Title: Lotriga Granular Capsules Special Drug Use Surveillance [Long-term use survey]

NCT Number: NCT02153073

Statistical analysis plan Approve Date: 22-Sep-2017

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

Statistical Analysis Plan
(for Periodic Safety Reporting/Reexamination Application)
<Lotriga Granular Capsules>
[Long-term use]

Takeda Pharmaceutical Company Limited
Japan Development Center
Director of Biostatistics Division

PPD

Ver. 4.0: Prepared on September 22, 2017

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1.0 Definitions of Terms

1.1 Definitions

Item	Definition
Survey unit period (periodic safety report)	Periodic Safety Report 1: July 22, 2012 to January 21, 2013 Periodic Safety Report 2: January 22, 2013 to July 21, 2013 Periodic Safety Report 3: July 22, 2013 to January 21, 2014 Periodic Safety Report 4: January 22, 2014 to July 21, 2014 Periodic Safety Report 5: July 22, 2014 to July 21, 2015 Periodic Safety Report 6: July 22, 2015 to July 21, 2016 Periodic Safety Report 7: July 22, 2016 to July 21, 2017 Periodic Safety Report 8: July 22, 2017 to July 21, 2018
Drug	Lotriga Granular Capsules
SOC	System organ class of MedDRA.
HLGT	High level group term of MedDRA.
PT	Preferred term of MedDRA.
LLT	Lowest level term of MedDRA.
Enrolled patient	A patient approved for enrollment in the Study.
Patient with eCRF collected	An enrolled patient whose eCRF was submitted via CCI .
Patient with eCRF uncollected	An enrolled patient other than a patient with eCRF collected.
Locked patient	A patient who has completed the approval process in the PMS system.
Unlocked patient	A patient with eCRF collected other than a locked patient.
Safety-evaluable patient	A locked patient included in safety evaluation.
Safety-unevaluable patient	A locked patient excluded from safety evaluation.
Efficacy-evaluable patient	A safety-evaluable patient included in efficacy evaluation.
Efficacy-unevaluable patient	A safety-evaluable patient excluded from efficacy evaluation.
ADR	An abbreviated form of the term ‘adverse drug reaction or infection.’ Refers to an adverse event other than those judged by the investigator as ‘not related’ in causality to the Drug. In this plan, ‘adverse drug reactions or infections’ is used in headings, and ‘ADRs’ is used in the text and tables.
Serious adverse event (SAE)	[Prior-approval data] An adverse event (AE) judged as ‘serious’ by the trial investigator. [Surveillance data] An adverse event (AE) judged as ‘serious’ by the investigator. Note that events listed in the separate MedDRA code list of the Takeda Medically Significant AE List should be treated as serious even if judged as

Item	Definition
	'not serious' by the investigator.
Bleeding-related event	An event falling under Standardized MedDRA Query (SMQ) code 20000038 (hemorrhagic SMQ [narrow scope]).
Rate of patients	[For safety compilation with safety-evaluable patients] Calculated by the following equation: [Number of Patients] / [Number of Safety-Evaluable Patients] × 100. [For safety compilation with safety-unevaluable patients] Calculated by the following equation: [Number of Patients] / [Number of Safety-Unevaluable Patients] × 100.
Onset time	Calculated by the following equation: [Onset Date] - [Start Date] + 1. If the onset date is unknown, use the first day of the month as the onset date in this equation. However, use the start date as the onset date if [Start Year & Month] = [Onset Year & Month].
Liver patient	A patient with 'fatty liver,' 'alcoholic fatty liver,' 'chronic hepatitis' or 'hepatic cirrhosis' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000005 (hepatic SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Kidney patient	A patient with 'diabetic nephropathy,' 'glomerulonephritis' or 'chronic kidney disease (CKD)' check-marked in the Complication Details field. Or a patient with a complication falling under the Takeda MedDRA query (TMQ) (Renal Disease) in the Complication Details (Other Diseases) field.
Heart patient	A patient with 'myocardial infarction,' 'angina pectoris' or 'atrial fibrillation' check-marked in the Complication Details field. Or a patient with a complication falling under the SOC code 10007541 (cardiac disorders) in the Complication Details (Other Diseases) field.
Cerebrovascular patient	A patient with 'cerebral infarction' or 'cerebral hemorrhage' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000060 (cerebrovascular SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Diabetic patient	A patient with 'diabetes' check-marked in the Complication Details field. Or a patient with a complication falling under the TMQ code (Diabetes Mellitus Confirmed diagnosis, excl diagnostics) in the Complication Details (Other Diseases) field.
Hypertensive patient	A patient with 'hypertension' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000147 (hypertensive SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Myocardial infarction	A patient with 'myocardial infarction' check-marked in the Complication

Item	Definition
patient	Details field. Or a patient with a complication falling under the SMQ code 20000047 (myocardial infarction SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Anginal patient	A patient with 'angina pectoris' check-marked in the Complication Details field. Or a patient with a complication falling under the MedDRA PT code 10002383 (angina pectoris), 10002388 (unstable angina pectoris), 10036759 (Prinzmetal angina), or 10058144 (postinfarction angina) in the Complication Details (Other Diseases) field.
Atrial fibrillation patient	A patient with 'atrial fibrillation' check-marked in the Complication Details field. Or a patient with a complication falling under the MedDRA PT code 10003658 (atrial fibrillation) in the Complication Details (Other Diseases) field.
Ischemic cerebrovascular patient	A patient with 'cerebral infarction' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000063 (ischemic cerebrovascular disease SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Hemorrhagic cerebrovascular patient	A patient with 'cerebral hemorrhage' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000064 (hemorrhagic cerebrovascular disease SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Bleeding-related event patient	A patient with a complication falling under the SMQ code 20000038 (bleeding SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Age	Calculated by the following equation: [Start Year] - [Birth Year] - 1 if [Start Month & Day] < [Birth Month & Day]. Calculated by the following equation: [Start Year] - [Birth Year] if [Start Month & Day] ≥ [Birth Month & Day]. If the birth day is unknown, use the first day of the month instead in this equation.
BMI	Calculated by the following equation: [Weight (kg)] / (0.0001 × [Height (cm)] × [Height (cm)]). Indicated by rounding off to the first decimal place.
Disease duration (in years)	Calculated by the following equation: ([Start Year & Month] - [Year & Month of Hyperlipidemia Diagnosis] + 1) / 12. Indicated by rounding off to the first decimal place.
Start date	The start date of first administration of the Drug stated in the Treatment Duration field of the eCRF.
End date	The end date of last administration of the Drug stated in the Treatment Duration field of the eCRF. However, if the end date of last administration is in 'ongoing 12 months after

Item	Definition
	baseline,' the end date should be the start date plus 405 days.
Observation period (in days)	Refers to the entire period of observation. The start date and end date of observation period should be the same as the 'start date' and 'end date,' respectively. Calculated by the following equation: [End Date] - [Start Date] + 1.
Treatment duration (in days)	Refers to the entire period of treatment. A total of Drug dosing periods in the number of actual administration days, excluding washout period. Calculated as a total of ([End Date] - [Start Date] + 1) in the number of actual administration days, excluding washout period.
Mean daily dose	Calculated by the following equation: Total of ([Daily Dose] × [Total Period of Treatment with the Dose]) / [Observation Period]. See the above for calculation of observation period.
Concomitant medication	A drug used during the surveillance period. However, concomitant medications exclude drugs used for adverse events occurring during the period.
Antihyperlipidemic drug	A drug starting with any of the following drug codes: 218, 2190006, 2190101, 2190102, 2190103, 2190104, 290006, 3133001, 3133400, 3399004.
Statins drug	A drug starting with any of the following drug codes: 2189010, 2189011, 2189012, 2189015, 2189016, 2189017.
Fibrate drug	A drug starting with drug code: 2183.
Intestinal transporter inhibitor	A drug starting with drug code: 2189018.
Anion-exchange resin	A drug starting with any of the following drug codes: 2189009, 2189014.
Nicotinic acid derivative	A drug starting with any of the following drug codes: 2189004, 2189005, 2190006.
Probucol	A drug starting with drug code: 2189008.
Ethyl icosapentate (EPA)	A drug starting with drug code: 3399004.
Anticoagulant drug	A drug starting with any of the following drug codes: 333, 2190408, 6343424.
Antiplatelet drug	A drug starting with any of the following drug codes: 3399 (excluding 3399004), 2171010, 2171402.
Anticoagulant/antiplatelet drug	A drug that falls under the class of either anticoagulant or antiplatelet drugs
LDL cholesterol (Friedewald formula) (mg/dL)	Calculated the equation below if the patient is fasting at the time of blood collection for laboratory testing with triglyceride 400 mg/dL or over. Indicated by rounding off to an integer alone. Total cholesterol - HDL cholesterol - triglyceride / 5
Non-HDL cholesterol (mg/dL)	Calculated by the equation below if triglyceride is 400 mg/dL or over. Indicated by rounding off to an integer alone. Total cholesterol - HDL cholesterol

Item	Definition
TC/HDL-C ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. Total cholesterol / HDL cholesterol
LDL-C/HDL-C ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. LDL cholesterol (Friedewald formula) / HDL cholesterol
LDL-C/Apo-B ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. LDL cholesterol (Friedewald formula) / Apo-B (fasting)
Summary statistics	Number of patients, mean value, standard deviation, minimum value, first quartile, median, third quartile, maximum value

1.2 Number of Display Digits

Item	Definition
Percentage (%)	Rate of patients with ADRs: Indicated by rounding off to the second decimal place. Other than above: Indicated by rounding off to the first decimal place.
Summary statistics	Mean value: Indicated by rounding off to the first digit below the raw numerical data. Standard deviation: Indicated by rounding off to the second digit below the raw numerical data. First quartile, median, third quartile: Indicated by rounding off to the first digit below the raw numerical data. Minimum value, maximum value: Indicated at the same digits of the raw numerical data.
Confidence interval	Indicated by rounding off to the second digit below the raw numerical data.

