Clinical Study Protocol

Drug Substance	AZD0585
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A Randomised, Double-blind, Placebo controlled, Parallel Group, Phase III Long-term Study to Evaluate Efficacy and Safety of 12 Weeks and 52 Weeks of AZD0585 Administration, Respectively, in Patients with Hyperlipidemia Accompanied by Hypertriglyceridemia (TG in the Range 150-499 mg/dL)

Sponsor:

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Randomised, Double-blind, Placebo controlled, Parallel Group, Phase III Long-term Study to Evaluate Efficacy and Safety of 12 Weeks and 52 Weeks of AZD0585 Administration, Respectively, in Patients with Hyperlipidemia Accompanied by Hypertriglyceridemia (TG in the Range 150-499 mg/dL)

National Co-ordinating Investigator

[redacted]

Study site(s) and number of subjects planned

This study will include 375 patients to be randomised at about 25 sites. All sites are presented in Supplement A.

Study period		Phase of development
Estimated date of first subject enrolled	June 2015	Phase III
Estimated date of last subject completed	May 2017	

Study design

This is a randomised, multicentre, double-blinded, placebo controlled, parallel group study. The eligible patients will be randomised to any of the following 3 cohorts.

- AZD0585 2 g
- AZD0585 4 g
- Placebo

Objectives

Primary Objective:	Outcome Measure:
To demonstrate the short-term (up to 12 weeks) efficacy of AZD0585 2 g and 4 g compared to placebo (corn oil) in Japanese patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL)	Placebo-corrected percent change in serum TG level from baseline to the Week 12 Endpoint.
To evaluate the long-term (up to 52 weeks) safety of AZD0585 administration in Japanese patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL)	Adverse events (AEs), brief physical findings/clinical assessments, ECG assessments, vital signs and laboratory evaluations.

Secondary Objective:	Outcome Measure:
To assess the effect of each dose of AZD0585 on fasting serum lipid profile	Percent change in each serum lipid level from baseline to Week 12 Endpoint in serum lipid profile including total cholesterol (TC), HDL-C, LDL-C, VLDL-C and non-HDL-C.
To assess the effects of each dose of AZD0585 in parameters shown as outcome measure for the objective	• Apolipoprotein (Apo) A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, and Apo E based on percent changes from baseline to Week 12. • Plasma fatty acids profile: EPA, DHA, arachidonic acid (AA) and EPA/AA ratio based on percent changes from baseline to Week 12. • Small dense LDL and LDL-C/Apo B ratio based on percent changes from baseline to Week 12. • Lipoprotein(a) [Lp(a)], remnant like particles cholesterol (RLP-C), proprotein convertase subtilisin kexin 9 (PCSK9) and high sensitivity C-reactive protein (hs-CRP) based on percent changes from baseline to Week 12.

Exploratory Objective:	Outcome Measure:
To assess the time-course of efficacy-related parameters profile up to Week 52 and explore the efficacy characteristics of long-term use of AZD0585 2 g/4 g vs. placebo.	• Fasting serum lipid profile including TG, TC, HDL-C, LDL-C, VLDL-C and non-HDL-C. • Apo A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, and Apo E. • Plasma fatty acids profile: EPA, DHA, AA, and EPA/AA ratio. • Small dense LDL and LDL-C/Apo B ratio. • Lp(a), RLP-C, PCSK9 and hs-CRP.

Target subject population

Japanese patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL) aged 20 years and over.

Duration of treatment

52 weeks.

Investigational product, dosage and mode of administration

The following investigational product(s) will be used in this study.

- AZD0585 1 g soft gelatine capsules

All subjects will need to take 4 capsules from assigned bottle, once daily just after breakfast.

Statistical methods

Primary analyses will be carried out by analysis of covariance (ANCOVA) model including percent change from baseline in TG at Week 12 Endpoint as a response variable, treatment and baseline statin use as factors and baseline TG as a covariate. The primary analysis will be carried out on full analysis set (FAS).

Least square means and 95%CI for each treatment as well as treatment difference to placebo will be provided from the model. P-values will be provided for comparison of AZD0585 each dose vs. placebo.

The primary objective of this study is to demonstrate the superiority of AZD0585 2 g and 4 g when compared with placebo using the percent change from baseline in TG to Week 12 as a primary efficacy variable. In order to protect family wise error rate to be 5%, superiority of AZD0585 2 g vs. placebo and superiority of AZD0585 4 g vs. placebo will be tested based on Hochberg procedure using two-sided significance level of 0.05. If a p-value for each hypothesis is less than 0.05/2 = 0.025, the corresponding hypothesis claimed to be demonstrated. If both p-values are less than 0.05, then the both hypotheses are claimed to be demonstrated.

All analyses other than analysis of the primary efficacy endpoint will be interpreted descriptively. Consequently, no adjustments for multiplicity will be necessary for such analyses. Ninety-five percent confidence intervals will be calculated, where appropriate, as measures of study precision. P-values may be calculated but are to be regarded as descriptive.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AA	Arachidonic acid
AE	Adverse event
AP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
Apo A-I	Apolipoprotein A-I
Apo A-II	Apolipoprotein A-II
Apo B	Apolipoprotein B
Apo B48	Apolipoprotein B48
Apo C-II	Apolipoprotein C-II
Apo C-III	Apolipoprotein C-III
Apo E	Apolipoprotein E
AST	Aspartate aminotransferase
BMI	Body Mass Index
BP	Blood pressure
CSA	Clinical Study Agreement
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
eCRF	Electronic Case Report Form
EE	Ethyl ester
EPA	Eicosapentaenoic acid
FAS	Full analysis set
FDA	Food and Drug Administration
FFA	Free fatty acid

Abbreviation or special term	Explanation
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice' (ICH GCP) and the Japanese 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications' (GCP Ordinance).
Hb	Haemoglobin
HbA1c	Haemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HR	Heart rate
hs-CRP	high sensitivity C-reactive protein
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
Investigators	Principal Investigator + Sub-investigator
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JAS	Japan Atherosclerosis Society
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
non-HDL-C	Non-high-density lipoprotein cholesterol
OTC	Over-the-counter
PCSK9	Proprotein Convertase Subtilisin Kexin 9
PI	Principal Investigator
PPS	Per protocol set
PT	Prothrombin time
PTT	Partial thromboplastin time
RLP-C	Remnant like particles cholesterol
SAE	Serious adverse event

Abbreviation or special term	Explanation
TC	Total cholesterol
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
VLDL-C	Very low-density lipoprotein cholesterol
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

AZD0585 capsules (hereinafter referred to as AZD0585), which was developed by Omthera Pharmaceuticals, Inc., is a complex mixture of 1 g of omega-3 free fatty acid (FFA) derived from fish oils, and primarily composed of eicosapentaenoic acid (EPA: [redacted] and docosahexaenoic acid (DHA: [redacted] Omega-3 fatty acids are well-known to lower serum triglycerides (TG) levels by reducing the amount of hepatic TG secretion and by enhancing the rate of TG clearance from circulation. In Japan, Epadel® (S300, S600, S900 and capsules 300; hereinafter referred to as Epadel®) and Lotriga® granular capsule 2 g (hereinafter referred to as Lotriga®), drugs containing omega-3 fatty acid like AZD0585, are approved for the indication of hyperlipidemia. Epadel is composed mostly of EPA ethyl ester (EE) and Lotriga is composed of EPA EE and DHA EE.

