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

NCT Number: NCT02285166

Statistical analysis plan Approve Date: 20-AUG-2020

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

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

Statistical Analysis Plan

(For Application for Re-examination)

<Lotriga Granular Capsules>

[OCEAN3]

Takeda Pharmaceutical Company Limited

Takeda Development Center Japan

PPD

Version 1: Released August 20, 2020

Table of Contents

1.0 Definitions of Terms

1.1 Definition

Term	Definition
Lotriga	Lotriga Granular Capsules
SOC	MedDRA/J System Organ Class
HLGT	MedDRA/J High Level Group Term
PT	MedDRA/J Preferred Term
LLT	MedDRA/J Lowest Level Term
Enrolled patient	Patient whose enrollment as a subject was approved
Subject with electronic questionnaire collected	An enrolled patient for whom an electronic questionnaire was sent by CCI
Subject with electronic questionnaire not collected	An enrolled patient who is not a subject with electronic questionnaire collected
Locked subject	A subject with electronic questionnaire collected for whom the questionnaire completion date was entered in the PMS system and the status of the questionnaire is "Final Approval"
Non-locked subject	A subject with electronic questionnaire collected who is not a locked subject
Enrolled subject administered Lotriga	A locked subject enrolled as a patient administered Lotriga at time of enrollment
Enrolled subject not administered Lotriga	A locked subject enrolled as a patient not administered Lotriga at time of enrollment
Patient not administered Lotriga	A locked subject not administered Lotriga
Patient administered Lotriga	A locked subject who is not a patient not administered Lotriga
Safety-evaluable subject	A locked subject included as a safety-evaluable subject, i.e., a subject to whom none of the following apply • Treated before the contract period • Enrolled 15 or more days after prescribing Lotriga • No data after start of observation • Not administered Lotriga
Safety-unevaluable subject	A locked subject excluded from the safety analysis set
Efficacy-evaluable subject	A locked subject included as efficacy-evaluable, i.e., a subject who has no major protocol violations, is evaluable for efficacy, and none of the following apply • Not on a statin • Does not have hyperlipidemia
Efficacy-unevaluable	A locked subject excluded from the efficacy analysis set
Primary prevention subject	An efficacy-evaluable subject who is not a secondary prevention subject

Term	Definition
Secondary prevention subject	An efficacy-evaluable subject who meets any of the following conditions • Has the risk factor "history of myocardial infarction or angina pectoris." • Has a history of PCI/CABG
Age	If observation start month and day < birthday, calculated as observation start year - birth year - 1 If observation start month and day ≥ birthday, calculated as observation start year - birth year If day of birth is unknown, calculated as 1st day of the month.
BMI	Calculated as Body weight (kg) / (0.0001 x Height (cm) x Height (cm)). Displayed to 1 decimal place, rounding off the second decimal place.
Observation start date	In patients administered Lotriga, treatment start date. In patients not administered Lotriga, patient enrollment date.
Observation end date	The last day of observation
Observation period (days)	The total observation period. The first and last day of the observation period are the same as "observation start date" and "observation end date," respectively. Calculated as Observation end date - Observation start date +1.
Duration of treatment (days)	The total period of time that Lotriga is administered. The total of each duration of Lotriga treatment recorded on the questionnaire. (The total number of days that the drug was actually administered, excluding times off the drug) Calculated as Treatment end date - Treatment start date + 1 for each duration of treatment.
Mean daily dose	Calculated as Daily dose x Total duration of treatment at each dose / Observation period. See above for calculation of observation period.
LDL cholesterol (Friedewald formula) (mg/dL)	Blood will be drawn for the laboratory test when the subject is fasting. Triglycerides will be calculated with the following equation if less than 400mg/dL. Displayed as an integer only, rounding off the first decimal place. Total cholesterol - HDL cholesterol - Triglycerides / 5 Note that LDL cholesterol is not calculated if "Total cholesterol - HDL cholesterol - Triglycerides / 5" ≤ 0.
non-HDL cholesterol (mg/dL)	Blood will be drawn for the laboratory test after a meal. Triglycerides will be calculated with the following equation if ≥ 400mg/dL. Displayed as an integer only, rounding off the first decimal place. Total cholesterol - HDL cholesterol
TC / HDL-C ratio	Calculated with the following equation. Displayed to 1 decimal place, rounding off the second decimal place. Total cholesterol / HDL cholesterol