1.3 Confidence Coefficient

Two-sided 95%

1.4 Handling of Evaluation Timepoint Data

The evaluation timepoints are the start of treatment with the Drug (baseline), Month 3, Month 6, Month 9, Month 12, and final evaluation timepoint.

If multiple data exist within each evaluation timepoint, calculate absolute values of difference in measurement intervals from the basic day count and adopt the minimum absolute value as date for that evaluation timepoint. If all the absolute values are the same, adopt one for the latest date of testing/measurement. Test/Measurement values should not be adopted that have been obtained after completion of treatment with the Drug. The final evaluation timepoint test/measurement should be one taken on the latest date within 405 days elapsed since the start date (including values tested/measured during washout period). Note that the number days elapsed since the start date should be counted with the start date as day 0 and the previous day as day -1.

Evaluation Timepoint	Tolerance (Number of Days Since Baseline)	Basic Day Count
Baseline	-90 to 0	0
Month 3	1 to 135	90
Month 6	136 to 225	180
Month 9	226 to 315	270
Month 12	316 to 405	360
Final evaluation timepoint	1 to 405	–

2.0 Results of Special Drug Use Surveillance (Survey 1)

<Lotriga Granular Capsules Special Drug Use Surveillance [long-term use survey]>

2.1 Patient Breakdown (Patient Disposition)

Statistical Analysis Set	Enrolled patients in this special drug use surveillance
Details of Statistical Analysis	Number of enrolled patients, number of patient enrollment sites, number of patients with eCRFs collected, number of patients with eCRFs uncollected, number of locked patients, number of unlocked patients, number of safety-evaluable patients, number of safety-unevaluable patients, number of efficacy-evaluable patients, number of efficacy-unevaluable patients Do not double-count the same medical institution with different participating clinical departments when counting the number of patient enrollment sites. Count the number of patients per reason below for not collecting and total the numbers when the number of patients with eCRFs uncollected. <Reasons for not collecting> • Survey under way • eCRFs uncollectable • Investigator transferred • Investigator's health reasons • Patients enrolled 15 days after Drug prescription [before eCRF collection] • Others Count the number of patients per reason below for exclusion and total the numbers when counting the numbers of safety- and efficacy-unevaluable patients. If the same patient falls under multiple reasons for exclusion, they should be counted separately. <Reasons for exclusion from safety evaluation> • Drug administered before contract period • Patient enrolled 15 days after Drug prescription • No data available after Drug administration • Drug not administered <Reasons for exclusion from efficacy evaluation> • Other than target disease • Exclusion criteria violation No output needs to be generated for items for which the number of patients is zero. For periodic safety reports, the numbers of efficacy-evaluable and unevaluable patients should not be counted.
Figure/Table No.	Figure 2.1, Table 2.1

2.2 Patient Demographics

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize the patient population by the following categories for each item and compile the number of patients and incidence.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td rowspan="2">Age</td><td>Summary statistics</td></tr>
<tr><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>Treatment category</td><td>Outpatient, inpatient</td></tr>
<tr><td rowspan="2">BMI</td><td>Summary statistics</td></tr>
<tr><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Complications</td><td>No, Yes</td></tr>
<tr><td>Complication breakdown</td><td>Hypertension, Diabetic, Liver disorder, Kidney disorder, Cardiac disorders [myocardial infarction, angina pectoris, atrial fibrillation, others], Cerebrovascular diseases [hemorrhagic cerebrovascular disease, ischemic cerebrovascular disease, others], Bleeding-related event, Others</td></tr>
<tr><td>Drinking history (Does the patient drink alcoholic beverages nearly every day?)</td><td>Yes, No, Unknown</td></tr>
<tr><td rowspan="2">Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
<tr><td>Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
</table></td></tr>
</table>

			Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured
		Smoking history	Never, Current, Former, Unknown
		Hypersensitivity disposition	No, Yes, Unknown
		Disease duration	Summary statistics
			Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
		Presence or absence of surgery within one month before baseline	No, Yes
		Pregnancy status during treatment (only for female)	No, Yes
Figure/Table No.	Table 2.2		

2.3 Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize the patient population by the following categories for each item and compile the number of patients and incidence.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, Other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Presence or absence of concomitant antihyperlipidemic drug use (during observation period)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant antihyperlipidemic drugs (during observation period)</td><td>Statins drugs, fibrate drugs, intestinal transporter inhibitors, anion-exchange resin, nicotinic acid derivatives, probucol, ethyl icosapentate (EPA), others</td></tr>
<tr><td>Presence or absence of concomitant anticoagulant/antiplatelet drug use (during observation period)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant anticoagulant/antiplatelet drugs (during observation period)</td><td>Anticoagulant drugs, antiplatelet drugs</td></tr>
<tr><td>Completion of treatment with the Drug</td><td>No, Yes</td></tr>
<tr><td>Reason for treatment</td><td>Treatment goal achieved, AE developing, Patient no</td></tr>
</table></td></tr>
</table>

	completion	longer visiting hospital due to hospital transfer or otherwise, Insufficient effect, Other
Figure/Table No.	Table 2.3	

2.4 Safety Statistical Analysis

2.4.1 Onset Status of Adverse Drug Reactions or Infections (Exhibit 2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies in Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items for the prior-approval status and per survey unit period of the special drug use surveillance.
Statistical analysis of ‘number of study sites,’ ‘number of surveyed patients,’ ‘number of patients with ADRs,’ and ‘number of ADRs’ should cover safety-evaluable patients locked during each survey unit period.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients with ADRs</td><td>Number of patients in which ADRs occurred.</td></tr>
<tr><td>Number of ADRs</td><td>Number of ADRs that occurred.
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients with ADRs</td><td>Calculated by the following equation: [Number of Patients with ADRs] / [Number of Safety-Evaluable Patients] × 100</td></tr>
<tr><td>ADR type</td><td>The calculation method in performing each analysis should be as follows:
[Number of patients with ADRs]
• Number of patients in which ADRs occurred.
[Number of ADRs]
• Number of ADRs that occurred. If the same ADR occurs more than once in the same patient, a total of frequencies of the ADR should be counted.
[Rate of patients with ADRs]
• Calculated by the following equation: [Number of Patients with ADRs] / [Number of Safety-Evaluable Patients] × 100.
[ADR type]
• ADRs should be replaced by MedDRA terms. Categorize by SOC and compile ADRs by PT in each category. If SOC is ‘Investigations,’ classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile ADRs by PT.

• At SOC level, the numbers and rates of patients with ADRs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, ADRs should be counted as one patient in the SOC.
At PT level, the numbers and rates of patients with ADRs should be presented by PT code in</td></tr>
</table>
</td></tr>
</table>

		ascending order. If the same PT occurs more than once in the same patient, ADRs should be counted as one patient in the PT.
	Cumulative total for special drug use surveillance	A respective total of the numbers of study sites and patients per survey unit period. Do not double-count the same medical institution when counting the number of study sites.
Figure/Table No.	Table 2.4.1	

2.4.2 Onset Status of Adverse Drug Reactions/Infections in Safety-Unevaluable Patients

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-unevaluable patients in this specified drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-unevaluable patients.</td></tr>
<tr><td>Number of patients with ADRs</td><td>Number of patients in which ADRs occurred.</td></tr>
<tr><td>Number of ADRs</td><td>Number of ADRs that have occurred.
Every PT occurring should be counted as one event.</td></tr>
<tr><td>ADR type</td><td>The calculation method in performing each analysis should be as follows:
[Number of patients with ADRs]
• Number of patients in which ADRs occurred.
[Number of ADRs]
• Number of ADRs that occurred. If the same ADR occurs more than once in the same patient, a total of frequencies of the ADR should be counted.
[ADR type]
• ADRs should be replaced by MedDRA terms. Categorize by SOC and compile ADRs by PT in each category. If SOC is ‘Investigations,’ classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile ADRs by PT.

• At SOC level, the numbers of patients with ADRs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, ADRs should be counted as one patient in the SOC.
At PT level, the numbers of patients with ADRs should be presented by PT code in ascending order. If the same PT occurs more than once in the same patient, ADRs should be counted as one patient in the PT.</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.2</td></tr>
</table>

2.4.3 Onset Status of AE

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	The compilation method is the same as described in section 2.4.1. However, adverse drug reactions should be replaced by adverse events.
Figure/Table No.	Table 2.4.3

2.4.4 Onset Status of Adverse Events in Safety-Unevaluable Patients

Statistical Analysis Set	Safety-unevaluable patients in this specified drug use surveillance
Details of Statistical Analysis	Compilation method is the same as described in section 2.4.2. However, adverse drug reactions should be replaced by adverse events.
Figure/Table No.	Table 2.4.4

2.4.5 Onset Status of Adverse Drug Reactions or Infections by Seriousness, Onset Time, and Outcome

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Categorize ADRs by the following categories for each item and compile ADR types.