AZD0585 was initially developed for an indication to enhance the remission of Crohn's Disease (Investigational New Drug application No. 65,440). While investigating this indication in two large, placebo-controlled, randomised, double-blind, Phase III trials (AZD0585 Program in Crohn's Disease [EPIC]-1 in Europe and Canada, and EPIC-2 in North America and Europe), it was recognized that AZD0585 lowered TG levels in patients with TG levels in the slightly elevated range. Since then, in overseas AZD0585 has been clinically developed for the indication of hypertriglyceridemia.

AZD0585 containing omega-3 fatty acid as FFA, unlike the existing drugs containing omega-3-acid EE, does not require hydrolysis at absorption from the small intestine to the systemic circulation, and provides favourable bioavailability regardless of taking meals containing fat. Actually, in the clinical pharmacology study of AZD0585 (ECLIPSE-2), the bioavailability of AZD0585 4 g per day and Lovaza®4 g per day administered up to 14 days with low-fat diet (evaluated by plasma total EPA, DHA and total[1] EPA + total DHA levels) was significantly higher compared to Lovaza®, a drug containing omega-3-acid EE.

In two Phase III studies (EVOLVE (OM-EPA-003) and ESPRIT (OM-EPA-004)) conducted out of Japan, consistent dose-dependent TG-lowering response with AZD0585 treatment was observed and clinical benefit on improving lipid parameters was demonstrated in both studies.

In EVOLVE study conducted with severe hypertriglyceridemia, TG levels were between ≥500 mg/dL and <2000 mg/dL after a washout period of lipid-altering medications other than statins and ezetimibe, median baseline TG level was 694 mg/dL. Treatment with AZD0585 led to statistically significant reductions in fasting TG levels (median % changes from baseline in TG were -10%, -25%, and -31% for placebo, AZD0585 2 g, and AZD0585 4 g, respectively; $p<0.01$ and $p<0.001$ for AZD0585 2 g and 4 g vs. placebo, respectively).

[1] "total" = the combined unesterified and esterified forms of EPA or DHA

Treatment with AZD0585 also resulted in statistically significant reductions in non-HDL-C levels compared with placebo, but increased LDL-C levels were observed.

In ESPRIT study conducted with fasting TG levels ≥200 mg/dL and <500 mg/dL and at high risk for a future cardiovascular disease (CVD) event, median baseline TG levels were approximately half those seen in EVOLVE (~265 mg/dL). The results showed a consistent, dose-dependent TG-lowering response with AZD0585 treatment that was similar to those in EVOLVE. Median percent changes from baseline in TG were -4%, -15%, and -21%, respectively.

An integrated safety analysis of both studies demonstrated that AZD0585 was safe and well tolerated for up to 12 weeks in subjects with hypertriglyceridemia.

Outside Japan, development of AZD0585 has been moved ahead in the United States (US). AZD0585 was approved by the US Food and Drug Administration (FDA) for treatment of severe hypertriglyceridemia in May 2014. Submission for this indication is under consideration in other regions.

In Japan, one single- and multiple-dose Phase I study (D5881C00005) with daily doses of 2 and 4 g up to 14 days was completed to evaluate the safety, tolerability and pharmacokinetics in 16 healthy adult male Japanese subjects. In this study, AZD0585 was administered under the low-fat diet conditions (~10% of total meal kcal). According to preliminary data from this study, AZD0585 was safe and well tolerated in healthy male Japanese subjects. In total, 5 adverse events (AEs) (3 cases of alanine aminotransferase [ALT] increased, 1 case of aspartate aminotransferase [AST] increased and 1 case of diarrhea) were reported in 4 of 12 subjects (33.3%) who received AZD0585 treatments (2 and 4 g/day), but all of them were of mild intensity. Mild ALT increased was also found in 2 of 6 subjects (33.3%) who received placebo treatment. The same subject in the placebo group developed mild rash. All AE resolved without intervention. Overall, no serious AE were reported and no subject discontinued the study due to AE.

[redacted] The other one, this study is aim to confirm the short-term efficacy and long term safety of AZD0585 compared to placebo.

In addition, the strategy of submission of AZD0585 with the indication of mixed dyslipidemia and the prevention of ischaemic cardiac events global study (STRENGTH) has been initiated in October 2014. This study has also started in Japan.

1.2 Rationale for study design, doses and control groups

The results of two Phase III studies (EVOLVE and ESPRIT) conducted out of Japan, administration of AZD0585 daily dose 2 or 4 g is expected TG-lowering response with patients with hypertriglyceridemia. Though placebo was extra virgin olive oil for both EVOLVE and ESPRIT studies, corn oil is used for placebo instead of extra virgin olive oil in

this study. Although placebo was extra virgin olive oil for both EVOLVE and ESPRIT studies, corn oil is used for placebo instead of extra virgin olive oil in this study, because it is reported that no statistically significant changes were observed in human plasma TG concentrations by corn oil and extra virgin olive oil (Sirtori et al 1986, Lichtenstein et al 1993).

This study is a randomised, double-blinded, placebo controlled, parallel group study designed to evaluate the efficacy of 12 weeks and safety of 52 weeks of AZD0585 treatment, respectively, in Japanese subjects with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL). The effect of 2 g or 4 g dose of AZD0585 once daily on %TG reduction will be evaluated by comparing with that of 4 g dose of placebo (corn oil). In addition, a long-term safety of 2 g or 4 g dose of AZD0585 once daily will be evaluated by comparing with the placebo control in a double-blinded fashion so that the relationship between AZD0585 administration and AEs including abnormalities in safety parameters such as clinical laboratory test can be better assessed with some insights of AZD0585 dose-dependency on the AEs.

An interim analysis is planned in this study. The data of interim analysis will be cut off when the last subject goes through Visit 11. An interim analysis will include all patients' data available until data cut-off even if patients withdraw prior to Visit 11 including analysis at Week 12 Endpoint for primary efficacy endpoint as well as safety evaluation up to Visit 11.

1.3 Benefit/risk and ethical assessment

AZD0585 contains omega-3-acid as FFA and has an advantage of greater bioavailability over existing omega-3-acid EE alternatives because absorption of EEs is significantly dependent on stimulated intestinal hydrolysis (food-activated) for mucosal uptake (Ikeda et al 1995, Small 1991, El Boustani et al 1987, Hazra et al 1999, Lawson and Hughes 1988a, Lawson and Hughes 1988b, Beckermann et al 1990, Hansen et al 1998).

The meal-fat independency of the AZD0585 formulation is important for full treatment effects, as patients with hypertriglyceridemia are advised to restrict fat intake in order to reduce TG and the associated risk of pancreatitis or CVD events (NCEP 2002).

The total intake of EPA plus DHA in subjects will not exceed 3 g per day since the planned 4 g per day dose of AZD0585 contains approximately 75% EPA plus DHA. This dose level is in agreement with the 1997 FDA ruling of 3 g per day as Generally Recognized as Safe for this aggregate amount (FDA 1997). In a previous Phase I study with AZD0585 in healthy adult male Japanese subjects (D5881C00005), 4 g AZD0585 was safe and well tolerated following single- and multiple-dose and once-daily administration up to 14 days.

