modifying agent, or re-checking a borderline TG and/or HDL-C value (see footnote 2 of Table 6-1 for details on lipid reassessments and on statin/ezetimibe dose adjustments during the

screening period). Repeated values at Visit 1a may be used directly to qualify if needed. At Visit 1b, if lab values do not satisfy all inclusion criteria, the patient will be screen failed.

Note c): Once the patient qualifies, they should be randomized within 14 days. Atleast 50% of randomized patients should satisfy 3a CVD secondary prevention criteria, and <50% of patients should satisfy 3b and 3c primary prevention criteria combined; the proportions will be monitored and controlled via an Interactive Web Response System (IWRS).

4.2 Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. Allergy or intolerance to omega-3 carboxylic acids, omega-3 fatty acids, omega-3-acid ethyl esters or corn oil.
2. Known hypersensitivity to fish and/or shellfish
3. Use of fibrates, bile acid sequestrants, or niacin or its analogues (>250 mg/day) within 4 weeks prior to Visit 2. Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued for 4 weeks or more prior to Visit 2. However, niacin or its analogues at a dose less than or equal to 250 mg/day is permissible.
4. Statin naïve at Visit 1.
5. Use of simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg within 4 weeks prior to Visit 2. Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued and replaced with a protocol acceptable statin treatment that is stabilized for 4 weeks or more prior to Visit 2.
6. Use of any prescription medications containing eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA), e.g. Lovaza® or Vascepa®, within 4 weeks prior to Visit 2. Patients taking these agents may be considered for inclusion in the study if these therapies have been discontinued for 4 weeks or more prior to Visit 2.
7. More than one capsule/day (any dose) of omega-3 dietary supplements. Patients taking >1 capsule/day of omega-3 supplements before Visit 1 DO NOT require a washout period but must agree to reduce the number of capsules per day to more than 1 capsule of 1 g promptly after signing the informed consent. No new omega-3 supplements are permitted following initiation of screening procedures at Visit 1.

8. Use of prescription or over-the-counter (OTC) weight loss drugs at any time after Visit 1.

9. Chronic use of oral corticosteroids during screening (acute use for inflammation for example from poison ivy, or intranasal or inhaled steroids for allergies/asthma, or intraarticular injections are allowed).

10. Use of tamoxifen, estrogens, progestins, or testosterone, that has not been stable for >4 weeks at Visit 1, or is unstable prior to Visit 2.

11. Known lipoprotein lipase impairment or deficiency, or apolipoprotein C-II deficiency.

12. Hemoglobin A_{1c} (Hb A_{1c}) >12% at Visit 1.

13. Poorly controlled hypertension (resting blood pressure ≥180 mm Hg systolic and/or ≥100 mm Hg diastolic) at two consecutive visits prior to randomization at Visit 2.

14. Uncontrolled hypothyroidism, or thyroid stimulating hormone (TSH) >2.0 times upper limit of normal (ULN) at Visit 1. Patients who are clinically euthyroid, on stable thyroid replacement therapy for 2 months prior to Visit 1 are allowed.

15. History of cancer (except non-melanoma skin cancer, or carcinoma *in situ* of cervix) within the previous two years.

16. Patients on dialysis.

17. Females who are pregnant, planning to be pregnant during the study period, lactating, or women of childbearing potential who are not using an acceptable method of contraception. A woman is considered of childbearing potential if she is not surgically sterile or if her last menstrual period was <12 months prior to Visit 1. Acceptable methods of contraception for this study include use of double barrier contraception, intrauterine device , all oral, patch, etc. hormonal contraceptives as long as dose and type is stable for 3 months prior to Visit 1. In addition, true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject.

18. Creatine kinase >5.0 times ULN; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0 times ULN; or total bilirubin (TBL) >2.0 times ULN (except with a confirmed diagnosis of Gilbert's disease), at Visit 1. A diagnosis of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) with stable elevations of AST and/or ALT (>3.0 times ULN) is eligible for participation in the study.

19. Excessive use of alcohol or other substance abuse that in the investigator's opinion would jeopardize the patient's participation in the study or interpretation of the data.

20. Exposure to any investigational agent within 4 weeks prior to Visit 1, including randomization in this study.

21. Previous clinical myocardial infarction (MI) <30 days prior to randomization

22. Percutaneous coronary intervention (PCI) including balloon angioplasty and coronary stenting<6 months prior to randomization

23. Coronary artery bypass grafting (CABG) <30 days prior to randomization

24. History of peripheral arterial revascularization (surgical or percutaneous) <30 days prior to randomization

25. Carotid endarterectomy or more than or equal to 50% stenosis in a carotid artery determined by carotid ultrasound or angiogram <30 days prior to randomization

26. History of abdominal aortic aneurysm diagnosed <30 days prior to randomization

27. Ischemic stroke <30 days prior to randomization

28. Any other condition the investigator believes would interfere with the patient's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the patient at undue risk.

29. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca or its representative and/or staff at the study site).

4.3 Discontinuation of Investigational Product Criteria

Every effort should be made by site study staff to encourage patients to remain in the study. Patients may discontinue the IP for reasons including the following:

1. Patient is unwilling to continue taking IP or has difficulties to comply with study visit schedule or investigational procedures.

2. During the study, patient has the need for medications or dietary products that are excluded (see Section 7.4, "Prohibited Medications and Dietary Products").

3. Occurrence of any adverse event (AE) or condition that could, in the Investigator's opinion, interfere with the evaluation of the treatment effect or put the patient at undue risk. See Appendix B (Actions Required in Cases of Combined Increase of

Aminotransferase and Total Bilirubin Hy´s Law) which provides criteria for determining potential serious hepatotoxicity of the IP according to Hy's Law. Patients will discontinue for drug-induced liver injury (DILI).

Patients must discontinue IP and statin during pregnancy.

Patients who permanently discontinue taking IP for any reason will be asked to continue the regular study visits after the scheduled ET visit and (for permanent discontinuation due to an SAE) the 3-week Follow-up visit unless they withdraw consent for further participation and the use of their data. In this case, patient will be asked to provide written documentation (when possible) of withdrawal of consent and complete the ET visit only. Therefore, all patients who are permanently discontinued from study medication and agree to continue in the protocol should have regularly scheduled study visits.

SAEs will be recorded at all visits for the patients who prematurely discontinue IP. Non-serious AEs will be collected until the final visit but not more than 30 days after last dose of IP.

Data collection and procedures should continue according to the study protocol until study closure. If the patient does not agree to this option (which must be documented), a modified follow-up (e.g., regular telephone contacts or a contact at study closure) should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices in order to collect at least the study endpoint information. It is recommended that anyone being followed by regular telephone contacts or a contact at study closure attend the final visit in person. If Visit 13 (Month 60) is done in person then all protocol required procedures (Treatment Visits 6-12) must be done except IP dispensing/collection. The approach taken should be documented in the electronic case report form (eCRF), medical records and informed consent (IC) form.
Administration of IP may be interrupted for any reason during the study. The Investigator will judge if re-starts of the IP will provide a potential benefit that outweighs the risk in any patient. If judged by the investigator to be necessary, the protocol allows for unlimited statin interruptions. Temporary IP interruption of 7 days or more will be recorded in the eCRF.

4.4 Withdrawal from study (withdrawal of consent)

Patients are at any time free to withdraw from study (study medication and assessments), without prejudice to further treatment. Withdrawal of consent must be ascertained and documented by the Investigator who must consult with the Quintiles Medical Monitor and document the withdrawal of consent in the eCRF as well as in the IC form and medical records. The IC form should be resigned and dated by both the patient and the

investigator, if possible. Such patients will always be asked about the reason(s) and the presence of any adverse events.

At the time of withdrawal, patients should, if possible do the Early Termination (ET) visit. The patient should return study medication. To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at study closure. AstraZeneca or its delegate will therefore attempt to collect information on all patients' vital status from publicly available sources at study closure, even if informed consent has been withdrawn completely.

Adequate documentation of withdrawal of consent for follow-up is present only if both criteria below are met:

1) The patient explicitly refused all possible avenues for follow-up

2) There is written documentation by the PI that the patient has declined even a single telephone call at the end of the trial and follow-up through medical records.

5 STUDY TREATMENTS

5.1 Identity of Investigational Product

The IP will be 1 g capsules of either corn oil or Epanova. The IP will be supplied in bottles of 60 and/or 120 capsules.

Investigational product	Dosage form and strength	Manufacturer
Omega-3 carboxylic acids (Epanova)	1g capsules*	Catalent Germany Eberbach GmbH (encapsulation) Catalent Germany Schorndorf GmbH (capsule coating/bulk packaging)
Corn oil	1g capsules*	Catalent Germany Eberbach GmbH (encapsulation) Catalent Germany Schorndorf GmbH (capsule coating/bulk packaging)

* The lot number will be recorded in the study master file and identified in the Clinical Study Report (CSR).

The methods used in, and the facilities and controls used for the manufacturing, processing, packaging, and holding of this drug substance conform with Current Good Manufacturing Practices (cGMP) in accordance with 21 Code of Federal Regulations (CFR) Parts 210 and 211. AstraZeneca will maintain certificates of analysis for each ingredient, documenting its purity and potency.

Study labels will be consistent with the requirements of local regulatory authorities in each country.

5.2 Investigational Product Storage and Accountability

Investigational product will be stored at controlled room temperature (77 °F, 25 °C) in a locked area with limited access. Excursions between 59-86 °F (15-30 °C) are permitted as per USP controlled room temperature criteria with minor excursions of 2 °C to 40 °C, which could occur during shipment and storage. Investigational product should not be frozen.

Investigational product will be shipped to the study site. The Principal Investigator (PI) or designee will inventory and acknowledge receipt of all shipments of IP. The PI or designee must keep accurate records of IP via the master IP accountability logs and the patient IP accountability logs. Supplies of IP will be checked and accountability records

will be reviewed by the Clinical Research Associate (CRA) at monitoring visits. When the final accountability review has been completed, the original, completed accountability logs will be collected by the CRA and all unused, partially used, empty or unopened kits or bottles will be returned or destroyed according to the instructions from AstraZeneca or its representative. Written explanation will be required for any missing product. Investigational supplies should be used only in accordance with this protocol and under supervision of the PI. All records must be available for inspection by the contract research organization (CRO) and AstraZeneca personnel or their designees, and are subject to inspections by the regulatory authorities (e.g., FDA) at any time.

5.3 Methods of Assigning Patients to Treatment Groups

Each clinical site will be assigned a unique number. At each clinical site, a unique screening number will be assigned to each patient after written informed consent is obtained. Patient screening numbers will be assigned sequentially by an IWRS. Each patient will have a unique identifier that combines both the site and screening number. At Visit 2 (Month 0), a randomization number will be assigned to each patient by an IWRS in a sequential manner as he or she becomes eligible for randomization. The randomization number will correspond to a predetermined sequence of treatments that will provide a balanced allocation of patients to the treatment arms. Randomization numbers must not be re-used once assigned, even if the patient does not take the IP.

5.4 Administration of Investigational Product

Starting at Visit 1, patients will continue with, or adjust, their previous statin treatment throughout the study period. If a patient is not at their LDL-C goal of 100 mg/dL at Visit 1, and not using a high intensity statin (atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg) , the statin must be titrated to the maximum tolerable statin dose or to a high intensity statin. If the patient is already at the maximum tolerated dose then ezetimibe 10 mg may be added (if available in the country). On the days of all clinic visits throughout the study, the daily dose of statin, with or without ezetimibe, and investigational product should not be taken until after the fasting blood draws.

After randomization at Visit 2 (Month 0), all patients will be treated with either 4 g once/day Epanova (4 capsules) or 4 g once/day placebo (corn oil) (4 capsules). Patients should take the first dose at the clinic at Visit 2 (Month 0) and the final dose should be taken no later than the night before the last visit (Visit 13 or ET). The IP may be taken without regard to meals.