Term	Definition
LDL-C / HDL-C ratio	Calculated with the following equation. Displayed to 1 decimal place, rounding off the second decimal place. LDL cholesterol (Friedewald formula) / HDL cholesterol
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting
TG	Triglycerides
Summary statistics	Number of subjects, mean, standard deviation, minimum, first quartile, median, third quartile, maximum

1.2 Number of digits displayed

Term	Definition
Summary statistics	Mean: Displayed to one place of the source data, rounding off the second place of the source data. Standard deviation: Displayed to two places of the source data, rounding off the third place of the source data. First quartile, median, third quartile: Displayed to one place of the source data, rounding off the second place of the source data. Minimum, maximum: The same number of places as the source is displayed.
Confidence interval	Displayed to two places of the source data, rounding off the third place of the source data.
P value	Displayed to 4 decimal places, rounding off the fifth place. If less than 0.0001, displayed as "<.0001."

1.3 Significance level, confidence coefficient

Significance level: 5% (two-sided test)

Confidence coefficient 95% (two-sided estimation)

1.4 Handing of assessment period data

Assessment periods are defined as start of observation, 6, 12, 18, 24, 30, and 36 months after start of observation, and last assessment time point.

In the case of multiple data for a particular period, the absolute value of the difference in the number of days from the basis number of days will be calculated and the date with the smallest absolute value will be used for that assessment period. If the absolute value is the same, the latter date of testing or measurement will be used.

The last assessment time point is defined as the value tested or measured on the latest date within the period of 1170 days from the observation start date (including values tested or measured during off-drug periods). In counting the number of days elapsed from the observation start date, the observation start date is defined as Day 0 and the previous day as Day -1.

Assessment period	Time window (Number of days from the observation start date)	Basis Number of Days
Start of observation	-90 to 0	0
6 months after start of observation	1 to 270	180
12 months after start of observation	271 to 450	360
18 months after start of observation	451 to 630	540
24 months after start of observation	631 to 810	720
30 months after start of observation	811 to 990	900
36 months after start of observation	991 to 1170	1080
Last assessment time point	1 to 1170	—

2.0 Special Drug Use Surveillance

<Lotriga Granular Capsules [OCEAN3]>

2.1 Disposition of Subjects (Composition of subject population)

Subjects tabulated for analysis	Enrolled patients in relevant Special Drug Use Surveillance
Information tabulated for analysis	Number of enrolled patients, number of study sites with enrolled patients, number of subjects with electronic questionnaire collected, number of subjects with electronic questionnaire not collected, number of locked subjects, number of non-locked subjects, number of enrolled subjects administered Lotriga, number of enrolled subjects not administered Lotriga, number of safety-evaluable subjects, number of safety-unevaluable subjects, number of efficacy-evaluable subjects, and number of efficacy-unevaluable subjects A site where subjects are enrolled in different departments should not be counted more than once in the number of study sites with enrolled patients. For subjects with electronic questionnaires not collected, the number of subjects with electronic questionnaires not collected for each of the following reasons and total number of subjects <Reason for not collecting questionnaire> • Survey in progress • Questionnaire could not be collected – Investigator moved – Due to the health of the investigator – Enrolled 15 or more days after prescribing Lotriga (before collection of electronic questionnaire) – Other For safety- and efficacy-unevaluable subjects, number of subjects excluded for each of the following reasons and total number of subjects. If multiple reasons apply to the same subject, the subject will be tabulated more than once. <Reasons for exclusion from safety analysis set> • Treated before the contract period • Enrolled 15 or more days after prescribing Lotriga • No data after start of observation • Not administered Lotriga <Reasons for exclusion from efficacy analysis set> • Non-target disease • Exclusion criteria violation Items for which the number of subjects is 0 are not to be output. A listing with the reasons for exclusion will be prepared for safety- and efficacy-

