



Title: Lipoprotein-Modifying Effects of Omega-3 Fatty Acids Ethyl Esters Analyzed by High Performance Liquid Chromatography in Patients with Hypertriglyceridemia (LOTUS)

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Note; This document was translated into English as the language on original version was Japanese.

PROTOCOL

*Lipoprotein-Modifying Effects of Omega-3 Fatty Acids Ethyl Esters Analyzed by
High Performance Liquid Chromatography in Patients s with Hypertriglyceridemia
(LOTUS)*

Sponsor	Takeda Pharmaceutical Company Limited 12-10 Nihonbashi 2-chome, Chuo-ku, Tokyo
Protocol number	TAK-085-4002
Version number/Revision number	Version 1
Study drug	Omega-3-acid ethyl esters
Creation date	July 7, 2016

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1.0 STUDY ADMINISTRATIVE INFORMATION AND CLINICAL STUDY PRINCIPLES

1.1 Clinical study principles

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Ethical Guideline for Clinical Research (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, December 22, 2014).
- Good Clinical Practice: Consolidated Guideline (ICH: International Conference on Harmonization of Technical Requirement for Registration on Pharmaceuticals for Human Use. E6)
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

1.2 Clinical study implementation system

This study will be conducted in accordance with the requirements of this clinical study protocol designed and prepared by the sponsor and also in accordance with the following:

Sponsor

Takeda Pharmaceutical Company Limited

Japan Pharma Business Unit

Strategic Medical Research Planning Group, Medical Affairs Department

The sponsor shall be responsible for matters related to planning/preparation, implementation/operation, and results/reporting in this clinical study. Methods of supervision of the contractor entrusted with the services related to this clinical study will be described in the procedure to be prepared separately.

Expenses* required for the operation of this clinical study will be paid by the sponsor.

* : Based on the “Consignment Service Contract,” expenses incurred for the services of Office of Clinical Study, monitoring, registration/allocation center, statistical processing, and audit shall

be paid to the contractor entrusted with services related to this clinical study. Expenses agreed by the study site shall be paid to the site based on the “Research Expense Standard.”

Chair of the Clinical Study Steering Committee:

PPD

Member of the Clinical Study Steering Committee:

PPD

The chair and member of the Clinical Study Steering Committee shall supervise implementation and reporting of the clinical study, secure medical guidance of a high degree of professionalism and a high-level scientific quality, and revise the study protocol appropriately.

Terms in this protocol are defined as follows:

Study site:

A corporation, governmental agency and sole proprietor conducting the study, excluding cases where only a part of the services related to storage of samples/information, statistical processing and other studies is entrusted.

Collaborative study site:

A study site that conducts collaborative study in accordance with the protocol, including a study site that obtains new samples/information from study subjects and provides other study sites.

Investigators, etc:

Principal investigators and other parties involved in conduction of the study (including operations at institutions involved in collection/distribution of samples/information). Those involved only in providing existing samples/information outside the study sites and those engaged in part of the entrusted operations related to the study are excluded.

Principal Investigator:

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An investigator who is engaged in implementation of the study and integrates the operations involved in this study at an affiliated study site.

Chief executive of the study site:

A representative of a corporation, head of a governmental agency, or a sole proprietor

Study subject:

A subject (including a dead subject) who meets any of the following:

1. Subjects being studied (including those who have been asked to be studied)
2. Subjects from whom existing samples/information to be used in the study have been obtained.

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2.0 STUDY SUMMARY

Sponsor: Takeda Pharmaceutical Company Limited	Study drug: Omega-3-acid ethyl esters
Study title: Exploratory study of the effects of omega-3-acid ethyl esters on the lipid and lipoprotein profile in the blood	
Protocol number: TAK-085-4002	
Clinical study design: <p>To explore the effects of omega-3-acid ethyl esters on the lipid and lipoprotein profile in the blood in hyperlipidemic patients receiving a hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor in comparison with the control group of patients not treated with omega-3-acid ethyl esters in an unblinded manner by use of high performance liquid chromatography (HPLC) using highly-sensitive gel filtration columns, which is a technique for analyzing lipoprotein.</p> <p>Study subjects who gave consent and were assessed as eligible in the eligibility assessment will be stratified by the factors of “fasting triacylglycerol (TG; < 300 mg/dL or ≥ 300 mg/dL) and age (< 65 years or ≥ 65 years) at the start of the screening period” and allocated to either the group treated with omega-3-acid ethyl esters or the group not treated with omega-3-acid ethyl esters (1:1 ratio).</p>	
Objectives: <p>To explore the effects of 8-week treatment with omega-3-acid ethyl esters on the lipid and lipoprotein profile in the blood in hyperlipidemic patients receiving a HMG-CoA reductase inhibitor by use of HPLC in comparison with the control group of patients not treated with omega-3-acid ethyl esters.</p>	
Subjects: Hyperlipidemic patients receiving a HMG-CoA reductase inhibitor	
Planned number of study subjects: <p>50 patients evaluable for the primary endpoint (25 patients in the group treated with omega-3-acid ethyl esters, 25 patients in the group not treated with omega-3-acid ethyl esters)</p>	Number of study sites: <p>Around 5 sites</p>
Dose and method of administration: <p>Omega-3-acid ethyl esters 2 g is orally administered immediately after meal twice daily.</p>	Route of administration: <p>Oral</p>
Duration of treatment: <p>8 weeks</p>	Duration of evaluation: <p>Screening period: 4 weeks</p>

	<p>Treatment period: 8 weeks</p> <p>Total: 12 weeks</p>
<p>Main criteria for inclusion:</p> <ol style="list-style-type: none"> 1. Patients diagnosed as hyperlipidemia. 2. Patients constantly receiving a HMG-CoA reductase inhibitor at a stable dose for at least 4 weeks at the start of observation period. 3. Patients with fasting TG of $150 \leq$ to <400 mg/dL measured at the start of observation period at Visit 1 (Week -4). 4. Patients who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical study and complying with the study protocol requirements. 5. Patients who can provide written informed consent prior to the conduction of the clinical study procedures. 6. Patients aged ≥ 20 years at the time of informed consent. 	
<p>Main criteria for exclusion:</p> <ol style="list-style-type: none"> 1. Patients who had clinically significant hemorrhagic disorders (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, and vitreous hemorrhage) within 24 weeks prior to the start of observation period, or those who concurrently have the above disorders. 2. Patients who had thyroid disorders (hyperthyroidism or hypothyroidism) within 24 weeks prior to the start of observation period, those who concurrently have the above disorders, or those who are orally receiving a therapeutic drug for thyroid disorder. 3. Patients in whom the type of HMG-CoA reductase inhibitors was changed within 12 weeks prior to the start of observation period. 4. Patients who received an eicosapentaenoic acid (EPA) preparation or an EPA/docosahexaenoic acid (DHA) preparation (including supplements) within 12 weeks prior to the start of observation period. 5. Patients who started antidyslipidemic agents within 4 weeks prior to the start of observation period. 6. Patients with severe hepatic impairment (e.g., Child-Pugh classification C) 7. Patients who were previously diagnosed as lipoprotein lipase deficiency or apoprotein C-II deficiency. 	

8. Patients who are concurrently having Cushing's syndrome, uremia, systemic lupus erythematosus (SLE), or serum dysproteinemia.
9. Diabetic patients who are currently receiving thiazolidine or insulin.
10. Patients who are concurrently having hypertension of grade III^{Note 1)}.

Note 1: Patients with systolic blood pressure of ≥ 180 mm Hg or diastolic blood pressure of ≥ 110 mm Hg regardless of treatment with antihypertensive drugs.
11. Patients who are habitual drinkers drinking an average of over 100 mL per day (expressed in terms of quantity of alcohol), or patients with or with a history of drug abuse or addiction.
12. Pregnant, lactating or postmenopausal women.
13. Patients with a history of hypersensitivity or allergy for omega-3-acid ethyl esters.
14. Patients participating in other clinical studies
15. Patients assessed ineligible in the study by the principal investigator or the investigator

STATISTICAL ANALYSIS METHODS:

(1) Analysis set

Two analysis sets, "Full Analysis Set (FAS)" and "Safety Analysis Set (SAS)" are used in this study.

Define FAS as the population of enrolled study subjects who satisfy the following criterion:

- Study subjects who were randomized and given at least one dose of the study drug.

Define SAS as the population of enrolled study subjects who satisfy the following criterion:

- Study subjects who were given at least one dose of the study drug during this clinical study.

(2) Efficacy analysis

[Primary endpoints]

Change in mean particle sizes of small dense LDL (sdLDL)-C and LDL-C in the specific 20-lipoprotein fraction assay

[Analytical method]

- 1) At each evaluation time point during the treatment period, summary statistics (number of subjects, mean, standard deviation [SD], minimum value, maximum value, quartiles) and a two-sided 95% confidence interval for the mean will be calculated in each treatment group, and a diagram illustrating the change in the mean \pm SD will be prepared.
- 2) At each evaluation time point during the treatment period, percentage of change from baseline will be calculated and analyzed in the same manner as in the above 1).

- 3) At each evaluation time point during the treatment period, study subjects will be stratified by fasting TG and ages at the start of study drug administration, and summary statistics (number of subjects, mean, SD, minimum value, maximum value, quartiles) and a two-sided 95% confidence interval for the mean will be calculated and analyzed in each treatment group.
- 4) At each evaluation time point during the treatment period, percentage of change from baseline will be calculated and analyzed in the same manner as in the above 3).

[Secondary endpoints]

- 1) Change in major lipid constituents in the specific 20-lipoprotein fraction assay
- 2) Change in fatty acids and sdLDL-C in total lipids
- 3) Change in concentration and particle number of lipids, apoprotein and lipoprotein in the blood

[Analytical method]

- 1) At each evaluation time point during the treatment period, summary statistics (number of subjects, mean, SD, minimum value, maximum value, quartiles) and a two-sided 95% confidence interval for the mean will be calculated in each treatment group, and a diagram illustrating the change in the mean \pm SD will be prepared.
- 2) At each evaluation time point during the treatment period, percentage of change from baseline will be calculated and analyzed in the same manner as in the above 1).
- 3) At each evaluation time point during the treatment period, study subjects will be stratified by fasting TG and ages at the start of study drug administration, and summary statistics (number of subjects, mean, SD, minimum value, maximum value, quartiles) and a two-sided 95% confidence interval for the mean will be calculated and analyzed in each treatment group.