If the patient has intolerability symptoms with study drug dose of 4 g/day, a dose reduction may be required. The investigator should contact Quintiles Medical Monitor or designee to discuss alternative dosing strategies if needed, it is essential to try to maintain study treatment at a tolerated dose. Even a low dose of study medication is preferred to no study medication. Titrations may be performed through telephone contacts, if judged appropriate by the investigator.

If the patient has mild intolerability symptoms with 4 g/day, the recommendation is that the patient reduces the dose to 1 capsule twice a day with meals.

A temporary stop of study treatment for 1-2 weeks may be necessary if symptoms persist despite dose reduction, or as a first step if suspected adverse symptoms are intolerable to the extent that rapid resolution is required. Once symptoms subside, every attempt to titrate the patient back to 4 g/day, or the highest tolerable dose, should be made. The up-titration can, if judged appropriate by the investigator, be performed stepwise with weekly increases up to the highest tolerable dose. The patient can begin with 1 capsule once daily for a week, then 1 capsule twice a day, thereafter 3 capsules per day and finally 4 capsules per day, if the increasing doses are tolerated by the patient. If a dose increase results in recurrence of symptoms the patient should go back to the highest tolerated dose. Unlimited temporary stops of intake of the study drug during the study period are allowed. Even after a longer stop of several months, a restart of slowly up-titrated study treatment can be attempted if acceptable to the patient.

At randomization Visit 2, and all following visits, the daily dose of IP should not be taken until after the fasting blood draws.

5.5 Treatment Accountability and Compliance

Accountability of IP consumption will be evaluated by site staff through patient interview and the counting of unused IP returned to the clinic at Visits 3 through 13 (Months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60). The patient will be asked to bring the used and unused containers to each visit. Compliance (percent) = (the number consumed) ÷ (the number prescribed) x 100. Lost or discarded IP should not be included in the calculation. If compliance is less than 80%, patients will receive additional instructions about treatment regimens.

5.6 Blinding and Unblinding Method

Investigational product will be administered in a double-blinded fashion. Access to the randomization schedule and treatment codes will be maintained through the IWRS.

Routines for this will be described in the IVRS/IWRS user manual that will be provided to each site.

In an emergency, the study blind may be broken only if:

- in the opinion of the Medical Monitor and/or the PI, it is in the patient's best interest to do so
- knowledge of the treatment will alter the clinical management of the patient

In the case of an emergency that requires unblinding, the Investigator can enter IWRS to unblind the patient without prior contact with the Medical Monitor although follow-up between the Investigator and Medical Monitor must occur so that all parties are aware of the unblinding. A series of questions must be answered to ensure that the Investigator does not accidently unblind a patient. Although it is recommended that the Investigator contact the Medical Monitor prior to unblinding any patient, in instances where this is not feasible or advisable the PI directly access the patient's treatment assignment using the IWRS.

The emergency contact telephone number will be provided for each Medical Monitor.

Sponsor AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

6 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Table 6-1 represents the schedule of procedures and assessments at each of the scheduled visits. Details of each visit are provided in Sections 6.1 through 6.13.

Table 6-1. SCHEDULE OF PROCEDURES

Study Period	**Screening[2]**			**Randomization and treatment**					**EOT/ET**	**EOT/ET Follow-up for SAE**
Visit[1]	**1**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6 – 12**	**13**	**14**
Month (±2 weeks)				**0**	**3**	**6**	**12**	**18, 24, 30, 36, 42, 48 and 54**	**60[15]**	**3 weeks after EOT/ET for SAE[17]**
Informed Consent	X									
Medical History	X	X	X	X						
Prior Medications	X	X	X	X						
Physical Exam	X						X		X	
Clinical Assessments[3]	X	X	X	X	X	X	X	X	X	
Fasting Lipid Panel[4,5]	X	X	X	X			X[13]	X[13]	X[13]	
Hemoglobin A_{1c}	X			X			X[13]	X[13]	X[13]	
Eligibility Review	X	X	X	X						
hs-CRP	X			X					X	
Serum Chemistry[6]	X			X			X	X[7]	X[7]	
TSH	X									
Urine Pregnancy Test[8]	X									
Fasting Plasma Glucose				X			X[13]	X[13]	X[13]	
Hematocrit							X[13]	X[13]	X[13]	
ECG				X						
Fasting Special Lipid Markers[4,9]				X			X		X	
Plasma and RBC Fatty Acids[4,10]				X			X		X[9]	
Fasting CV Risk Markers[4,11]				X	X					
Genetic sample[14]				X						
Counseling on TLC or Equivalent Diet	X									
AEs, Concomitant Medications and Endpoint					X	X	X	X	X[16]	X[18]

Assessments[11]										
Telephone Calls[12]							→			
Randomization				X						
Dispense IP				X	X	X	X	X		
Assess IP Compliance					X	X	X	X	X	

AE = adverse event;
EOT = End of treatment; EOT is defined for patients who 1) permanently discontinue IP before the study has ended but agree for further follow-up assessments (on-site visits or telephone or via third party) until end of study 2) complete Visit 12 (Month 60) and have not discontinued IP early;
ET = Early Termination. ET is defined for patients who permanently discontinue IP before the study has ended and decide **not** to participate with any follow-up assessments (on-site visits or telephone or via third party);
TSH = thyroid stimulating hormone;
hs-CRP = high-sensitivity C-reactive protein;
ECG = electrocardiogram;
CV = cardiovascular;
TLC = Therapeutic Lifestyle Changes;
IP = Investigational Product.
RBC= red blood cell

1. If fasting is not normal routine clinical practice, informed consent should be obtained prior to request for fasting for the Screening visit. If this is the case, the Screening visit should be split into 2 separate visits with informed consent obtained and IWRS accessed to obtain the patient number at the initial visit; and all other procedures obtained at the subsequent visit. In the event that the Screening visit is split into 2 separate visits, the screening visit lab draw must be completed within 3 days. At any subsequent visit, if the patient did not fast for the recommended 9-14 hours, the fasted lab may be drawn the next day.
2. If at Visit 1 the patient's TG, LDL-C, and HDL-C meet the inclusion criteria and the patient has been on a stable diet and has met all other inclusion criteria and none of the exclusion criteria the patient should return within 2 weeks for randomization at Visit 2.

   If at Visit 1 the patient requires an adjustment to their statin regimen and/or a washout of other excluded lipid medications, the patient should return 4-6 weeks later to have their lipids re-drawn at Visit 1a.

   If at Visit 1 the patient does not require an adjustment to their statin regimen and/or a washout of other excluded lipid medications and either the patient's TG and/or HDL-C are borderline: TG ≥160 - 179 mg/dL (>1.81 – 2.02 mmol/L) or TG ≥500 and <575 mg/dL (>5.65 and <6.49 mmol/L) and/or HDL-C ≤45 mg/dL (1.17 mmol/L) for men and ≤50 mg/dL (1.30 mmol/L) for women, the patient can return within 2 weeks later to have all lipids re-drawn at Visit 1a.

If at Visit 1 the patient does not require an adjustment to their statin regimen and/or a washout of other excluded lipid medications, and TG and HDL-C values are outside of borderline boundaries, the patient is considered screen failed.

The TG, LDL-C and HDL-C results from Visit 1a will be used to determine eligibility in the same way as for Visit 1. If re-drawn TG and HDL-C values are again borderline (as above), lipids can be repeated once more at Visit 1b to determine eligibility. Note that all lipid parameters qualifying for randomization should be obtained from the same visit.

If the TG, LDL-C and HDL-C criteria are not met after Visit 1b, the patient should be screen failed.

Please note the possibility to rescreen in the some situations, please see section 6.4.

3. Includes height (Visit 1 only), waist circumference and weight (Visit 1, 5, 7, 9, 11, 13 only), blood pressure, and heart rate.
4. Fasting blood samples should be drawn after the recommended 9-14 hour fast.
5. Lipid panel includes serum TG, TC, calculated LDL-C (in patients with triglycerides > 400 mg/dl LDL-C will be directly measured), HDL-C, calculated non-HDL-C, VLDL-C and TC: HDL-C ratio.
6. Serum chemistry includes creatine kinase, ALT, AST, total and direct bilirubin, and creatinine. Glomerular Filtration Rate (GFR) will be calculated only at Visits 1 and 5.
7. Only ALT, AST and total bilirubin will be analyzed, and only at Visits 7, 9, 11 and 13.
8. Females of childbearing potential only (see Exclusion No. 17).
9. Special lipid markers include serum apolipoprotein B-100 (Apo B-100), and apolipoprotein C-III (Apo C-III).
10. Plasma and RBC fatty acids (EPA, DHA, DPA and AA) will be measured from the recommended 9-14 hour fasting samples. Note: Plasma and RBC assessments are performed only at Visits 2 and 5, or ET before Visit 5.
11. Blood samples will be collected for future analyses on a subset of patients located in the US, of lipid fractions, inflammatory markers and other CV markers that may be identified during the course of the study.
12. In addition to these scheduled procedures, a well-being phone call will be made every 6 months (±2 weeks) starting after Visit 4 that will occur at Months 9, 15, 21, 27, 33, 39, 45, 51, and 57, except at scheduled visits, to question about adverse events, endpoint assessment, changes in medications and any major issues with the IP (losses or noncompliance). For further assessment of any identified

potential or confirmed AE, a physical examination should be carried out if clinically appropriate.

13. Fasting lipid panel, Hb A_{1c}, fasting plasma glucose and hematocrit will be measured annually at Visits 5, 7, 9, 11 and 13.
14. Genetic samples will be collected for future analysis on approximately 2000 patients in the US, see Appendix F for details. The sample should be taken at Visit 2.
15. Patients who permanently discontinue taking IP for any reason will be asked to continue the regular study visits after the scheduled ET visit and (for permanent discontinuation of IP due to SAE) the 3-week Follow-up visit unless they withdraw consent for further participation and the use of their data. In this case, patient will be asked to provide written documentation (when possible) of withdrawal of consent and complete the ET Visit procedures only. If the patient is permanently discontinued from study medication and agrees to continue in the protocol, then the patient, if possible, should have regularly scheduled study visits.
16. Patients who have early permanent discontinuation of IP due to an SAE and have an ET visit, will be required to schedule a 3-week Follow-up (Visit 14) to assess the SAE and concomitant medications. The patients should be asked to continue the regular study visits as described above thereafter.
17. Visit window is ±1 week for Visit 14 (ET/EOT Follow-up for SAE).
18. At Follow-up Visit 14, other assessments from the procedures table may be performed upon investigator discretion to further evaluate the SAE causing ET or for SAE identified at EOT.

6.1 Screening Period (Visit 1)

- Written IC
- Relevant medical history
- Prior medications taken within the last 4 weeks. Doses will be recorded only for statins, anticoagulants and diabetes medications
- Physical examination
- Clinical assessments (height, weight, waist circumference measured at the umbilicus, blood pressure, heart rate)
- Fasting lipid panel (recommended 9-14 hour fast)
- Hemoglobin A_{1c} (Hb A_{1c})
- Eligibility review
- hs-CRP
- Serum chemistry

- TSH
- Urine pregnancy test
- TLC or equivalent diet counseling
- Remind patients of the recommended 9-14 hour fast prior to next visit

This visit may be conducted over two days in order to complete all procedures and obtain fasting laboratory tests. At Visit 1, if LDL-C is <100 mg/dL (2.59 mmol/L), OR ≥100 mg/dL and patient is on high intensity statin treatment (atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg) or on maximum tolerated medium-low intensity statin dosing regimen, with or without ezetimibe, patient will qualify to return for Visit 2 provided all other inclusion criteria are met and no exclusion criteria are met. If neither of the LDL-C criteria are met at Visit 1, patient will have statin/ezetimibe adjustment and return 4-6 weeks later at Visit 1a. At Visit 1a, if neither LDL-C criteria are met and patient is not on high intensity statin or on maximum tolerated dose of a medium- or low intensity statin, patient will have a second statin/ezetimibe adjustment and return 4-6 weeks later at Visit 1b. At Visit 1a or 1b, patients who meet either LDL-C Inclusion Criteria will qualify to return for randomization at Visit 2 provided that all inclusion and none of the exclusion criteria are met at the same visit.