Item Name	Details of Statistical Analysis
Number of patients	Compile the number of patients with ADRs.
Number of ADRs	At SOC, the number of ADRs should be compiled by totaling associated PTs that occurred. At PT level, every PT occurring should be counted as one event.

Item Name	Category
Seriousness	Serious, Not serious
Onset time	1 to 15 days, 16 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over, Unknown
Outcome	Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown

Figure/Table No.	Table 2.4.5

2.4.6 Onset Status of Adverse Events by Seriousness, Onset Time, and Outcome

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize AEs by the following categories for each item and compile AE types.
The compilation method of AE types is the same as described in section 2.4.5. However, adverse drug reactions should be replaced by adverse events.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Seriousness</td><td>Serious, Not serious</td></tr>
<tr><td>Onset time</td><td>1 to 15 days, 16 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over, Unknown</td></tr>
<tr><td>Outcome</td><td>Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown</td></tr>
<tr><td>Causal relationship with the Drug</td><td>Related, Not related, Unevaluable
If AEs (LLTs) occur more than once in the same patient, they should be counted as one event in the following order of priority:
(1) Related, (2) Unevaluable, (3) Not related</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.6</td></tr>
</table>

2.4.7 Onset Status of Adverse Drug Reactions (Bleeding-Related Events) by Seriousness, Onset Time, and Outcome

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Categorize adverse drug reactions (bleeding-related events) by the following categories for each item, and count the types of adverse drug reactions (bleeding-related events). The categories and the compilation method of adverse drug reactions are the same as described in section 2.4.5.
Figure/Table No.	Table 2.4.7

2.4.8 Rate of Patients of Adverse Drug Reactions or Infections by Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize ADRs by the following categories for each item and compile the rate of patients with ADRs.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>BMI</td><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Complications</td><td>No, Yes</td></tr>
<tr><td>Complication breakdown</td><td>Hypertension, Diabetic, Liver disorder, Kidney disorder, Cardiac disorders Cerebrovascular diseases, Bleeding-related event, Others</td></tr>
<tr><td rowspan="2">Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
<tr><td rowspan="2">Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, other</td></tr>
<tr><td>Breakdown of presence of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Presence or absence of concomitant antihyperlipidemic drug use (during observation period)</td><td>No, Yes</td></tr>
</table></td></tr>
</table>

		Breakdown of concomitant antihyperlipidemic drugs (during observation period)	statins drugs, fibrate drugs, intestinal transporter inhibitors, anion-exchange resin, nicotinic acid derivatives, probucol, ethyl icosapentate (EPA), others
		Presence or absence of concomitant anticoagulant/antiplatelet drug use (during observation period)	No, Yes
		Breakdown of concomitant anticoagulant/antiplatelet drugs (during observation period)	Anticoagulant drugs, antiplatelet drugs
Figure/Table No.	Table 2.4.8		

2.4.9 Onset Status of Adverse Drug Reactions or Infections by Sex Group

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Classify the patient population into males and females, and compile ADR types. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.9

2.4.10 Onset Status of Adverse Drug Reactions or Infections by Age Group

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Classify the patient population into 64 years or below, 65 to 74 years, and 75 years or over, and compile ADR types. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.10

2.4.11 Onset Status of Adverse Drug Reactions or Infections by BMI

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Classify the patient population into less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, and compile ADR types. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.11

2.4.12 Onset Status of Adverse Drug Reactions or Infections by Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.12

2.4.13 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Hypertension Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of hypertension complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.13

2.4.14 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Diabetes Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of diabetes complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.14

2.4.15 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Liver Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of liver complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.15

2.4.16 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Kidney Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of kidney complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.16

2.4.17 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Cardiac Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of cardiac complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.17

2.4.18 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Cerebrovascular Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of cerebrovascular complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.18

2.4.19 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Bleeding-related Event Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of bleeding-related event complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.19

2.4.20 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Anticoagulant and/or Antiplatelet Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant anticoagulant or antiplatelet drugs (Concomitant anticoagulant / antiplatelet , Anticoagulant only, Antiplatelet only, Neither). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.20

2.4.21 Onset Status of Adverse Drug Reactions (Bleeding-Related Events) by Presence or Absence of Concomitant Anticoagulant and/or Antiplatelet Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile the types of adverse drug reactions (bleeding-related events) by presence or absence of concomitant anticoagulant or antiplatelet drugs (Concomitant anticoagulant / antiplatelet , Anticoagulant only, Antiplatelet only, Neither). The compilation method of the types of adverse drug reactions is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.21

2.4.22 Onset Status of Adverse Drug Reactions or Infections by Baseline Fasting Triglyceride Level

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance whose fasting triglyceride levels were measured at baseline
Details of Statistical Analysis	Compile ADR types by baseline fasting triglyceride level (Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.22

2.4.23 Onset Status of Adverse Drug Reactions or Infections by Baseline Random Triglyceride Level

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance whose random triglyceride levels were measured at baseline
Details of Statistical Analysis	Compile ADR types by baseline random triglyceride level (Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.23

2.4.24 Onset Status of Adverse Drug Reactions or Infections by Initial Dose

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by initial dose. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.24

2.4.25 Onset Status of Adverse Drug Reactions or Infections by Breakdown of Change in Daily Dose

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by breakdown of change in daily dose (2 g → 4 g, 4 g → 2 g, Other). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.25

2.4.26 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Antihyperlipidemic Drug Use (during observation period)

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant antihyperlipidemic drug use. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.26

2.4.27 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Statins Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant statins drugs. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.27

2.4.28 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Fibrate Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant fibrate drugs. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.28

2.4.29 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Intestinal Transporter Inhibitors

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant intestinal transporter inhibitors. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.29

2.4.30 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Anion-exchange Resin

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant anion-exchange resin. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.30

2.4.31 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Nicotinic Acid Derivatives

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant nicotinic acid derivatives. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.31

2.4.32 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Probucol

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant probucol. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.32

2.4.33 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Ethyl Icosapentate (EPA)

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant ethyl icosapentate (EPA). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.33

2.4.34 Changes in Laboratory Test Values (Glucose Metabolism)

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline.
Figure/Table No.	Table 2.4.34

2.4.35 Changes in Laboratory Test Values (Glucose Metabolism) <With Diabetic Complications>

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline.
Remarks	Stratification factor: With diabetic complications
Figure/Table No.	Table 2.4.35

2.4.36 Changes in Laboratory Test Values (Glucose Metabolism) <Without Diabetic Complications>

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline.
Remarks	Stratification factor: Without diabetic complications
Figure/Table No.	Table 2.4.36

2.4.37 Summary of Onset Status of Serious Adverse Events (Exhibit 2-2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies in Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items per survey unit period of the prior-approval status and of the special drug use surveillance.
Statistical analysis of ‘number of study sites,’ ‘number of surveyed patients,’ ‘number of patients,’ and ‘number of SAEs’ should cover safety-evaluable patients locked during each survey unit period.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients</td><td>Number of patients with SAEs</td></tr>
<tr><td>Number of SAEs</td><td>Number of SAEs
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients</td><td>Calculated by the following equation: [Number of Patients with SAEs] / [Number of Safety-Evaluable Patients] × 100.</td></tr>
<tr><td>SAE type</td><td>The calculation method in performing each analysis should be as follows:
[Number of patients with SAEs]
• Number of patients in which SAEs occurred.
[Number of SAEs]
• Number of SAEs that occurred. If the same SAE occurs more than once in the same patient, a total of frequencies of the SAE should be counted.
[Rate of patients with SAEs]
• Calculated by the following equation: [Number of Patients with SAEs] / [Number of Safety-Evaluable Patients] × 100.
[SAE type]
• SAEs should be replaced by MedDRA terms. Categorize by SOC and compile SAEs by PT in each category. If SOC is ‘Investigations,’ classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile SAEs by PT.

• At SOC level, the numbers and rates of patients with SAEs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, SAEs should be counted as one patient in the SOC.
At PT level, the numbers and rates of patients with SAEs should be presented by PT code in ascending order. If the same PT occurs more than once in the same patient, SAEs should be counted as one patient in the PT.</td></tr>
</table>
</td></tr>
</table>

			The number of SAEs of which causal relationship to the Drug has been denied should be entered in the [ ] brackets. In that case, if the same PT events which are both "related" and "not related" in causality to the Drug occur in the same patient, the SAEs should be counted as one patient in the "related" category.	
		Cumulative total of special drug use surveillance	A respective total of the numbers of study sites and patients per survey unit period. Do not double-count the same medical institution when counting the number of study sites.	
Figure/Table No.	Table 2.4.37			

2.4.38 Summary of Onset Status of Serious Adverse Drug Reactions or Infections

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients</td><td>Number of patients with serious ADRs</td></tr>
<tr><td>Number of serious ADRs</td><td>Number of serious ADRs
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients</td><td>Calculated by the following equation: [Number of Patients with serious ADRs] / [Number of Safety-Evaluable Patients] × 100.</td></tr>
<tr><td>Serious ADR type</td><td>The calculation method in performing each analysis should be as follows:
[Number of patients with serious ADRs]
• Number of patients in which serious ADRs occurred.
[Number of serious ADRs]
• Number of serious ADRs that occurred. If the same serious ADR occurs more than once in the same patient, a total of frequencies of the serious ADR should be counted.
[Rate of patients with serious ADRs]
• Calculated by the following equation: [Number of Patients with serious ADRs] / [Number of Safety-Evaluable Patients] × 100.
[Serious ADR type]
• Serious ADRs should be replaced by MedDRA terms. Categorize by SOC and compile serious ADRs by PT in each category. If SOC is ‘Investigations,’ classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile serious ADRs by PT.