Additionally, AZD0585 4 g daily dose was safe and well tolerated for up to 3 years in subjects with Crohn's disease. Therefore it is considered that 52-week treatment period is applicable for this study.

The patients who are allocated to placebo group continue placebo treatment for 52 weeks. From ethical point of view, patients are allowed to use lipid lowering drugs and/or supplements except for omega-3-acid after Visit 8.

1.4 Study Design

This is a randomised, double-blinded, placebo controlled, study employing 3 arm parallel groups to evaluate efficacy of 12 weeks and safety of 52 weeks of AZD0585 administration in patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL).

Total 375 subjects will be randomised to 3 cohorts, A) placebo, B) Epanova 2 g, and C) Epanova 4 g, at a ratio of 1:2:2, respectively. The efficacy will be evaluated as placebo-corrected percent change TG reduction at 12 weeks from the baseline TG level (see Section 8.1). The safety will be evaluated as AEs and other safety parameters (vital sign, clinical laboratory test, etc) during 52-week treatment period.

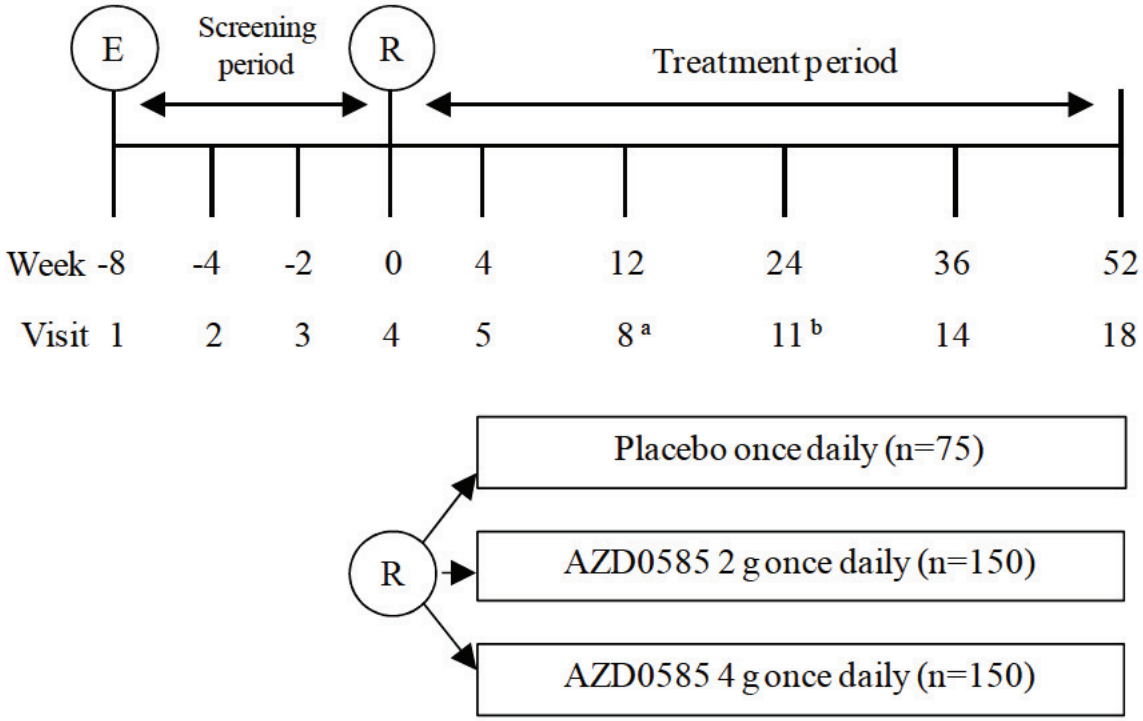
A. Placebo (corn oil) 4 g once daily (n=75)
B. AZD0585 2 g (+placebo 2 g) once daily (n=150)
C. AZD0585 4 g once daily (n=150)

Randomisation will be stratified by the following factors to ensure equal representation across all treatment groups;

- Current use of statin (yes vs. no) at baseline
- Baseline TG level <300 or ≥300 mg/dL

Stratified randomisation will be conducted so that approximately 50% or more of total randomised patients are statin users.

Figure 1 Study flow chart



E : Enrolment, R : Randomisation

a An efficacy primary analysis will be done at Visit 8.

b The data of interim analysis will be cut off when last subject goes through by Visit 11. An interim analysis will include all patients' data available until data cut-off even if patients withdraw prior to Visit 11 including analysis at Week 12 Endpoint for primary efficacy endpoint as well as safety evaluation up to Visit 11.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To demonstrate the short-term (up to 12 weeks) efficacy of AZD0585 2 g and 4 g compared to placebo (corn oil) in Japanese patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL)	Placebo-corrected percent change in serum TG level from baseline to Week 12 Endpoint.
To evaluate the long-term (up to 52 weeks) safety of AZD0585 administration in Japanese patients with hyperlipidemia accompanied by hypertriglyceridemia (TG in the range 150-499 mg/dL)	AEs, brief physical findings/clinical assessments, ECG assessments, vital signs and laboratory evaluations.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To assess the effect of each dose of AZD0585 on fasting serum lipid profile	Percent change in each serum lipid level from baseline to Week 12 Endpoint in serum lipid profile including total cholesterol (TC), HDL-C, LDL-C, VLDL-C and non-HDL-C.
To assess the effects of each dose of AZD0585 in parameters shown as outcome measure for the objective	• Apolipoprotein (Apo) A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, and Apo E based on percent changes from baseline to Week 12. • Plasma fatty acids profile: EPA, DHA, AA and EPA/AA ratio based on percent changes from baseline to Week 12. • Small dense LDL and LDL-C/Apo B ratio based on percent changes from baseline to Week 12. • Lp(a), RLP-C, PCSK9 and hs-CRP based on percent changes from baseline to Week 12.

2.3 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To assess the time-course of efficacy-related parameters profile up to Week 52 and explore the efficacy characteristics of long-term use of AZD0585 2 g/4 g vs. placebo.	• Fasting serum lipid profile including TG, TC, HDL-C, LDL-C, VLDL-C and non-HDL-C. • Apo A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, and Apo E. • Plasma fatty acids profile: EPA, DHA, AA, and EPA/AA ratio. • Small dense LDL and LDL-C/Apo B ratio. • Lp(a), RLP-C, PCSK9 and hs-CRP.

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Japanese men or women, ≥20 years of age.

2. Subjects must meet all of the following criteria;

   (a) Fasting TG level: average of Visit 2 and Visit 3 must be in the range 150 - 499 mg/dL

   (b) %TG change between Visit 2 and Visit 3 must be within 30%

   (c) %LDL-C change between Visit 2 and Visit 3 must be within 25%

   If subjects do NOT meet one of above criteria but the average values are very close to inclusion cut-offs, and are quite willing to join the study and the investigators decide that an additional test is appropriate, an additional Visit (Visit 3a) is allowed between Visit 3 and 4. To be included after Visit 3a the subjects must meet all the following criteria;

   (d) Fasting TG level: average of Visit 2, 3 and 3a must be in the range 150-499 mg/dL

(e) %TG change between Visit 2 and the average of Visit 3 and 3a must be within 30%

(f) %LDL-C change between Visit 2 and the average of Visit 3 and 3a must be within 25%

3. Subjects must be willing and able to give written informed consent by signing an Institutional Review Board (IRB)-approved Informed Consent Form prior to admission to this study and follow the restrictions and procedures outlined for the study.