(3) Analysis of safety endpoints

[Adverse events]

The following analyses will be performed for each treatment group. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT).

- Tabulation of frequency of all adverse events
- Tabulation of frequency of adverse events with a causal relationship to the study drug
- Tabulation of frequency of all adverse events by severity
- Tabulation of frequency of adverse events with a causal relationship to the study drug by severity
- Tabulation of frequency of adverse events leading to study drug discontinuation

- Tabulation of frequency of serious adverse events
- Tabulation of frequency of all adverse events by time of onset

Rationale for the number of planned study subjects:

The number of planned study subjects is based on the feasibility to explore the effects of omega-3-acid ethyl esters on the lipid and lipoprotein profile in the blood. The number of planned study subjects is same in the group treated with omega-3-acid ethyl esters and the group not treated with omega-3-acid ethyl esters, which is not based on a statistical consideration.

3.0 ABBREVIATION

AE	adverse event
BMI	body mass index
CKD	chronic kidney disease
COI	conflict of interest
CRO	contract research organization
DHA	docosahexaenoic acid
EDC	electronic data capture
EPA	eicosapentaenoic acid
FAS	full analysis set
FMD	flow mediated dilation
GCP	Good Clinical Practice
HDL-C	high density lipoprotein-cholesterol
ICH	International Conference on Harmonisation
JAPIC	Japan Pharmaceutical Information Center
LDL-C	low density lipoprotein-cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAS	safety analysis set
sdLDL	small dense low density lipoprotein
SLE	systemic lupus erythematosus
SOC	System Organ Class
TG	triacylglycerol

4.0 INTRODUCTION

4.1 Background

In recent years, metabolic syndrome has been socially concerned, posing multiple risks including for coronary artery disease in association with visceral obesity-induced insulin resistance. Dyslipidemia, characteristically observed, represents a series of abnormal findings including increased TG, decreased HDL-C, sdLDL and remnant cholesterol in the blood. When one becomes highly resistant to insulin, TG increases and LDL quality alters, i.e., sdLDL with particles with small diameters increases. SdLDL is easily engulfed by macrophages and thus may accelerate formation of atherosclerotic plaque. Among other LDL, sdLDL is a small particle with the mean diameter of ≤ 25.5 nm. An overseas report showed 3-fold higher incidence of myocardial infarction in the patient population predominantly having sdLDL.¹⁾ There is another report that sdLDL was found in $\geq 70\%$ of Japanese patients with myocardial infarction²⁾, suggesting importance of measurement of particle sizes of LDL as a part of risk assessment for coronary artery disease.

Given the above situation, especially after LDL-C was successfully lowered with a HMG-CoA reductase inhibitor, it may be important to lower sdLDL in order for further reduction of coronary artery disease risk. Recently, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are omega-3 fatty acids have been highlighted as drugs having such activity. EPA and DHA have TG-lowering and antiatherosclerosis activities but the mechanism has not been completely elucidated. Omega-3-acid ethyl esters (an EPA/DHA preparation, Lotriga[®]) released in 2013 lower TG levels in a dose-dependent manner³⁾ and are expected to have the potential to lower RLP, enlarge the LDL particle size, improve FMD, and lower IL-6 levels for example.⁴⁾

The outcomes previously obtained in clinical studies for omega-3-acid ethyl esters indicated that efficacy of the product is comparable to of an EPA-E preparation in hyperlipidemic patients for which an EPA preparation is indicated. However, change and course of LDL-C after administration of omega-3-acid ethyl esters are remain to be elucidated.⁵⁾

In this clinical study, Lotriga[®] (an EPA/DHA preparation) will be administered to hyperlipidemic patients receiving a HMG-CoA reductase inhibitor, and the specific 20-lipoprotein fraction including sdLDL will be assayed with HPLC using gel filtration columns, an established assay for precise analysis⁶⁾, for exploration of “quality of lipids,” i.e., numbers of particles of lipids and lipoprotein in the blood and their change.

4.2 Rationale for the proposed study

This clinical study was planned to explore the effects of omega-3-acid ethyl esters on the lipid and lipoprotein (including sdLDL) profile in the blood in hyperlipidemic patients receiving a HMG-CoA reductase inhibitor for elucidation of “quality of lipids.”

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

To explore the effects of 8-week treatment with omega-3-acid ethyl esters on the lipid and lipoprotein profile in the blood in hyperlipidemic patients receiving a HMG-CoA reductase inhibitor by use of HPLC in comparison with the control group of patients not treated with omega-3-acid ethyl esters.

5.2 Definition of endpoints

5.2.1 Primary endpoints

Change in mean particle sizes of sdLDL-C and LDL-C in the specific 20-lipoprotein fraction assay

5.2.2 Secondary endpoints

- 1) Change in major lipid constituents in the specific 20-lipoprotein fraction assay
- 2) Change in fatty acids and sdLDL-C in total lipids
- 3) Change in concentration and particle number of lipids, apoprotein and lipoprotein in the blood

5.2.3 Safety endpoints

Adverse events

6.0 CLINICAL STUDY DESIGN

6.1 Clinical study design

<Clinical study design>

This is an multicenter, randomized, open-label study to explore the effects of omega-3-acid ethyl esters on the lipid and lipoprotein profile in the blood in hyperlipidemic patients receiving a HMG-CoA reductase inhibitor in comparison with the control group of patients not treated with omega-3-acid ethyl esters in an unblinded manner by use of HPLC using highly-sensitive gel filtration columns, which is a technique for analyzing lipoprotein.

Considering the factors potentially biasing the lipid and lipoprotein profile in the blood between the treatment groups, study subjects who gave consent and were assessed as eligible in the eligibility assessment will be stratified for allocation by the factors of “fasting TG (< 300 mg/dL or \geq 300 mg/dL) and age (< 65 years or \geq 65 years) at the start of the screening period” (1:1 ratio).

<Treatment>

[1] Study drug

Omega-3-acid ethyl esters

[2] Dosage regimen

The group treated with omega-3-acid ethyl esters: Hyperlipidemic patients receiving a HMG-CoA reductase inhibitor* will orally receive omega-3-acid ethyl esters 2 g immediately after meal twice daily.

The group not treated with omega-3-acid ethyl esters: Hyperlipidemic patients receiving a HMG-CoA reductase inhibitor* will continue to receive the HMG-CoA reductase inhibitor at the same dose regimen as at the time of informed consent.

*: Irrespective of the treatment groups, patients will receive a HMG-CoA reductase inhibitor at a consistent dose regimen that should have been stable for \geq 4 weeks prior to informed consent. Change of the HMG-CoA reductase inhibitor and its dose regimen is not allowed throughout the screening period and the treatment period.

[3] Duration of treatment

8 weeks

<Planned number of study subjects>

50 patients evaluable for the primary endpoint

(25 patients in the group treated with omega-3-acid ethyl esters, 25 patients in the group not treated with omega-3-acid ethyl esters)

<Number of study sites>

Around 5 sites

<Duration of treatment and number of visits for a study subject>

[1] Duration of treatment

The duration of the treatment period is 8 weeks. Visit 1 is to obtain informed consent (Day -29 to Day -1 before the start of study drug administration), Visit 2 is to administer the study drug for the first time (Day -15 to Day -1 before the start of study drug administration), Visit 3 takes place in the 4th week after the start of study drug administration (Week 4), and Visit 4 is to administer the study drug for the last time (Week 8).

[2] Number of visits

Screening period: 1 visit

Treatment period: 3 visits

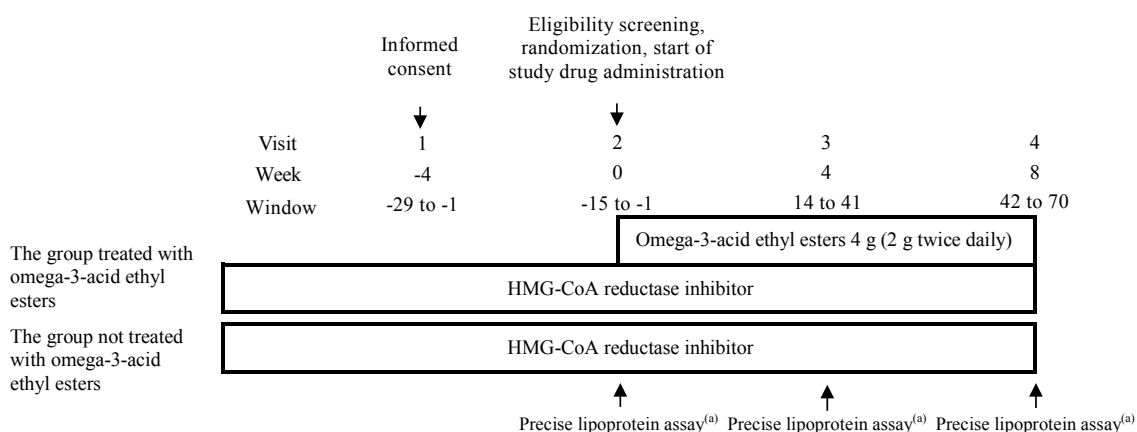
Figure 6 (a) shows an outline of the clinical study design. Refer to Appendix A for schedule of examinations, observations, and evaluations.

Figure 6.a Outline of the clinical study design

<Outline of the clinical study>

Duration of treatment: 8 weeks

Number of visits: 4 visits



(a) by HPLC

6.2 Rationale for the clinical study design

<Rationale>

This clinical study was designed as an open-label study with the control group of patients who will not be treated with omega-3-acid ethyl esters, because the objective is to explore the effects of 8-week, twice-daily, oral treatment with omega-3-acid ethyl esters 2 g on the lipid and lipoprotein profile in the blood in hyperlipidemic patients receiving a HMG-CoA reductase inhibitor. Subjects are to be stratified for allocation (1:1 ratio) by the factors of “fasting TG (< 300 mg/dL or ≥ 300 mg/dL) and age (< 65 years or ≥ 65 years) at the start of the screening period” that may potentially bias the lipid and lipoprotein profile in the blood, so that the potential bias between the treatment groups is minimized.