• At SOC level, the numbers and rates of patients with serious ADRs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, serious ADRs should be counted as one patient in the SOC.
At PT level, the numbers and rates of patients with serious ADRs should be presented by PT code in ascending order. If the same PT occurs more than once in the same patient, serious ADRs should be counted as one patient in the PT.
The number of serious ADRs of which causal relationship to the Drug has been denied should be</td></tr>
</table></td></tr>
</table>

			entered in the [ ] brackets. In that case, if the same PT events which are both "related" and "not related" in causality to the Drug occur in the same patient, the SAEs should be counted as one patient in the "related" category.
Figure/Table No.	Table 2.4.38		

2.4.39 Summary of Onset Status of Serious Adverse Events in Safety-Unevaluable patients

Statistical Analysis Set	Safety-unevaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile the following items.

Item Name	Details of Statistical Analysis
Number of study sites	Number of medical institutions that have collected eCRFs
Number of surveyed patients	Number of safety-unevaluable patients.
Number of patients	Number of patients with SAEs
Number of SAEs	Number of SAEs Every PT occurring should be counted as one event.
Rate of patients	Calculated by the following equation: [Number of Patients with SAEs] / [Number of Safety-unevaluable Patients] × 100.
SAE type	The calculation method in performing each analysis should be as follows: [Number of patients with SAEs] • Number of patients in which SAEs occurred. [Number of SAEs] • Number of SAEs that occurred. If the same SAE occurs more than once in the same patient, a total of frequencies of the SAE should be counted. [SAE type] • SAEs should be replaced by MedDRA terms. Categorize by SOC and compile SAEs by PT in each category. If SOC is 'Investigations,' classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile SAEs by PT. • At SOC level, the numbers and rates of patients with SAEs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, SAEs should be counted as one patient in the SOC. At PT level, the numbers of patients with SAEs should be presented by PT code in ascending order. If the same PT occurs more than once in the same patient, SAEs should be counted as one patient in the PT.

			The number of SAEs of which causal relationship to the Drug has been denied should be entered in the [ ] brackets. In that case, if the same PT events which are both "related" and "not related" in causality to the Drug occur in the same patient, the SAEs should be counted as one patient in the "related" category.
Figure/Table No.	Table 2.4.39		

2.4.40 Summary of Onset Status of Serious Adverse Drug Reactions or Infections in Safety-Unevaluable patients

Statistical Analysis Set	Safety-unevaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile the following items.

Item Name	Details of Statistical Analysis
Number of study sites	Number of medical institutions that have collected eCRFs
Number of surveyed patients	Number of safety-unevaluable patients.
Number of patients	Number of patients with serious ADRs
Number of serious ADRs	Number of serious ADRs Every PT occurring should be counted as one event.
Rate of patients	Calculated by the following equation: [Number of Patients with serious ADRs] / [Number of Safety-unevaluable Patients] × 100.
Serious ADR type	The calculation method in performing each analysis should be as follows: [Number of patients with serious ADRs] • Number of patients in which serious ADRs occurred. [Number of serious ADRs] • Number of serious ADRs that occurred. If the same serious ADR occurs more than once in the same patient, a total of frequencies of the serious ADR should be counted. [Serious ADR type] • Serious ADRs should be replaced by MedDRA terms. Categorize by SOC and compile serious ADRs by PT in each category. If SOC is 'Investigations,' classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile serious ADRs by PT. • At SOC level, the numbers and rates of patients with serious ADRs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, serious ADRs should be counted as one patient in the SOC. At PT level, the numbers of patients with serious

			ADRs should be presented by PT code in ascending order. If the same PT occurs more than once in the same patient, serious ADRs should be counted as one patient in the PT. The number of serious ADRs of which causal relationship to the Drug has been denied should be entered in the [ ] brackets. In that case, if the same PT events which are both "related" and "not related" in causality to the Drug occur in the same patient, the serious ADRs should be counted as one patient in the "related" category.
Figure/Table No.	Table 2.4.40		

2.5 Efficacy Statistical Analysis

2.5.1 Changes in Laboratory Test Values (Fasting Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting measurements and rates of change from baseline (%) of triglyceride (mg/dL), LDL cholesterol (Friedewald formula) (mg/dL), VLDL cholesterol (mg/dL), VLDL cholesterol (%),Apo-B (mg/dL), Apo-CIII (mg/dL), lipoprotein(a) (mg/dL), and remnant lipoprotein cholesterol (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%).
Figure/Table No.	Table 2.5.1

2.5.2 Changes in Laboratory Test Values (Random Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for random measurements and rates of change from baseline (%) of triglyceride (mg/dL), VLDL cholesterol (mg/dL), VLDL cholesterol (%),Apo-B (mg/dL), Apo-CIII (mg/dL), lipoprotein(a) (mg/dL), and remnant lipoprotein cholesterol (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%).
Figure/Table No.	Table 2.5.2

2.5.3 Changes in Laboratory Test Values (Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for random measurements and rates of change from baseline (%) of total cholesterol (mg/dL), LDL cholesterol (direct measurement) (mg/dL), HDL cholesterol (mg/dL), non-HDL cholesterol (mg/dL), Apo-AI (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%).
Figure/Table No.	Table 2.5.3

2.5.4 Changes in Fasting Lipid-Related Ratio

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for TC/HDL-C, LDL-C/HDL-C, and LDL-C/Apo-B.
Figure/Table No.	Table 2.5.4

2.5.5 Changes in Fasting Triglyceride by Patient Demographics and Treatment Details

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics by stratification for each item for baseline and final evaluation timepoint measurements and rates of change from baseline (%) of fasting triglyceride.

Item Name	Category
Sex	Male, Female
Age	Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown
BMI	Less than 18.5kg/m^2, 18.5 to less than 25kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown
Fasting triglyceride at baseline (mg/dL)	Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Unknown
Disease duration	Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
Initial dose	2 g, 4 g, other
Change in daily dose	No, Yes
Breakdown of change in daily dose	2 g → 4 g, 4 g → 2 g, Other
Mean daily dose	Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over
Treatment duration	1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over
Presence or absence of concomitant antihyperlipidemic drug use (during observation period)	No, Yes
Breakdown of concomitant antihyperlipidemic drugs (during	Statins drugs, Fibrate drugs, Intestinal transporter inhibitors, Anion-exchange resin, Nicotinic acid derivatives, Probucol, Ethyl icosapentate (EPA), Others

		observation period)	
Figure/Table No.	Table 2.5.5		

2.5.6 Changes in Random Triglyceride by Patient Demographics and Treatment Details

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics by stratification for each item for baseline and final evaluation timepoint measurements and rates of change from baseline (%) of random triglyceride.

Item Name	Category
Sex	Male, Female
Age	Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown
BMI	Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown
Random triglyceride at baseline (mg/dL)	Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Unknown
Disease duration	Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
Initial dose	2 g, 4 g, other
Change in daily dose	No, Yes
Breakdown of change in daily dose	2 g → 4 g, 4 g → 2 g, Other
Mean daily dose	Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over
Treatment duration	1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over
Presence or absence of concomitant antihyperlipidemic drug use (during observation period)	No, Yes
Breakdown of concomitant antihyperlipidemic drugs (during observation period)	Statins drugs, Fibrate drugs, Intestinal transporter inhibitors, Anion-exchange resin, Nicotinic acid derivatives, Probucol, Ethyl icosapentate (EPA), Others

Figure/Table No.	Table 2.5.6

Statistical Analysis Plan
(for Periodic Safety Reporting/Reexamination Application)
<Lotriga Granular Capsules>
[Long-term use]

Takeda Pharmaceutical Company Limited
Japan Development Center
Director of Biostatistics Division

PPD

Ver. 3.0: Prepared on July 31, 2017

Table of Contents

1.0 Definitions of Terms

1.1 Definitions

Item	Definition
Survey unit period (periodic safety report)	Periodic Safety Report 1: July 22, 2012 to January 21, 2013 Periodic Safety Report 2: January 22, 2013 to July 21, 2013 Periodic Safety Report 3: July 22, 2013 to January 21, 2014 Periodic Safety Report 4: January 22, 2014 to July 21, 2014 Periodic Safety Report 5: July 22, 2014 to July 21, 2015 Periodic Safety Report 6: July 22, 2015 to July 21, 2016 Periodic Safety Report 7: July 22, 2016 to July 21, 2017
Drug	Lotriga Granular Capsules
SOC	System organ class of MedDRA.
HLGT	High level group term of MedDRA.
PT	Preferred term of MedDRA.
LLT	Lowest level term of MedDRA.
Enrolled patient	A patient approved for enrollment in the Study.
Patient with eCRF collected	An enrolled patient whose eCRF was submitted via CCI [redacted].
Patient with eCRF uncollected	An enrolled patient other than a patient with eCRF collected.
Locked patient	A patient who has completed the approval process in the PMS system.
Unlocked patient	A patient with eCRF collected other than a locked patient.
Safety-evaluable patient	A locked patient included in safety evaluation.
Safety-unevaluable patient	A locked patient excluded from safety evaluation.
Efficacy-evaluable patient	A safety-evaluable patient included in efficacy evaluation.
Efficacy-unevaluable patient	A safety-evaluable patient excluded from efficacy evaluation.
ADR	An abbreviated form of the term ‘adverse drug reaction or infection.’ Refers to an adverse event other than those judged by the investigator as ‘not related’ in causality to the Drug. In this plan, ‘adverse drug reactions or infections’ is used in headings, and ‘ADRs’ is used in the text and tables.
Serious adverse event (SAE)	[Prior-approval data] An adverse event (AE) judged as ‘serious’ by the trial investigator. [Surveillance data] An adverse event (AE) judged as ‘serious’ by the investigator. Note that events listed in the separate MedDRA code list of the Takeda Medically Significant AE List should be treated as serious even if judged as ‘not serious’ by the investigator.