4. If a statin is prescribed, the patient should be on an optimal statin dose for achieving LDL-C goals based on Japan Atherosclerosis Society (JAS) guideline 2012 or on a maximally tolerated statin dose (i.e., without muscles aches/weakness, liver or muscle enzyme elevations). Statin dose must have been stable for at least 4 weeks prior to screening.

5. Subjects who is willing to follow the diet and/or exercise therapy recommended by JAS guideline 2012 during the study.

3.2 Exclusion criteria

Subjects must not be randomised in the study if any of the following exclusion criteria are fulfilled:

1. Allergy or intolerance to omega-3 fatty acids and omega-3-acid ethyl esters.

2. Use of fibrates, bile acid sequestrants, or niacin or its analogues (greater than 200 mg/day) or any drug for the purpose of lowering plasma cholesterol (except for statin) during screening.

3. Use of any EPA or DHA products, fish oil, or medications (e.g., Lotriga®, Epadel®) or investigational drugs (e.g., AMR101) containing EPA or DHA within 8 weeks prior to randomisation.

4. Use of any supplement for the purpose of lowering plasma cholesterol during screening (e.g., red rice yeast supplements).

5. Use of weight loss drugs (including over-the-counter [OTC] preparations), supplements or programs during screening.

6. Use of anticoagulants (e.g. warfarin, coumarin, heparin, enoxaparin or Prazaxa®) during screening.

7. Use of oral or injected corticosteroids (other than intranasal or inhaled steroids used for allergies/asthma) during screening.

8. Use of tamoxifen, estrogens, progestins, or testosterone, that has not been stable for >4 weeks at Visit 1, or is unstable during screening.

9. Known lipoprotein lipase impairment or deficiency, or Apo C-II deficiency or familial dysbetalipoproteinemia.

10. Current or history of pancreatitis.

11. Type I diabetes mellitus, use of insulin, or haemoglobin A1c (HbA1c) >10% at Visit 1.

12. Poorly controlled hypertension (resting blood pressure [BP] ≥160 mmHg systolic and/or ≥100 mmHg diastolic) at two consecutive visits prior to randomisation at Visit 4.

13. Uncontrolled hypothyroidism, thyroid stimulating hormone (TSH) >1.5 x upper limit of normal (ULN) or Cushing's syndrome at Visit 1.

14. Within six months prior to Visit 1 or current significant nephritic syndrome, pulmonary, hepatic, biliary, gastrointestinal or immunologic disease.

15. Current or history of cancer (except non-melanoma skin cancer, or carcinoma in situ of cervix) within the previous five years.

16. Female patients who is considered of childbearing potential if she is not surgically sterile or if her last menstrual period was <12 months prior to Visit 1 meet any following criteria:

    - Have a positive pregnancy test
    - Be breast feeding
    - Be planning to be pregnant during the study period
    - Cannot use acceptable methods of contraception

    Acceptable methods of contraception for this study include use of double barrier contraception, intrauterine device or abstinence, all oral, hormonal or selective estrogen receptor modulator contraceptives as long as dose and type is stable for 3 months prior to Visit 1.

17. Creatine kinase >5.0 times ULN; AST or ALT >2.5 times ULN at Visit 2.

18. Current or within 12 months prior to Visit 1 of drug or alcohol abuse.

19. Exposure to any investigational agent within 4 weeks prior to Visit 1.

20. Any other condition the investigators believe would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.

21. Patients who are at known risk for bleeding including congenital disorder of coagulation system, recent severe external injury and/or any known conditions that will require surgery during the study period.

22. Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study site)

23. Previous participation in a clinical study with AZD0585.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment and randomisation

The Principal Investigator (PI) will ensure:

1. Signed informed consent is obtained from each potential subject before any study specific procedures are performed.

2. The eligibility of each subject is determined see Sections 3.1 and 3.2.

3. Each potential subject is assigned a unique enrolment number, beginning with "E".

4. Each eligible subject is assigned a unique randomisation code.

Randomisation will be performed before the first dose treatment at Visit 4.

Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation.

If a subject withdraws his participation in the study, then his/her enrolment/randomisation code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomised subjects

Subjects 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. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigators should inform the AstraZeneca Study Team Physician immediately, and a discussion should occur between the AstraZeneca Study Team Physician and the investigators regarding whether to continue or discontinue the patient from

treatment. The AstraZeneca Study Team Physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Patients will be randomised to placebo, AZD0585 2g and AZD0585 4 g with the ratio of 1:2:2.

Randomisation will be stratified by concomitant statin use (yes / no) at baseline and baseline TG value (<300, ≥300 mg/dL).

Stratified randomisation will be conducted so that approximately 50% or more of total randomised patients are statin users.

3.6 Methods for ensuring blinding

The treatment allocation in this study will be double-blind. To ensure the blinding of the treatments, matching AZD0585 placebo capsules will be used. Each pack will be labelled with a unique kit ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the investigators or patient.

An un-blinded interim report will be provided based on Visit 11 data, in order to submit Japan New Drug Application. Investigators and patients will be kept blinded to randomized treatment up-to study closure.

The plasma fatty acids profile (EPA, DHA, AA and EPA/AA ratio) data from Visit4 or later and the serum TG values between Visit4 and Visit8 will also be kept double-blinded until the interim database lock. These data will not be disclosed to Investigators and patients up-to study closure.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator(s) or pharmacists from the interactive voice response system (IVRS) / interactive web response system (IWRS). Routines for this will be described in the IVRS/IWRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigators documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca representative.

AstraZeneca representatives who are independent to the study evaluation at the Patient Safety Department retains the right to break the code for serious adverse event (SAE) 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 subject have been made and documented.

3.8 Restrictions

Subjects will be instructed as follows for a specified period during the study:

1. Any new prescription medications or OTC preparations, supplements must be reported to study site staff during study period.

2. Continue existing therapy (if applicable) with antihypertensive agents at current dosages unless needed by the Investigators discretion during study period.

3. Fast overnight for at least 8 hours prior to each study visit, i.e., no food or beverage except water.

4. Withhold alcohol and refrain from intense exercise 24 hours prior to each study visit.

5. Do not donate blood for the duration of the study.

6. Statin dose should not be changed up to Visit 8 unless needed for safety reason at investigators discretion. Do not take lipid lowering drug except for statin up to Visit 8. Thereafter any lipid lowering drugs and/or supplements are allowed except for omega-3.

7. Subjects should not take investigational products on the morning of the study visit. Subjects bring study drug to each study visit and take investigational products just after the nearest meal after study procedure of the study visit.

8. Subjects must make every attempt to adhere to the dietary and physical activity changes and goals as discussed with the Investigator(s) during study period.

9. Women of child-bearing potential must immediately contact the Investigators if they suspect they might be pregnant and if they have changed, or plan to change their birth control method during study period.

The sponsor or designee should be contacted if the investigator is informed of any restriction violations. The sponsor will decide whether a subject with restriction violations will be allowed to continue study participation.

3.9 Discontinuation of investigational product

Subjects may be discontinued from investigational product in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Severe non-compliance with the study protocol, as judged by the investigator(s) or AstraZeneca

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (see Section 6); diary cards and all study drugs should be returned by the subject. If the patient discontinues the study during the treatment period (by Visit 18), the test and evaluations planned at Visit 18 should be performed unless the patient refuses the procedure.