If LDL-C, TG or HDL-C do not meet Inclusion Criterion No. 2 at Visit 1, the patient may return twice during the screening period to reassess lipids. For example, if TG ≥160-179 mg/dL (≥1.81-2.02 mmol/L) or TG ≥500 and <575 mg/dL (>5.65 and <6.49 mmol/L) the patient will return within 2 weeks for a scheduled repeat test.

6.2 Screening Period (Visit 1a)

- Medical history
- Prior medications – any relevant changes since last visit
- Clinical assessments (blood pressure, heart rate)
- Fasting lipid panel (recommended 9-14 hour fast)
- Eligibility review
- Remind patients of the recommended 9-14 hour fast prior to next visit

At Visit 1a, patient will qualify to return for Visit 2 provided all other inclusion criteria, including the **LDL-C criteria, are met** and no exclusion criterion is met at the same visit.

If neither LDL-C criteria are met and patient is not on maximum tolerated dose, patient will have a second statin/ezetimibe adjustment and return 4-6 weeks later at Visit 1b.

If the TG or HDL-C value for Inclusion Criteria is borderline (TG ≥160-179 mg/dL [≥1.81-2.02 mmol/L] or TG ≥500 and <575 mg/dL (>5.65 and <6.49 mmol/L) and/or HDL-C ≤ 45 mg/dL (1.17 mmol/L) for men and ≤50 mg/dL (1.30 mmol/L) for women at Visit 1a, the patient will return within two weeks for a scheduled repeat test of all lipid parameters. Values at Visit 1a may be used directly to qualify if needed. If TG or HDL-C results from visit 1a are exclusionary, the subject will be screen failed.

6.3 Screening Period (Visit 1b)

- Medical history
- Prior medications – any relevant changes since last visit
- Clinical assessments (blood pressure, heart rate)
- Fasting lipid panel (recommended 9-14 hour fast)
- Eligibility review
- Remind patients of the recommended 9-14 hour fast prior to next visit

At Visit 1b, patient will qualify to return for Visit 2 provided all other inclusion criteria are met and no exclusion criteria are met at the same visit.

If LDL-C criteria are not met and patient is still not on maximum tolerated dose, patient will be screen failed.

If any TG or HDL-C value for Inclusion Criteria is borderline at Visits 1b, the patient will be screen failed.

6.4 Re-screening

In some circumstances, the patient is allowed for re-screening. A patient can return on one occasion to redo screening procedures, starting from a re-screening Visit 1, if:

- A permanent change has occurred in eligibility criteria (medical status or laboratory findings) that previously led to screen failure.
- Any of the 3 a-c inclusion criteria or any of the exclusion criteria for age, or time elapsed after a previous event,were not fulfilled at initial screening but the patient becomes eligible after additional time has elapsed.

In addition, any patient that based on criteria used in a previous protocol version failed to be randomized due to TGs between 180 to 200 mg/dL (≥2.23 to 2.26 mmol/L) and/or

HDL-C 40 to 41 mg/dL (1.04 and 1.06mmol/L) for men or 45 to 46 mg/dL (1.17 to 1.19 mmol/L) for women can return for re-screening.

6.5 Randomization (Visit 2, Month 0)

- Medical history
- Prior medications
- Clinical assessments (blood pressure, heart rate)
- Fasting lipid panel (recommended 9-14 hour fast)
- Eligibility review
- Hb A_{1c}
- hs-CRP
- Serum chemistry
- Fasting plasma glucose (recommended 9-14 hour fast)
- ECG
- Fasting plasma and RBC fatty acids (recommended 9-14 hour fast)
- Fasting blood samples for CV risk markers (on a subset of approximately 2000 patients located in the US)
- Genetic sample (on a subset of approximately 2000 patients in the US)
- Randomization
- Dispense IP (Epanova/placebo (corn oil)) and dosing instructions. Patients will take first dose at the clinic.

6.6 Treatment (Visit 3, Month 3)

- Clinical assessments (blood pressure, heart rate)
- Fasting blood samples for CV risk markers (on a subset of approximately 2000 patients located in the US)
- Adverse events: selected collection see Section 9.2
- Endpoint Assessment
- Concomitant medications - relevant changes since last visit to be recorded for statins, anticoagulants or diabetes medications
- Dispense IP (Epanova/placebo (corn oil))
- Collect IP (Epanova/placebo (corn oil)) and assess compliance

6.7 Treatment (Visit 4, Month 6)

- Clinical assessments (blood pressure, heart rate)
- Adverse events: selected collection see Section 9.2
- Endpoint Assessment
- Concomitant medications - relevant changes since last visit to be recorded for statins, anticoagulants or diabetes medications

- Dispense IP (Epanova/placebo (corn oil))
- Collect IP (Epanova/placebo (corn oil)) and assess compliance
- Remind patients of the recommended 9-14 hour fast prior to next visit

6.8 Treatment (Visit 5, Month 12)

- Physical examination
- Clinical assessments (waist circumference, weight, blood pressure, heart rate)
- Fasting lipid panel (recommended 9-14 hour fast)
- Hb A_{1c}
- Serum chemistry
- Fasting plasma glucose
- Hematocrit
- Fasting plasma and RBC fatty acids (recommended 9-14 hour fast)
- Adverse events: selected collection see Section 9.2
- Endpoint Assessment
- Concomitant medications - relevant changes since last visit to be recorded for statins, anticoagulants or diabetes medications
- Dispense IP (Epanova/placebo (corn oil))
- Collect IP (Epanova/placebo (corn oil)) and assess compliance

6.9 Treatment (Visits 6-12; Months 18, 24, 30, 36, 42, 48, and 54)

- Clinical assessments (blood pressure, heart rate)
- Clinical assessments (waist circumference and weight at visits 7, 9, and 11 only)
- Fasting lipid panel (Visits 7, 9, 11)
- Hb A_{1c} (Visits 7, 9, 11)
- Serum chemistry (ALT, AST, total bilirubin only) (Visits 7, 9, 11)
- Fasting plasma glucose (Visits 7, 9, 11)
- Hematocrit (Visits 7, 9, 11)
- Adverse events: selected collection see Section 9.2
- Endpoint Assessment
- Concomitant medications - relevant changes since last visit to be recorded for statins, anticoagulants or diabetes medications
- Dispense IP (Epanova/placebo (corn oil))
- Collect IP (Epanova/placebo (corn oil)) and assess compliance
- Remind patients of the recommended 9-14 hour fast prior to next visit

6.10 Telephone Calls (Months 9, 15, 21, 27, 33, 39, 45, 51, and 57)

A well-being telephone call will be made to assess:

- Adverse event experiences
- Endpoint assessment
- Changes in concomitant medications -relevant changes since last phone call to be recorded for statins, anticoagulants or diabetes medication
- Issues with IP (losses, compliance)

For further assessment of any identified potential or confirmed AE, a physical examination should be carried out if clinically appropriate.

6.11 End of Treatment (Visit 13; Month 60) or ET

- Physical examination
- Clinical assessments (blood pressure, heart rate, waist circumference and weight)
- Fasting lipid panel (recommended 9-14 hour fast)
- Hb A_{1c}
- hs-CRP
- Fasting plasma glucose (recommended 9-14 hour fast)
- Serum chemistry (ALT, AST & total bilirubin only)
- Hematocrit
- Fasting plasma and RBC fatty acids (recommended 9-14 hour fast) assessed only for ET before Visit 5
- Adverse events: selected collection see Section 9.2
- Endpoint Assessment
- Concomitant medications - relevant changes since last visit to be recorded for statins, anticoagulants or diabetes medication
- Collect IP (Epanova/placebo (corn oil)) and assess compliance

Note: Patients will be treated by their primary care provider after the study is completed. The Sponsor does not intend to keep supplying the treatment to patients after the study ends.

6.12 Follow-up for SAE causing ET (3 weeks after ET visit)*

Patients who have an Early Termination (ET) of IP due to a serious adverse event (SAE) will be required to schedule the 3-week Follow-up visit. The patient may be contacted by telephone if they are not available to attend an onsite visit. After the 3-week Follow-up visit the patient should be asked to follow the regular scheduled study visits.

- Adverse events: selected collection see Section 9.2
- Concomitant medications - relevant changes since last visit to be recorded for statins, anticoagulants or diabetes medication

*Note: other assessments from the procedures table may be performed upon investigator discretion to further evaluate the SAE causing permanent IP discontinuation.

6.13 Early Termination Procedures

The term "Early Termination" refers to a patient's non-completion of a study whether by his or her own choice, or the investigator's decision, or due to discontinuation of the study by the Sponsor. Non-completion by a patient's choice is defined for those who withdraw consent via written notification by the patient, discontinue IP, and who decide not to participate with any follow-up assessments (visit or telephone). The primary reason for a patient withdrawing prematurely should be recorded on the eCRF. In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Investigator to keep the patient in the study. For patients who withdraw from the study, direct ascertainment of health status at the end of the study will be performed in compliance with local privacy laws/regulations/practices.

Patients who discontinue IP but agree to participate with any follow-up assessments (visit or telephone) will undergo the ET visit, and the 3-week Follow-up visit for discontinuation from an SAE, and be asked to follow the regularly scheduled study visit assessments thereafter.

The investigator must contact the Quintiles Medical Monitor promptly when deciding if a patient should be withdrawn, or if the study is stopped at their site by the IRB/IEC, or if the investigator elects to stop the study.

6.14 Patient Completion Criteria

For purposes of this study, patients who complete Visit 13 (Month 60) or are active participants when the specified number of patients with MACE endpoints is reached, and who have not discontinued IP early, will be defined as study completers.

6.15 Protocol Deviations

This study is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must notify the Medical Monitor by submitting a form that

documents the deviation for approval for the patient to continue participation in the study unless it is necessary to stop IP for safety/tolerability reasons.

Significant deviations that require review by the Medical Monitor include deviations from inclusion/exclusion criteria and use of prohibited medications during the study.

7 DETAILED DESCRIPTION OF ASSESSMENTS

7.1 Informed Consent

Written IC for the study will be obtained from each patient. For each country or region, a copy of the IC form, as approved by the respective IRB/IEC, will be given to all potentially eligible patients to read.

The protocol will be discussed in detail with each potentially eligible patient. The PI or qualified designee will explain all aspects of the study in lay language and answer all the patient's questions regarding the study. The PI or qualified designee will inform the patient as to the nature, aims, duration, potential hazards, and procedures to be performed during the study and that his or her medical records may be reviewed. The PI or qualified designee will also explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

The study patient must sign the IC form if he/she decides to participate in the study. No study procedures will be performed and IP will not be administered to any patient who has not signed the IC form.

Withdrawal of consent must be ascertained and documented by the Investigator who must consult with the Quintiles Medical Monitor and document the withdrawal of consent in the eCRF as well as in the IC form and medical records. The IC form should be resigned and dated by both the patient and the investigator, if possible. Such patients will always be asked about the reason(s) for withdrawal and the presence of any adverse events.

7.2 Medical History

A relevant medical history, will be obtained at Visit 1. Medical History will also be updated until randomization at Visit 2. Medical information necessary for the enrollment in the study can, if no written information is available, be based on the patients´ verbal confirmation.

7.3 Prior Medications and Concomitant Medications

Any therapy taken by the patient during the 4 weeks before Visit 1 or during screening and stopped before Visit 2 will be defined as a prior medication. Doses will only be recorded for statins, anticoagulants and diabetes medication. Any therapy started or

stopped by the patient after randomization (Visit 2) will be regarded as concomitant therapy.

Relevant prior and concomitant medications will be documented and must include the following information:

- Medication name
- Indication
- Treatment prior to study start
- Stop date or "Ongoing"
- Dose for statin, anticoagulants and diabetes medications only.

