Title: Specified drug-use survey of Lotriga Granular Capsules: OCEAN3 (Outcome prevention on Cardiovascular Events by Antihyperlipidemic therapy with N3-fatty acid in Japan)

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

Specified Drug-Use Survey Protocol

Specified Drug-Use Survey of Lotriga Granular Capsules

OCEAN3

Outcome prevention on Cardiovascular Events by Antihyperlipidemic therapy with N3-fatty acid in Japan

Version Number	**Version 8**
Date of Preparation	**June 1, 2019**
Sponsor	**Takeda Pharmaceutical Company Limited**

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1.0 Background

Lotriga Granular Capsules (Lotriga) is an omega-3 fatty acid preparation containing highly pure eicosapentaenoic acid ethyl ester (EPA-E) and docosahexaenoic acid ethyl ester (DHA-E) made from oceanic fish oil. Lotriga has been confirmed to have triglyceride (TG)-lowering effect and ameliorate lipid quality, including a larger LDL particle size, in clinical studies in patients with hypertriglyceridemia and is indicated for hyperlipidemia.

The goal of the treatment of hyperlipidemia is not only to ameliorate lipid parameters but also to inhibit cardiovascular events attributable to arterial sclerosis associated with hyperlipidemia.

An epidemiological study conducted overseas [1] suggests a combination therapy with an omega-3 fatty acid preparation and an HMG-CoA reductase inhibitor (statin) decreases all-cause deaths, onset of cardiac failure, etc. as compared with statin monotherapy in patients with myocardial infarction.

In addition, in Study GISSI-Prevenzione [2] conducted overseas, the secondary prevention effect of Lotriga on cardiovascular events has been demonstrated in patients with myocardial infarction, and Lotriga is indicated for prevention of recurrence of myocardial infarction in EU nations, such as the UK, France, Germany, Norway, and Austria.

However, there have been no results of epidemiological studies showing the status of onset of cardiovascular events in patients treated with Lotriga in Japan.

Therefore, in order to clarify the status of onset of cardiovascular events under long-term treatment with Lotriga in patients with hyperlipidemia on statin therapy with a high risk of cardiovascular events (patients with high-risk hyperlipidemia), this specific drug-use survey (survey) has been planned.

This survey will be conducted in compliance with the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) and relevant regulatory requirements.

2.0 Objectives

To reveal the status of onset of cardiovascular events associated with long-term treatment with Lotriga in high-risk hyperlipidemic patients on statin therapy in daily medical practice and to collect data from patients treated with Lotriga in this survey in order to compare the status of onset of cardiovascular events between patients treated with and without Lotriga just for information.

3.0 Survey Design

Prospective cohort study with control (patients treated without Lotriga)

4.0 Planned Sample Size and Rationale

4.1 Planned sample size

Patients treated with Lotriga: 7,000 patients

Patients treated without Lotriga: 7,000 patients

However, 8,400 patients will be enrolled as patients treated without Lotriga. By doing

this, approximately 7,000 patients are expected to be gathered as the control.

4.2 Rationale

In order to gather as many patients as possible within the feasible range in this survey, the planned sample size was set with 7,000 patients treated with Lotriga and 7,000 patients treated without Lotriga.

In JELIS [3] conducted in Japanese hypercholesterolemic patients, in terms of patients with a history of coronary artery disease, the incidences of cardiovascular events in the EPA-E group and the control group 5 years after the start of the observation period were 8.7% and 10.7%, respectively. By reference to the above, the incidences of cardiovascular events in patients treated with Lotriga and patients treated without Lotriga 3 years after the start of the observation period are estimated to be 4.8% and 6.0%, respectively. Given that patients are uniformly enrolled and the observation period is 3 years (36 months) in every patient, according to the method of Schoenfeld and Richter [4], a power of 80% will be ensured on log-rank test with the significance level of 5% (two-sided) in 5,600 each of patients treated with Lotriga and patients treated without Lotriga. Therefore, even with dropout of 20% of patients to be surveyed, assessment can be made at a certain level.