	unevaluable subjects.
Figure and Table Nos.	Figure 2.1, Table 2.1

2.2 Patient demographics

Subjects tabulated for analysis	Efficacy-evaluable subjects in relevant Special Drug Use Surveillance
Information tabulated for analysis	Each item will be classified by the following categories, and the number of subjects and frequency will be tabulated. These tabulations will be performed in enrolled subjects administered Lotriga, enrolled subjects not administered Lotriga, and in a pooled population of the two.

Item	Category
Category of patient in surveillance	Enrolled subjects administered Lotriga, enrolled subjects not administered Lotriga
Sex	Male, female
Age	Summary statistics
	< 65 years, ≥ 65 years to < 75 years, ≥ 75 years
Number of risk factors	2, 3, 4, 5, 6
(Itemization)	
Hypertension	Absent, Present
Type 2 diabetes mellitus	Absent, Present
Chronic kidney disease	Absent, Present
History of myocardial infarction or angina pectoris	Absent, Present
History of cerebral infarction	Absent, Present
Peripheral artery disease	Absent, Present
Breakdown of risk factors (history of myocardial infarction or angina pectoris) (may be counted more than once) *Only if history of myocardial infarction or angina pectoris "present"	Myocardial infarction, angina pectoris
Myocardial infarction /	

		angina pectoris	
		Details on history of myocardial infarction *Only if history of myocardial infarction "present" Time of onset (closest to observation start date) Number of past episodes	 Within last year, prior to last year 1, 2, 3 or more
		Details on history of cerebral infarction *Only if history of cerebral infarction "present" Time of onset (closest to observation start date) Number of past episodes	 Within last year, prior to last year 1, 2, 3 or more
		History of PCI/CABG	Absent, Present
		Details on history of PCI/CABG *Only if history of PCI/CABG "present" Time performed (closest to observation start date)	 Within last year, prior to last year
		History of peripheral artery intervention	Absent, Present
		Details on history of peripheral artery intervention *Only if history of peripheral artery intervention "present" Time performed (closest to observation start date)	 Within last year, prior to last year
		BMI	Summary statistics < 25 kg/m^2, 25 to < 30 kg/m^2, ≥ 30 kg/m^2, Unknown
		Smoking history	Never smoked, Current smoker, Previous smoker/current non-smoker
		Alcohol use (Drinks alcoholic beverages almost daily [≥ 5 days a week])	Yes, No
		Hospital visit frequency	≥ Twice a month, About once a month, 1-2 times every 3 months, Other

		Fish consumption frequency	Almost every day, About once every 2 days, Once-twice a week, Almost never, Missing data
		Previous or concurrent cerebral or cardiac vascular disorders	Absent, Present
		Details on previous or concurrent cerebral or cardiac vascular disorders *Only if previous or concurrent cerebral or cardiac vascular disorders "present" (Itemization) Atrial fibrillation Left ventricular hypertrophy Cardiac failure Cerebral hemorrhage Subarachnoid hemorrhage Transient ischemic attack (TIA) Aortic aneurysm Aortic dissection	 Absent, Present Absent, Present Absent, Present Absent, Present Absent, Present Absent, Present Absent, Present Absent, Present
		Details on previous or concurrent cerebral hemorrhage *Only if previous or concurrent cerebral hemorrhage "present" Time of onset (closest to observation start date) Number of past episodes	 Within last year, prior to last year 1, 2, 3 or more
		Details on previous or concurrent subarachnoid hemorrhage *Only if previous or concurrent subarachnoid hemorrhage "present" Time of onset (closest to observation start date) Number of past episodes	 Within last year, prior to last year 1, 2, 3 or more
		Family history of coronary artery	Absent, Present

	disorders (parents, siblings)	
	Family history of cerebrovascular disorders (parents, siblings)	Absent, Present
	TG (mg/dL) within 3 months before start of observation (Start of observation)	Summary statistics < 200 mg/dL, ≥ 200 mg/dL
Figure and Table Nos.	Table 2.2	