<Rationale for the dose regimen>

In accordance with the approved dosage and administration of omega-3-acid ethyl esters, omega-3-acid ethyl esters 2 g is to be orally administered immediately after meal twice daily as the dose regimen in this study. In the Phase 3 confirmatory study in patients with hypertriglyceridemia, superiority of the product 4 g group to the EPA-E group as well as non-inferiority of the product 2 g group to the EPA-E group were confirmed for percentage of change in TG from baseline at the completion of administration of omega-3-acid ethyl esters 2 or 4 g or the control EPA preparation 1.8 g/day. Patients receiving omega-3-acid ethyl esters in actual clinical practice are likely to have increased TG, therefore the dose of 4 g daily was selected as having more marked TG-lowering effect, so that the effects of omega-3-acid ethyl esters on the lipid profiles may be investigated in detail.

<Rationale for the study period>

In the Phase 3 confirmatory study in patients with hypertriglyceridemia, decrease of TG was observed in an early stage (Week 4) after the start of administration with omega-3-acid ethyl

esters 4 g/day, and the product 2 and 4 g/day showed comparable or more marked TG-lowering effect as compared to the control EPA-E preparation 1.8 g/day. For LDL-C, another lipid parameter than TG, decrease was observed since Week 4 after the start of administration with the product 4 g/day. Therefore, the 8-week treatment duration including additional 4-week treatment is set to investigate the effects of omega-3-acid ethyl esters on the lipid profiles in detail in this study. As a result of the Phase 3 confirmatory study, no tendency for LDL-C to increase constantly was observed in association with treatment with the product, while it is still unknown what induced transient LDL-C increase after treatment with the product.

<Rationale for the number of planned study subjects>

See Section 13.3.

6.3 Premature termination of entire clinical study or premature termination of clinical study at a study site

6.3.1 Premature termination criteria of entire clinical study

The sponsor should immediately discontinue the study when at least one of the following criteria is applicable:

- When new information or other evaluation on the safety or efficacy of the study drug becomes available that shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for study subject participation in the study.
- When there is serious deviation from Ethical Guidelines or ICH-GCP for medical and health study involving human subjects.

6.3.2 Criteria for premature termination of study sites

Termination of involvement of a study site in the study may be requested prematurely at the discretion of the sponsor if the entity (e.g., principal investigator) is found to have significant violation of the ethical guidelines, protocol, or contractual agreement for medical and health study involving human subjects or becomes unable to ensure proper conduct of the study, or otherwise as specified in the contractual agreement.

6.3.3 Procedures of clinical study suspension and premature termination of entire clinical study or clinical study at a study site

In the event that the sponsor or a study site committee such as an Ethical Review Board decides to prematurely suspend or terminate the entire clinical study or clinical study at a study site, a study-specific procedure shall be provided by the sponsor. The procedure shall be followed by applicable study sites during the course of clinical study suspension or premature termination.

6.4 Procedures for protocol revision

If the protocol needs to be revised, the sponsor shall consider and decide whether to revise the protocol.

The principal investigator of each study site shall be informed of the details of each protocol revision. Principal investigators shall confirm the content of the revision of the protocol and submit a letter of agreement to the sponsor as evidence of agreement with the protocol revision.

Upon notification, the principal investigator at each study site shall submit the revised contents to committees such as the Ethical Review Board, as necessary according to institutional regulations for review, and obtain approval from the director of the entity.

7.0 SELECTION AND WITHDRAWAL CRITERIA OF STUDY SUBJECTS

The principal investigator or investigator shall check for all the inclusion/exclusion criteria including the test results prior to randomization.

7.1 Inclusion criteria

Eligibility of study subjects shall be determined in accordance with the following criteria.

1. Patients diagnosed as hyperlipidemia.
2. Patients receiving a HMG-CoA reductase inhibitor continuously at a stable dose regimen for at least 4 weeks at the start of observation period at Visit 1 (Day -29 to Day -1 before the start of study drug administration)
3. Patients with fasting TG of ≥ 150 to < 400 mg/dL at the start of observation period at Visit 1 (Day -29 to Day -1 before the start of study drug administration)
4. Patients who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical study and complying with the study protocol requirements.
5. Patients who can provide written informed consent prior to the conduction of the clinical study procedures.
6. Patients aged ≥ 20 years at the time of informed consent

[Rationale for the inclusion criteria]

1. These patients were subjected in the clinical study because omega-3-acid ethyl esters is indicated for “hyperlipidemia.”
2. This was set so that the lipid and lipoprotein profile in the blood may be investigated in detail when omega-3-acid ethyl esters is added to a HMG-CoA reductase inhibitor. Change in the dose regimen of the HMG-CoA reductase inhibitor is not allowed during the study, so that efficacy may be assessed accurately.
3. The lower limit was set according to the diagnostic criteria for hypertriglyceridemia in “Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012.” The upper limit was set as using a reference in the clinical settings when adding omega-3-acid ethyl esters to a HMG-CoA reductase inhibitor.
4. 5. These were set as fundamental items for the study.
6. Patients should be ≥ 20 years of age, so that they may make up their mind to participate in the study at their own discretion.

7.2 Exclusion criteria

Study subjects meeting any of the criteria below shall not be included in this study.

1. Patients who had clinically significant hemorrhagic disorders (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, and vitreous hemorrhage) within 24 weeks prior to the start of observation period (Day -29 to Day -1 before the start of study drug administration), or those who concurrently have the above disorders
2. Patients who had thyroid disorders (hyperthyroidism or hypothyroidism) within 24 weeks prior to the start of observation period (Day -29 to Day -1 before the start of study drug administration), those who concurrently have the above disorders, or those who are orally receiving a therapeutic drug for thyroid disorder.
3. Patients in whom the type of HMG-CoA reductase inhibitors was changed within 12 weeks prior to the start of observation period (Day -29 to Day -1 before the start of study drug administration)
4. Patients who have received an EPA preparation or an EPA/DHA preparation (including supplements) within 12 weeks prior to the start of observation period (Day -29 to Day -1 before the start of study drug administration)
5. Patients who have started antidyslipidemic agents within 4 weeks prior to the start of observation period (Day -29 to Day -1 before the start of study drug administration)
6. Patients with severe hepatic impairment (e.g., Child-Pugh classification C)
7. Patients who were previously diagnosed as lipoprotein lipase deficiency or apoprotein C-II deficiency.
8. Patients who are concurrently having Cushing's syndrome, uremia, systemic lupus erythematosus (SLE), or serum dysproteinemia.
9. Diabetic patients who are currently receiving thiazolidine or insulin.
10. Patients who are concurrently having hypertension of grade III^{Note 1)}.

Note 1: Patients with systolic blood pressure of ≥ 180 mm Hg or diastolic blood pressure of ≥ 110 mm Hg regardless of treatment with antihypertensive drugs.

11. Patients who are habitual drinkers drinking an average of over 100 mL per day (expressed in terms of quantity of alcohol), or patients with or with a history of drug abuse or addiction.
12. Pregnant, lactating or postmenopausal women.

13. Patients with a history of hypersensitivity or allergy for omega-3-acid ethyl esters.
14. Patients participating in other clinical studies
15. Patients assessed ineligible in the study by the principal investigator or the investigator

Note 2: Alcohol conversion table (reference)

Alcohol	Type	Alcohol content	Amount corresponding to 100 mL alcohol
Brewage	Sake	15%	670 mL (approx. 3 cups)
	Beer	5%	2,000 mL (approx. 3 large bottles)
	Sparkling liquor	5%	2,000 mL
	Wine	12%	830 mL
	Chinese rice wine	18%	560 mL
Distilled liquor	Ko-rui Shochu	35%	290 mL
	Otsu-rui Shochu	25%	400 mL
	Whiskey	40%	250 mL (approx. 3 doubles)
	Brandy	40%	250 mL (approx. 3 doubles)
	Vodka	40%	250 mL (approx. 3 doubles)
Mixed liquor	Plum wine	13%	770 mL
	Synthetic sake	16%	630 mL

[Rationale for the exclusion criteria]

- 1.13. The product is contraindicated for these patients.
2. Lipids and lipoproteins in the blood may be affected by thyroid disorders and the therapeutic drugs.
- 3.4.5. Efficacy may not be assessed accurately in these patients.
- 6.10. These were set to ensure safety of the study subjects.
7. Patients who genetically produce less lipoprotein and apoprotein should be excluded.
8. Patients with underline diseases commonly seen with secondary hypertriglyceridemia should be excluded.
9. Production of hepatic lipid parameters including TG may not be assessed accurately in these patients.
11. These were set to ensure safety of the study subjects and accurate efficacy assessment.
12. For the product, safety has not been established for the use during pregnancy, and the product should preferably not be administered to lactating women. In addition, production of lipid parameters including TG may be affected by estrogen, a female hormone.
- 14.15. These were set as fundamental items for the study.

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7.3 Prohibited concomitant drugs and permitted concomitant drugs

7.3.1 Prohibited concomitant drugs

[Prohibited concomitant drugs]

The concomitant use of the following drugs* will be prohibited during the clinical study [Visit 1 (Day -29 to Day -1 before the start of study drug administration) to Visit 4 (Week 8)].

(*: including concomitant drugs that were administered at the start of observation period and prohibited in the package insert of the HMG-CoA reductase inhibitor)

1. EPA preparations or EPA/DHA preparations (including supplements)
2. Antidyslipidemic agents (except for HMG-CoA reductase inhibitors administered at the start of observation period)
Anion exchange resin, fibrates, nicotinic acid derivatives, probucol, phytosterols and others (elastase ES, dextran sulfate sodium, polyenephosphatidylcholine, pantethine, ezetimibe)
3. Pancreatic hormones
Insulin preparation
4. Androgens
Testosterone, methyltestosterone
5. Follicle hormone and luteinizing hormone
Estrogen and progestogen
6. Systemic steroids
7. Thyroid hormone

<Rationale>

1 to 7 Efficacy of the study drug may not be assessed accurately with these concomitant drugs.

7.3.2 Permitted concomitant drugs

Concomitant use of “HMG-CoA reductase inhibitors,” “antidiabetic drugs (except for insulin)” or “antihypertensive drugs” is allowed during the study period. However, for “HMG-CoA reductase inhibitors” and “antidiabetic drugs (except for insulin),” dose modification, addition of new treatment drugs, or change of treatment drugs shall not be allowed unless the principal investigator or investigator considers it necessary due to adverse events, etc.