7.4 Prohibited Medications and Dietary Products

Use of the following medications or dietary products are prohibited during the study at any time after Visit 1:

The following 4 types of medications or dietary supplements are prohibited as they may have an effect on lipids that interferes with the ability to evaluate the results of the study:

- Bile acid sequestrants, fibrates, or niacin or its analogues (>250 mg/day)
- Use of any prescription medications containing EPA and/or DHA (e.g., Lovaza® or Vascepa®). Patients taking >1 capsule/day of omega-3 dietary supplements before Visit 1 DO NOT require a washout period but must agree to reduce the number of capsules per day to no more than 1 capsule of 1 g promptly after signing the informed consent. No new omega-3 supplements are permitted following initiation of screening procedures at Visit 1.
- Prescription or OTC weight loss drugs such as phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat (Xenical® prescription; Alli™ OTC), sibutramine, lorcaserin, topiramate+phentermine (Qsymia®), bupropion+naltrexone , and bupropion+zonisamide
- Chronic use of oral corticosteroids is prohibited (acute use for inflammation for example from poison ivy, or intranasal or inhaled steroids for allergies/asthma, or intraarticular injections is allowed)

The following 2 types of prohibited medications are related to the background statin treatment and are prohibited as they are known to have a potential for side effects or a potential for interactions with statins:

- Specific instructions for simvastatin: The dose should always be lower than Simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg. Patients taking verapamil or diltiazem should not exceed 10 mg/day simvastatin. Patients taking amiodarone, amlodipine or ranolazine should not exceed 20 mg/day simvastatin. All statins should always be prescribed in compliance with the local product label/prescribing information, including dose adjustments if drugs potentially interacting with the statin need to be prescribed.

- Oral erythromycin, telithromycin, clarithromycin, cyclosporine, itraconazole, ketoconazole, protease inhibitors, or nefazodone are examples of drugs that should generally be avoided during the study. If such treatment is clinically important the statin should be stopped, or the doses of statins should be adjusted, according to local prescribing information.

If a patient begins taking a prohibited medication or dietary product, the Medical Monitor should be notified of the deviation. Approval of certain medications or dietary products may generally be considered if the exposure was brief. Prohibited medications started in violation of the protocol (for example, those instituted by the patient's general practitioner) should ideally be stopped, but may be continued if the concomitant medication treatment in addition to study drug will not put the patient at risk. If a prohibited medication is to be continued, but the concomitant treatment with study drug is judged to infer risk to the patient, the study drug must be stopped. These decisions will be left at the discretion of the investigator but should be communicated to the Medical Monitor as indicated above.

Patients who need to discontinue IP should always be asked to continue the regular study visits after the scheduled ET visit.

7.5 Permitted Medications

A statin adjustment period(s) will be permitted after Visit 1 under the following circumstances:

- Patients who are on simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg at Visit 1 (see Section 7.4 for all restricted simvastatin dosing) an adjustment must be made to a lower dose of simvastatin, or an alternative statin in order to continue in

the study. If patients are taking simvastatin 20-40 mg/day and a coumarin anticoagulant (e.g. warfarin) the International Normalized Ratio (INR) should be appropriately monitored

- Patients who require a statin/ezetimibe adjustment at Visit 1 to achieve LDL-C criteria, will be permitted to return 4-6 weeks later at Visit 1a to qualify. If the LDL-C criteria are not met, another repeat visit will be scheduled for Visit 1b as needed. If the lab criteria are not met by Visit 1b, the patient will be screen failed.

Note: if ezetimibe is added to warfarin, a coumarin anticoagulant, the International Normalized Ratio (INR) should be appropriately monitored.

Every attempt should be made to maintain LDL-C levels at National Guidelines goals (e.g. NCEP goals1), at a minimum achieving LDL-C below 100 mg/dL (2.59 mmol/L) by adjusting statin dose to the maximum tolerated dose or combination therapy with ezetimibe. However, if LDL-C is ≥100 mg/dL and the patient is on a high intensity statin according to the 2013 ACC/AHA guidelines (i.e. atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) or on the maximum tolerated moderate or low-intensity statin dose (with or without ezetimibe coadministration), then the patient may be eligible for randomization. The maximum tolerated dosage of a statin is defined as the maximum approved dose per local label or the maximal dose that the patient can tolerate without unacceptable adverse effects such as muscle pain or elevations in liver enzymes or CK as determined by the investigator to be clinically relevant and due to statin therapy. Statin dose adjustments during the study can be made at the discretion of the investigator, if needed for safety reasons. If judged by the investigator to be necessary, the protocol allows for unlimited statin interruptions.

Acute use of inhaled or intranasal corticosteroids (such as products commonly used for asthma or seasonal allergies) is permitted. Topical antifungals, corticosteroids, and limited use of oral or intra-articular corticosteroids are permitted.

Stable use (≥4 weeks prior to Visit 1) of estrogens, tamoxifen, progestins or selective estrogen receptor modulator is allowed. All oral, patch, etc. hormonal or contraceptives are allowed as long as dose and type are stable for 3 months prior to screening. Topical estrogens for local vaginal symptoms, and daily use of testosterone patches will be allowed.

Patients who are clinically euthyroid, on stable thyroid replacement therapy for 2 months prior to screening will be allowed adjustment during the study.

7.6 Eligibility Review

Eligibility criteria are reviewed at each screening visit and the randomization visit and the patient must meet all of the inclusion and none of the exclusion criteria prior to randomization. If lipid laboratory values are abnormal and are reasonably expected to fall within the allowable range upon repeat testing, the test may be repeated at the additional screening visits 1a and 1b. All repeat laboratory testing will be performed by the central laboratory.

Screen Failure: A screen failure is defined as a patient who has consented but who has not been randomized.

7.7 Clinical Assessments

Height (at Visit 1 only). Weight and waist circumference will be measured at Visit 1, 5, 7, 9, 11, 13. Resting blood pressure and heart rate will be measured at all clinic visits. Three blood pressure and heart rate measurements 3 minutes apart will be taken after at least 3 minutes of seated rest. The first measurement will be ignored. The average of the last 2 measurements will be recorded for both blood pressure and heart rate.

7.8 Physical Examination

A physical examination consisting of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems will be performed at Visit 1 and Visits 5 as well as on Visit 13/EOT/ET.

For further assessment of any identified potential or confirmed AE, a physical examination should be carried out if clinically appropriate.

Any clinically significant finding observed up to and including Visit 2 will be considered Medical History. Any new or worsened clinically significant finding observed after Visit 2 through Visit 13/EOT/ET will be considered an adverse event and recorded in the source documents. Findings associated with a change in dose or discontinuation of IP should be reported in the eCRF.

7.9 Electrocardiogram

A 12-lead ECG will be performed after patient has been supine at rest for at least 5 minutes at Visit 2. The ECG will be read by the investigator at each clinical site. Any clinically significant finding observed at Visit 2 will be included in the Medical History.

7.10 Diet

At the first clinic visit, patients will receive dietary counseling regarding the NCEP TLC or equivalent diet at the discretion of the investigator and be willing to adhere to during the treatment period. (see Appendix A for details).

A weight maintenance version of the TLC or equivalent diet will be employed.

7.11 Safety Assessments – Adverse Events

Information on SAEs, AE criteria in accordance with Section 9.1, and adverse events leading to a change of IP dose or interruption of IP will be collected at each clinic visit and at each well-being telephone call. Temporary IP interruption of 7 days or more will be recorded in the eCRF. A DMC will review safety data periodically and may recommend stopping the study for safety concerns at any time. At each DMC meeting, the committee will review all individual cases of LDL-C increases, AST/ALT increases or other increases in liver-related chemistries, new onset diabetes mellitus, or bleeding related events, in addition to other safety and laboratory data (i.e. fasting glucose, hemoglobin A_{1c} and hematocrit) refer to Section 9.2 for details on selected adverse event collection. For this study, it will be assumed that all undetermined cases of bleeding are included in the hemorrhagic category since use of other omega-3 agents has been associated with an increase in bleeding risk. See Appendices B and C for details regarding “increases in liver related chemistries” and hemorrhagic stroke. A sensitivity analysis will be performed in which the undetermined strokes are included with the ischemic stroke category. See Section 9.3 for details about bleeding definitions.

7.12 Laboratory Assessments and Procedures

An approximate maximum of 160 mL of whole blood will be collected from each patient throughout the study.

7.12.1 Screening Laboratory Assessments

For the screening period, a maximum of 5.4 mL of blood will be collected to assess lipids, chemistry, hs-CRP and TSH. Two mL of blood will be collected at Visit 1 for assessment Hb A_{1c}.

7.12.2 Efficacy Laboratory Assessments

For efficacy laboratory testing of fasting lipids (TG, TC, calculated LDL-C [in patients with triglycerides > 400mg/dl LDL-C will be directly measured], HDL-C, calculated

non-HDL-C, VLDL-C and TC: HDL cholesterol ratio) 1-mL blood samples are collected at Visits 2, 5, 7, 9, 11 and 13/EOT/ET. Three 1-mL blood samples will be collected for measurement of Apo C-III, and three 2-mL samples will be collected for Apo B-100 at Visits 2, 5 and 13/EOT/ET. A 6 mL blood sample for plasma and RBC fatty acids (EPA, DHA, DPA and AA) will be collected at each Visit 2, 5 and ET for early termination before Visit 5.

Starting at Visit 2, the lipid panel, special lipid markers, and fatty acids are blinded. All fasting blood samples will be drawn after the recommended 9-14 hour fast.

7.12.3 Safety Laboratory Assessments

Safety laboratory testing on all patients in the study, on IP or not, includes serum chemistry (creatine kinase, ALT, AST, total and direct bilirubin, and creatinine) at Visits 2 and 5; approximately 2 mL of blood will be collected at each visit. At Visits 7, 9, 11 and 13/EOT/ET, only ALT, AST and total bilirubin are measured; , approximately 2 mL of blood will be collected at each visit. The eGFR will be calculated only at Visits 1 and 5. Two mL of blood will be collected to measure fasting plasma glucose at Visits 2, 5, 7, 9, 11 and 13/EOT/ET. Hb A_{1c} is measured at Visits 2, 5, 7, 9, 11 and 13/EOT/ET; approximately 2 mL of blood will be collected at each visit. Hematocrit is evaluated at Visits 5, 7, 9, 11 and 13/EOT/ET; approximately 2 mL of blood will be collected at each visit. Assessment of hs-CRP at Visits 2 and 13/EOT/ET will be sampled from the chemistry blood draws.

Urine pregnancy tests will be conducted only on women of childbearing potential. A woman is considered of childbearing potential if she is not surgically sterile or is less than 1 year since last menstrual period. Urine pregnancy tests will be conducted by the site.

7.12.4 Collection, Shipment, and Retention of Laboratory Samples

7.12.4.1 Safety and Efficacy Analyses

All safety and efficacy laboratory analyses (except urine pregnancy tests) will be performed by a central laboratory. The central laboratory (Quintiles Laboratory) will provide all collection materials and instructions for sample collection, packaging, and shipment

7.12.5 Exploratory CV Risk Markers (on a subset of patients located in the US)

The subject's consent to the use of donated biological samples is mandatory (included in the Inform Consent for the main trial). Blood samples will be collected at baseline (Visit 2) and 12 weks (Visit 3) for future analyses of lipid fractions, inflamatary markers and other CV markers that may be identified during the course of the study. The samples will be collected on a subset of approximately 2000 patients located in the US. Two tubes of blood will be collected at baseline and 1 tube at 12 weeks after randomization. Plasma and serum will be extracted by the central laboratory, aliquoted into 250-300 µL samples and stored at -80 ºC until analysis is performed. The samples will be transferred from Quintiles Laboratory to the AstraZeneca BioBank.

7.12.5.1 Storage, re-use and destruction of exploratory CV risk marker samples (on a subset of patients located in the US).