2.3 Description of treatment (status of Lotriga treatment)

Subjects tabulated for analysis	Efficacy-evaluable subjects in relevant Special Drug Use Surveillance
Information tabulated for analysis	Each item will be classified by the following categories, and the number of subjects and frequency will be tabulated. These tabulations will be performed in a pooled population of enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga.

Item	Category
Lotriga treatment (during the observation period)	Absent, Present
Details of Lotriga treatment *Only if Lotriga treatment "present"	
Starting dose	2 g, 4 g, other
Change in daily dose	Absent, Present
Description of change in daily dose	2 g → 4 g, 4 g → 2 g, Other
Mean daily dose	< 2 g, 2 to < 4 g, 4 to < 6 g, ≥ 6 g
Duration of treatment	1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 to 720 days, 721 to 1080 days, ≥ 1081 days

Figure and Table Nos.	Table 2.3

2.4 Description of treatment (status of statin treatment)

<table>
<tr><td>Subjects tabulated for analysis</td><td>Efficacy-evaluable subjects in relevant Special Drug Use Surveillance</td></tr>
<tr><td>Information tabulated for analysis</td><td>Each item will be classified by the following categories, and the number of subjects and frequency will be tabulated. These tabulations will be performed in enrolled subjects administered Lotriga, enrolled subjects not administered Lotriga, and in a pooled population of the two.
<table>
<tr><th>Item</th><th>Category</th></tr>
<tr><td>Statin treatment</td><td>Absent, Present</td></tr>
<tr><td>Details of statin treatment
*Only if statin treatment “present”
Type (may be counted more than once)</td><td>Pravastatin sodium, simvastatin, fluvastatin sodium, atorvastatin calcium, pitavastatin calcium, rosuvastatin calcium</td></tr>
<tr><td>Duration of treatment (during observation period)</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 to 720 days, 721 to 1080 days, ≥ 1081 days</td></tr>
</table></td></tr>
<tr><td>Figure and Table Nos.</td><td>Table 2.4</td></tr>
</table>

2.5 Description of treatment (status of EPA product treatment)

Subjects tabulated for analysis	Efficacy-evaluable subjects in relevant Special Drug Use Surveillance

<table>
<tr><td>Information tabulated for analysis</td><td>Each item will be classified by the following categories, and the number of subjects and frequency will be tabulated. These tabulations will be performed in enrolled subjects administered Lotriga, enrolled subjects not administered Lotriga, and in a pooled population of the two.

<table><tr><th>Item</th><th>Category</th></tr><tr><td>EPA product treatment</td><td>Absent, Present</td></tr><tr><td>Details of EPA treatment
*Only if EPA product treatment “present”
Reason for treatment (may be counted more than once)</td><td>Lipid control, occurrence of cardiovascular event (or increased risk thereof), request of patient, other</td></tr></table></td></tr>
<tr><td>Figure and Table Nos.</td><td>Table 2.5</td></tr>
</table>

2.6 Description of treatment (status of active vitamin D treatment)

<table>
<tr><td>Subjects tabulated for analysis</td><td>Efficacy-evaluable subjects in relevant Special Drug Use Surveillance</td></tr>
<tr><td>Information tabulated for analysis</td><td>Each item will be classified by the following categories, and the number of subjects and frequency will be tabulated. These tabulations will be performed in enrolled subjects administered Lotriga, enrolled subjects not administered Lotriga, and in a pooled population of the two.