If a subject is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

Subjects may be withdrawn from the study in the following situations:

- Subject decision. The subject is at any time free to withdraw from study
- AE
- Severe non-compliance with the study protocol, as judged by the investigator(s) or AstraZeneca
- Incorrect enrolment of the patient
- Patient falls into exclusion criteria, e.g., pregnancy
- Death
- Patient lost to follow up

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigators will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

If possible, they will be seen and assessed by investigators. Unresolved AEs will be followed up (see Sections 6.3.2); investigational products should be returned by the subject.

3.11 Discontinuation of the study

AstraZeneca may terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD0585.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan

	Screening period				Treatment period															With-drawal visit [a]
Week	**-8**	**-4**	**-2**		**0**	**4**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Visit	**1**	**2**	**3**	**3a [b]**	**4 [c]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Visit window (days)	**± 3**	**± 3**	**± 2**		**0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Informed Consent	X																			
Eligibility Review	←	—	—	—	→															
Randomisation					X															
Demography	X																			
Medical History/Surgical History, Prior Medications	←	—	—	—	→															
Brief Physical Findings [d]	X								X										X	X
Clinical Assessments [e]	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Sign	X				X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipid Panel (TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting special lipid markers (RLP-C, Apo B and Apo B48)	X				X				X			X			X				X	X
Fatty acids profile (EPA, DHA, AA, and EPA/AA ratio)	X				X				X			X			X				X	X
Small dense LDL					X				X			X			X				X	X

Table 1 Study Plan

	Screening period				Treatment period															With-drawal visit [a]
Week	**-8**	**-4**	**-2**		**0**	**4**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Visit	**1**	**2**	**3**	**3a [b]**	**4 [c]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Visit window (days)	**± 3**	**± 3**	**± 2**		**0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Apo except Apo B (A-I, A-II, C-II, C-III and E)					X				X			X			X				X	X
hs-CRP					X				X			X			X				X	X
Fasting special lipid markers (Lp(a), PCSK9)					X				X			X							X	X
Clinical Chemistry	X	X			X	X	X		X	X		X			X				X	X
Haematology	X	X			X	X	X		X	X		X			X				X	X
Thromboplastin time (PT), Partial thromboplastin time (PTT)		X			X				X			X			X				X	X
Urinalysis	X	X			X	X	X		X	X		X			X				X	X
HbA1c	X				X				X			X			X				X	X
Assessment of renal function (Estimated glomerular filtration rate [eGFR], Albumin Creatinine Ratio [ACR])	X																			
TSH	X																			
Urine Pregnancy Test	X				X														X	X

Table 1 Study Plan

	Screening period				Treatment period															With-drawal visit [a]
Week	**-8**	**-4**	**-2**		**0**	**4**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Visit	**1**	**2**	**3**	**3a [b]**	**4 [c]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Visit window (days)	**± 3**	**± 3**	**± 2**		**0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
ECG	X				X				X			X			X				X	X
Diet Counselling on Therapeutic Lifestyle Changes (TLC) diet	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Question Adherence to TLC diet		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Investigational Product					X	X	X		X	X	X	X	X	X	X	X	X	X		
Assess Investigational Product Compliance						X	X		X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs [f]	←																			→
Concomitant and other treatments	←																			→

a If a patient withdraws before completion of 52 weeks of treatment, withdrawal visit should be carried out to evaluate the patient's safety.
b If the investigators decide that an additional test is appropriate, Visit 3a is allowed. See section 3.1, 2nd inclusion criterion for details.
c All examinations to be completed before randomisation.
d Brief physical findings consisting of an evaluation of general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.
e Clinical assessments: Subjects will be questioned regarding the occurrence and nature of any symptoms and signs. Weight will be measured at each time; however, height will be measured only at Visit 1 to determine the body mass index (BMI).
f SAEs will be recorded from the time of informed consent (Visit 1), and non-serious AEs will be collected from time of randomisation (Visit 4).

4.1 Screening period

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening. Investigators will obtain signed informed consent from a potential subject before starting screening period. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

Screening period takes 8 weeks. Concomitant medications for hyperlipidemia except for statins are not allowed to use.

Subjects will take 3 study visits during screening period (Visit 1, Visit 2 and Visit 3). TG, LDL-C and other laboratory data will be measured at each visit, then only the subjects with TG and LDL-C values within acceptable ranges of variability will be randomised (see Sections 3.1). In case repeat of Visit 3 test (Visit 3a) is performed between Visit 3 and 4 at investigators discretion, eligibility should be re-evaluated with using Visit 3a data (see Section 3.1).

The following assessments and procedures should be performed during screening period as per Table 1.

- Demography (date of birth, sex, race and ethnicity)
- Medical history/Surgical history and prior medications
- Brief physical findings
- Clinical assessments (occurrence and nature of any symptoms and signs, body weight, height)
- Vital signs (BP and pulse)
- Clinical Chemistry/Haematology/Urinalysis
- ECG
- Urine pregnancy test for women of childbearing potential
- Diet counselling on TLC diet/Question adherence to TLC diet
- AEs must be captured from time of consent. However, screening period of the study only SAEs will be collected.
- Concomitant and other treatments

The investigators should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

4.2 Treatment period

The following assessments and procedures should be performed during treatment period as per Table 1.

- Brief physical findings

- Clinical assessments (occurrence and nature of any symptoms and signs, body weight)
- Vital signs (BP and pulse)
- Clinical Chemistry/Haematology/Urinalysis
- ECG
- Urine pregnancy test for women of childbearing potential
- Diet counselling on TLC diet/Question adherence to TLC diet
- Dispense investigational product
- Assess investigational product compliance
- AEs
- Concomitant and other treatments

The Investigators should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

4.3 Withdrawal visit

The following assessments and procedures should be performed if subjects withdraw from the study before they complete 52 weeks treatment, i.e., Visit 18 (see Table 1).

- Brief physical findings
- Clinical assessment (occurrence and nature of any symptoms and signs, body weight)
- Vital signs (BP and pulse)
- Clinical Chemistry/Haematology/Urinalysis
- Urine pregnancy test for women of childbearing potential
- ECG
- Question adherence to TLC diet
- Assess investigational product compliance
- AEs
- Concomitant and other treatments

The Investigators should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigators will ensure that data are recorded on the Electronic Case Report Form (eCRF) as specified in the study protocol and in accordance with the instructions provided.

The PI ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The PI will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

5.1 Efficacy assessments

Blood samples will be taken at the times indicated in the Study Plan (see Table 1).

The samples are measured by SRL Medisearch Inc. The detailed procedure of sampling, handling and shipping is described in the standard operating procedure made by AstraZeneca.

The valuables for efficacy assessment are as follows;

- Fasting serum TG
- Fasting serum lipid profile: TC, LDL-C*, VLDL-C, HDL-C and non-HDL-C* (*direct method)
- Apolipoprotein: Apo A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, and Apo E
- Plasma fatty acids profile: EPA, DHA, AA, and EPA/AA ratio
- Small dense LDL and LDL-C/Apo B ratio
- Lp(a), RLP-C, PCSK9 and hs-CRP

The plasma fatty acids profile (EPA, DHA, AA and EPA/AA ratio) data from Visit 4 or later and the serum TG values between Visit 4 and Visit 8 must not be disclosed to Investigators and patients until the study closure.