7.4 Study subject management

The principal investigator or investigator shall instruct study subjects regarding the following:

- (1) Guidance for study subjects for improving lifestyle should not be changed or modified during the clinical study. Study subjects shall be instructed to avoid excessive exercise to the extent possible during the study period.
- (2) Study subjects shall be instructed not to consume alcohol after 9:00 pm 2 days before the hospital visit and not to consume food after 9:00 pm the day before the hospital visit until the test to be performed in the fasting state. Although water can be taken as desired on the day of blood collection, study subjects shall be instructed to visit the hospital in a fasting state in order that fasting morning samples can be collected.
- (3) Study subjects shall be instructed to avoid eating/drinking to excess, extreme change in dietary content (eating a high-fat meal, etc.) or excessive exercise, and spend time on a routine basis the day before the hospital visit.
- (4) Study subjects shall be instructed to visit the hospital according to the schedule and take the test as prescribed during the study period.
- (5) Study subjects shall be instructed to comply with the instructions or restrictions (taking the study drug, prohibited drugs for concomitant use, those allowed for concomitant use, etc.) during the study period.
- (6) Upon concomitant use of anticoagulants (warfarin potassium, etc.) or antiplatelet drugs (aspirin, etc.) listed under Precautions for Coadministration in the package insert of the study drug, study subjects shall be instructed to promptly report in the event of an adverse drug reaction, such as bleeding.
- (7) Study subjects must notify the principal investigator or investigator in advance if they receive treatment from other physicians. If treated by other physicians, the study subjects shall be instructed to promptly report the details of the treatment.

7.5 Criteria for discontinuation or withdrawal of a study subject

The principal investigator or investigator shall record the main reason for discontinuation of protocol treatment on the case report form (CRF) according to the classification described below. Refer to Section 9.1.11 for study subjects who withdraw from the study before randomization.

1. Adverse events

When the study subject had an adverse event that requires withdrawal of the study subject from the study because continued participation in the study would impose an unacceptable risk to the study subject's health, or when the study subject is unwilling to continue study participation because of the adverse event.

2. Major protocol deviation

When it is discovered after randomization that a study subject does not meet the eligibility criteria or is not adhering to the protocol, and continued participation in the study would impose an unacceptable risk to the study subject's health.

3. Lost to follow-up

When the study subject failed to make visits and could not be contacted despite the attempts to contact the study subject.

4. Voluntary termination

When the study subject wishes to withdraw from the study. The reason for discontinuation shall be obtained to the extent possible.

5. Study termination

When the sponsor or a committee such as the Ethical Review Board or regulatory authority has decided to terminate the study. Refer to Section 6.3.1 for details.

6. Pregnancy

When a female study subject was found to be pregnant.

Note: The study subject must discontinue the study immediately after she was found to be pregnant. Refer to Section 9.1.13 for the procedures.

7. Lack of efficacy

When efficacy of the study drug is not evident and continuation of the study may pose an unacceptable risk to the study subjects in the opinion of the principal investigator or investigator.

8. Others

When the principal investigator or investigator determined to terminate the study for other reasons.

The specific reasons should be recorded on the CRF.

7.6 Procedures for discontinuation of individual study subjects

The principal investigator or investigator shall terminate a study subject's study participation when the study subject meets the criteria described in Section 7.5. Individual study subjects may discontinue their study participation without giving a reason at any time during the study. Should a study subject's participation be discontinued, the primary reason for termination shall be recorded on

the CRF by the principal investigator or investigator. In addition, efforts shall be made to perform all tests/observations/evaluations scheduled at the time of discontinuation.

8.0 STUDY TREATMENT

8.1 Study drug

Generic name: Omega-3-acid ethyl esters

Chemical name: Ethyl icosapentate;

ethyl(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenoate

Docosahexaenoic acid ethyl ester;

ethyl(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate

8.1.1 Dose and administration method

For subjects who were allocated to the omega-3 group, omega-3-acid ethyl esters 2 g is to be orally administered immediately after meal twice daily for 8 weeks. The principal investigator or investigator chose patients needed treatment with omega-3-acid ethyl esters 4 g/day as a result of assessment. In principle, the dosage prescribed to the study subject should not be changed until the end of the study. Since the study subject should visit the study site in the fasting state, the post-breakfast dose, if any, should be administered immediately after the first meal in the day after completion of the prescribed test.

Medication should be started the day after completion of all the tests at Week 0.

8.1.2 Concomitant drugs

The “HMG-CoA reductase inhibitors” or “antidiabetic drugs (except for insulin)” taken at the start of observation period should continue without dose modification during the study period. Addition or change of these drugs are not allowed.

8.1.3 Overdose of the study drug

Overdose is defined as intentional or accidental administration of the study drug at a higher dose than that specified in the protocol, either by a health professional or by the study subject.

To consistently collect important safety information about overdose, the principal investigator or investigator(s) shall record all cases of overdose on the “Overdose” page of the CRF, irrespective of the presence or absence of accompanying adverse event. Adverse events associated with overdose shall be recorded on the “Adverse events” page of the CRF, in accordance with the procedures described in Section 10.0, “Adverse Events.”

In addition, serious adverse events associated with overdose shall be recorded in accordance with the procedures described in Section 10.2.2, "Collection and reporting of serious adverse events."

In the event of overdose, the principal investigator or investigator shall treat the subject as required based on symptoms.

8.2 Allocation of the study drug and administration procedure

The principal investigator or investigator shall access the Case Registration Web System to allocate the study subjects. The principal investigator or the designee shall notify the information required for allocation in addition to the study subject identification (ID) code. Then, subjects will allocate to omega-3 group or control group through the Case Registration Web System. The principal investigator or investigator shall prescribe the study drug and/or HMG-CoA reductase inhibitor according to the notification, and record the prescribed dose for each study subject in the CRF.

8.3 Preparation and storage of allocation list

The allocation responsible person (designated by the sponsor) shall create an allocation procedure. Information on the allocation shall be kept in a safe place and shall not be available to anyone other than authorized persons, to secure independency from the clinical study.

Using fasting TG values and ages as stratified factors, stratified allocation shall be performed at the Registration Center at the start of treatment period. For allocation, the Registration Center shall use the Allocation Procedure for Stratified Allocation prepared by the allocation responsible person.

9.0 CLINICAL STUDY PROTOCOL

9.1 Clinical study procedures

The principal investigator or investigator shall collect data in accordance with the procedure below. In principle, all the tests, observations, and evaluations of study subjects shall be performed by the same principal investigator or investigator with the exception of the specific 20-lipoprotein fraction. The study schedule is provided in Appendix A.

9.1.1 Informed consent

The procedures for obtaining informed consent are described in Section 15.3.

Consent shall be obtained from the study subject before initiation of study procedures.

Study subject ID code is given to each study subject from whom informed consent was acquired and who was randomized. The study subject ID code shall be used throughout the study period and shall not be changed.

9.1.2 Demographic data, medical history, and previous treatment drugs

Demographic data shall be collected regarding date of birth, gender, time (year/month) of onset (or diagnosis) of hyperlipidemia, frequency of consumption of fish (almost every day, once/2 days, 1 to 2 times/week, almost never), HMG-CoA reductase inhibitor administered before start of observation period, and smoking and drinking history.

Medical history data shall be collected regarding clinically problematic diseases or symptoms that disappeared or were terminated within 1 year from initiation of screening period and that related to target conditions. When the symptoms or disease continues, it shall be considered as a concurrent disease (Refer to Section 9.1.7).

Previous treatment drug data shall be collected regarding all drugs used within 12 weeks before the initiation of screening period and that are related to criteria for eligibility and assessment of efficacy.

9.1.3 Physical examination

All subsequent physical examinations after the start of study drug administration shall be assessed for clinically significant changes from the baseline examination.

9.1.4 Body weight, height, and BMI

Body weight and height shall be measured. The sponsor shall calculate the BMI using the following formula.

Body Mass Index: $BMI = \text{body weight (kg)} / [\text{height (m)}]^2$

Height shall be measured to the nearest whole number in centimeters. Body weight shall be measured to one decimal place in kilograms. The result of BMI shall be shown to one decimal place.

Example:

Height = 176 cm, body weight = 79.2 kg, BMI = $79.2/1.76^2 = 25.6 \text{ kg/m}^2$

9.1.5 Vital signs

For vital signs, blood pressure in sitting position (after resting for at least 5 minutes) and a pulse rate (bpm) shall be measured.

When timing for the vital signs measurement overlaps with blood collection, priority shall be given to blood collection, and the vital signs shall be measured within 30 minutes before or after the blood collection.

9.1.6 Concomitant drugs

Concomitant drugs are all drugs to be given in addition to the study drug. Drugs prescribed by doctors or the over-the-counter medicines purchased by the study subjects shall be included. At every hospital visit of the study subject, the name, dose and dose regimen, route of administration and treatment duration should be investigated for the drugs (including vitamin compound, over-the-counter medication, and Chinese medicine) used other than the study drug from the start of the screening period to the completion of the clinical study. HMG-CoA reductase inhibitor administered before start of observation period is not treated as concomitant drug.

9.1.7 Concurrent disease

A concurrent disease shall be defined as a disease or symptom present at the start of the screening period or observed from the start of the screening period until before the start of study drug administration. Clinically problematic laboratory test data, ECG findings, and abnormal physical examination findings observed at the start of the screening period shall be considered as a concurrent disease at the discretion of the principal investigator or investigator. The content of concurrent disease (diagnosis) shall be investigated.

9.1.8 Food and drink consumption before the visit

The principal investigator or investigator shall confirm with the study subject about food and drink consumed before the visit at every visit.

- Alcohol should not be consumed from 9:00 pm 2 days before the visit, and food should not be consumed from 9:00 pm the day before the visit until the fasting test.
- Excessive eating/drinking and extreme change in dietary content should be avoided on the day before the fasting test.

9.1.9 Laboratory tests and the specific 20-lipoprotein fraction assay

According to the observation schedule (Appendix A), samples are to be collected in each study site for the following laboratory tests and the specific 20-lipoprotein fraction assay. The fasting test is to be performed under ≥ 10 -h fasting.