<table><tr><th>Item</th><th>Category</th></tr><tr><td>Active vitamin D treatment</td><td>Absent, Present</td></tr></table></td></tr>
<tr><td>Figure and Table Nos.</td><td>Table 2.6</td></tr>
</table>

2.7 Pregnancy during the observation period

Subjects tabulated for analysis	Safety-evaluable women who received Lotriga in the relevant Special Drug Use Surveillance

<table>
<tr><td>Information tabulated for analysis</td><td>Each item will be classified by the following categories, and the number of subjects and frequency will be tabulated.

<table><tr><th>Item</th><th>Category</th></tr><tr><td>Presence/absence of pregnancy during the observation period</td><td>Absent, Present</td></tr></table></td></tr>
<tr><td>Figure and Table Nos.</td><td>Table 2.7</td></tr>
</table>

2.8 Treatment status of dietary therapy, exercise therapy, OTC or supplement use, and concomitant medications other than statins and EPA products

<table>
<tr><td>Subjects tabulated for analysis</td><td>Efficacy-evaluable subjects in relevant Special Drug Use Surveillance</td></tr>
<tr><td>Information tabulated for analysis</td><td>Each item will be classified by the following categories, and the number of subjects and frequency will be tabulated for each assessment period. These tabulations will be performed in enrolled subjects administered Lotriga, enrolled subjects not administered Lotriga, and in a pooled population of the two. The tabulations will be based on the assessment time points on the questionnaire.
However, any data at 12 months after start of observation or at discontinuation will be handled as data at 6 months if there is no data at 6 months and will be handled as data at 12 months if there is data at 6 months. In the same manner, data at 36 months after start of observation or at discontinuation of observation will be handled as data at 18 months if there is no data at 18 months and will be handled as data at 24 months if there is data at 18 months. Further, data from 24, 30, and 36 months will be handled in the same manner.

<table><tr><th>Item</th><th>Category</th></tr><tr><td>Presence or absence of dietary therapy</td><td>Absent, Present</td></tr><tr><td>Presence or absence of exercise therapy</td><td>Absent, Present</td></tr><tr><td>Use of OTC or supplements
(Breakdown for “present”; may be counted more than once)</td><td>Absent, Present, Unknown

EPA, DHA, vitamin D, other</td></tr><tr><td>Administration of hyperlipidemia treatment (other than statins, Lotriga, or EPA)
(Breakdown for “present”; may be counted more than once)</td><td>Absent, Present

Anion exchange resin, small intestinal cholesterol transporter inhibitors, probucol, fibrates,</td></tr></table></td></tr>
</table>

		nicotinic acid products, other
	Administration of antihypertensives (Breakdown for "present"; may be counted more than once)	Absent, Present ARB, ACE-I, CCB, α-blockers, β-blockers, αβ-blockers, diuretics, renin inhibitors, other
	Administration of antidiabetics (Breakdown for "present"; may be counted more than once)	Absent, Present SUs, BG agents, α-GIs, TZDs, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, glinides, insulin products, other
	Administration of antiplatelet drugs (Breakdown for "present"; may be counted more than once)	Absent, Present Aspirin, ticlopidine, clopidogrel, cilostazol, other
	Administration of anticoagulants (Breakdown for "present"; may be counted more than once)	Absent, Present Warfarin, factor Xa inhibitors, thrombin inhibitors, other
	Administration of nitrates	Absent, Present
Figure and Table Nos.	Table 2.8	