In addition, the plasma fatty acids profile data from Visit 4 or later and the serum TG values between Visit 4 and Visit 8 will be kept double-blinded until the interim database lock.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Plan (see Table 1).

Blood samples will be measured by SRL Medisearch Inc.

The detailed procedure of sampling, handling and shipping is described in the standard operating procedure made by AstraZeneca. In addition, the PI ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances

that do not meet Category A criteria), see Appendix C 'International Airline Transportation Association (IATA) 6.2 Guidance Document'. Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

Urinalysis will be performed at each study site by dipstick provided by SRL Medisearch Inc.

The following laboratory variables will be measured:

Table 2 Laboratory Safety Variables

Haematology/Haemostasis	**Clinical Chemistry**
B-Haemoglobin (Hb)	S-Creatinine
B-Leukocyte count	S-Bilirubin, total
B-Leukocyte differential count (absolute count)	S-Alkaline phosphatise (AP)
B-Platelet count	S-AST
B-Haematocrit	S-ALT
P-PT	S-Albumin
P-PTT	S-Potassium
Urinalysis	S-Calcium, total
U-Hb	S-Sodium
U-Protein/Albumin	S-Creatine kinase (CK)
U-Glucose	S-TSH
U-Pregnancy	B-HbA1c
	P-Glcouse
	S-LDL-C
	S-Apo B

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at site as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

5.2.2 Physical examination

5.2.2.1 Brief Physical Findings

A brief physical findings will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears,

eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

5.2.2.2 Clinical Assessments

Subjects will be questioned by investigators at every visit regarding the occurrence and nature of any symptoms and signs. Body weight will be measured at each time, however, height will be measured only at Visit 1 to determine the BMI.

5.2.3 ECG

For timing of assessments refer to the Study Plan (Table 1).

A 12-lead ECG will be performed after patient has been supine at rest for at least 5 minutes.

All ECGs will be evaluated for heart rate, QT interval, ECG interval measured from the onset of the QRS complex to the onset of the P wave (PR), ECG interval measured from the onset of the QRS complex to the J point (QRS), and the time between corresponding points on 2 consecutive R waves on ECG (RR) intervals from the 12-lead ECG, and the Investigators will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant and the reason for the abnormality will be recorded. ECG will be measured using the same recording device during this study as much as possible.

All ECG readings will be stored as source documents as a paper printout if the data will not be able to kept electronically.

5.2.4 Vital signs

BP and pulse will be measured by standard BP recording device using at study site(s) with an appropriate cuff size. BP and pulse will be measured using the same recording device during this study as much as possible.

For timings of assessments refer to the Study Plan (Table 1).

5.3 Other assessments (Not Applicable)

5.4 Pharmacokinetics (Not Applicable)

5.5 Pharmacodynamics (Not Applicable)

5.6 Pharmacogenetics (Not Applicable)

5.7 Biomarker analysis (Not Applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including screening periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (i.e., screening and treatment), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from randomisation (Visit 4) until Visit 18 (or Visit 19).

SAEs will be recorded from the time of informed consent (Visit 1) until Visit 18 (or Visit 19).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum Intensity
- Whether the AE is serious or not
- Investgators causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investgators became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE

Intensity rating scale:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The PI will assess causal relationship between investigational product and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since you were last asked?", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses are preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs and other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low Hb value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives promptly, 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 the necessary information is provided to the AstraZeneca patient safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE promptly, or **no later than 24 hours** of when he or she becomes aware of it.

Once the investigator or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

6.5 Overdose

There are no human data on overdosing and no known antidote.

It will be considered the taking investigational product that is ≥ 5 capsules per day to be the overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

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.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must be provided to the AstraZeneca Patient Safety data entry site within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication.

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives promptly, 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 within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

There are no restrictions against fathering a child when treated with AZD0585.

If paternal exposure pregnancy occurs in the course of the study, then investigators or other centre personnel should inform appropriate AstraZeneca representatives within 24 hours as described in the maternal exposure Section 6.6.1.

6.7 Management of investigational product related toxicities (Not Applicable)

6.8 Study governance and oversight

6.8.1 Steering Committee

A Steering Committee will be set up in this clinical study. The Steering Committee charter will be prepared to detail responsibilities. The Steering Committee constitutions are presented in Supplement A.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 3 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
AZD0585 capsule	1 g soft gelatine capsules [redacted]	Catalent Germany Eberbach GmbH (encapsulation) Catalent Germany Schondorf GmbH (capsule coating / bulk packing)
AZD0585 capsule placebo	1 g soft gelatine capsules (corn oil)	Catalent Germany Eberbach GmbH (encapsulation) Catalent Germany Schondorf GmbH (capsule coating / bulk packing)

7.2 Dose and treatment regimens

Patients start treatment of AZD0585 administration at Visit 4 (Randomisation).
Eligible patients will be randomly assigned to 1 of 3 treatment groups: AZD0585 2 g with placebo (corn oil) 2 g once daily, or AZD0585 4 g once daily, or placebo (corn oil) 4 g once daily. The capsules of AZD0585 and placebo are identical in appearance of 1 g soft gelatine capsules, and all patients will need to take 4 capsules once daily just after breakfast.

7.3 Labelling

Labels will be prepared in accordance with Good Clinical Practice (GCP) Ordinance. Details are specified in the document "explaining the reconstitution procedures and other handling procedures for the investigational products".

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions.

A description of the appropriate storage conditions is specified in the document "explaining the reconstitution procedures and other handling procedures for the investigational products".

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

The investigator(s) will check drug accountability. If the patient's compliance rate is low due to missing doses, etc, the investigator(s) will instruct the patient to comply with the treatment.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'explaining the reconstitution procedures and other handling procedures for the investigational products' which describes the specific requirements. The Investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

7.7 Concomitant and other treatments

Concomitant use of following medications or therapies is not allowed during study period.

- Fibrates, bile acid sequestrants, or niacin or its analogues (greater than 200 mg/day) or any drug for the purpose of lowering plasma cholesterol (except for statin) from the screening to Visit 8.
- Any EPA or DHA products, fish oil, or medications (e.g., Lotriga®, Epadel®) or investigational drugs (e.g., AMR101) containing EPA or DHA during study period.
- Any supplement for the purpose of lowering plasma cholesterol (e.g., red rice yeast supplements) from the screening to Visit 8.
- Weight loss drugs (including OTC preparations) or programs during study period.
- Ketoconazole, erythromycin, clarithromycin, cyclosporine, itraconazole, or protease inhibitors during study period only for statin users.
- Any anticoagulants (e.g., warfarin, coumarin, heparin, Prazaxa® or enoxaparin) during study period.
- Oral or injected corticosteroids (other than intranasal or inhaled steroids used for allergies/asthma) during study period.
- Grapefruit juice >750 mL/day during study period only for statin users.
- Insulin during study period.

Concomitant use of tamoxifen, estrogens, progestins, and testosterone are allowed during study period without change of the dose regimen, if the treatment of those drugs is stable during screening.

Fixed dose statin can be used until Visit 8. No limit is set to use statin after Visit 8.

7.8 Post Study Access to Study Treatment (Not Applicable)

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.