The principal investigator or investigator shall evaluate and keep the reported laboratory test results. Results of the specific 20-lipoprotein fraction assay shall be assessed by the chair and member of the Clinical Study Steering Committee.

Table 9.a Laboratory tests

Hematology ^(a)	Serum chemistry ^(a)
Platelet count	Total cholesterol, TG, HDL-C, LDH, AST, ALT, ALP, γ -GTP, CK(CPK)
Specific 20-lipoprotein fraction^(b), lipid content of each lipoprotein fraction^(b), mean particle size of LDL^(b), mean particle size of HDL^(b)	
Apoprotein, remnant lipoprotein	
Apolipoprotein A1 ^(a) , A2 ^(a) , B ^(a) , B-48 ^(a) , B-100 ^(c) , C-II ^(a) , C-III ^(a) , C-II/III ^(a) , E ^(a) , RemL-C ^(a)	
Others	Fatty acid fraction in total lipids ^(a)
Lipoprotein lipase ^(c) , high-sensitive CRP ^(a)	24-fatty acid fraction, T/T, EPA/AA

- (a) To be measured in PPD
- (b) To be assayed for the sub-class⁽⁶⁾ specified for each fraction number using HPLC
CCI in PPD

Fraction No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Particle diameter	>90	75	64	53.6	44.5	36.8	31.3	28.6	25.5	23	20.7	18.6	16.7	15	13.5	12.1	10.9	9.8	8.8	7.6
Sub-Class	Chylomicrons		large VLDL			medium VLDL	small VLDL	large LDL	medium LDL	small LDL	very small LDL			very large HDL	large HDL	medium HDL	small HDL	very small HDL		

- (c) To be measured in PPD

The principal investigator shall keep laboratory test reference values including the historical data with the exception of the specific 20-fraction assay using CCI

9.1.10 Contraception

Female subjects of childbearing potential (e.g., nonsterilized or premenopausal female subjects) must use adequate contraception from signing on the informed consent throughout the study period. At the time of acquisition of informed consent from an applicable study subject, signature on the informed consent should be acquired only after explanation is made about what is the adequate

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contraception and that the subject must avoid to be pregnant during the study period by use of the informed consent form until the subject thoroughly understands them.

9.1.11 Pregnancy

When a study subject was found to be pregnant during the study period, the fact that the female study subject participated in the study when she became pregnant with the details of the study drug should be transferred to her obstetrician upon agreement with her.

Pregnancy during the study period and until the day of the last study drug administration should be reported to the sponsor with the format separately specified.

9.1.12 Record of study subjects who are withdrawn before randomization

A CRF shall be created for all study subjects who have signed the consent form and withdrawn before randomization.

The following items are to be described on the CRF.

- Date of consent obtainment
- Date of birth
- Gender
- Eligibility
- Adverse events (with details, if any)
- Reason for discontinuation

The primary reason for withdrawal before randomization shall be recorded on the CRF according to the following classification:

- Adverse events
- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria
- Major protocol deviation
- Lost to follow-up
- Voluntary discontinuation (specify the reason)
- Study termination
- Pregnancy
- Others (specify the reason)

Study subject ID codes assigned to study subjects withdrawn from the study before randomization shall not be reused.

9.1.13 Record of randomization

Study subjects to be randomized shall meet all of the inclusion criteria and shall not meet any of the exclusion criteria according to 8.2 Section 8.2. The principal investigator or investigator shall specify the primary reason why the study subject cannot be randomized.

9.2 Compliance with study treatment of study subjects

The principal investigator or investigator shall confirm compliance with the study treatment with study subject at every visit. Throughout the study period, overall treatment compliance shall be checked in the interview and categorized into the 2 categories of “ $\geq 50\%$ or $< 50\%$ of the prescribed dose.” If poor compliance with study treatment (e.g., $< 50\%$ of the prescribed dose) has been found through the interview and does not improve, the study subject may be withdrawn from the study if appropriate for the circumstances.

9.3 Implementation time point of the tests and observation

The schedule for all tests, observations, and evaluations is shown in Appendix A. The principal investigator or investigator shall perform the tests, observations, and evaluations at the time points shown below.

9.3.1 Screening period (Visit 1)

At Visit 1 (Day -29 to Day -1 before the start of study drug administration), the study shall be explained using the informed consent form to the study subjects who meet the inclusion criteria (except for 3) in Section 7.1 and do not meet any of the exclusion criteria in Section 7.2, and consent shall be obtained in accordance with Section 15.3.

Tests, observations, and evaluations to be performed at Visit 1 (Day -29 to Day -1 before the start of study drug administration) are shown below.

- Informed consent
- Demographic data, medical history, previous treatment drug(s)
- Physical examination
- Height, body weight and BMI
- Vital signs
- Concomitant drugs
- Concurrent disease
- Laboratory tests (fasting)

Items to be checked: Food and drink consumption before visit

- Confirm that alcohol was not consumed from 9:00 pm 2 days before the visit and food was not consumed from 9:00 pm the day before the visit

- Confirm that excessive eating/drinking and extreme change in dietary content were not made on the day before the visit.

9.3.2 Treatment period (Visit 2)

In consideration of the results of tests and observation at Visit 1 (Day -29 to Day -1 before the start of study drug administration), the principal investigator and the investigator shall perform the following tests, observations, and evaluations for each study subject.

Items to be checked: Food and drink consumption before visit

- Confirm that alcohol was not consumed from 9:00 pm 2 days before the visit and food was not consumed from 9:00 pm the day before the visit
 - Confirm that excessive eating/drinking and extreme change in dietary content were not made on the day before the visit.
-
- Physical examination
 - Vital signs
 - Concomitant drugs
 - Concurrent disease
 - Laboratory tests

The principal investigator or the investigator shall give notification to the Registration Center (accessing to the Case Registration Web System) regarding study subjects in whom all the tests, observation and evaluation at Visit 2 (Day -15 to Day -1 before the start of study drug administration) have been completed and study drug administration was considered possible.

The principal investigator or the investigator shall prescribe the study drug at a dose notified from the Registration Center and tell the study subject to take the drug starting from the next day.

Refer to Section 9.1.11 for preparation of records relating to the study subjects withdrawn before randomization.

9.3.3 Treatment period (Visit 3)

In consideration of the results of tests and observation at Visit 2 (Day -15 to Day -1 before the start of study drug administration), the principal investigator and the investigator shall perform the following tests, observations, and evaluations for each study subject. If the study drug administration is discontinued, study subjects should, to the extent possible, undergo tests, observations, and evaluations required for the last visit within 3 days from the last dose taken.

Items to be checked: Food and drink consumption before visit

- Confirm that alcohol was not consumed from 9:00 pm 2 days before the visit and food was not consumed from 9:00 pm the day before the visit
 - Confirm that excessive eating/drinking and extreme change in dietary content were not made on the day before the visit.
-
- Physical examination
 - Vital signs
 - Concomitant drugs
 - Laboratory tests
 - Treatment compliance
 - Evaluation of adverse events

9.3.4 Completion (Visit 4) or discontinuation

Visit 4 is the last visit, and the principal investigator or the investigator shall perform the following tests, observations, and evaluations for each study subject. If the study drug administration is discontinued, study subjects should, to the extent possible, undergo tests within 3 days from the last dose taken.

Items to be checked: Food and drink consumption before visit

- Confirm that alcohol was not consumed from 9:00 pm 2 days before the visit and food was not consumed from 9:00 pm the day before the visit
 - Confirm that excessive eating/drinking and extreme change in dietary content were not made on the day before the visit.
-
- Physical examination
 - Vital signs
 - Concomitant drugs
 - Laboratory tests
 - Treatment compliance
 - Evaluation of adverse events

At completion of the clinical study, the status of all study subjects administered the study drug shall be recorded on the CRF.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse events

An adverse event is defined as any untoward medical occurrence in a patient or a study subject receiving a pharmaceutical product (including the study drug). It does not necessarily have an apparent causal relationship with this pharmaceutical product (including study drug).

An adverse event can therefore be any unfavorable and unintended sign (e.g., a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug), regardless of whether it is considered related to the pharmaceutical product (including the study drug) or not.

10.1.2 Considerations for adverse events

Generally unfavorable findings are described below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of an existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation or a change in the dose of the study drug or a concomitant medication
- Considered unfavorable by the principal investigator or the investigator

Diagnosis name and signs/symptoms:

Adverse events shall be recorded by diagnosis name. Accompanying signs (including abnormal laboratory values) and symptoms shall not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, the signs or symptoms shall be recorded as the adverse event.

Laboratory test values:

Abnormal laboratory values shall be recorded as adverse events when the principal investigator or the investigator judges the results are clinically problematic (in other words, when certain action or medical practice is required, or when the principal investigator or the investigator judges the change has exceeded the normal physiological variation range of the study subject). Retest and/or continued monitoring of an abnormality are not considered medical practice. Also, repeated or additional

conduction of non-invasive tests for verification, evaluation, and monitoring of an abnormality are not considered medical practice.

However, when abnormal laboratory values are the accompanying symptoms of a disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the adverse event shall be handled by its diagnosis name.

Pre-existing conditions (a disease or symptom that is present at the start of the screening period or that is observed from the start of the screening period until before the start of study drug administration):

A disease or symptom that is present at the start of the screening period or that is observed from the start of the screening period until before the start of study drug administration are considered a concurrent disease and not considered an adverse event. When a concurrent disease is aggravated, the aggravation shall be determined as an adverse event and the principal investigator or the investigator shall record on the CRF that the adverse event is an aggravation of the concurrent disease (e.g., “aggravation of hypertension,” etc.).

If a study subject has a pre-existing episodic condition (e.g., asthma, epilepsy), each episode shall be recorded as an adverse event if the episodes become more frequent, serious, or severe in nature. If a study subject has a chronic concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition shall be recorded as adverse event if the degree of the worsening exceeds that which would be expected. The principal investigator or the investigator shall ensure that the adverse event term to be reported represents the change in the condition from baseline (e.g. “worsening of...”).

Worsening of adverse events:

If a study subject experiences a worsening of the adverse event after a change of the study drug, or secondary signs and symptoms are caused by the adverse event, the worsening or the secondary signs and symptoms shall be recorded as a new adverse event on the CRF. The principal investigator or the investigator shall use an adverse event term that explicitly means a change of the condition (e.g., “worsening of...”).