2.9 Analysis of primary outcome measures

Subjects tabulated for analysis	Efficacy-evaluable subjects in relevant Special Drug Use Surveillance
Information tabulated for analysis	[Analysis of primary outcome measures] First onset of any of the following cardiovascular events − The following key major cardiovascular events 1. Major cardiovascular event 1) Cardiovascular death (sudden death, fatal myocardial infarction, fatal cardiac failure, fatal stroke [cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage], other cardiovascular death) 2) Non-fatal myocardial infarction 3) Non-fatal stroke (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage) − Anginal pectoris requiring coronary revascularization (PCI or CABG) − Peripheral artery disease requiring surgery or peripheral artery intervention [Description of analysis] The following analysis will be performed. If no events occur during the observation period (the period from the observation start date to the observation end date), the

	censoring time point will be the observation period end date. I. Kaplan-Meier estimates of cumulative incidence every 6 months in enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga II. Comparison of enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga, based on a Cox proportional hazards model, using as covariates age (continuous value), sex, BMI, smoking history, fish consumption frequency, presence or absence of previous or concurrent cerebral or cardiac vascular disorders, fasting triglycerides (continuous value), presence or absence of administration of antihypertensives, presence or absence of administration of antidiabetics, presence or absence of administration of antiplatelet drugs, presence or absence of administration of anticoagulants, and number of risk factors (continuous value). III. For covariates whose interactions with the treatment group are statistically significant at a significance level of 5% when a Cox proportional hazard model with all of the covariates in II., treatment group, and interactions between the covariates and the treatment group is applied to the primary endpoint, the following analyses will be performed: Estimates of cumulative incidence by every 6 months by each category* of the covariates by the treatment group based on Kaplan-Meier methods Comparison of the treatment group based on a Cox proportional hazard model with only the treatment group. (*: for the continuous covariates, the following categorization will be made. age: "< 65 years, ≥ 65 years to < 75 years, ≥ 75 years," BMI: "< 25 kg/m2, 25 to < 30 kg/m2, ≥ 30 kg/m2," fasting triglycerides: "< 200 mg/dL, ≥ 200 mg/dL," and number of risk factors: "2, 3, or 4 to 6") The level at which smoking history and fish consumption frequency are collected on the questionnaire will be changed according to the following logic. Smoking history: "Current smoker," "previous smoker/current non-smoker," and "missing data" will be consolidated into one level. Fish consumption frequency: Missing data will be handled as one level. The same analysis as in III. will be performed in the respective subgroups of primary prevention subjects and secondary prevention subjects by presence or absence of history of myocardial infarction, angina pectoris, cerebral infarction, or cerebral hemorrhage and by presence or absence of history of coronary revascularization. For reference, the same analyses as in I and II will be performed in "patients administered Lotriga and patients not administered Lotriga" instead of "enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga."
Figure and Table	Table 2.9

Nos.	

2.10 Analysis of secondary outcome measures

Subjects tabulated for analysis	Efficacy-evaluable subjects in relevant Special Drug Use Surveillance
Information tabulated for analysis	[Secondary outcome measures] [1] All deaths (cardiovascular deaths and deaths other than cardiovascular deaths) [2] First onset of any of the following key major cardiovascular events [3] First onset of any of the following cardiovascular events 1. Major cardiovascular events 1) Cardiovascular death (sudden death, fatal myocardial infarction, fatal cardiac failure, fatal stroke [cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage], other cardiovascular death) 2) Non-fatal myocardial infarction 3) Non-fatal stroke (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage) 2. Angina pectoris requiring hospitalization* 3. Anginal pectoris requiring coronary revascularization (PCI or CABG) 4. Cardiac failure requiring hospitalization 5. Transient ischemic attack requiring hospitalization 6. Peripheral artery disease requiring hospitalization* 7. Peripheral artery disease requiring surgery or peripheral artery intervention *Including percutaneous revascularization performed on an out-patient basis. [4] Onset of individual cardiovascular events [Description of analysis] The same analysis will be performed as the analysis in I. and II. for the primary outcome measure.
Figure and Table Nos.	Table 2.10