8.2 Sample size estimate

A common standard deviation of 24% is assumed for primary efficacy variable (percent change from baseline to Week 12 Endpoint in serum TG). One hundred and fifty patients in both of AZD0585 2 g and AZD0585 4 g and 75 patients in placebo will ensure the power for detecting 12.5% difference of AZD0585 each dose vs. placebo to be at least 92%, based on t-test with two-sided significance level of 0.05/2= 0.025.

In the above calculation, it was assumed that a total of 375 patients are to be randomised to placebo, AZD0585 2 g, AZD0585 4 g with ratio of 1:2:2 and that proportion of randomised patients not contributing primary analysis at Week 12 Endpoint is negligible.

In addition, the above sample size is expected to be sufficient to provide long term safety data of more than 100 Japanese patients treated by AZD0585 2 g or by AZD0585 4 g for 1 year.

8.3 Definitions of analysis sets

Randomised set: all patients who received randomisation number.

8.3.1 Efficacy analysis set

Full Analysis Set (FAS): all randomised set who had both any baseline and any post-baseline efficacy measurements. Patients will be analyzed according to their randomised treatment. FAS will be considered primary analysis set used for all efficacy evaluation.

Per Protocol Set (PPS): all patients in FAS who completed the first 12-week treatment period without any significant protocol deviations affecting primary efficacy evaluations. All criteria to exclude patients from the PPS will be made prior to the unblinding of the study. Patients will be analyzed according to their randomised treatment. Analyses on PPS will be of supportive purpose and limited to primary and important secondary efficacy variables.

8.3.2 Safety analysis set

Safety set: all patients who took at least on dose of double-blind study medication. Patients will be analyzed according to actual medication received.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy variable

Primary efficacy variable is percent change from baseline to the Week 12 Endpoint in serum TG.

8.4.2 Secondary efficacy variables

- Percent change from baseline to the Week 12 Endpoint in TC
- Percent change from baseline to the Week 12 Endpoint in HDL-C
- Percent change from baseline to the Week 12 Endpoint in non-HDL-C
- Percent change from baseline to the Week 12 Endpoint in LDL-C
- Percent change from baseline to the Week 12 Endpoint in VLDL-C
- Percent change from baseline to Week 12 in Apo A-I
- Percent change from baseline to Week 12 in Apo A-II
- Percent change from baseline to Week 12 in Apo B
- Percent change from baseline to Week 12 in Apo B48
- Percent change from baseline to Week 12 in Apo C-II
- Percent change from baseline to Week 12 in Apo C-III
- Percent change from baseline to Week 12 in Apo E
- Percent change from baseline to Week 12 in EPA
- Percent change from baseline to Week 12 in DHA
- Percent change from baseline to Week 12 in AA
- Percent change from baseline to Week 12 in EPA/AA ratio
- Percent change from baseline to Week 12 in Small dense LDL
- Percent change from baseline to Week 12 in LDL-C/Apo B ratio
- Percent change from baseline to Week 12 in Lp(a)
- Percent change from baseline to Week 12 in RLP-C
- Percent change from baseline to Week 12 in PCSK9
- Percent change from baseline to Week 12 in hs-CRP

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variable (s)

Primary analyses will be carried out by analysis of covariance (ANCOVA) model including percent change from baseline in TG at Week 12 Endpoint as a response variable, treatment and baseline statin use as factors and baseline TG as a covariate. The primary analysis will be carried out on FAS.

Least square means and 95%CI for each treatment as well as treatment difference to placebo will be provided from the model. P-values will be provided for comparison of AZD0585 each dose vs. placebo.

As a sensitivity analysis, log-transformed TG at Week 12 Endpoint will also be analyzed by ANCOVA model including treatment and baseline statin use as factors and log-transformed baseline TG as a covariate. Least square means and 95%CI for treatment difference to placebo will be back transformed and presented as relative treatment difference to placebo in percent change from baseline of TG.

Definition of Endpoint and baseline & missing values

Baseline is defined as average of Week -4, -2 and 0.
Week 12 Endpoint is defined as an average of measurements Week 10 and Week 12.

If patients drop out before Week 12, average of the last two consecutive post-treatment values will be used for Week 12 Endpoint evaluation. If only one post-baseline measurement is available, it will be employed for Endpoint evaluation. Data obtained after Week 12 visit will not be used for evaluation of Week 12 Endpoint.

It is assumed that most patients will complete 12-week treatment without major deviations and the above approach would provide approximately unbiased estimates for treatment effects. However, further sensitivity checks may be planned and documented in Statistical Analysis Plan.

Confirmatory Hypothesis Family & Multiplicity

The primary objective of this study is to demonstrate the efficacy of AZD0585 2 g and 4 g when compared with placebo using the percent change from baseline in TG to Week 12 as a primary efficacy variable. In order to protect family wise error rate to be 5%, superiority of AZD0585 2 g vs. placebo and superiority of AZD0585 4 g vs. placebo will be tested based on Hochberg procedure using two-sided significance level of 0.05. If a p-value for each hypothesis is less than 0.05/2 = 0.025, the corresponding hypothesis claimed to be demonstrated. If both p-values are less than 0.05, then the both hypotheses are claimed to be demonstrated.

All analyses other than analysis of the primary efficacy endpoint will be interpreted descriptively. Consequently, no adjustments for multiplicity will be necessary for such analyses. Ninety-five percent confidence intervals will be calculated, where appropriate, as measures of study precision. P-values may be calculated but are to be regarded as descriptive.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Efficacy variables

Percent change from baseline to the Week 12 Endpoint in TC, HDL-C, LDL-C, VLDL-C and non-HDL-C

Analyses will be carried out by ANCOVA model including percent change from baseline at Week 12 Endpoint as a response variable, treatment and baseline statin use and baseline TG strata (<300, ≥300 mg/dL) as factors, and the corresponding baseline values as a covariate.

Percent change from baseline to Week 12 in Apo A-I, Apo A-II, Apo B, Apo B48, Apo C-II, Apo C-III, Apo E

Percent change from baseline to Week 12 in EPA, DHA, AA, EPA/AA ratio

Percent change from baseline to Week 12 in Small dense LDL, LDL-C/Apo B ratio

Percent change from baseline to Week 12 in Lp(a), RLP-C, PCSK9, hs-CRP

Analyses will be carried out by ANCOVA model including percent change from baseline at Week 12 as a response variable, treatment and baseline statin use and baseline TG strata (<300, ≥300 mg/dL) as factors, and the corresponding baseline values as a covariate.

8.5.2.2 Safety variables

Safety for AZD0585 2 g and 4 g will be mainly evaluated via AEs, brief physical findings/clinical assessments, laboratory measurements, vital signs and ECGs.

The analysis of safety was based on the safety analysis set. Safety data obtained during the treatment period were evaluated descriptively by treatment group. No formal statistical hypothesis testing will be performed. Details will be specified in Statistical Analysis Plan.

8.5.3 Subgroup analysis

Subgroup analyses for primary efficacy variable and selected secondary variables will be carried out to explore internal consistency. Descriptive summary would be provided by gender, by age (<65, ≥65 years), by concurrent statin use at baseline, by baseline TG level (<300, ≥300 mg/dL) and by other clinically relevant factors if appropriate.