Change of severity of adverse events:

If the study subject experiences changes in the severity of an adverse event, the event shall be recorded once, at its peak severity.

Previously planned surgery or treatment:

Preplanned surgeries or treatment that were scheduled before the start of study drug administration shall not be considered adverse events. However, when the existing symptom is aggravated to a degree requiring emergency surgery or treatment, the condition or the event shall be considered an

adverse event. A concurrent disease that resulted from previously planned surgery shall be reported as an adverse event.

Non-urgent surgery or treatment:

Non-urgent surgery or treatment that does not induce a change in the condition of a study subject (cosmetic surgery, etc.) shall not be considered an adverse event; However, it shall be recorded in the source documents. Concurrent diseases due to a non-urgent surgery shall be reported as an adverse event.

The Insufficient clinical response (lack of efficacy):

Insufficient clinical response, efficacy, or pharmacological action shall not be recorded as an adverse event. The principal investigator or the investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

Overdose:

Overdose of any medication without manifested symptoms shall not be recorded as an adverse event, but the overdose shall be recorded on the “Overdose” page of the CRF. Any manifested symptoms shall also be recorded as adverse events on the “Adverse events” of the CRF.

10.1.3 Serious adverse event

Of all the unfavorable medical events that develop with administration of a pharmaceutical product (including study drug) (irrespective of dose), a serious adverse event is an event that:

1. results in death,
2. is life threatening*,
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. leads to a congenital anomaly/birth defect, or
6. other medically significant condition: a medically important event that causes a risk to a study subject even if it is not immediately life-threatening and does not result in death or hospitalization, or requires an action or treatment to prevent the results described in 1 to 5 above. In addition, points described in the Takeda Medically Significant Adverse Event List (Table 10 (a)) are included in this section.

* The term “life threatening” refers to an event in which the study subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Table 10.a Takeda Medically Significant AE List

Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsades de pointes/ ventricular fibrillation/ventricular tachycardia	Acute hepatic failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/	Neuroleptic malignant syndrome/ malignant hyperpyrexia
Oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Spontaneous abortion/ stillbirth and fetal death
	Confirmed or suspected transmission of infection by a medicinal product
	Confirmed or suspected endotoxin shock

10.1.4 Severity of adverse events

The severity of adverse events shall be classified and defined as shown below.

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities.

10.1.5 Causality of adverse events

The causal relationship of each adverse event to the study drug shall be classified and defined as shown below.

Related	An adverse event that follows a temporal sequence (including clinical course after discontinuation), or an adverse event in which there is at least a reasonable probability that a causal relationship to the study drug cannot be ruled out, although other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment are also suspected.
Not related	An adverse event that does not follow a temporal sequence from administration of the study drug. Very likely due to other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment.

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10.1.6 Relationship to study procedures

The relationship shall be recorded as “Yes” if the principal investigator or the investigator considers that there is reasonable possibility that an adverse event is due to a study procedure. Otherwise, the relationship shall be recorded as “No.”

10.1.7 Date of onset

The date of onset of adverse event shall be determined according to the following rules:

Adverse events	Date of onset
Signs, symptoms, diseases (diagnoses)	The date on which the first signs/symptoms were noted by the study subject and/or the principal investigator or investigator.
Asymptomatic diseases	The date on which a diagnosis was confirmed through a test(s). The date on which a diagnosis was confirmed, even when the test results indicate an old sign(s) of the disease or an approximate time of its onset.
Exacerbation of concurrent diseases	The date on which the first worsening of diseases/symptoms was noted by the study subject and/or the principal investigator or investigator.
Onset of a test abnormality after the start of study drug administration	The date on which a clinically significant laboratory abnormality was detected.
Worsening of a baseline test abnormality after initiation of study treatment	The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter.

10.1.8 Date of resolution

The date of resolution of an adverse event is the date on which the study subject recovered (including resolution with sequelae). If a study subject died due to the adverse event concerned, it shall be the date of death. The adverse event shall be recorded as “ongoing” if the study subject has not yet recovered by the end of the study.

10.1.9 Actions taken for the study drug

Actions taken for the study drug shall be classified or defined as shown below.

Drug withdrawn	<p>The study drug is discontinued because of an adverse event (including withdrawal by the study subject at his/her own discretion).</p> <p>When the study is discontinued but study drug administration is still continued, the classification should be “Dose not changed.”</p>
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Dose not changed	<p>The dose was not changed after the onset of the adverse event.</p> <p>The study drug was discontinued, reduced, or increased because of another adverse event.</p> <p>The study drug was discontinued or reduced for a reason other than the adverse event, e.g., inadvertence of the study subject.</p>
Unknown	It has not been possible to determine what action has been taken because the study subject is lost to follow-up.
Not Applicable	The administration of the study drug had already been completed or discontinued before the onset of the adverse event.
Dose reduced	The dose of the study drug is reduced because of an adverse event (including dose reduction by the study subject at his/her own discretion).

10.1.10 Outcome

Outcome of adverse events is classified as follows:

Category	Criteria
Recovered	<ul style="list-style-type: none"> - Disappearance or recovery of symptoms and findings - Laboratory values returned to normal or baseline
Improved	<ul style="list-style-type: none"> - The intensity is lowered by one or more stages - Symptoms or findings mostly disappeared - Laboratory values improved, but have not returned to normal or baseline - The study subject died from a cause other than the concerned adverse event while the condition was resolving (recording of the date of death unnecessary)
Not recovered	<ul style="list-style-type: none"> - No change in symptoms, findings, or laboratory data - The symptoms, findings, or laboratory data on the final day of observable period were aggravated compared with the date of onset - Irreversible congenital anomaly - The study subject died from another cause before resolution of the concerned adverse event (recording of the date of death unnecessary)
Recovered with sequelae	<ul style="list-style-type: none"> - Disability that disturbs daily life
Death	<ul style="list-style-type: none"> - Direct relationship between death and the concerned adverse event, etc. "Direct relationship" means that the concerned adverse event, etc. was the cause of death, or the concerned adverse event, etc. was clearly responsible for death. - Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same study subject is not considered as death. - The date of death shall be recorded.
Unknown	<ul style="list-style-type: none"> - Follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc.

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Adverse event collection period

Adverse events shall be collected from the start of administration with the study drug until completion of the treatment period (or discontinuation).

10.2.1.2 Reporting of adverse events

At each study visit, the principal investigator or investigator shall check for the presence of any onset of subjective symptoms. A neutral question, such as “How have you been feeling since your last visit?” may be asked to collect any adverse events that occurred between the previous and present visits.

The principal investigator or investigator shall follow up all study subjects experiencing an adverse event irrespective of the causal relationship with the study drug, until the symptom resolve, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent and irreversible adverse events, etc.). All adverse events shall be recorded in the CRF. For the adverse event, the name, date of onset, date of resolution, category, severity, causal relationship with the study procedures (the procedure possibly having causal relationship, if applicable), causal relationship with the study drug (i.e. "Not related" or "Related"), action taken for the study drug, outcome, and seriousness shall be recorded.

Follow-up period of adverse events shall be until recovery of the adverse events, or the time when the principal investigator or investigator judges that further follow-up would be unnecessary.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it shall be reported according to the following procedures.

At the time of onset of a serious adverse event or after notification of the onset by the study subject, the principal investigator shall report the serious adverse event to the chief executive of the study site immediately, and the sponsor or CRO to whom the sponsor has entrusted responsibility shall notify the principal investigator of the study site.

The principal investigator shall then report the serious adverse event to the sponsor (for the contact information, refer to the attachment) within 1 working day after notification of the onset. Further, the investigator shall submit a formal report within 10 calendar days to the sponsor.

Furthermore, it shall be mandatory to include the contents below in the report to be submitted to the sponsor within 1 working day, and other items shall be reported as far as possible.

- Brief description of adverse event and the reason for why it was determined as serious
- Study subject ID code
- Name of principal investigator or the investigator
- Name of the study drug
- Determined causal relationship

10.2.3 Reporting of additional information concerning adverse events

If the sponsor requests provision of additional information concerning adverse events for reporting to regulatory authorities, the principal investigator or the investigator shall confirm the necessary additional information and enter in the Electronic Data Capture (EDC) system or submit a report within the period specified by the sponsor.

10.3 Follow-up of serious adverse events

When information that was not included in the detailed report was obtained later, principal investigator or the investigator shall state it in the copy of the report on serious adverse events, or create another document and submit it to the contact address shown on the attached sheet. Relevant data collected at the study site (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the sponsor or the committee such as the Ethical Review Board upon request.

The principal investigator or the investigator shall follow-up all serious adverse events, etc., until recovery is confirmed, or the final outcome is determined.

10.3.1 Reporting of serious adverse events to Ethical Review Board, etc., and regulatory authorities

When the chief executive of study site receives a report of a serious adverse event from the principal investigator, the chief executive of study site shall consult the Ethical Review Board, etc., and notify the study sites that are conducting the clinical study through the sponsor or the CRO consigned by the sponsor.

When the principal investigator reported a serious adverse event for which a causal relationship to the study (study drug) cannot be ruled out and is unexpected, the chief executive of the study site shall prepare a written report of the unexpected serious adverse event containing the information reported by the principal investigator plus the information below, and submit the report to the

Minister of Health, Labour and Welfare, and notify other study sites conducting the clinical study. (The chief executive of the study site may report it to the Minister of Health, Labour and Welfare via the sponsor, and notify it to other clinical study sites via the sponsor.)

- Actions taken for serious adverse events
(discontinuation of new enrollment, revision of informed consent form, re-consents to other study subjects, etc.)
- Date of review, summary of review, result, necessary action, etc., related to Ethical Review Board, etc.
- Notification to other collaborative study sites

The sponsor shall report, in accordance with regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the principal investigators, and the chief executive of study site.

From the time point of first acknowledging the event or receiving additional information, the sponsor or the CRO consigned by the sponsor shall comply with regulatory required time frames for reporting, and make emergency reports concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, the sponsor shall, in the same way, make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, or continuation of clinical study. The study site shall submit copies of emergency report documents to the Ethical Review Board, etc.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

Neither Clinical Study Steering Committee, Independent Data Monitoring Committee nor Clinical Endpoint Committee are to be employed in this study.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Data management operations shall be performed according to the standard operating procedure by the data management department of the sponsor independent from the medical affairs department. Adverse events, medical history and concurrent disease shall be coded using the MedDRA. Drugs shall be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Case report form

The principal investigator or investigator shall complete a CRF for each study subject who has signed the informed consent form.