Item	Definition
Bleeding-related event	An event falling under Standardized MedDRA Query (SMQ) code 20000038 (hemorrhagic SMQ [narrow scope]).
Rate of patients	[For safety compilation with safety-evaluable patients] Calculated by the following equation: [Number of Patients] / [Number of Safety-Evaluable Patients] × 100. [For safety compilation with safety-unevaluable patients] Calculated by the following equation: [Number of Patients] / [Number of Safety-Unevaluable Patients] × 100.
Incidence	[For safety compilation with safety-evaluable patients] Calculated by the following equation: [Number of Events] / [Number of Safety-Evaluable Patients] × 100. [For safety compilation with safety-unevaluable patients] Calculated by the following equation: [Number of Events] / [Number of Safety-Unevaluable Patients] × 100.
Onset time	Calculated by the following equation: [Onset Date] - [Start Date] + 1. If the onset date is unknown, use the first day of the month as the onset date in this equation. However, use the start date as the onset date if [Start Year & Month] = [Onset Year & Month].
Liver patient	A patient with ‘fatty liver,’ ‘alcoholic fatty liver,’ ‘chronic hepatitis’ or ‘hepatic cirrhosis’ check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000005 (hepatic SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Kidney patient	A patient with ‘diabetic nephropathy,’ ‘glomerulonephritis’ or ‘chronic kidney disease (CKD)’ check-marked in the Complication Details field. Or a patient with a complication falling under the Takeda MedDRA query (TMQ) (Renal Disease) in the Complication Details (Other Diseases) field.
Heart patient	A patient with ‘myocardial infarction,’ ‘angina pectoris’ or ‘atrial fibrillation’ check-marked in the Complication Details field. Or a patient with a complication falling under the SOC code 10007541 (cardiac disorders) in the Complication Details (Other Diseases) field.
Cerebrovascular patient	A patient with ‘cerebral infarction’ or ‘cerebral hemorrhage’ check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000060 (cerebrovascular SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Diabetic patient	A patient with ‘diabetes’ check-marked in the Complication Details field. Or a patient with a complication falling under the TMQ code (Diabetes Mellitus Confirmed diagnosis, excl diagnostics) in the Complication Details (Other Diseases) field.

Item	Definition
Hypertensive patient	A patient with 'hypertension' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000147 (hypertensive SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Myocardial infarction patient	A patient with 'myocardial infarction' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000047 (myocardial infarction SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Anginal patient	A patient with 'angina pectoris' check-marked in the Complication Details field. Or a patient with a complication falling under the MedDRA PT code 10002383 (angina pectoris), 10002388 (unstable angina pectoris), 10036759 (Prinzmetal angina), or 10058144 (postinfarction angina) in the Complication Details (Other Diseases) field.
Atrial fibrillation patient	A patient with 'atrial fibrillation' check-marked in the Complication Details field. Or a patient with a complication falling under the MedDRA PT code 10003658 (atrial fibrillation) in the Complication Details (Other Diseases) field.
Ischemic cerebrovascular patient	A patient with 'cerebral infarction' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000063 (ischemic cerebrovascular disease SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Hemorrhagic cerebrovascular patient	A patient with 'cerebral hemorrhage' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000064 (hemorrhagic cerebrovascular disease SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Bleeding-related event patient	A patient with a complication falling under the SMQ code 20000038 (bleeding SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Age	Calculated by the following equation: [Start Year] - [Birth Year] - 1 if [Start Month & Day] < [Birth Month & Day]. Calculated by the following equation: [Start Year] - [Birth Year] if [Start Month & Day] ≥ [Birth Month & Day]. If the birth day is unknown, use the first day of the month instead in this equation.
BMI	Calculated by the following equation: [Weight (kg)] / (0.0001 × [Height (cm)] × [Height (cm)]). Indicated by rounding off to the first decimal place.
Disease duration (in years)	Calculated by the following equation: ([Start Year & Month] - [Year & Month of Hyperlipidemia Diagnosis] + 1) / 12. Indicated by rounding off to the first decimal place.

Item	Definition
Start date	The start date of first administration of the Drug stated in the Treatment Duration field of the eCRF.
End date	The end date of last administration of the Drug stated in the Treatment Duration field of the eCRF. However, if the end date of last administration is in 'ongoing 12 months after baseline,' the end date should be the start date plus 405 days.
Observation period (in days)	Refers to the entire period of observation. The start date and end date of observation period should be the same as the 'start date' and 'end date,' respectively. Calculated by the following equation: [End Date] - [Start Date] + 1.
Treatment duration (in days)	Refers to the entire period of treatment. A total of Drug dosing periods in the number of actual administration days, excluding washout period. Calculated as a total of ([End Date] - [Start Date] + 1) in the number of actual administration days, excluding washout period.
Mean daily dose	Calculated by the following equation: Total of ([Daily Dose] × [Total Period of Treatment with the Dose]) / [Observation Period]. See the above for calculation of observation period.
Concomitant medication	A drug used during the surveillance period. However, concomitant medications exclude drugs used for adverse events occurring during the period.
Antihyperlipidemic drug	A drug starting with any of the following drug codes: 218, 2190006, 2190101, 2190102, 2190103, 2190104, 290006, 3133001, 3133400, 3399004.
Statins drug	A drug starting with any of the following drug codes: 2189010, 2189011, 2189012, 2189015, 2189016, 2189017.
Fibrate drug	A drug starting with drug code: 2183.
Intestinal transporter inhibitor	A drug starting with drug code: 2189018.
Anion-exchange resin	A drug starting with any of the following drug codes: 2189009, 2189014.
Nicotinic acid derivative	A drug starting with any of the following drug codes: 2189004, 2189005, 2190006.
Probucol	A drug starting with drug code: 2189008.
Ethyl icosapentate (EPA)	A drug starting with drug code: 3399004.
Anticoagulant drug	A drug starting with any of the following drug codes: 333, 2190408, 6343424.
Antiplatelet drug	A drug starting with any of the following drug codes: 3399 (excluding 3399004), 2171010, 2171402.
Anticoagulant/antiplatelet drug	A drug that falls under the class of either anticoagulant or antiplatelet drugs

Item	Definition
LDL cholesterol (Friedewald formula) (mg/dL)	Calculated the equation below if the patient is fasting at the time of blood collection for laboratory testing with triglyceride 400 mg/dL or over. Indicated by rounding off to an integer alone. Total cholesterol - HDL cholesterol - triglyceride / 5
Non-HDL cholesterol (mg/dL)	Calculated by the equation below if triglyceride is 400 mg/dL or over. Indicated by rounding off to an integer alone. Total cholesterol - HDL cholesterol
TC/LDL-C ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. Total cholesterol / LDL cholesterol (Friedewald formula)
LDL-C/HDL-C ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. LDL cholesterol (Friedewald formula) / HDL cholesterol
LDL-C/Apo-B ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. LDL cholesterol (Friedewald formula) / Apo-B
Summary statistics	Mean value, standard deviation, minimum value, first quartile, median, third quartile, maximum value

1.2 Number of Display Digits

Item	Definition
Percentage (%)	Rate of patients with ADRs: Indicated by rounding off to the second decimal place. Other than above: Indicated by rounding off to the first decimal place.
Summary statistics	Mean value: Indicated by rounding off to the first digit below the raw numerical data. Standard deviation: Indicated by rounding off to the second digit below the raw numerical data. First quartile, median, third quartile: Indicated by rounding off to the first digit below the raw numerical data. Minimum value, maximum value: Indicated at the same digits of the raw numerical data.
Confidence interval	Indicated by rounding off to the second digit below the raw numerical data.

1.3 Confidence Coefficient

Two-sided 95%

1.4 Handling of Evaluation Timepoint Data

The evaluation timepoints are the start of treatment with the Drug (baseline), Month 3, Month 6, Month 9, Month 12, and final evaluation timepoint.