8.5.4 Interim analysis

An interim analysis will include all patients' data available until data cut-off, including primary/secondary analysis at Week 12 Endpoint for efficacy as well as safety evaluation based on 24-week or longer exposure to study drug. Sponsor will be unblinded at the time of interim analysis but investigators, patients and site-staff will not be informed of assigned treatment in order to maintain integrity as much as possible. Data cut off date is defined as a day when 24 weeks have passed after Last Subject In (LSI). This interim analysis will be documented as an interim clinical study report.

8.5.5 Sensitivity analysis

Primary analysis will be repeated for PPS. Also, several exploratory analyses based on different missing handling may be carried out for the purpose of sensitivity check. Details will be specified in Statistical Analysis Plan.

8.5.6 Exploratory analysis

For efficacy and pharmacodynamic parameters, baseline and post-baseline measurements up to Week 52 will be summarized by treatment group. In addition, percent change from baseline to Week 52 Endpoint will also be presented. Week 52 Endpoint will be defined as last non-missing measurement after start of treatment.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the site needs information and advice about the study conduct.

9.2.1 Source data

Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records. Original data recorded on the eCRFs and regarded as source data are listed in the CSA.

9.2.2 Study agreements

The PI at each/the site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The PI follows the principles outlined in the CSA.

9.3 Study timetable and end of study

Planned duration of the study:

Study period: June 2015 - May 2017

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD0585.

9.4 Data management

Data management will be performed by Cognizant Technology Solution and AstraZeneca Data Management Centre staff according to the Data Management Plan.

The data collected through third party sources will be obtained and reconciled against study data.

AEs and medical/surgical history will be classified according to the terminology of the latest version the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Affairs (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team of Cognizant Technology Solution.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

SAE Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Management of genotype data

N/A

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to the clinical database. Data Management will assure that the data collection tools (e.g., IVRS/IWRS, etc) are tested and validated. External data reconciliation will be done with the clinical database as defined in the Data Management plan.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The head of the study site will ensure the distribution of these documents to the applicable IRB, and the PI to the Investigators and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as the IRB written approval to AstraZeneca and the PI before enrolment of any subject should into the study.

The IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The PI should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the PI with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

10.4 Informed consent

The PI at each site will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator’s Study File

- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the Head of the Study Site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular site's Informed Consent Form, then AstraZeneca and the site's IRB should be notified by the PI. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site.

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Clinical Study Protocol Administrative Change

Amendment Number	2
Drug Substance	Epanova®
Study Code	D5881C00004
Date	5 November 2015
Protocol Dated	March 2014

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

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden.

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

All changes refer to Global Amended Protocol version 4.0, dated May 2015

Section of protocol affected:

Page 16 and 64, Schedule of Procedures

Previous text:

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						

New text:

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									
Genetic Informed Consent (for US only)				**X**						
Medical History	X	X	X	X						

Section of protocol affected:

Page 19 and 67, Footnote 14

Previous text:

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.

New text:

Genetic samples will be collected for future analysis on approximately 2000 patients in the US, see Appendix **G** for details. **Written informed consent and the Genetic sample should only be collected at Visit 2.**

Section of protocol affected:

Page 89, section 8.5 Interim Analysis

Preious text:

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**).

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**).

New text:

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 **8.1**).

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 **8.7**).

Section of protocol affected:

Page 19, 67 and 83, bullet 14 and section 7.12.6

Previous text:

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

New:

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

Section of protocol affected:

Page 69, section 6.4 Re-screening

Previous text:

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.

New text:

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 (>**2.03** 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.

Section of protocol affected:

Page 16 and 64, section Schedules of Procedures

Previous text:

Plasma and RBC Fatty Acids[4,10]				X			X		**X[9]**	

New text:

Plasma and RBC Fatty Acids[4,10]				X			X		**X[10]**	

Section of protocol affected:

Page 17 and 65, section Schedule of Procedures

Previous:

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,

New:

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,

Section of protocol affected:

Page 44, section 3.1 Overall Study Design

Previous text:

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.

Revised text:

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.

Section of protocol affected:

Page 68, section 6.1 Screening Period (Visit 1)

Previous text:

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.

New text:

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.

Section of protocol affected:

Page 69, section 6.2 Screening Period (Visit 1a)

Previous text:

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,

New text:

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,

Section of protocol affected:

Page 65, section 6 Schedule of Procedures

Previous text:

AEs, Concomitant Medications and Endpoint Assessments[11]					X	X	X	X	X[16]	X[18]

New text:

AEs, Concomitant Medications and Endpoint Assessments[12]					X	X	X	X	X[16]	X[18]

Section of protocol affected:

Page 8, Protocol Synopsis, Exclusion Criteria, bullet no 7

The same change applies to page 55, Section 4.2 Exclusion Criteria, bullet no 7

Previous text:

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 **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.

Revised text:

More than one capsule/day 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 **1 capsule not containing more than a maximum of 1 g of total active EPA + DHA** promptly after signing the informed consent. No new omega-3 supplements are permitted following initiation of screening procedures at Visit 1.

Section of Protocol affected:

Page 76, Section 7.4 Prohibited Medications and Dietary Products

Previous text:

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.

New text:

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 **1 capsule not containing more than a maximum of 1 g of total active EPA + DHA** promptly after signing the informed consent. No new omega-3 supplements are permitted following initiation of screening procedures at Visit 1.

Section of protocol affected:

Page 82, section 7.12.5, Exploratory CV Risk Markers (on a subset of patients located in the US)

Previous text:

The samples will be transferred from Quintiles Laboratory to the **AstraZeneca BioBank**.

New text :

The samples will be transferred from Quintiles Laboratory to the **Fisher Bioservices**.

Section of protocol affected:

Page 82, section 7.12.5.1, Storage, re-use and destruction of exploratory CV risk marker samples (on a subset of patients located in the US).

Previous text:

The CV risk marker samples will be shipped from the **cental** lab to the **AstraZeneca BioBank in United Kingdom**.

New text:

The CV risk marker samples will be shipped from the **central** lab to the **Fisher Bioservices**.

Section of protocol affected:

Page 82, section 7.12.5.3, Chain of custody of exploratory CV risk marker samples (on a subset of patients located in the US)

Previous text:

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

New text:

Samples retained for further use will be registered in the AstraZeneca **assigned** Biobank during the entire life cycle.

Reason for Administrative Change:

Genetic Informed Consent for US only in the Schedule of Procedures has been added for clarification.

Typos related to borderline values of TG have been corrected.

Changes to Fisher Bioservices have been made as well as the administrative updates for consistency.

Persons who initiated the Administrative Change:

The AstraZeneca Clinical Program Team

Signed agreement to the Administrative Change:

I hereby approve the Administrative Change to the Clinical Study Protocol.

Study Code: D5881C00004 [redacted]

....

Date AstraZeneca Study Leader

5 November 2015 [redacted]

[redacted]

Signed agreement to the Administrative Change:

<<The Study Leader should sign approval of the CSP Administrative Change. The Local Study Leader/Monitor should also sign approval according to local procedures. For local CSP Administrative Change(s) it should be signed off by the Local Study Leader/Monitor.>>

I hereby approve the Administrative Change to the Clinical Study Protocol.

Study Code: D5881C00004

.....	.....
Date	AstraZeneca Local Study <<Leader/Monitor/Physician, *According to local procedures*>>
(Day Month, Year)	<<Name and Address. Please delete as appropriate>>