The CV risk marker samples will be shipped from the cental lab to the AstraZeneca BioBank in United Kingdom. Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in scientific report or publication.

7.12.5.2. Labelling and shipment of exploratory CV risk marker samples (on a subset of patients located in the US)

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual.

7.12.5.3 Chain of custody of exploratory CV risk marker samples (on a subset of patients located in the US)

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment..

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca Biobank during the entire life cycle.

7.12.5.4 Withdrawal of Informed Consent for donated exploratory CV risk marker samples (on a subset of patients located in the US)

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the subject may continue in the study.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

7.12.6 Pharmacogenetics (on a subset of patients located in the US)

Genetic samples will be collected for future analysis on approximately 2000 patients in the US, see Appendix F for details.

8 STATISTICAL METHODS

8.1 Sample Size Determination

This event-driven study is designed to have 90% power to detect a 15% reduction in risk of primary efficacy MACE rate (hazard ratio=0.85) for patients treated with Epanova compared to placebo (corn oil) on top of a background of standard care (statin therapy). With an overall type I error rate (alpha level) of 5%, a total of 1,600 primary efficacy events are required to achieve approximately 90% power to detect the difference between Epanova and placebo (corn oil) (a constant hazard ratio of 0.85). The estimate of 4% annual event rate for control is based on previous studies investigating MACE, considering populations with documented cardiovascular disease and populations with cardiovascular risk factors only. **The enrollment of patients with documented CVD will be ≥50% of all randomized patients; the enrollment of patients with risk factors only (primary prevention) will be less than 50% of all randomized patients; these proportions will be monitored and controlled via IWRS.**

Assuming a total study duration of 4.5 years and a placebo (corn oil) event rate of approximately 4% per year, a sample size of 13,000 patients (6,500 per treatment group) is required.

8.2 Analysis Populations

Intent-to-Treat Population

The intent-to-treat (ITT) population will comprise all patients who were randomized. If patients stop taking IP, patients should continue to be followed for the study duration. A patient will be considered randomized as soon as a treatment number is assigned by an IWRS. Patients will be summarized by their randomized treatment. All data collected throughout the duration of the study will be analyzed based on randomized treatment.

Safety Population

All randomized patients who received at least 1 dose of IP will be included in the safety population.

8.3 Randomization

An IWRS will be implemented to obtain a balanced allocation to each treatment group.

8.4 Statistical Analyses

A Statistical Analysis Plan (SAP) will describe in detail the statistical analyses for the study. If circumstances arise during the study that make these analyses inappropriate or if improved methods become available, the SAP may be revised. Any revisions (both alternative and additional methods) to the SAP, and reasons for such revisions, will only be made while study is still blinded and will be described in the final Clinical Study Report (CSR). In general, descriptive statistics, unless otherwise noted, will include the number of patients (n), mean, standard deviation (SD), median, minimum value, and maximum value. Median will be presented together with Q1 and Q3. Percentages will be calculated using the number of patients within each treatment. Unless otherwise stated, all summary tables will present descriptive statistics and/or frequency by visit for each treatment group.

8.4.1 Primary Outcome Analysis

The primary outcome measure is the time to first occurrence (TTE; time-to-event) of any component of the composite of MACE (cardiovascular death, non-fatal MI, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina). The primary outcome will be based on the ITT population using adjudicated events.

A Cox proportional hazards model for time to first MACE event will be assessed for comparing the two treatment groups, with treatment arm, established CV disease at baseline, multiple risk factors without established CV disease at baseline and geographic region as covariates (Appendix E). Event rates will be expressed as the percentage of events per follow-up year, taking into account censoring of follow-up data.

For each TTE endpoint, a patient will be censored no later than the date of the last available information on that patient, from any source captured in the database. The specific rule(s) for each individual TTE will be explicitly specified in the SAP. Kaplan–Meier estimates will be used to quantify event rates during the course of the trial.

The assumption for proportional hazards for the treatment groups will be assessed:

1. visually by using log-cumulative hazard plots. The effects of any departures from the proportional hazards will be discussed as part of the presentation of results of the analyses.

2. Treatment-by-time interaction, defined as time-varying covariate, will be tested. In the event of a statistically meaningful interaction, an additional analysis will be carried out with the interaction term in the model
3. Schönfeld Residual will be plotted for each covariate versus log(time) and for treatment group versus observation

Sensitivity analyses of the primary efficacy endpoint will also be performed to assess the robustness of the primary results. The sensitivity analyses will be performed for only on-treatment MACE events in the ITT population.

Further details will be provided in the SAP. All comparisons described above will use a Cox proportional hazards model to estimate the relative effect of Epanova versus placebo (corn oil). The treatment effect will be assessed at a nominal 5% significance level. Analysis results will be presented as hazard ratios, 95% confidence intervals and p-value.

8.4.2 Secondary Outcomes Analyses

The secondary outcomes measures will be analyzed using the same model as outlined above for the primary outcomes measure, on the ITT population. The respective censoring rules will be defined explicitly in the SAP. The evaluation will be carried out in a hierarchical fashion. Specifically, if the primary endpoint objective is met(2-sided p-value<0.05), the secondary outcomes will be evaluated hierarchically at an overall alpha of 0.05 for each comparison, sequentially. Once a key secondary endpoint is not met at alpha 0.05, all subsequent comparisons will be considered exploratory.

The hierarchy for sequential testing the following key secondary outcome measures will be defined as:

KEY SECONDARY (tested at α=0,05, conditional on success of the primary)

1. The composite measure of CV events that include the first occurrence of cadiovascular death, non-fatal MI and non-fatal stroke

2.The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), non-fatal MI, emergent/elective coronary revascularization, or hospitalization for unstable angina.

3.Time to CV Death

Other SECONDARY (evaluated at α=0,05; NOT part of the hierarchical testing sequence; that is, exploratory)

Time to:

1. Emergent/elective coronary revascularization
2. Hospitalization for unstable angina
3. Fatal or non-fatal MI
4. Non-fatal MI
5. Fatal or non fatal stroke
6. Non-fatal stroke
7. All-cause death

Further details (including individual censoring rules) will be provided in the SAP.

8.4.3 Tertiary Outcome Analysis

Tertiary outcome measures will include:

- The first occurrence of new onset AF.
- The composite measure of total thrombotic events that include the first occurrence of documented coronary stent thrombosis, any systemic thromboembolism including arterial stent thrombosis (except coronary) or venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) and/or pulmonary embolism (PE).
- First occurrence of a heart failure event.

The tertiary outcome measures will be analyzed using methods similar to those for the primary and secondary analyses. The analysis of the tertiary outcomes will be considered observational only. Further details will be provided in the SAP.

8.4.4 Biomarkers of Efficacy

The analysis of biomarkers (e.g. lipids or other biomarkers) will be based on the differences in change from baseline (Month 0) to Month 12 (primary), between placebo (corn oil) and Epanova treatments. In addition, biomarker data after Month 12, will be presented in a descriptive manner. The biomarker variables include:

- non-HDL-C, TG and HDL-C;

- TC, VLDL cholesterol, TC:HDL-C ratio and calculated LDL-C (in patients with triglycerides > 400mg/dl LDL-C will be directly measured);
- Apo B-100 and Apo C-III;
- EPA, DHA, DPA and AA in plasma and RBC; and
- hs-CRP

A mixed model will be used for each biomarker endpoint with patient fitted as a random effect and terms included for treatment, visit, baseline value, treatment by visit and baseline by visit interactions using log-transformations where appropriate. A point estimate, 95% confidence interval and p-value for the mean difference between Epanova and placebo (corn oil) patients from Month 0 to Month 12 (primary) will be produced based on this repeated measures model. Further details in the SAP will specify how each biomarker variable will be analyzed, i.e. whether as mean change or as percent change.

The CEC will adjudicate all components of the primary and secondary endpoints as well as the tertiary heart failure events endpoint.

8.4.5 Evaluation of Efficacy and Safety

The DMC will review data periodically throughout the study and will have the ability to recommend stopping the study for safety at any time. Details will be defined in the DMC charter.

8.4.6 Safety Analyses

Safety analyses will include, where appropriate, descriptive statistics, counts and percentages.

Adverse Events

Adverse experiences will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term for each treatment group. Only AEs that are considered serious, lead to discontinuation or result in a dose modification, new onset diabetes mellitus, TIA, potential Hy´s Law (PHL) cases or bleeding-related events will be captured starting after randomization through the final visit (Visit 13/ EOT/ET (see Section 9).

SAEs will be recorded at all visits for the patients who prematurely discontinue IP. Non-serious AEs will be collected until the final visit but not more than 30 days after last dose of IP.

Adverse events and suspected adverse reactions will be summarized by presenting:

- the number and percentage of patients experiencing any AE
- the number and percentage of patients experiencing any AE by SOC
- the number and percentage of patients experiencing any SAE
- the number and percentage of patients experiencing any AE associated with study discontinuation.

8.5 Interim analyses

Accrual of a total of 1600 MACE (primary efficacy) events are required to maintain a power of at least 90% in this study (See section 0). The study is designed to continue until this number of events is observed. However, 2 interim analyses of the primary endpoint are planned and the study may be recommended for termination by the DMC early if the stopping rule for superiority or futility is met. The Executive Steering Committee and the Sponsor may choose to enforce the DMC´s recommendation.

A blinded independent statistician will carry out all analyses in support of the "open" session of DMC meetings. For more information about the DMC (see Section 0).

A group sequential design will be used to preserve the overall type 1 error probability of 0.05.

Planned interim analyses on MACE will be performed around the time when 50% (800) of MACEs have occurred and again when 75% (1200) of MACEs have occurred. The final analysis is scheduled when at least 1600 MACEs have occurred. The group sequential superiority boundaries abs(z-score) for the 1st and 2nd interim analyses are 3.719. Boundaries abs(z-score) for futility at the 1st and 2nd interim look are 0.3085 and 1.2375, respectively. The significance threshold (z-score) for the final analysis is 1.9602, which correspond to a nominal p-value if 0.025. Confidence interval for the main Primary analysis on MACE will be constructed at the 95% level. All thresholds are constructed accounting for DMC recommendations for stopping for efficacy to be "non-binding".

Superiority boundaries are defined based on Haybittle-Peto rule. Specifically, this uses a 1-sided p-value threshold held constant at 0.0001 for each look prior to final. The final comparison will be carried out at a 2-sided alpha of 0.05. Futility boundaries are based on Lan-DeMets alpha spending function that approximates an O'Brien-Fleming boundary in the setting of unequal analysis times. More details on the thresholds for stopping are

displayed in Table 8-1. Parallel thresholds in the hazard-ratio and the p-value scale are also presented.

In the event that this trial is stopped for overwhelming benefit at either of the two interim looks then all hierarchical Secondary tests will be carried out at α=0.0001.

Table 8-1. INTERIM ANALYSIS PLAN

Interim analysis	Number of Events (%)	Approximate Time from FPFV (months)[a]	Boundaries (z-scale)[b]	
			Superiority	Futility
1	800 (50%)	32	$abs(z_{obs}) > 3{,}719$	$abs(z_{obs}) < 0.3085$
			$HR < 0{,}7682$	$HR > 0{,}9785$
			$p < 0{,}0002$[c]	$p > 0{,}7578$[c]
2	1200 (75%)	43	$abs(z_{obs}) > 3{,}719$	$abs(z_{obs}) < 1{,}2375$
			$HR < 0{,}8063$	$HR > 0{,}9312$
			$p < 0{,}0002$[c]	$p > 0{,}216$[c]
Final	1600 (100%)	54	$abs(z_{obs}) > 1{,}9602$	
			$HR < 0{,}9064$	
			$p < 0{,}05$	

FPFV = First Patient First Visit

[a] Based on simulations of 10000 trials

[b] Non-binding boundaries

[c] 2-sided

8.6 Missing Values

Extensive efforts will be made to collect data from patients after premature discontinuation of study treatment, if agreed to by the patient and in compliance with local privacy laws/regulations/practices, to avoid missing MACE status as much as possible. Patients who are not reporting any event in the primary composite efficacy endpoint will be censored at the time of study closure, the time of death from non-cardiovascular causes, or at the time point after which the occurrence of any components of the primary endpoint could not be assessed. Since the absence of laboratory measurements for each patient may not be "completely at random", missing laboratory data will be analyzed using approaches assuming Missing At Random (MAR) two-step procedure[80]. Further details will be provided in the SAP.