2.11 Analysis of other outcome measures

Subjects tabulated for analysis	Efficacy-evaluable subjects in relevant Special Drug Use Surveillance
Information tabulated for analysis	[Other outcome measures] [1] First onset of any of fatal myocardial infarction, non-fatal myocardial infarction, and angina pectoris requiring hospitalization [2] First onset of any of fatal stroke, non-fatal stroke, and transient ischemic attack

	requiring hospitalization [3] Time-course of vital signs (systolic blood pressure, diastolic blood pressure, and heart rate), time course of laboratory test results (TG, TC, HDL-C, LDL-C, non-HDL-C, TC/HDL-C ratio, LDL-C/HDL-C ratio, EPA, DHA, AA, DHLA, and HbA1c [NGSP value]), and occurrence of clinically significant changes in electrocardiogram [Description of analysis] The same analysis will be performed as the analysis in [1] and [2] for the primary outcome measure. Among the items in [3], summary statistics for test values and change (Test value for each testing time point - Test value at start of observation) at each testing time point will be calculated for the time-courses of vital signs and laboratory test results. The results of electrocardiogram interpretations will be tabulated at each assessment time point.
Figure and Table Nos.	Table 2.11

2.12 Supplemental analysis of primary outcome measures

Subjects tabulated for analysis	Efficacy-evaluable subjects in relevant Special Drug Use Surveillance
Information tabulated for analysis	[Analysis of primary outcome measures] First onset of any of the following cardiovascular events - The following key major cardiovascular events 1. Major cardiovascular events 1) Cardiovascular death (sudden death, fatal myocardial infarction, fatal cardiac failure, fatal stroke [cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage], other cardiovascular death) 2) Non-fatal myocardial infarction 3) Non-fatal stroke (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage) - Anginal pectoris requiring coronary revascularization (PCI or CABG) - Peripheral artery disease requiring surgery or peripheral artery intervention [Description of analysis] The following supplemental analysis of the above primary outcome measures will be performed using propensity scores. The propensity scores for each subject will be estimated using a logistic regression model in which the probability of assignment to the Lotriga treatment group

converted to a logit is the response variable and the following items are the objective variables.

The covariates to be included in the propensity score model are defined as follows.

Age (continuous value), sex, BMI, smoking history, fish consumption frequency, presence or absence of previous or concurrent cerebral or cardiac vascular disorders, fasting triglycerides (continuous value), presence or absence of administration of antihypertensives, presence or absence of administration of antidiabetics, presence or absence of administration of antiplatelet drugs, presence or absence of administration of anticoagulants, number of risk factors (continuous value)

The level at which smoking history and fish consumption frequency are collected on the questionnaire will be changed according to the following logic.

Smoking history: "Current smoker," "previous smoker/current non-smoker," and "missing data" will be consolidated into one level.

Fish consumption frequency: Missing data will be handled as one level.

[1] Distribution of propensity scores

Summary statistics will be calculated for estimated propensity scores. In addition, the number and proportion of subjects in categories produced by demarcating propensity scores by the quartiles will be tabulated. This tabulation will be performed separately from that performed by enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga.

[2] Weighted analysis using inverse probability weighting (IPW)*

Using IPW for each subject, Kaplan-Meier estimates of cumulative incidence every 6 months in enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga and Cox regression with treatment group (enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga) included in the model will be performed. As necessary, logistic regression (where the model includes treatment group) and doubly robust estimation with IPW will be performed, handling events in the primary outcome measure as binary data (presence or absence of event). The explanatory variables included in the outcome regression model in the doubly robust estimation will be the same as in the propensity score model. Estimates, standard error, and two-sided 95% confidence interval will be calculated for the treatment groups in the Cox regression, logistic regression, and doubly robust estimation. Robust decentralization will be used for the standard error.