If multiple data exist within each evaluation timepoint, calculate absolute values of difference in measurement intervals from the basic day count and adopt the minimum absolute value as date for that evaluation timepoint. If all the absolute values are the same, adopt one for the latest date of testing/measurement. Test/Measurement values should not be adopted that have been obtained after completion of treatment with the Drug. The final evaluation timepoint test/measurement should be one taken on the latest date within 405 days elapsed since the start date (including values tested/measured during washout period). Note that the number days elapsed since the start date should be counted with the start date as day 0 and the previous day as day -1.

Evaluation Timepoint	Tolerance (Number of Days Since Baseline)	Basic Day Count
Baseline	-90 to 0	0
Month 3	1 to 135	90
Month 6	136 to 225	180
Month 9	226 to 315	270
Month 12	316 to 405	360
Final evaluation timepoint	1 to 405	–

2.0 Results of Special Drug Use Surveillance (Survey 1)

<Lotriga Granular Capsules Special Drug Use Surveillance [long-term use survey]>

2.1 Patient Breakdown (Patient Disposition)

Statistical Analysis Set	Enrolled patients in this special drug use surveillance
Details of Statistical Analysis	Number of enrolled patients, number of patient enrollment sites, number of patients with eCRFs collected, number of patients with eCRFs uncollected, number of locked patients, number of unlocked patients, number of safety-evaluable patients, number of safety-unevaluable patients, number of efficacy-evaluable patients, number of efficacy-unevaluable patients Do not double-count the same medical institution with different participating clinical departments when counting the number of patient enrollment sites. Count the number of patients per reason below for not collecting and total the numbers when the number of patients with eCRFs uncollected. <Reasons for not collecting> • Survey under way • eCRFs uncollectable • Investigator transferred • Investigator's health reasons • Patients enrolled 15 days after Drug prescription [before eCRF collection] • Others Count the number of patients per reason below for exclusion and total the numbers when counting the numbers of safety- and efficacy-unevaluable patients. If the same patient falls under multiple reasons for exclusion, they should be counted separately. <Reasons for exclusion from safety evaluation> • Drug administered before contract period • Patient enrolled 15 days after Drug prescription • No data available after Drug administration • Drug not administered <Reasons for exclusion from efficacy evaluation> • Pre- or post-administration lipid-related values (fasting or random) unavailable No output needs to be generated for items for which the number of patients is zero. For periodic safety reports, the numbers of efficacy-evaluable and unevaluable patients should not be counted.
Figure/Table No.	Figure 2.1, Table 2.1

2.2 Patient Demographics

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize the patient population by the following categories for each item and compile the number of patients and incidence.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td rowspan="2">Age</td><td>Summary statistics</td></tr>
<tr><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>Treatment category</td><td>Outpatient, inpatient</td></tr>
<tr><td rowspan="2">BMI</td><td>Summary statistics</td></tr>
<tr><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Complications</td><td>No, Yes</td></tr>
<tr><td>Complication breakdown</td><td>Hypertension, Diabetic, Liver disorder, Kidney disorder, Cardiac disorders [myocardial infarction, angina pectoris, atrial fibrillation, others], Cerebrovascular diseases [hemorrhagic cerebrovascular disease, ischemic cerebrovascular disease, others], Bleeding-related event, Others</td></tr>
<tr><td>Drinking history (Does the patient drink alcoholic beverages nearly every day?)</td><td>Yes, No, Unknown</td></tr>
<tr><td rowspan="2">Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
<tr><td rowspan="2">Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
</table></td></tr>
</table>

	Smoking history	Never, Current, Former, Unknown
	Hypersensitivity disposition	No, Yes, Unknown
	Disease duration	Summary statistics
		Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
	Presence or absence of surgery within one month before baseline	No, Yes
	Pregnancy status during treatment (only for female)	No, Yes
Figure/Table No.	Table 2.2	

2.3 Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize the patient population by the following categories for each item and compile the number of patients and incidence.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, Other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Presence or absence of concomitant antihyperlipidemic drug use (during observation period)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant antihyperlipidemic drugs (during observation period)</td><td>Statins drugs, fibrate drugs, intestinal transporter inhibitors, anion-exchange resin, nicotinic acid derivatives, probucol, ethyl icosapentate (EPA), others</td></tr>
<tr><td>Presence or absence of concomitant anticoagulant/antiplatelet drug use (during observation period)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant anticoagulant/antiplatelet drugs (during observation period)</td><td>Anticoagulant drugs, antiplatelet drugs</td></tr>
<tr><td>Completion of treatment with the Drug</td><td>No, Yes, Unknown</td></tr>
</table></td></tr>
</table>

		Reason for treatment completion	Treatment goal achieved, AE developing, Patient no longer visiting hospital due to hospital transfer or otherwise, Insufficient effect, Other
Figure/Table No.	Table 2.3		

2.4 Safety Statistical Analysis

2.4.1 Onset Status of Adverse Drug Reactions or Infections (Exhibit 2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies in Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items for the prior-approval status and per survey unit period of the special drug use surveillance.
Statistical analysis of ‘number of study sites,’ ‘number of surveyed patients,’ ‘number of patients with ADRs,’ and ‘number of ADRs’ should cover safety-evaluable patients locked during each survey unit period.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients with ADRs</td><td>Number of patients in which ADRs occurred.</td></tr>
<tr><td>Number of ADRs</td><td>Number of ADRs that occurred.
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients with ADRs</td><td>Calculated by the following equation: [Number of Patients with ADRs] / [Number of Safety-Evaluable Patients] × 100</td></tr>
<tr><td>ADR type</td><td>The calculation method in performing each analysis should be as follows:
[Number of patients with ADRs]
• Number of patients in which ADRs occurred.
[Number of ADRs]
• Number of ADRs that occurred. If the same ADR occurs more than once in the same patient, a total of frequencies of the ADR should be counted.
[Rate of patients with ADRs]
• Calculated by the following equation: [Number of Patients with ADRs] / [Number of Safety-Evaluable Patients] × 100.
[ADR type]
• ADRs should be replaced by MedDRA terms. Categorize by SOC and compile ADRs by PT in each category. If SOC is ‘Investigations,’ classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile ADRs by PT.

• At SOC level, the numbers and rates of patients with ADRs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, ADRs should be counted as one patient in the SOC.
At PT level, the numbers and rates of patients with ADRs should be presented by PT code in</td></tr>
</table>
</td></tr>
</table>

		ascending order. If the same PT occurs more than once in the same patient, ADRs should be counted as one patient in the PT.
	Cumulative total for special drug use surveillance	A respective total of the numbers of study sites and patients per survey unit period. Do not double-count the same medical institution when counting the number of study sites.
Figure/Table No.	Table 2.4.1	

2.4.2 Onset Status of Adverse Drug Reactions/Infections in Safety-Unevaluable Patients

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-unevaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this specified drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-unevaluable patients.</td></tr>
<tr><td>Number of patients with ADRs</td><td>Number of patients in which ADRs occurred.</td></tr>
<tr><td>Number of ADRs</td><td>Number of ADRs that have occurred.
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients with ADRs</td><td>Calculated by the following equation: [Number of Patients with ADRs] / [Number of Safety-Unevaluable Patients] × 100</td></tr>
<tr><td>ADR type</td><td>The calculation method in performing each analysis should be as follows:
[Number of patients with ADRs]
• Number of patients in which ADRs occurred.
[Number of ADRs]
• Number of ADRs that occurred. If the same ADR occurs more than once in the same patient, a total of frequencies of the ADR should be counted.
[Rate of patients with ADRs]
• Calculated by the following equation: [Number of Patients with ADRs] / [Number of Safety-Unevaluable Patients] × 100.
[ADR type]
• ADRs should be replaced by MedDRA terms. Categorize by SOC and compile ADRs by PT in each category. If SOC is ‘Investigations,’ classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile ADRs by PT.

• At SOC level, the numbers and rates of patients with ADRs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, ADRs should be counted as one patient in the SOC.
At PT level, the numbers and rates of patients with ADRs should be presented by PT code in ascending order. If the same PT occurs more than once in the same patient, ADRs should be counted as one patient in the PT.</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.2</td></tr>
</table>

2.4.3 Onset Status of AE

Statistical Analysis Set	Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance
Details of Statistical Analysis	The compilation method is the same as described in section 2.4.1. However, adverse drug reactions should be replaced by adverse events.
Figure/Table No.	Table 2.4.3

2.4.4 Onset Status of Adverse Events in Safety-Unevaluable Patients

Statistical Analysis Set	Safety-unevaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this specified drug use surveillance
Details of Statistical Analysis	Compilation method is the same as described in section 2.4.2. However, adverse drug reactions should be replaced by adverse events.
Figure/Table No.	Table 2.4.4

2.4.5 Onset Status of Adverse Drug Reactions or Infections by Seriousness, Onset Time, and Outcome

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Categorize ADRs by the following categories for each item and compile ADR types.

Item Name	Details of Statistical Analysis
Number of patients	Compile the number of patients with ADRs.
Number of ADRs	At SOC, the number of ADRs should be compiled by totaling associated PTs that occurred. At PT level, every PT occurring should be counted as one event.