5.0 Target Patient Population

Patients who meet the following inclusion criteria and do not meet any of the exclusion criteria will be included. Among the patients, patients who will newly receive Lotriga will be enrolled as patients treated with Lotriga, and the other patients will be enrolled as patients treated without Lotriga. The PRECAUTIONS section of the Lotriga package insert should also be referenced for patients treated with Lotriga.

5.1 Inclusion criteria

Patients who meet all of the following criteria will be included.

[1] Patients with hyperlipidemia on statin therapy
[2] Outpatients
[3] Male patients aged ≥ 50 years or female patients aged ≥ 60 years
[4] Patients with a fasting TG level ≥ 150 mg/dL (within 3 months prior to the start of the observation period*[1])
[5] Patients with two or more of the following risk factors:
- Hypertension*[2]
- Type 2 diabetes mellitus*[3]
- Chronic kidney disease*[4]
- History of myocardial infarction or angina pectoris
- History of cerebral infarction
- Peripheral arterial disease*[5]

*1 Start date of Lotriga for patients treated with the drug; patient enrollment date (the date on which information concerning patient enrollment was entered in PostMaNet and an electronic signature was provided (See Section 8.3-2); the same is applicable to the below) for patients treated without Lotriga

*2 Systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or under antihypertensive therapy

*3 HbA1c ≥ 6.5% (NGSP value) or under treatment with antidiabetic drugs (including insulin)

*4 Persistence of either/both of eGFR < 60 mL/min/1.73 m^2 or/and positive urinary protein for ≥ 3 months prior to the start of observation period

*5 Ankle-brachial index ≤ 0.9

5.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded.

[1] Patients who have experienced coronary artery disease within a month prior to the start of the observation period

[2] Patients who have experienced cerebrovascular accident within a month prior to the start of the observation period

[3] Patients who have undergone cardiac surgery or revascularization (including coronary intervention and peripheral artery intervention) within a month prior to the start of the observation period

[4] Patients scheduled to undergo cardiac surgery or revascularization (including coronary intervention and peripheral artery intervention)

[5] Patients receiving treatment of malignant tumors

[6] Patients who have received eicosapentaenoic acid (EPA) preparations within a month prior to the start of the observation period or who are scheduled to receive EPA preparations after the start of the observation period

[7] Patients with bleeding (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, vitreous hemorrhage)

[8] Patients with a history of hypersensitivity to the ingredients of Lotriga (applicable only to patients who will receive Lotriga)

[9] Patients with a history of receiving Lotriga

6.0 Dosage and Administration

The usual adult dosage is 2 g of omega-3 fatty acid ethyl ester administered orally immediately after a meal once daily. The dose can be increased up to 2 g twice daily. The PRECAUTIONS section of the package insert should also be referenced.

7.0 Planned Number of Survey Sites by Specialty

Approximately 3,000 medical institutions (cardiology, internal medicine, etc.)

8.0 Methods

8.1 Duration of observation

36 months from the start date of observation period*. In patients treated with Lotriga, observation will be performed for 36 months even in the case of discontinuation of the drug.

*Start date for patients treated with Lotriga and patient enrollment date for patients treated without Lotriga

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<Matching factors of patient demographics>

- Age
  < 65 years, ≥ 65 years and < 75 years, ≥ 75 years
- Sex
  Male, female
- Important risk factors
  Presence/absence of a history of myocardial infarction, angina pectoris, or cerebral infarction
- Fasting TG level
  < 200 mg/dL, ≥ 200 mg/dL

Table 1 Patient Groups based on Matching Factors of Patient Demographics

			< 65 years	≥ 65 years and < 75 years	≥75 years
Male	With important risk factors*	Fasting TG < 200 mg/dL	[1]	[2]	[3]
		Fasting TG ≥ 200 mg/dL	[4]	[5]	[6]
	Without important risk factors*	Fasting TG < 200 mg/dL	[7]	[8]	[9]
		Fasting TG ≥ 200 mg/dL	[10]	[11]	[12]
Female	With important risk factors*	Fasting TG < 200 mg/dL	[13]	[14]	[15]
		Fasting TG ≥ 200 mg/dL	[16]	[17]	[18]
	Without important risk factors*	Fasting TG < 200 mg/dL	[19]	[20]	[21]
		Fasting TG ≥ 200 mg/dL	[22]	[23]	[24]