[3] Propensity score matching

One-to-one nearest neighbor matching without replacement using 0.2-fold the standard deviation of estimated propensity scores converted to logits as the calipers will be applied. The standard difference between enrolled subjects

	administered Lotriga and enrolled subjects not administered Lotriga will be calculated for variables used for estimating propensity scores before and after matching. In propensity-matched populations, Kaplan-Meier estimates of cumulative incidence every 6 months in enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga and Cox regression analysis with treatment group (enrolled subjects administered Lotriga and enrolled subjects not administered Lotriga) included in the model will be performed. As necessary, logistic regression (where the model includes treatment group) will be performed, handling events in the primary outcome measure as binary data (presence or absence of event). Estimates, standard error, and two-sided 95% confidence interval will be calculated for the treatment groups in the Cox regression and logistic regression. Robust decentralization will be used for the standard error. [4] Weighted analysis using matching weight (MW)* The same analysis as in [2] will be performed with MW weighting for each subject. However, a bootstrap approach will be used in the doubly robust estimation. [5] Other As necessary, analysis with a marginal structural Cox model will be performed using covariates, etc., estimated every 6 months.
Figure and Table Nos.	Table 2.12

*Li. L and Greene. T (2013). A Weighting Analogue to Pair Matching in Propensity Score Analysis. Int J Biostat, 31;9(2):215-34.

3.0 Safety analysis

3.1 Listing of Occurrence of Adverse Reactions and Infections in Postmarketing Surveillance, Etc.

(Attached Form 15)

<table>
<tr><td>Subjects tabulated for analysis</td><td colspan="2">Safety-evaluable subjects in relevant Special Drug Use Surveillance</td></tr>
<tr><td>Information tabulated for analysis</td><td colspan="2">The following items will be tabulated from each postmarketing surveillance, etc.
<table>
<tr><th>Item</th><th>Information tabulated for analysis</th></tr>
<tr><td>Number of safety-evaluable subjects</td><td>Number of subjects in the “subjects tabulated for analysis” (above) from the relevant analysis.</td></tr>
<tr><td>Number of subjects with adverse drug reactions, etc.</td><td>Number of subjects who experienced adverse drug reactions, etc.</td></tr>
<tr><td>Percentage of subjects with adverse drug reactions, etc.</td><td>This will be calculated as Number of subjects with adverse drug reactions, etc. / Number of safety-evaluable subjects x 100.</td></tr>
<tr><td>Types of adverse drug reactions, etc.</td><td>When performing the analysis the following method will be employed.
[Types of adverse drug reactions, etc.]
• MedDRA/J will be used for coding adverse drug reactions, etc. Adverse drug reactions, etc., will be tabulated by SOC and then by PT within the SOCs. For the SOC of “Investigations,” adverse drug reactions, etc. will be tabulated by HLGT (arranged in ascending order of HLGT codes, but not output) and then by PT.
• The number of subjects with and incidence of adverse drug reactions, etc. will be listed in the Internationally Agreed Order of SOCs. If the same SOC occurs multiple times in the same subject, it will be counted as 1 subject in that SOC.
• For PTs, the number of subjects with and incidence of adverse drug reactions, etc. will be listed in ascending order of PT codes. If the same PT occurs multiple times in the same subject, it will be counted as 1 subject with that PT.</td></tr>
</table></td></tr>
</table>

Figure and Table Nos.	Table 3.1

4.0 Summary of the subjects in the postmarketing surveillance, etc.

4.1 Summary of Subjects in Postmarketing Surveillance, Etc. (Attached Form 16)

Subjects tabulated for analysis	Subjects with collected questionnaires in relevant Special Drug Use Surveillance
Information tabulated for analysis	Listings will be prepared for the following items in accordance with (Notes 1-3) of Attached Form 16 in "Re-examination Notification," Notification No. 1128-2, of the Pharmaceutical Evaluation Division, PSEHB, dated November 28, 2017.

Item
Subject No.
Site
Sex
Date of birth
Reason for use (disease code, disease name)
Complications (disease code, disease name)
Route of administration
Maximum dose
Mean dose
Unit
Duration of use
Concomitant drugs (drug code, drug name)
Extent of effect
Adverse drug reactions (disease code, disease name, outcome)
Questionnaire No.
Dropouts

Figure and Table Nos.	Table 4.1