Item Name	Category
Seriousness	Serious, Not serious
Onset time	1 to 15 days, 16 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over, Unknown
Outcome	Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown

Figure/Table No.	Table 2.4.5

2.4.6 Onset Status of Adverse Events by Seriousness, Onset Time, and Outcome

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize AEs by the following categories for each item and compile AE types.
The compilation method of AE types is the same as described in section 2.4.5. However, adverse drug reactions should be replaced by adverse events.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Seriousness</td><td>Serious, Not serious</td></tr>
<tr><td>Onset time</td><td>1 to 15 days, 16 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over, Unknown</td></tr>
<tr><td>Outcome</td><td>Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown</td></tr>
<tr><td>Causal relationship with the Drug</td><td>Related, Not related, Unevaluable
If AEs (LLTs) occur more than once in the same patient, they should be counted as one event in the following order of priority:
(1) Related, (2) Unevaluable, (3) Not related</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.6</td></tr>
</table>

2.4.7 Onset Status of Adverse Drug Reactions (Bleeding-Related Events) by Seriousness, Onset Time, and Outcome

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Categorize adverse drug reactions (bleeding-related events) by the following categories for each item, and count the types of adverse drug reactions (bleeding-related events). The categories and the compilation method of adverse drug reactions are the same as described in section 2.4.5.
Figure/Table No.	Table 2.4.7

2.4.8 Rate of Patients of Adverse Drug Reactions or Infections by Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize ADRs by the following categories for each item and compile the rate of patients with ADRs (point estimate and 95% confidence interval).
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>BMI</td><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Complications</td><td>No, Yes</td></tr>
<tr><td>Complication breakdown</td><td>Hypertension, Diabetic, Liver disorder, Kidney disorder, Cardiac disorders [myocardial infarction, angina pectoris, atrial fibrillation, others], Cerebrovascular diseases [hemorrhagic cerebrovascular disease, ischaemic cerebrovascular disease, others], Bleeding-related event, Others</td></tr>
<tr><td>Drinking history (Does the patient drink alcoholic beverages nearly every day?)</td><td>Yes, No, Unknown</td></tr>
<tr><td rowspan="2">Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
<tr><td rowspan="2">Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
<tr><td>Smoking history</td><td>Never, Current, Former, Unknown</td></tr>
</table>
</td></tr>
</table>

		Hypersensitivity disposition	No, Yes, Unknown
		Disease duration	Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
		Presence or absence of surgery within one month before baseline	No, Yes
		Pregnancy status during treatment (only for female)	No, Yes
		Initial dose	2 g, 4 g, other
		Change in daily dose	No, Yes
		Breakdown of change in daily dose	2 g → 4 g, 4 g → 2 g, Other
		Mean daily dose	Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over
		Treatment duration	1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over
		Presence or absence of concomitant antihyperlipidemic drug use (during observation period)	No, Yes
		Breakdown of concomitant antihyperlipidemic drugs (during observation period)	Statins drugs, fibrate drugs, intestinal transporter inhibitors, anion-exchange resin, nicotinic acid derivatives, probucol, ethyl icosapentate (EPA), others
		Presence or absence of concomitant anticoagulant/antiplatelet drug use (during observation period)	No, Yes
		Breakdown of concomitant anticoagulant/antiplatelet drugs (during observation period)	Anticoagulant drugs, antiplatelet drugs
Figure/Table No.	Table 2.4.8		

2.4.9 Onset Status of Adverse Drug Reactions or Infections by Age Group

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Classify the patient population into 64 years or below, 65 to 74 years, and 75 years or over, and compile ADR types. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.9

2.4.10 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Liver Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of liver complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.10

2.4.11 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Kidney Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of kidney complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.11

2.4.12 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Anticoagulant and/or Antiplatelet Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant anticoagulant and/or antiplatelet drugs (Both, Anticoagulant only, Antiplatelet only, Neither). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.12

2.4.13 Onset Status of Adverse Drug Reactions (Bleeding-Related Events) by Presence or Absence of Concomitant Anticoagulant and/or Antiplatelet Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile the types of adverse drug reactions (bleeding-related events) by presence or absence of concomitant anticoagulant and/or antiplatelet drugs (Both, Anticoagulant only, Antiplatelet only, Neither). The compilation method of the types of adverse drug reactions is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.13

2.4.14 Onset Status of Adverse Drug Reactions or Infections by Baseline Fasting Triglyceride Level

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance whose fasting triglyceride levels were measured at baseline
Details of Statistical Analysis	Compile ADR types by baseline fasting triglyceride level (Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.14

2.4.15 Onset Status of Adverse Drug Reactions or Infections by Baseline Random Triglyceride Level

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance whose random triglyceride levels were measured at baseline
Details of Statistical Analysis	Compile ADR types by baseline random triglyceride level (Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.15

2.4.16 Changes in Laboratory Test Values (Glucose Metabolism)

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline.
Figure/Table No.	Table 2.4.16

2.4.17 Changes in Laboratory Test Values (Glucose Metabolism) <With Diabetic Complications>

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline.
Remarks	Stratification factor: With diabetic complications
Figure/Table No.	Table 2.4.17

2.4.18 Changes in Laboratory Test Values (Glucose Metabolism) <Without Diabetic Complications>

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline.
Remarks	Stratification factor: Without diabetic complications
Figure/Table No.	Table 2.4.18

2.5 Efficacy Statistical Analysis

2.5.1 Changes in Laboratory Test Values (Fasting Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting measurements and rates of change from baseline (%) of triglyceride (mg/dL), total cholesterol (mg/dL), LDL cholesterol (direct measurement) (mg/dL), LDL cholesterol (Friedewald formula) (mg/dL), HDL cholesterol (mg/dL), non-HDL cholesterol (mg/dL), VLDL cholesterol (mg/dL), VLDL cholesterol (%), Apo-AI (mg/dL), Apo-B (mg/dL), Apo-CIII (mg/dL), lipoprotein(a) (mg/dL), and remnant lipoprotein cholesterol (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%).
Figure/Table No.	Table 2.5.1

2.5.2 Changes in Laboratory Test Values (Random Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom random blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for random measurements and rates of change from baseline (%) of triglyceride (mg/dL), total cholesterol (mg/dL), LDL cholesterol (direct measurement) (mg/dL), HDL cholesterol (mg/dL), non-HDL cholesterol (mg/dL), VLDL cholesterol (mg/dL), VLDL cholesterol (%), Apo-AI (mg/dL), Apo-B (mg/dL), Apo-CIII (mg/dL), lipoprotein(a) (mg/dL), and remnant lipoprotein cholesterol (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%).
Figure/Table No.	Table 2.5.2

2.5.3 Changes in Fasting Lipid-Related Ratio

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for TC/LDL-C, LDL-C/HDL-C, and LDL-C/Apo-B.
Figure/Table No.	Table 2.5.3

2.5.4 Changes in Fasting Triglyceride by Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Calculate summary statistics by stratification for each item for baseline and final evaluation timepoint measurements and rates of change from baseline (%) of fasting triglyceride.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>BMI</td><td>Less than 18.5kg/m^2, 18.5 to less than 25kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Unknown</td></tr>
<tr><td>Disease duration</td><td>Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown</td></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Presence or absence of concomitant antihyperlipidemic drug use</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant antihyperlipidemic drugs (during observation period)</td><td>Statins drugs, Fibrate drugs, Intestinal transporter inhibitors, Anion-exchange resin, Nicotinic acid derivatives, Probucol, Ethyl icosapentate (EPA), Others</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.5.4</td></tr>
</table>

2.5.5 Changes in Random Triglyceride by Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Efficacy-evaluable patients in this special drug use surveillance for whom random blood collection was performed at baseline</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Calculate summary statistics by stratification for each item for baseline and final evaluation timepoint measurements and rates of change from baseline (%) of random triglyceride.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>BMI</td><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Unknown</td></tr>
<tr><td>Disease duration</td><td>Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown</td></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Presence or absence of concomitant antihyperlipidemic drug use (during observation period)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant antihyperlipidemic drugs (during observation period)</td><td>Statins drugs, Fibrate drugs, Intestinal transporter inhibitors, Anion-exchange resin, Nicotinic acid derivatives, Probucol, Ethyl icosapentate (EPA), Others</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.5.5</td></tr>
</table>

3.0 Summary of Onset Status of Serious Adverse Events (Exhibit 2-2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies in Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items per survey unit period of the prior-approval status and of the special drug use surveillance.
Statistical analysis of ‘number of study sites,’ ‘number of surveyed patients,’ ‘number of patients,’ and ‘number of SAEs’ should cover safety-evaluable patients locked during each survey unit period.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients</td><td>Number of patients with SAEs</td></tr>
<tr><td>Number of SAEs</td><td>Number of SAEs
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients</td><td>Calculated by the following equation: [Number of Patients with SAEs] / [Number of Safety-Evaluable Patients] × 100.</td></tr>
<tr><td>SAE type</td><td>The calculation method in performing each analysis should be as follows:
[Number of patients with SAEs]
• Number of patients in which SAEs occurred.
[Number of SAEs]
• Number of SAEs that occurred. If the same SAE occurs more than once in the same patient, a total of frequencies of the SAEs should be counted.
[Rate of patients with SAEs]
• Calculated by the following equation: [Number of Patients with SAEs] / [Number of Safety-Evaluable Patients] × 100.
[SAE type]
• SAEs should be replaced by MedDRA terms. Categorize by SOC and compile SAEs by PT in each category. If SOC is ‘Investigations,’ classify by HLGT (sort by HLGT code in ascending order but without outputting) and compile SAEs by PT.