The sponsor or the designee shall provide access rights to the EDC system to the study site. Before use of the EDC system, the sponsor shall provide training to the principal investigator, investigators, and study collaborators. The CRF shall be used to report the information collected during the study period to the sponsor. CRF must be completed in Japanese. Data shall be directly entered in preparing the CRF.

A change or correction of the CRF shall be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The principal investigator shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the CRF. The principal investigator shall bear full responsibility for the accuracy and reliability of all data entered on the CRF.

The following data shall be recorded on the CRF directly (unless recorded in the source document).

- Eligibility, completion status, reason for discontinuation, seriousness of adverse events, severity of adverse events and causal relationship between adverse events and the study drug or the study procedures, and outcome

The following data shall not be recorded directly into the CRF.

- Laboratory test values
- Data on the specific 20-lipoprotein fraction assay

When the principal investigator or the investigator makes a change or correction in the data entered on the CRF after fixation of clinical data base, a record (Data Clarification Form; DCF) of change or correction on the CRF provided by the sponsor shall be used. The principal investigator shall confirm that the record of change or correction on the CRF is accurate and complete, and sign or write name/affix a seal, and date it.

The sponsor or the designee shall confirm that the CRFs are completed appropriately according to the procedures set by study. The sponsor or the designee shall have access to the medical records of the study subjects and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF is the property of the sponsor, and the principal investigator or the investigator shall not disclose the information to a third party without a written permission from the sponsor.

12.2 Timing of data entry into the EDC system

The sponsor or the designee shall request the principal investigator and investigator to promptly enter data into the EDC following enrolment of the study subject, each visit during study treatment, completion/discontinuation of the study, and follow-up period.

12.3 Storage of records

The principal investigator or the chief executive of the study site shall store the following materials, including those specified in Section 12.1, and study-specific documents to be investigated or audited by the regulatory authority and the sponsor or the designee. The documents include the list of study subject ID code, medical records, clinical study worksheets (if used), original signed and dated informed consent forms, the record (copy) of modification or correction on the CRF, and electric copies of EDC including audit trail. The principal investigator and the chief executive of the study site shall appropriately retain the material/information related to this study for at least 5 years from the date of reporting the end of the study by the principal investigator, or for 3 years from the date of reporting final publication of the study result, whichever date is later. However, when the sponsor requires a longer storage period, the chief executive of the study site shall discuss the period and methods of storage with the sponsor.

13.0 STATISTICAL ANALYSIS METHODS

The person in charge of analysis and the designee [analysis personnel, who belongs to contract research organization (CRO) independent from the sponsor] shall perform the statistical analysis. The sponsor will not be involved in the statistical analysis.

13.1 Statistical and analytical plans

The analysis personnel shall prepare a statistical analysis plan (SAP) before the acquisition of the informed consent of the earliest study subject, and issue the first edition. Detailed definition of endpoints and analytical methods should be specified in the SAP to deal with all the purposes of the study.

13.1.1 Analysis set

Two analysis sets, “FAS” and “SAS” are used in this study. The FAS primarily used for efficacy analysis will be defined as “study subjects who have been randomized and received the study drug at least once,” and the SAS as “study subjects who have received the study drug at least once during the clinical study.”

13.1.2 Analysis of demographic and other baseline characteristics

From “SAS” primary study subject background items will be tabulated.

13.1.3 Efficacy analysis

From FAS the following shall be analyzed.

13.1.3.1 Analysis of the primary endpoint

Change in mean particle sizes of sdLDL-C and LDL-C in the specific 20-lipoprotein fraction assay

[Analytical method]

- 1) At each evaluation time point during the treatment period, summary statistics (number of subjects, mean, standard deviation [SD], minimum value, maximum value, quartiles) and a two-sided 95% confidence interval for the mean will be calculated in each treatment group, and a diagram illustrating the change in the mean \pm SD will be prepared.
- 2) At each evaluation time point during the treatment period, percentage of change (Visit 3 or 4 - Visit 2 in the treatment period) will be calculated in each treatment group and analyzed in the same manner as in the above 1).
- 3) At each evaluation time point during the treatment period, study subjects will be stratified by fasting TG and ages at the start of study drug administration, and summary statistics (number

of subjects, mean, SD, minimum value, maximum value, quartiles) and a two-sided 95% confidence interval for the mean will be calculated and analyzed in each treatment group.

- 4) At each evaluation time point during the treatment period, percentage of change from baseline will be calculated and analyzed in the same manner as in the above 3).

13.1.3.2 Analysis of secondary endpoints

- 1) Change in major lipid constituents in the specific 20-lipoprotein fraction assay
- 2) Change in fatty acids and sdLDL-C in total lipids
- 3) Change in concentration and particle number of lipids, apoprotein and lipoprotein in the blood

[Analytical method]

- 1) At each evaluation time point during the treatment period, summary statistics (number of subjects, mean, SD, minimum value, maximum value, quartiles) and a two-sided 95% confidence interval for the mean will be calculated in each treatment group, and a diagram illustrating the change in the mean \pm SD will be prepared.
- 2) At each evaluation time point during the treatment period, percentage of change (Visit 3 or 4 - Visit 2 in the treatment period) will be calculated in each treatment group and analyzed in the same manner as in the above 1).
- 3) At each evaluation time point during the treatment period, study subjects will be stratified by fasting TG and ages at the start of study drug administration, and summary statistics (number of subjects, mean, SD, minimum value, maximum value, quartiles) and a two-sided 95% confidence interval for the mean will be calculated and analyzed in each treatment group.

13.1.4 Safety analysis

From SAS the following will be analyzed.

Adverse events

The following analyses will be performed for each treatment group. Adverse events will be coded using MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT).

- Tabulation of frequency of all adverse events
- Tabulation of frequency of adverse events with a causal relationship to the study drug
- Tabulation of frequency of all adverse events by severity

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- Tabulation of frequency of adverse events with a causal relationship to the study drug by severity
- Tabulation of frequency of adverse events leading to study drug discontinuation
- Tabulation of frequency of serious adverse events
- Tabulation of frequency of all adverse events by time of onset

13.2 Criteria for interim analysis and premature discontinuation

No interim analysis is planned.

13.3 Determination of the number of planned study subject

50 patients evaluable for the primary endpoint

(25 patients in the group treated with omega-3-acid ethyl esters, 25 patients in the group not treated with omega-3-acid ethyl esters)

[Rationale for the number of planned study subjects]

The number of planned study subjects is based on the feasibility to explore the effects of omega-3-acid ethyl esters on the lipid and lipoprotein profile in the blood. The number of planned study subjects is same in the group treated with omega-3-acid ethyl esters and the group not treated with omega-3-acid ethyl esters, which is not based on a statistical consideration.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the study site

The sponsor or the designee shall perform periodic monitoring of the study site during the study to confirm that the study is conducted in accordance with all specifications in the study protocol. In the monitoring, the data recorded on the CRF will be checked by comparing them with those in the source documents. Source documents are the original documents, data and records. The principal investigator and the chief executive of the study site shall ensure that the sponsor or the designee and the Ethical Review Board, etc., have access to the source documents.

The sponsor or the designee shall access the records, including the list of study subject ID codes, medical records of the study subjects, and signed and dated original consent forms to confirm that the study is appropriately conducted in compliance with the study protocol. Also, confirm the consistency between CRF and the related source documents. The principal investigator, investigator, and other personnel involved in the study shall spare sufficient time to facilitate monitoring procedures during visits to the study site.

Detailed procedures for monitoring shall be described separately in the written procedures.

14.2 Deviation from the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the study protocol

The principal investigator or investigator shall record all deviations from Ethical Guidelines for Medical and Health Research Involving Human Subjects, and study protocol.

If any deviation is found, the principal investigator shall promptly notify the chief executive of the study site for the clinical study and the sponsor. As necessary, the principal investigator will discuss protocol revisions with the sponsor to reach agreement. For protocol revisions, draft revisions should be submitted as early as possible to the chief executive of the study site for approval of the committee such as the Ethical Review Board.

14.3 Quality assurance audits and regulatory agency inspections

The sponsor or the designee shall perform audit at the study site as necessary. In such a case, the auditor designated by the sponsor shall contact the study site in advance to determine the date of audit. The auditor may ask to visit the facilities where laboratory specimens are collected and any other facilities used during the clinical study. In addition, this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified promptly. The

principal investigator and the chief executive of the study site shall ensure that the auditor has access to all the study-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL STUDY

This clinical study shall be conducted with the highest respect for the individual participants (i.e., study subjects) according to the study protocol, the ethical principles that have their origin in the Declaration of Helsinki, and “Ethical Guidelines for Medical and Health Research Involving Human Subjects.” Each principal investigator will conduct the study according to regulatory requirements and in accordance with “Responsibilities of the Principal Investigator” in Appendix B.

15.1 Approval of the Ethical Review Board, etc.

The Ethical Review Board, etc., shall be constituted in accordance with the regulations.

The sponsor or the designee should obtain the document listing the name and title of each committee member. When a committee member directly participates in this clinical study, the document describing that he/she is not participating in deliberation or voting for the study will be obtained.

The sponsor or the designee shall supply relevant documents for submission to study site committee such as the Ethical Review Board for the protocol’s review and approval. In addition to the study protocol, a copy of the informed consent form and information sheet, written materials related to study subject recruitment, advertisement, and other documents required by regulations, when necessary, shall be submitted to the central committee or a study site committee such as the Ethical Review Board to obtain approval. The sponsor or the designee must obtain written approval of the protocol and the informed consent form and information sheet from the study site committee such as the Ethical Review Board before commencement of the study. The study site committee such as the Ethical Review Board’s approval must refer to the study by exact protocol title, number and version date; identify versions of other documents (e.g., informed consent form and information sheet) reviewed; and state the approval date. The sponsor shall notify the study site, the principal investigator, and investigator after confirming the validity of the regulatory documents of the study site. Protocol procedures such as obtainment of consent shall not be started until the study site, the principal investigator, and investigator receive notification.