*history of myocardial infarction, angina pectoris, or cerebral infarction

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Table 2 Definition of an Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product. Note that the following events will also be handled as adverse events: • Any manifestation in an infant breastfed by a mother taking this drug • Any untoward manifestation in a child given this drug • Any manifestation due to occupational exposure to this drug • Any manifestation due to a counterfeit product of a prescription drug marketed by Takeda

Table 3 Criteria for Seriousness Assessment

An adverse event is assessed as "serious" if it results in any of the following outcomes:

1. results in death (Death),
2. is life-threatening (Life-threatening),
3. requires hospitalization or prolongation of existing hospitalization (Hospitalization/Prolongation of hospitalization),
4. results in persistent or significant disability/incapacity (Disability),
5. leads to a congenital anomaly or birth defect (Congenital anomaly), or
6. is any other important medical event that does not fulfil 1 to 5 above.

Serious adverse events include events described in the "Takeda Medically Significant AE List."

Takeda Medically Significant AE List

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

9.0 Planned Survey Period

Survey period: October 2014 to December 31, 2019

Patient enrollment period*

Patients treated with Lotriga: October 2014 to December 31, 2016

Patients treated without Lotriga: October 1, 2015 to December 31, 2016

*Patients treated with Lotriga shall not be enrolled (entered in PostMaNet) on or after January 1, 2017 even though they have received a prescription of the drug by December 31, 2016.
If the total number of the patients enrolled in the entire survey reach the planned sample size before December 31, 2016, patient enrollment may be closed before the end of the patient enrollment period.

If the patient enrollment period is shortened, the surveillance period will also be changed according to the shortened enrollment period.

10.0 Survey Items

The survey investigator shall enter the following data in PostMaNet. The schedule of this survey is shown in Appendix 1.

10.1 Patient enrollment

1) Survey items

Category of the target patients of the survey (patients treated with Lotriga or patients treated without Lotriga), prescription date (patients treated with Lotriga), enrollment date (patients treated without Lotriga: automatically entered), patient identification number, patient initials, sex, date of birth, assessment on the basis of the inclusion criteria, fasting TG level within 3 months prior to the start of observation, time of the onset of the most recent myocardial infarction or cerebral infarction prior to the start of observation period and the number of previous episodes (in patients with a history of myocardial infarction or cerebral infarction), assessment on the basis of the exclusion criteria, presence/absence of a history of percutaneous transluminal coronary angioplasty (PCI), coronary artery bypass grafting (CABG), or peripheral artery intervention and the time of the most recent procedure prior to the start of observation period

2) Time of data collection

At enrollment of the patient

10.2 Patient demographics information

1) Survey items

Height, weight, smoking history, drinking history, frequency of hospital visits, frequency of fish intake, presence/absence of a history or concurrence of cerebral/cardiac/vascular disorders*, time of onset of the most recent episode of cerebral hemorrhage or subarachnoid hemorrhage prior to the starting day of observation period and the number of previous episodes (if the patient has a history of cerebral hemorrhage or subarachnoid hemorrhage), family history of coronary artery disease and cerebrovascular accident (parents, brothers/sisters)

*Atrial fibrillation, left ventricular hypertrophy, cardiac failure, cerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack (TIA), aortic aneurysm, aortic dissection

2) Time of data collection

At the start of the observation period

10.3 Treatment information

1) Survey items

Status of the treatment with statin (drug name, daily dose, start and end dates), status of the treatment with Lotriga (daily dose, start and end dates), status of the treatment with EPA preparations (presence/absence, if present, with start and end dates, and indication), status of the treatment with activated vitamin D preparations

(presence/absence, if present, with start and end dates), presence/absence of diet therapy*, presence/absence of exercise therapy*, status of intake of OTC or dietary supplements (presence/absence and the details if present)*, status of treatment with antihyperlipidemic drugs (other than statins/Lotriga/EPA preparations), antihypertensives, antidiabetics, antiplatelets, and anticoagulants (presence/absence, if present, with details)*, presence/absence of the treatment with nitrates*