8.7 Data Monitoring Committee

The DMC is responsible for monitoring the safety of the study participants, ensuring that the study is being conducted with the highest scientific and ethical standards and making appropriate recommendations based on the data seen. The DMC may recommend at any time during the conduct of the STRENGTH trial, modification of the protocol or discontinuation of the study for safety reasons. In addition, should outstanding benefit of the investigational drug compared with placebo be demonstrated during the STRENGTH trial, the DMC may recommend that consideration be given to stopping the study while taking into account the need to accumulate further safety data to allow adequate assessment of benefit- risk.

9 ADVERSE EVENT MONITORING

9.1 Definitions

An AE is defined as any untoward medical occurrence associated with use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition (including the physical examination), or abnormal results of diagnostic procedures (including laboratory test abnormalities).

Events should be considered AEs if they:

- result in discontinuation from the study,
- require treatment or any other therapeutic intervention,
- require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality),
- are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact

In this study, only AEs that are considered serious, lead to discontinuation or result in a dose modification, overdose, new onset diabetes mellitus, TIA, PHL cases or bleeding-related events will be captured starting after randomization through the final visit.

For further assessment of any identified potential or confirmed AE, a physical examination should be carried out if clinically appropriate.

Clinically Significant Laboratory Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. For each abnormal result, the investigator needs to ascertain whether the abnormality presents a clinically significant change from baseline. If the change is due to the expected course of the patient's underlying disease, it is not considered an adverse event unless the abnormality is more severe than expected. A laboratory test may be confirmed by repeat testing or other diagnostic tests before being considered an adverse event. If the laboratory abnormality is a significant change from baseline for the patient, then it should be considered an adverse event. See Appendix B (Actions Required in Cases of Combined Increase of

Aminotransferase and Total Bilirubin Hy´s Law) which provides criteria for determining potential serious hepatotoxicity of the IP according to Hy's Law.

At each DMC meeting, the committee will review all individual cases of LDL-C increases, AST/ALT increases or other increases in liver-related chemistries, new onset diabetes mellitus type II, or bleeding related events, in addition to other safety and laboratory data (i.e. fasting glucose, hemoglobin A_{1c} and hematocrit) refer to Section 9.2 for details on selected adverse event collection.

An Adverse Event is not:

- A surgical procedure
- A situation where an untoward event did not occur, (e.g. a social hospitalization)
- The disease being studied, unless progression is more severe than anticipated
- Lack of efficacy
- Baseline conditions that have not worsened in severity or frequency
- Clinically significant abnormal laboratory findings or test results related to the disease being studied (unless more severe than expected)
- A study endpoint described in Section 9.8

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to believe the drug caused the event. Suspected adverse drug reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

9.2 Procedures

An untoward event that occurs after screening (Visit 1) and before the first dose of IP at Visit 2 will be recorded as an update to the medical history. Some events may make the patient ineligible for randomization. Unanticipated events, including those associated with withdrawal from prior medications, should be reported to the IRB/IEC, according to its requirements.

Patients will be questioned at every visit and will receive well-being telephone calls after the randomization until the last visit regarding the occurrence and nature of any AEs.

A description of the event or diagnosis including dates, severity, relationship to the IP, action taken and outcome, and seriousness must be reported on the AE eCRF for each adverse event recorded in the patient's chart.

For the STRENGTH trial, selective collection of AEs will be conducted in accordance with FDA Draft Guidance dated February 2012 "Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post approval Clinical Investigations" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291158.pdf). Only AEs that are considered serious, lead to discontinuation or result in a dose modification, new onset diabetes mellitus, TIA, or bleeding-related events will be captured starting after randomization through the final visit. The rationale for selective AE collection is based on the extensive safety information of Epanova already provided in 10 clinical trials, and the well-known safety profile of omega-3 products (see Section 1.2 Clinical Safety of Epanova) .

SAEs will be recorded at all visits for the patients who prematurely discontinue IP. Non-serious AEs will be collected until the final visit but not more than 30 days after last dose of IP.

9.3 Bleeding definitions

The investigator will report any blood loss in the eCRF and the bleedings will in the Clinical Study Report be classified according to the TIMI non- CABG bleeding definitions [81] shown below:

Major

-Any intracranial bleeding (excluding microhemorrhages)

-Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dL

-Fatal bleeding (bleeding that directly results in death within 7 days)

Minor

-Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL

Requiring medical attention

-Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above

-Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)

-Leading to or prolonging hospitalization

-Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Minimal

-Any overt bleeding event that does not meet the criteria above.

9.4 Severity

Adverse events are first graded according to seriousness and then severity. The seriousness of an event is determined by the regulatory criteria in Section 9.8.

The investigator will evaluate the severity of each AE. Adverse events will be graded as:

Mild: Awareness of symptoms but easily tolerated

Moderate: Discomfort enough to interfere with but not prevent daily activity

Severe: Unable to perform usual activity

9.5 Relationship

The investigator will judge the likelihood that the AE was related to the IP according to the following criteria:

Not related: There is no temporal or causal relationship to the IP.

Suspected: There is a reasonable possibility of a causal relationship to the IP.

Related: The adverse event was caused by the IP.

9.6 Action Taken and Outcome

The Action Taken with IP for every AE will be reported as either "Dose Not Changed", "Dose Reduced", "Dose Interrupted", or "Dose Withdrawn". The Outcome of each AE will be entered as either: Recovered/Resolved, Recovered/Resolved with Sequelae, Not Recovered/Not Resolved, Fatal, or Unknown.

9.7 Adverse Event Follow-up

Investigators should follow AEs until the event has resolved, the condition has stabilized, is well characterized, or referred to appropriate medical management, whichever comes first. Events and follow-up information occurring after the last visit should be recorded in the source documentation.

9.8 Serious Adverse Events

An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death (note that death is the outcome of an SAE and the cause of death should be listed as the AE)
- Life-threatening event
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect
- Other important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. DILI should be reported as an SAE, if laboratory abnormalities meet the criteria in Appendix B (Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin Hy´s Law).

Hospitalization for elective surgery for a prior condition that did not worsen or hospitalization for social reasons will not be treated as serious.

Events that are related to the primary efficacy endpoints or outcomes will not be reported as SAEs and will not be subject to expedited reporting regardless of expectedness or causality before termination of the study. This includes all cardiovascular deaths, MI, non-ischemic stroke, unstable angina or event associated with emergent/elective coronary revascularization procedure. Test results associated with these events will not be reportable as SAEs. These events will be adjudicated by an Endpoint Committee and safety will be evaluated by the DMC. If the committees find that an increased frequency of an endpoint is a suspected serious adverse reaction, then these events will become reportable by the Sponsor.

9.8.1 Serious Adverse Event Reporting

Any SAE which occurs after randomization and until Visit 13/EOT/ET must be reported to the Quintiles Medical Monitor whether or not it is judged related to the IP. SAEs will be recorded at all visits also for patients who prematurely discontinue IP.

To report the SAE, complete the SAE form electronically in the Electronic Data Capture (EDC) system for the study. When the form is completed, CRO personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the internet, send an email to the CRO @ Redacted, or call the CRO SAE hotline (toll free phone and fax number will be listed in the safety manual), and fax the completed SAE report form to the designated CRO fax number within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available. CRO personnel are available for SAE reporting on a 24-hour basis. Reports are reviewed during normal U.S.business hours.

The investigator will provide, at a minimum, the protocol number, patient's initials, patient number, date of the SAE, SAE term and relationship to IP. Information identifying the patient must be obliterated before transmitting to the CRO.

The PI will notify the IRB or IEC of the SAE according to its requirements. The CRO may also notify the IRB/IEC on behalf of investigators, where permitted. An initial report followed promptly by a complete report will be forwarded to the IRB, or in accordance with the IRB policy.

9.8.2 Serious Adverse Event Follow-Up

The patient will be observed and monitored carefully until

- the event resolves, or
- the event/condition has stabilized (e.g., in the case of persistent impairment), or
- the event returns to baseline, if a baseline value is available.

The investigator and Medical Monitor will determine if additional follow-up is required. Follow-up information relating to an SAE must be submitted to the regional designee as soon as additional data related to the event are available. All efforts must be taken to obtain follow-up information promptly.

Follow-up information may consist of:

- A hospital discharge summary for patients who are hospitalized. If possible, the discharge summary should be obtained when it becomes available.
- A copy of the autopsy report, if a death occurs and an autopsy is performed, should be obtained if possible when it becomes available.

Any SAEs that are ongoing at Visit 13 (Month 60) or ET should be followed as described above and a visit should be scheduled 3 weeks after Visit 13 to assess the SAE. Data after the 3-weeks FU Visit should be recorded on the source documents and submitted to the CRO on a SAE report form. For ongoing SAEs, the investigator must submit follow-up SAE reports to the regional designee regarding the patient's subsequent course until the case is closed.

9.9 Reporting of Serious Adverse Events that are also Endpoints in the Study

Primary efficacy endpoints in the study will not be reported to health authorities as SAEs to avoid unnecessary unblinding of efficacy endpoints that are also SAEs. Events identified as suspected endpoints will be reported on separate event form in the eCRF to support central adjudication. Clinical data reported as AEs/SAEs will also be reviewed for possible endpoint events. The initial notification of a suspected efficacy endpoint should be sent within the same time frames as defined for SAEs (see above). Selected events (leading to discontinuation or resulting in a dose modification, new onset diabetes mellitus, TIA, PHL cases or bleeding-related events) will be reported as AE/SAEs.

In addition to the normal monitoring of the study, a DMC will review all endpoint data and selected AEs/SAEs. Information will be sent to the Executive Committee and regulatory authorities if the DMC expresses safety concerns that suggest that study conduct should be amended.

9.10 Pregnancy

Any pregnancy occurring during this study will be reported within 24 hours of notification of the investigator. The investigator will promptly notify the Medical Monitor about the pregnancy and complete a pregnancy report form. The pregnancy report form will be faxed to the Medical Monitor via the SAE fax number. If a patient becomes pregnant during the study, she must discontinue taking IP, but will continue to be followed in the protocol. Her obstetrician should be made aware of her study participation. The investigator should request information from the patient and her obstetrician about the outcome of the pregnancy, including any possible fetal abnormalities and congenital defects. If a congenital abnormality is reported, then it should be recorded in the source documents and reported to the Medical Monitor as a Serious Adverse Event.

9.11 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of investigational product that is considered both excessive and medically important. Once an investigator decides that a particular occurrence is an overdose, it must be reported as a Serious Adverse Event. If an overdose is suspected, monitoring of vital functions as well as treatment as appropriate should be performed.

In this study, a dose of more than 8 g of Epanova® (>8 capsules) during one day should be considered as an overdose.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

10 INVESTIGATOR OBLIGATIONS

10.1 Ethical and Regulatory Considerations

This study will be conducted in accordance with Good Clinical Practice (GCP) Guidelines, 21 CFR Parts 11, 50 Subparts A and B, 54, 56, and International Conference on Harmonisation (ICH) GCP E6(R1).

10.2 Institutional Review Board/Independent Ethics Committee

The PI will ensure that AstraZeneca or its representative approves any changes to the IC template prior to submission to the IRB/IEC.

Should changes to the IC form become necessary during the study, the PI will ensure that the changes are approved by AstraZeneca or its representative prior to submission to the IRB/ IEC. Should changes to the study protocol become necessary, the PI will ensure that the protocol amendment is approved by the IRB/IEC prior to implementation. The PI will ensure that protocol administrative changes have been reviewed by the IRB/IEC.