The study site shall observe all requirements that the Ethical Review Board, etc. prescribe. The requirements may include notifications to committees such as the Ethical Review Board, for example, revision of the protocol, revision of the informed consent form and information sheet, revision of materials related to study subject recruitment, reports on safety in accordance with the regulatory requirements, reports on status of implementation of the study at intervals determined by a study site committee such as the Ethical Review Board, and submission of the study completion report. The sponsor or the designee shall obtain written approval from the Ethical Review Board, etc. related to the above mentioned items and all related materials.

15.2 Conflict of interest

This clinical study shall be conducted with the support of the sponsor.

Prior to the conduction of this clinical study, the principal investigators involved in this clinical study shall ensure appropriate management of any conflicts of interest (COI) in the conduct of the study in accordance with the rules of the study site.⁷⁾⁻¹¹⁾

The study site shall observe all requirements that the Ethical Review Board, etc. prescribe. This will include self-declaration of COI, clinical study protocol, informed consent form and information sheet.

15.3 Informed consent form and information sheet, and the agreement of the study subjects

The informed consent form shall contain specific requirements of the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of study subjects in this clinical study (both in and outside Japan: supply to a third party), and disclosure. The informed consent form will explain in detail the nature of the clinical study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that study subject is free to withdraw at any time without giving a reason and without any negative effect on further medical care.

The principal investigator is responsible for the preparation, contents, and approval of the informed consent form and information sheet by the committee such as the Ethical Review Board. The informed consent form and information sheet must be approved by the committee such as the Ethical Review Board prior to use.

The informed consent form shall be written in language that can be easily understood by the potential study subjects. The principal investigator or investigator shall be responsible for providing detailed explanation of the informed consent form to the potential study subjects. Information should be given in both oral and written form whenever possible and in manner deemed appropriate by the committee such as the Ethical Review Board.

The principal investigator or investigator must (1) give the opportunity to ask questions and (2) sufficient time to consider whether to participate in the study to the potential study subjects. If the potential study subject decides to participate, the informed consent form must be signed and dated by the potential study subject prior to entering into the study. The principal investigator or investigator shall instruct the potential study subject or representative to sign using their legal names, not

nicknames, using a blue or black ball point ink pen. Also the principal investigator or investigator shall sign and date the informed consent form prior to entering into the study.

Once signed, the original informed consent form shall be retained by the principal investigator or investigator. The principal investigator or investigator shall record the date that the potential study subject signed the informed consent form in the subject's medical record. A copy of the signed informed consent form shall be given to the study subject.

The principal investigator or investigator shall follow the same procedure as for obtaining the initial consent when newly obtaining re-consent from the concerned study subject when the informed consent form and information sheet is revised. The date of obtaining new consent shall be recorded in the study subject's medical record, and a copy of the revised consent form shall be provided to the study subject.

15.4 Personal information of the study subjects

The sponsor or the designee shall affirm the principle of the protection of study subjects' private/personal information. Throughout this study, study subject ID codes shall be used to link the subject's source data to the sponsor's study database and study-related documents. Limited information on study subjects such as gender, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of study subjects and confirmation of accuracy of study subject ID code.

For verification of the conduct of the study in compliance with this protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, the sponsor shall require the principal investigator to provide the study sponsor's designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to study subjects' original medical records (source data or documents), including laboratory test results, admission and discharge records during a subject's study participation, and autopsy reports. The principal investigator or investigator shall obtain specific authorization of the study subject as part of the informed consent process for access to study subject's original medical records by study sponsor's designee and representatives of regulatory authorities (see Section 15.3).

When providing a copy of source documents to the sponsor, the principal investigator or investigator shall delete information that may lead to identification of an individual (name and address of study subject, other personal information not recorded on the CRF of the study subject).

15.5 Consultation windows for the study subjects or persons related to the study concerned

The principal investigator shall establish a contact service to respond to inquiries concerning this clinical study from study subjects or concerned people. Details of the contacts for inquiries will be described in the informed consent form and information sheet.

15.6 Financial burden or reward to the study subjects

Of the expenses for this clinical study, the sponsor shall offer compensation for medical treatment not covered by health insurance as study expenses. The study subjects shall pay expenses for medical treatment covered by ordinary health insurance.

In addition, the principal investigator shall pay expenses such as transportation expenses for participation in this clinical study to the study subjects at each visit from the research funds. Details of the financial burden on the study subjects and rewards shall be described in the informed consent form and information sheet.

15.7 Benefits and inconveniences to the study subjects

15.7.1 Benefits to study subjects

By participating in this clinical study, the study subjects may understand one's own condition of vascular endothelial function in detail.

15.7.2 Inconveniences to study subjects

By participating in this clinical study the burden of the study subject may increase as number of visits will increase compared to daily medical care.

15.8 Attribution of study results and access rights

15.8.1 Attribution of study results

The study results and data obtained from this study shall belong to the sponsor.

15.8.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by the sponsor. In addition, secondary use (meta-analysis, etc.) of the data obtained in this clinical study may be possible if used in such a way that the data shall not be linked to personal identification information.

15.9 Reporting of results, publication, disclosure, and clinical study registration policy

15.9.1 Reporting of results, publication and disclosure

The principal investigator shall report a written summary of results of the study to the chief executive of the study site and provide the sponsor with all the results and data obtained from the study. Only the sponsor may disclose the study information to other principal investigators, investigators or regulatory authorities during the study period, except when required by laws and regulations. The sponsor shall be responsible for publication of the study protocol and study-related results (including the public web site) except for other cases permitted in the study contract.

During the study period and after the end of study, the sponsor or the designee should promptly summarize the results and present it to medical journals and academic conferences, etc. The sponsor may publish any data or information obtained from the study (including data and information provided by the principal investigator) without obtaining agreement of the principal investigator.

The principal investigator or the investigator should obtain the prior written approval from the sponsor when publishing the information obtained in this study at an academic conference, etc.

15.9.2 Clinical study registration

To ensure that information on clinical study is made accessible to the public in a timely manner and to comply with applicable laws, regulations, and guidelines, Takeda Pharmaceutical Company Limited shall register all clinical study being conducted in patients around the world at public trial registration sites, including at least the website(s) of ClinicalTrials.gov (and) Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC), before initiation of the clinical study. On such websites, the study location (city, country), study subject recruitment status, and contact information for Takeda Pharmaceutical Company Limited are open to the public.

15.9.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited shall post the study results, irrespective of the nature of the results, at the public trial registration site(s) of ClinicalTrials.gov (and) JAPIC in accordance with applicable laws and regulations.

15.10 Insurance and compensation for injury

In case of injuries, each study subject in the clinical study must be insured in accordance with the regulations applicable to the study site where the subject is participating. The sponsor or the designee shall buy an insurance policy to compensate for health injury in study subjects.

Healthy injury in a study subject will be compensated as specified in the study contract.

Compensation-related questions by the principal investigator or investigators should be made to the sponsor or the designee.

16.0 REFERENCES

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Appendix A Schedule for Study Procedures

		Screening period	Treatment period			Discontinuation ^(e)
Visit timing	Week	-4	0	4	8	
	Day		-1 ^(d)	28	56	
Window (day)		-29 to -1	-15 to -1	14 to 41	42 to 70	Within 3 days after the last dose
Visit No.		1	2	3	4	
Informed consent		X				
Inclusion/exclusion criteria		X				
Demographic data, medical history, previous treatment drug(s)		X				
Physical examination		X	X	X	X	X
Height		X				
Body weight		X				
BMI		X				
Vital signs		X	X	X	X	X
Concomitant drugs ^(a)		X	X	X	X	X
Concurrent disease		X	X			
Laboratory tests						
Hematology/ Serum chemistry		X ^(c)	X	X	X	X
Specific lipoprotein fraction assay ^(b)		X ^(c)	X	X	X	X
Lipoprotein assay ^(b)		X ^(c)	X	X	X	X
Mean particle diameter of LDL/HDL ^(b)		X ^(c)	X	X	X	X
Fatty acid fraction in total lipids		X ^(c)	X	X	X	X
Others		X ^(c)	X	X	X	X
Study drug prescription			X	X		
Treatment compliance				X	X	X
Food and drink consumption before the visit			X	X	X	X
Evaluation of adverse events			←X→	←X→	←X	←X

(a) All concomitant drugs will be recorded.

(b) By HPLC

(c) To be performed before the Visit 2 tests

(d) Medication will be started the day after the completion of all the tests of Week 0. The start date of medication will be referred to as Day 1.

(e) To be performed to the extent possible

Appendix B Responsibilities of the Principal Investigator

1. To appropriately conduct the clinical study in compliance with this study protocol and the “Ethical Guidelines for Medical and Health Research Involving Human Subjects” and with the highest respect for human rights, safety, and welfare of study subjects.
2. To prepare a list of any other investigators and/or study collaborators when certain important study-related activities are divided by investigators and/or study collaborators, and submit the list to the sponsor as required.
3. To prepare the informed consent form and information sheet and revise it as necessary.
4. To check the contents of the study contract.
5. To provide sufficient information on the protocol, drug and duties of each personnel to investigators and study collaborators, and give guidance and supervision.
6. To select study subjects who satisfy the inclusion criteria, give explanation using written information, and obtain consent in writing.
7. To be responsible for all medical judgments related to the clinical study.
8. Corresponding to request from the chief executive of the study site, to report the latest progress status at least once a year to the chief executive of the study site.
9. To confirm and comprehend the most update status regarding the COI of the investigators participating in the clinical study according to the procedure at an affiliated study site.
10. To ensure, together with the chief executive of the study site, that sufficient medical care is provided to study subjects for all study-related clinically problematic adverse events throughout the period of subjects’ study participation and thereafter.
11. When a study subject is treated at another medical institution or department, to inform the acting physician at the medical institution or department in writing of the study subject’s study participation and study completion/discontinuation after obtaining the study subject’s consent, and prepare a record.
12. When emergency reporting of serious adverse events, etc., is required, to immediately report it in writing to the chief executive of the study site and the sponsor.
13. To prepare correct and complete CRFs, and submit them to the sponsor with an electronic signature.
14. To verify any entries on the CRFs prepared by the investigator or transcribed by the study collaborator from source data, electronically sign and submit them to the sponsor.
15. To discuss a revision of the protocol, etc., when proposed by the sponsor.
16. To report the study completion in writing to the chief executive of the study site.