2) Time of data collection

From the start of observation until at 36 months (or at discontinuation of observation)
*At the start of observation period, at 6, 12, 18, 24, 30, and 36 months (or at discontinuation of observation)

10.4 Items of the tests and observation

10.4.1 Vital signs, electrocardiogram (ECG)

1) Measurement items

Blood pressure measured at a medical institution (systolic/diastolic), pulse rate, ECG

2) Time of data collection

At the start of the observation period, and the points of measurement at 6, 12, 18, 24, 30 and 36 months (or at discontinuation of observation)

10.4.2 Laboratory tests

1) Test items

TG*, total cholesterol (TC)[1)], HDL-cholesterol (HDL-C)[1)], LDL-cholesterol (LDL-C)[1)2)], EPA, docosahexaenoic acid (DHA), arachidonic acid (AA), dihomogammalinolenic acid (DHLA), HbA1c (NGSP value)

[1)] The status of a meal at blood collection (fasting or postprandial) will be investigated.

[2)] In the case of direct measurement

2) Time of data collection

At the start of the observation period, and the points of test at 6, 12, 18, 24, 30 and 36 months (or at discontinuation of observation)

10.4.3 Other observation items

1) Observation items

Presence/absence of pregnancy during the observation period (only in female patients treated with Lotriga)

Any pregnancy found during the observation period should be immediately notified to a Takeda representative. Based on a request by a Takeda representative, the survey investigator shall provide detailed information (wherever possible up to the outcome of pregnancy, such as premature delivery) separately using a pregnancy report form.

2) Time of data collection

From the start of observation period until at 36 months (or at discontinuation of observation)

10.4.4 Cardiovascular events

The following are defined as cardiovascular events. The definitions of the cardiovascular events are shown in Appendix 2.

- Major cardiovascular events

  Cardiovascular death [sudden death, fatal myocardial infarction, fatal cardiac failure, fatal stroke (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage), other cardiovascular deaths]

  Non-fatal myocardial infarction

  Non-fatal stroke (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage)
- Angina pectoris requiring hospitalization*
- Angina pectoris requiring coronary revascularization (PCI or CABG)
- Cardiac failure requiring hospitalization
- Transient ischemic attack requiring hospitalization
- Peripheral artery disease requiring hospitalization*
- Peripheral artery disease requiring surgery or peripheral artery intervention

*Including single-day percutaneous revascularization

1) Survey items

Presence/absence and details of cardiovascular events and non-cardiovascular deaths (cardiovascular events, etc.), rationale for diagnosis, presence/absence of diagnosis by a specialist, date of onset, date of death (in fatal cases), outcome, date of outcome assessment, causality between cardiovascular events, etc. and Lotriga (only in patients treated with Lotriga) (Table 4)

Follow-up investigation should be performed to the extent possible when the outcome of cardiovascular event, etc. is 'unresolved' or 'unknown' (non-fatal cardiovascular events) and when the causality between the cardiovascular event, etc. and Lotriga is determined to be unassessable.

2) Time of data collection

From the start of observation until at 36 months (or at discontinuation of observation)

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10.4.5 Continuation of observation

1) Survey items

Presence/absence of continuous observation, reason for discontinuation of observation, the last date of observation

2) Time of data collection

At 12 and 36 months after the start of the observation period (or at discontinuation of observation)

11.0 Items Concerning Evaluation

11.1 Primary endpoint

Time to the initial onset of one of the following cardiovascular events:

Any of the composite of the major cardiovascular events (See Section 10.4.4), angina pectoris requiring coronary revascularization (PCI or CABG), peripheral artery disease requiring surgery or peripheral artery intervention

11.2 Analysis of the primary endpoint

The cumulative incidence will be estimated using Kaplan-Meier method at each point.

Just for information, an analysis in consideration of the covariates (e.g., analysis using Cox proportional hazard model) will be performed for the period from the start of the observation period until the onset of an event to compare patients treated with Lotriga with patients treated without Lotriga. An analysis using propensity scores (e.g., propensity score matching) will be performed on an as-needed basis.