Prior to submission to the IRB/IEC, the PI will ensure that AstraZeneca or its representative approves the IC form. The PI will ensure that an appropriately constituted IRB/ IEC, in compliance with the requirements of 21 CFR 56 in the US or ICH GCP E6 elsewhere, reviews and approves the clinical study and IC form. IRB/IEC approval must refer to the study by exact protocol title, number, and amendment number (if applicable), identify the documents reviewed, and state the date of review.

The PI will ensure that AstraZeneca or its representative is provided with a copy of the IRB/IEC approval documents and a copy of the IRB/IEC-approved IC form before the study is initiated.

AstraZeneca or its representative must be copied on all correspondence, including submission documentation, initiated by the site to the IRB/IEC during the course of the study. The PI will ensure copies of all correspondence from the IRB/IEC, including approvals and revised IC forms are provided to AstraZeneca or its representative.

10.3 Informed Consent

A properly executed, written IC, in compliance with 21 CFR Part 56 and Health Insurance Portability and Accountability Act (HIPAA) authorization (where required), will be obtained from each patient prior to enrollment and the initiation of screening evaluations required by this protocol. A copy of the IC form planned for use will be

reviewed by AstraZeneca or its representative for acceptability and submitted by or on behalf of the investigator, together with the protocol, to the IRB/IEC for review and approval prior to the start of the study. Consent forms will be written in language fully comprehensible to the prospective patient.

All revisions of the protocol must be reflected in the IC form, if applicable, and reviewed by the IRB/IEC. Patients must be made aware of those applicable changes in the protocol and must consent to participate in the revised protocol.

10.4 Patient Confidentiality

All communications, reports, and patient samples will be identified by site number, and a coded number and/or initials to maintain patient confidentiality. All records will be kept confidential to the extent permitted by law. If a waiver or authorization separate from the statement in the IC is required for permitting access to a patient's medical records (e.g. HIPAA), the investigator will obtain such authorization prior to enrolling a patient in the study. The PI should keep a separate log of patients, codes, names, and addresses. Documents which identify the patient by name (for example, the IC form) should be kept in strict confidence.

AstraZeneca and its business associates agree to keep all patient information confidential. Only coded, blinded data will be released. Data resulting from analyses will be entered into a database that is not accessible to the public. Patient data will be identified only by the patient screen number, randomization number and initials, and not by any other annotation or identifying information.

AstraZeneca and its business associates will take every possible step to reduce the risk of releasing information to the public that would enable patients to be personally identified.

11 STUDY MONITORING

11.1 Clinical Monitoring

An initiation meeting will be conducted by the CRO or an approved representative. At this meeting the protocol, the procedure for completing the eCRFs, and pertinent aspects of the eCRFs will be reviewed with the PI and all study staff.

Monitoring visits will be conducted during the study. The PI will make a reasonable amount of time available to the CRA on reasonable notice to assist with monitoring.

At each visit, the CRA will review the eCRFs and source documents to ensure that all items have been completed and that the data provided are accurate and obtained in the manner specified in the monitoring plan.

11.2 Auditing Procedures

In addition to the monitoring visits outlined above, an investigational site may undergo a quality assurance audit. The CRO, its authorized representative, AstraZeneca representatives or a regulatory agency such as the FDA or European Medicines Agency (EMA) may conduct the audit. If a regulatory agency requests an audit of the study site, the investigator is required to inform the CRO (and/or AstraZeneca) immediately.

11.3 Executive Steering Committee

The Executive Steering Committee will have scientific responsibility for the study. They will review study conduct and progress, consider recommendations from the DMC, and resolve any other study related issues. The committee will also review all proposed ancillary studies and any proposed publications. Executive Steering committee members will remain blinded to the study data. The roles and responsibilities of the Committee will be documented in a Study Charter.

12 CHANGES TO THE PROTOCOL AND STUDY TERMINATION

12.1 Protocol Amendment and Administrative Change

All changes to the protocol must be documented by amendments, or administrative changes where applicable, and the amended protocol must be signed by AstraZeneca or its representative and the investigators. The amended protocol and a revised IC form, if necessary, will be submitted to the IRB/IEC for approval. If the protocol modifications affect the eCRFs, they will also be revised and provided to the site.

12.2 Termination of the Study

The Sponsor AstraZeneca reserves the right to terminate the study at any time. In terminating the study, AstraZeneca and the PI will ensure that adequate consideration is given to the protection of each patient's interest.

13 SOURCE DOCUMENTS, CASE REPORT FORMS AND RECORD RETENTION

13.1 Source Documents

The PI will complete and maintain source documents for each patient participating in the study. The source documents should contain all demographic and medical information, including laboratory data. The patient's source documents file should also indicate that the patient is participating in the clinical study, referencing the study number and the IP.

All information required by the protocol should be documented in the source records. An explanation must be given for any omissions. Each evaluation recorded will be performed at the time specified in the protocol.

13.2 Case Report Forms

The study will use EDC and all data will be recorded on eCRFs, which will be designed by the CRO. All information on the eCRFs must be traceable back to the source documents. All information must be entered on the eCRF and made available as soon as possible after the patient's visit, in order that the CRA may verify the validity and completeness of the data and permit prompt transmission of the data. The PI should review all eCRFs for completeness, accuracy, and legibility before the CRA reviews and collects the data.

13.3 Record Retention

The PI will maintain adequate records so that the conduct of the study can be fully documented and monitored. Copies of protocols, eCRFs or CD(s) with PDF files of all eCRFs, as well as the audit trial, test result originals, all IP accountability records, correspondence, patient IC forms, and any other documents relevant to the conduct of the study will be kept on file by the PI. Study documents will not be destroyed. For regulatory inspections, it will be necessary to have access to complete study patient records, provided that patient confidentiality is maintained.

Per the Clinical Development Agreement between AstraZeneca and its representative, investigators must retain patients' records for a period of 2 years after FDA approval or until written approval to destroy the documentation is provided by AstraZeneca. The documentation must be retained longer if so required by local law. Investigators must notify AstraZeneca and its representative, in writing, of changes in address, sales of

practices or site closures in order to make arrangements for the maintenance of study files.

14 FINAL REPORT/PUBLICATION STATEMENT

Any formal presentation or publication of data collected as a direct or indirect result of this study will be considered as a joint publication by the investigator(s) and AstraZeneca. In the case of multicenter studies, it is mandatory that the first publication be made based on the totality of data obtained from all centers, analyzed as stipulated in the protocol, and presented and interpreted as documented in the final CSR. The resulting publication will name PIs according to the policy of the chosen journal. Where it is not permitted for all PIs to be included as authors, the publication will acknowledge all PIs within the publication.

Individual investigators may publish data arising from their own patients only after publication of the main manuscript from this study. The PI will provide AstraZeneca with copies of written publications (including abstracts and posters) in advance of submission. This review is to permit AstraZeneca to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not inadvertently divulged (including patent protection), to allow adequate input or supplementary information that may not have been available to the PI, and to allow establishment of co-authorship.

Investigators participating in multicenter studies must agree not to engage in presentations based on data gathered individually or by a subgroup of centers before publication of the first main publication, unless this has been agreed otherwise by all other investigators and AstraZeneca. However, in the event that no publication of the overall results has been submitted after approval of the CSR, investigators may publish results of one or more center's patients to the same review as outlined above. AstraZeneca will circulate proposed multi-center publications to all PIs for review.

Data will be reviewed by all participating investigators prior to publication. AstraZeneca will review all definitive publications, such as manuscripts and book chapters, and abstracts.

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APPENDIX A: Therapeutic Lifestyle Changes Diet

The guidelines developed by the National Cholesterol Education Program recommend a multifaceted lifestyle approach to reduce the risk of coronary heart disease. (*NIH Publication 01-3670, http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm*).

The recommended ranges of intake for specific dietary components are listed in the Table below.

Nutrient Composition of the Therapeutic Lifestyle Changes Diet

Nutrient	Recommended Intake
Total Fat	25-35% of total calories
Saturated Fatty Acids	<7% of total calories
Monounsaturated Fatty Acids	Up to 20% of total calories
Polyunsaturated Fatty Acids	Up to 10% of total calories
Carbohydrates	50-60% of total calories
Fiber	20-30 grams per day
Protein	Approx. 15% of total calories
Cholesterol	<200 mg per day
Total Calories	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

The principles of the TLC diet or equivalent are as follows:

1. Start by choosing a target calorie level that best suits the patient's weight goals.
2. Focus on eating lots of fruits, vegetables, whole grains, low-fat or nonfat dairy products, fish, and skin-off poultry.
3. Cut saturated fat to less than 7 percent of daily calories, which means eating less high-fat dairy, such as butter, and eliminating fatty meats like salami.
4. Consume no more than 200 milligrams of dietary cholesterol a day-the amount in about 2 ounces of cheese.
5. Consider adding plant stanols or sterols and 10 to 25 grams of soluble fiber each day to further reduce LDL-C.

APPENDIX B: Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin Hy´s Law:

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Quintiles Medical Monitors, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to Quintiles Medical Monitor).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the Quintiles Medical Monitor
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Quintiles Medical Monitor
- Determine whether the patient meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform Quintiles Medical Monitor representative that the patient has not met PHL criteria. Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment
- Notify the Quintiles representative who will then inform Quintiles Medical Monitor.

The Quintiles Medical Monitor contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver eCRF Modules as information becomes available
- If at any time (in consultation with Quintiles Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of potential Hy's Law cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, Quintiles Medical Monitor contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI

caused by the IMP. The Sponsor Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow this study´s standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to this study´s standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the Quintiles representative, who will inform the Quintiles Medical Monitor, then follow the subsequent process described in Section "Potential Hy's Law Criteria met" of this Appendix.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX C: Standardized Definitions for Endpoint Events in Cardiovascular Trials

A. Death – All Cause Death (classified as CV death or Non-CV Death)

B. Non-fatal MI

C. Non-fatal Stroke

D. Hospitalization for Unstable Angina

E. Coronary Revascularization – Elective/Urgent

F. Heart Failure

A. Death

I. Cardiovascular Death

Cardiovascular death includes death resulting from: an acute MI, sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

CV mortality will be classified more specifically (MI, sudden cardiac death, etc.) as follows:

1. **Death due to Acute Myocardial Infarction** refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days[1] after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, it will be considered a death due to MI.

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI in this document or by autopsy findings showing recent MI or recent coronary thrombosis.

   Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from MI), should also be considered death due to acute MI.

   Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as death due to a CV procedure (see # 5 below).

[1] The 30-day cutoff is arbitrary.

2. **Sudden Cardiac Death** refers to death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
    a. Death witnessed and occurring without new or worsening symptoms
    b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
    c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
    d. Death after unsuccessful resuscitation from cardiac arrest
    e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
    f. Unwitnessed death in a patient seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

    General Considerations

    Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion 2f, above) should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death (see section III below) should be recorded (e.g., a patient found dead in bed, but who had not been seen by family for several days).

3. **Death due to Heart Failure** refers to death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure.
6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.
7. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease)

II. Non-Cardiovascular Death

Non-cardiovascular death is defined as any death with a specific cause not thought to be CV in nature, as described above (section I). The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., systemic inflammatory response syndrome [SIRS]/ immune [including autoimmune])
- Hemorrhage that is neither cardiovascular bleeding nor a stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription Drug Reaction or overdose
- Neurological (non-CV)
- Malignancy
- Other non-CV

III. Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be discouraged and should apply to a minimal number of patients.

For this study, it will be assumed that all undetermined cases are included in the cardiovascular category (e.g., presumed cardiovascular death, specifically "death due to other cardiovascular causes") since, in a CV population, it is the overwhelming likelihood in cases where data are missing or incomplete.

B. Non-fatal Myocardial Infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin (cTn)) with at least one value above the 99th percentile upper reference limit (URL) **and** with at least one of the following:
  - Symptoms of ischemia;
  - New or presumed new significant ST-T changes or new LBBB *;
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy.

*ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB):

- ST elevation: New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.
- ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. In general, troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

Criteria for prior myocardial infarction

Any one of the following criteria meets the definition for prior MI:

- Pathologic Q waves with or without symptoms in the absence of non-ischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.
- Pathologic findings of a prior MI.

For each MI identified by the CEC, a Type of MI will be assigned using the following guidelines:

- **Type 1 Spontaneous MI**
  Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

- **Type 2 Myocardial Infarction secondary to an ischemic imbalance**
  In instances of myocardial injury with necrosis where a condition OTHER THAN CAD contributes to an imbalance between myocardial oxygen supply and/or demand, (e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy).

- **Type 3 Myocardial infarction resulting in death when biomarker values are unavailable**
  Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker values could increase, or in rare cases were not collected. **Note: For this study, these will be classified as CV deaths.**

- **Type 4a Myocardial infarction related to percutaneous coronary intervention (PCI)**
  Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (< 99th percentile URL) or a rise of cTn values ≥20% if the baseline values are elevated and are stable or falling. In addition, either (i)

symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

- **Type 4b Myocardial Infarction related to stent thrombosis**
  Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

- **Type 4c Myocardial Infarction related to PCI restenosis**
  Myocardial infarction related to PCI restenosis is defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values >99th percentile URL and no other significant obstructive coronary artery disease (CAD) of greater severity following: (i) initially successful stent deployment, or (ii) dilation of a coronary artery stenosis with balloon angioplasty (<50%).

- **Type 5 Myocardial Infarction related to coronary artery bypass grafting (CABG)**
  Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (< 99th percentile URL) plus, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

C. Non-fatal Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction, generally lasting more than 24 hours, caused by brain, spinal cord, or retinal injury as a result of hemorrhage or infarction. For each stroke identified by the CEC, the event will be further categorized using the following guidelines:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Note: Subdural hematomas are intracranial hemorrhagic events and NOT strokes.

C. Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurologic dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B. In general, the use of this category of stroke should be discouraged and should apply to a minimal number of patients.

For this study, it will be assumed that all undetermined cases are included in the hemorrhagic category since use of other omega-3 agents has been associated with an increase in bleeding risk. A sensitivity analysis will be performed in which the undetermined strokes are included with the ischemic stroke category.

D. Disability Assessment for Patients Suffering a Stroke

The Modified Rankin Scale (mRS) will be used to assess patients who sustain a stroke.

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance

4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

D. Hospitalization for Unstable Angina

Hospitalization for Unstable Angina is defined as:

1. Ischemic discomfort (angina *or symptoms thought to be equivalent*) > 10 minutes in duration occurring:

- At rest, ***or***
- In an increasing pattern with frequent episodes associated with progressively decreased exercise capacity.

AND

2. Prompting an unscheduled hospitalization **within 24 hours** of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available).

AND

3. At least 1 of the following:
    a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders such as LVH and LBBB)
        - Transient ST elevation (duration < 20 minutes)
          New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.
        - ST depression and T-wave changes
          New horizontal or down-sloping ST depression ≥ 0.05 mV in 2 contiguous leads; and/or new T inversion ≥ 0.3 mV in 2 contiguous leads.

    b. Definite evidence of inducible myocardial ischemia as demonstrated by:
        - An early positive exercise stress test, defined as ST elevation or ≥2mm ST depression prior to 5 mets **OR**
        - stress echocardiography (reversible wall motion abnormality) **OR**

- myocardial scintigraphy (reversible perfusion defect), **OR**
- MRI (myocardial perfusion deficit under pharmacologic stress).

AND believed to be responsible for the myocardial ischemic symptoms/signs.

c. Angiographic evidence of new or worse ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

AND

4. Negative cardiac biomarkers and no evidence of acute MI.

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as IV nitrates or increasing doses of β-blockers, should be considered supportive but not diagnostic of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3 (above), would be insufficient to support classification as hospitalization for unstable angina.
2. If patients are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.
3. Planned hospitalization or rehospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example,

    - Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina.

- Rehospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina.

4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina end point.
5. A patient who has UA and subsequently dies should be adjudicated as defined above (see Section I) to determined cause of death.

E. Cardiac Revascularization Procedure

A cardiac (coronary) revascularization procedure is defined as either coronary artery bypass graft surgery (CABG) or a percutaneous coronary intervention (PCI) (e.g., angioplasty, coronary stenting). CABG is defined as the successful placement of at least one conduit with either a proximal and distal anastomosis or a distal anastomosis only. PCI is defined as placement of an angioplasty guidewire, balloon, or other device (e.g., stent, atherectomy catheter brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire will NOT be considered PCI. Coronary Artery Bypass Graft surgeries and Percutaneous Coronary Interventions will be categorized into two distinct categories, elective and urgent:

a. Elective: The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and NOT because the patient's clinical situation demands the procedure prior to discharge.
b. Urgent: The procedure does not meet “elective” criteria. This encompasses all non-elective procedures including those of an urgent, emergent or salvage nature.

F. Heart Failure

A **HF Event** may consist of a hospitalization, as well as urgent outpatient visits. All events identified as being representative of HF will be sub-classified as 1) **HF hospitalization** or 2) **urgent HF visit**. In addition, all events identified as being representative of HF will be sub-classified as 1) new or 2) exacerbation of existing HF.

I) A HF Hospitalization is defined as an event that meets **ALL 5** of the following criteria:

1) The patient is admitted to the hospital with a primary diagnosis of HF

2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:

a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
b. Decreased exercise tolerance
c. Fatigue
d. Other symptoms of worsened end-organ perfusion or volume overload

4) The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding **and at least ONE** laboratory criterion, including:

a. Physical examination findings considered to be due to heart failure, including new or worsened:
i. Peripheral edema
ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
iii. Pulmonary rales/crackles/crepitations
iv. Increased jugular venous pressure and/or hepatojugular reflux
v. S3 gallop
vi. Clinically significant or rapid weight gain thought to be related to fluid retention

b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of

heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

ii. Radiological evidence of pulmonary congestion

iii. Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)

OR

iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5) The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:

a. Augmentation in oral diuretic therapy
b. Intravenous diuretic, inotrope, or vasodilator therapy
c. Mechanical or surgical intervention, including:
i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

II) An **Urgent HF Visit** is defined as an event that meets all of the following:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization.

2) All signs and symptoms for HF hospitalization, i.e., symptoms, physical examination findings/laboratory evidence of new or worsening HF, (as indicated above) must be met.

3) The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Note: A HF event that results in death should be classified as a CV Death due to Heart Failure.

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APPENDIX D: 2013 ACC/AHA Guidelines for High-, Moderate- and Low-Intensity Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** ***(40)*** **mg**	**Atorvastatin 10** ***(20)*** **mg** **Rosuvastatin (*5*) 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** ***(80)*** **mg** **Lovastatin 40 mg** ***Fluvastatin XL 80 mg*** **Fluvastatin 40 mg bid** ***Pitavastatin 2–4 mg***	***Simvastatin 10 mg*** **Pravastatin 10–20 mg** **Lovastatin 20 mg** ***Fluvastatin 20–40 mg*** ***Pitavastatin 1 mg***

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (47).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

bid indicates twice daily; FDA, Food and Drug Administration; IDEAL, Incremental Decrease through Aggressive Lipid Lowering study; LDL–C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

List of References:

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, Journal of the American College of Cardiology 2014;63(25 Pt B):288.

APPENDIX E: Covariates

The following covariates will be included in the Cox proportional hazards model

1) Treatment arm:

TRT	Treatment arm
Epanova	Epanova 4g+ statin
Placebo	Corn oil 4g + statin

2) Regions:

REGION	Country
Asia	CHINA (MAINLAND)
Asia	JAPAN
Asia	SOUTH KOREA
Asia	TAIWAN
Asia	SOUTH AFRICA
Australia & NZ	AUSTRALIA
Australia & NZ	NEW ZEALAND
Europe	BELGIUM
Europe	CZECH REP
Europe	DENMARK
Europe	ESTONIA
Europe	HUNGARY

Europe	ITALY
Europe	LITHUANIA
Europe	NETHERLANDS
Europe	POLAND
Europe	RUSSIA
Europe	UK
Europe	UKRAINE
Latin America	MEXICO
North America	CANADA
North America	USA

3) Established CV disease at baseline:

ECVD_BL	Established CV disease at baseline
1 (YES)	Patient that meet one or more of the atherosclerotic CVD criteria as defined in 3a
0 (NO)	Patient that do not meet any of the 3a criteria

4) Multiple risk factors without established CV disease at baseline:

RISK_BL	Multiple risk factors without established CV disease at baseline
1	Patient that meet both primary prevention critera 3b and 3c
2	Patient that meet primary prevention critera 3b only
3	Patient that meet primary prevention criteria 3c only

APPENDIX F : Additional Safety Information

Clinical Study Protocol Appendix F	
Drug Substance	Epanova®
Study Code	D5881C00004
Edition Number	1
Date	May 2015

Appendix F
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

APPENDIX G

Clinical Study Protocol Appendix G	
Drug Substance	Epanova®
Study Code	D5881C00004
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Appendix G
Pharmacogenetics Research –for the US only

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
ECRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
GWAS	Genome wide association studies
HR	Hazard Ratio
ICH	International Conference on Harmonisation
LDL-C	Low density lipoprotein-cholesterol
LIMS	Laboratory information management system
MI	Myocardial Infarction
PGx	Pharmacogenetics
SNP	Single Nucleotide Polymorphism

Background and rationale

AstraZeneca intends to perform genetic research in the Epanova clinical development programme to explore how genetic variations may affect the clinical parameters associated with Epanova where appropriate. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic variation can contribute to an individual's risk of adverse clinical outcomes as well as to their response to pharmacotherapy. Specifically, genetic polymorphisms can identify individuals at increased risk of adverse clinical outcomes, through known and yet to be discovered biological pathways. Genetic variants that identify patients at higher risk for thrombotic events might be used to tailor therapy. Patients at higher risk for adverse events will, by definition, enjoy a greater absolute risk reduction for a given relative risk reduction from a therapy and hence require a smaller number needed to treat to prevent an adverse event. Moreover, pathobiologically relevant genetic variants may identify a specific subset of patients who enjoy a larger relative risk reduction with a given pharmacotherapeutic intervention, and thus an even greater absolute risk reduction.

For this study, it has been decided to collect genetic samples from 2000 patients in the US only.

Genetic Research Objectives

The objective of this research is to collect and store DNA for exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to omega-3 fatty acids and other cardiovascular medications and/or susceptibility to and/or prognosis of cardiovascular, metabolic and related diseases.

Selection of genetic research population

Study selection record

It is estimated that 2000 subjects in US will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, subjects must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 4.3 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. Only one

sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Genotyping

The genetic research conducted may use a variety of genotyping methodologies as needed. For example, specific sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, and areas linked to the study disease or related cardiovascular or metabolic diseases as well as associated with mechanisms underlying adverse events. In addition, genome-wide scans involving large numbers of polymorphic markers (e.g., single nucleotide polymorphisms (SNPs)) located throughout the genome may be employed for discovery of novel genetic variants linked to outcomes of interest. Additional methodologies may be used, but only as related the genetic objective stated earlier.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10.1 of the main Clinical Study Protocol.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data Management

Any genotype data generated in this study will be stored in an appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and determination of Sample Size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.

If decided that the result will be part of the CSR, then a statistical analysis plan will be prepared and signed before un-blinding.

All analyses for this Pharmacogenetics Research are exploratory and any p-value that is generated will be regarded as descriptive only. Analyses may be carried out to evaluate the degree of association between patient genotype (or haplotype) and selected phenotypes (e.g., outcomes). In addition to evaluating the main effects of the genotypes (haplotypes or alleles) on the selected phenotypes, the possibility of a treatment group by genotype (haplotype or allele) interaction will also be explored.

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