In addition, the same analysis will be performed respectively according to presence/absence of a history of myocardial infarction, angina pectoris, coronary revascularization, cerebral infarction, or cerebral hemorrhage.

11.3 Secondary endpoints

[1] Time to all-cause death (cardiovascular deaths and non-cardiovascular deaths)

[2] Time to the initial onset of any of the composite of the major cardiovascular events

[3] Time to the initial onset of any of all cardiovascular events (See Section 10.4.4)

[4] Time to the onset of individual cardiovascular events

11.4 Analysis of the secondary endpoints

The same analysis as that for the primary endpoint will be performed.

11.5 Other endpoints

[1] Time to the initial onset of any of the following: fatal myocardial infarction, non-fatal myocardial infarction, or angina pectoris requiring hospitalization

[2] Time to the initial onset of any of the following: fatal stroke, non-fatal stroke, or transient ischemic attack

[3] Changes in the vital signs (blood pressure and pulse rate), changes in the laboratory test values (serum lipids, EPA, DHA, AA, DHLA, and HbA1c), onset of any clinically problematic change on ECG

11.6 Analysis of other endpoints

The same analysis as that for the primary endpoint will be performed for [1] and [2] of Section 11.5.

Among the items listed in [3] of Section 11.5, the test values and the amounts of change

(values at each testing after the start of the observation period - baseline values) will be aggregated for vital signs and the changes in the laboratory test values. In addition, assessment results will be aggregated for ECG according to the point of testing.

12.0 Registration of Survey Information

Before the start of the survey, Takeda Pharmaceutical Company Limited will register the survey information with online public clinical trials registries:

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information
- National Institute of Health Clinical Trial Registration System: Clinical Trials.gov

13.0 Administrative Structure

13.1 Administrative manager

Post-marketing survey manager, Takeda Pharmaceutical Company Limited

13.2 Medical advisors

The medical advisors shall provide advice on interpretation, publication, etc. of the survey plan and the results.

PPD

13.3 Event assessment committee members

The committee members shall determine how to handle the cardiovascular events reported by the survey investigator and request additional information to the survey investigator on an as-needed basis. Event assessment shall be made with blinding of the surveyed patients (patients treated with Lotriga, patients treated without Lotriga).

PPD

13.4 Statistical advisor

The statistical advisor shall provide advice on preparation of the statistical analysis plan, etc.

PPD

14.0 Contract Research Organizations

PPD

Duty: Data management

PPD

Duties: Data management, statistical analysis, and medical writing

PPD

Duties: Storage of records, PDF conversion of AE reports and supportive activities related to provision of information

PPD

Duties: Construction and operation of PostMaNet

PPD

Duty: Management of progress of monitoring

PPD

Duty: Monitoring

PPD

Duty: Monitoring

PPD

Duty: Monitoring

15.0 Other Necessary Items

15.1 Protocol amendments

During the survey period, monitoring shall be performed regarding the progress of the surveillance, occurrence of ADRs unpredictable on the basis of the PRECAUTIONS and serious ADRs, any increase in the incidence of particular ADRs, appropriateness of the survey items, etc., and the protocol shall be reviewed and amended as necessary. If any partial change to the DOSAGE AND ADMINISTRATION, INDICATIONS, etc. is approved during the surveillance period, necessity of protocol amendments shall be discussed, and the protocol shall be amended as necessary.

15.2 Actions to be taken in response to detection of any issues or concerns

When any issue is found regarding the safety or efficacy, the data will be investigated in detail, and necessary actions will be determined.

16.0 References

[1] Macchia A, Romero M, D'Ettorre A, Tognoni G, Mariani J. Exploratory analysis on the use of statins with or without n-3 PUFA and major events in patients discharged for acute myocardial infarction: an observational retrospective study. PLoS One. 2013 May 6;8(5):e62772.

[2] Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI Prevenzione trial. Lancet. 1999;354:447-455.

[3] Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. Lancet. 2007;369:1090–1098.

[4] Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics. 1982 Mar;38(1):163-170.

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