• At SOC level, the numbers and rates of patients with SAEs should be presented by SOC internationally agreed order. If the same SOC occurs more than once in the same patient, SAEs should be counted as one patient in the SOC.
At PT level, the numbers and rates of patients with SAEs should be presented by PT code in ascending order. If the same PT occurs more than once in the same patient, SAEs should be counted as one patient in the PT.</td></tr>
</table>
</td></tr>
</table>

			The number of SAEs of which causal relationship to the Drug has been denied should be entered in the [ ] brackets. In that case, if the same PT events which is both "related" and "not related" in causality to the Drug occur in the same patient, the SAEs should be counted as one patient in the "related" category.	
		Cumulative total of special drug use surveillance	A respective total of the numbers of study sites and patients per survey unit period. Do not double-count the same medical institution when counting the number of study sites.	
Figure/Table No.	Table 3.0			

Statistical Analysis Plan

(for Periodic Safety Reporting/Reexamination Application)

<Lotriga Granular Capsules>

[Long-term use]

Takeda Pharmaceutical Company Limited
Pharmacovigilance Department, Japan Development Center
Postmarketing Surveillance Group Manager
PPD

Statistical Analysis Contractor
PPD

Ver. 2.0: Prepared on July 20, 2016

Table of Contents

1.0 Definitions of Terms

1.1 Definitions

Item	Definition
Survey unit period (periodic safety report)	Periodic Safety Report 1: July 22, 2012 to January 21, 2013 Periodic Safety Report 2: January 22, 2013 to July 21, 2013 Periodic Safety Report 3: July 22, 2013 to January 21, 2014 Periodic Safety Report 4: January 22, 2014 to July 21, 2014 Periodic Safety Report 5: July 22, 2014 to July 21, 2015 Periodic Safety Report 6: July 22, 2015 to July 21, 2016 Periodic Safety Report 7: July 22, 2016 to July 21, 2017
Drug	Lotriga Granular Capsules
SOC	System organ class of MedDRA.
HLGT	High level group term of MedDRA.
PT	Preferred term of MedDRA.
LLT	Lowest level term of MedDRA.
Enrolled patient	A patient approved for enrollment in the Study.
Patient with eCRF collected	An enrolled patient whose eCRF was submitted via CCI [redacted].
Patient with eCRF uncollected	An enrolled patient other than a patient with eCRF collected.
Locked patient	A patient who has completed the approval process in the PMS system.
Unlocked patient	A patient with eCRF collected other than a locked patient.
Safety-evaluable patient	A locked patient included in safety evaluation.
Safety-unevaluable patient	A locked patient excluded from safety evaluation.
Efficacy-evaluable patient	A safety-evaluable patient included in efficacy evaluation.
Efficacy-unevaluable patient	A safety-evaluable patient excluded from efficacy evaluation.
ADR	An abbreviated form of the term ‘adverse drug reaction or infection.’ Refers to an adverse event other than those judged by the investigator as ‘not related’ in causality to the Drug. In this plan, ‘adverse drug reactions or infections’ is used in headings, and ‘ADRs’ is used in the text and tables.
Serious adverse event (SAE)	[Prior-approval data] An adverse event (AE) judged as ‘serious’ by the trial investigator. [Surveillance data] An adverse event (AE) judged as ‘serious’ by the investigator. Note that events listed in the separate MedDRA code list of the Takeda Medically Significant AE List should be treated as serious even if judged as ‘not serious’ by the investigator.

Item	Definition
Bleeding-related event	An event falling under Standardized MedDRA Query (SMQ) code 20000038 (hemorrhagic SMQ [narrow scope]).
Rate of patients	[For safety compilation with safety-evaluable patients] Calculated by the following equation: [Number of Patients] / [Number of Safety-Evaluable Patients] × 100. [For safety compilation with safety-unevaluable patients] Calculated by the following equation: [Number of Patients] / [Number of Safety-Unevaluable Patients] × 100.
Incidence	[For safety compilation with safety-evaluable patients] Calculated by the following equation: [Number of Events] / [Number of Safety-Evaluable Patients] × 100. [For safety compilation with safety-unevaluable patients] Calculated by the following equation: [Number of Events] / [Number of Safety-Unevaluable Patients] × 100.
Onset time	Calculated by the following equation: [Onset Date] - [Start Date] + 1. If the onset date is unknown, use the first day of the month instead in this equation. However, use the start date if [Start Year & Month] = [Onset Year & Month].
Liver patient	A patient with ‘fatty liver,’ ‘alcoholic fatty liver,’ ‘chronic hepatitis’ or ‘hepatic cirrhosis’ check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000005 (hepatic SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Kidney patient	A patient with ‘diabetic nephropathy,’ ‘glomerulonephritis’ or ‘chronic kidney disease (CKD)’ check-marked in the Complication Details field. Or a patient with a complication falling under the Takeda MedDRA query (TMQ) (Renal Disease) in the Complication Details (Other Diseases) field.
Heart patient	A patient with ‘myocardial infarction,’ ‘angina pectoris’ or ‘atrial fibrillation’ check-marked in the Complication Details field. Or a patient with a complication falling under the SOC code 10007541 (cardiac disorders) in the Complication Details (Other Diseases) field.
Cerebrovascular patient	A patient with ‘cerebral infarction’ or ‘cerebral hemorrhage’ check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000060 (cerebrovascular SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Diabetic patient	A patient with ‘diabetes’ check-marked in the Complication Details field. Or a patient with a complication falling under the TMQ code (Diabetes Mellitus Confirmed diagnosis, excl diagnostics) in the Complication Details (Other Diseases) field.

Item	Definition
Hypertensive patient	A patient with ‘hypertension’ check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000147 (hypertensive SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Myocardial infarction patient	A patient with ‘myocardial infarction’ check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000047 (myocardial infarction SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Anginal patient	A patient with ‘angina pectoris’ check-marked in the Complication Details field. Or a patient with a complication falling under the MedDRA PT code 10002383 (angina pectoris), 10002388 (unstable angina pectoris), 10036759 (Prinzmetal angina), or 10058144 (postinfarction angina) in the Complication Details (Other Diseases) field.
Atrial fibrillation patient	A patient with ‘atrial fibrillation’ check-marked in the Complication Details field. Or a patient with a complication falling under the MedDRA PT code 10003658 (atrial fibrillation) in the Complication Details (Other Diseases) field.
Ischemic cerebrovascular patient	A patient with ‘cerebral infarction’ check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000063 (ischemic cerebrovascular disease SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Hemorrhagic cerebrovascular patient	A patient with ‘cerebral hemorrhage’ check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000064 (hemorrhagic cerebrovascular disease SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Bleeding-related event patient	A patient with a complication falling under the SMQ code 20000038 (bleeding SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Age	Calculated by the following equation: [Start Year] - [Birth Year] - 1 if [Start Month & Day] < [Birth Month & Day]. Calculated by the following equation: [Start Year] - [Birth Year] if [Start Month & Day] ≥ [Birth Month & Day]. If the birth day is unknown, use the first day of the month instead in this equation.
BMI	Calculated by the following equation: [Weight (kg)] / (0.0001 × [Height (cm)] × [Height (cm)]). Indicated by rounding off to the first decimal place.
Disease duration (in years)	Calculated by the following equation: ([Start Year & Month] - [Year & Month of Hyperlipidemia Diagnosis] + 1) / 12. Indicated by rounding off to the first decimal place.

Item	Definition
Start date	The start date of first administration of the Drug stated in the Treatment Duration field of the eCRF.
End date	The end date of last administration of the Drug stated in the Treatment Duration field of the eCRF. However, if the end date of last administration is in 'ongoing 12 months after baseline,' the end date should be the start date plus 360 days.
Observation period (in days)	Calculated by the following equation: [End Date] - [Start Date] + 1.
Treatment duration (in days)	A total of ([End Date] - [Start Date] + 1) in the number of actual administration days, excluding washout period.
Mean daily dose	Calculated by the following equation: Total of ([Daily Dose] × [Total Period of Treatment with the Dose]) / [Observation Period]. See the above for calculation of observation period.
Concomitant medication	A drug used during the surveillance period. However, concomitant medications exclude drugs used for adverse events occurring during the period.
Antihyperlipidemic drug	A drug starting with any of the following drug codes: 218, 2190006, 2190101, 2190102, 2190103, 2190104, 290006, 3133001, 3133400, 3399004.
Statins drug	A drug starting with any of the following drug codes: 2189010, 2189011, 2189012, 2189015, 2189016, 2189017.
Fibrate drug	A drug starting with drug code: 2183.
Intestinal transporter inhibitor	A drug starting with drug code: 2189018.
Anion-exchange resin	A drug starting with any of the following drug codes: 2189009, 2189014.
Nicotinic acid derivative	A drug starting with any of the following drug codes: 2189004, 2189005, 2190006.
Probucol	A drug starting with drug code: 2189008.
Ethyl icosapentate (EPA)	A drug starting with drug code: 3399004.
Anticoagulant drug	A drug starting with any of the following drug codes: 333, 2190408, 6343424.
Antiplatelet drug	A drug starting with any of the following drug codes: 3399 (excluding 3399004), 2171010, 2171402.
Anticoagulant/antiplatelet drug	A drug that falls under the class of either anticoagulant or antiplatelet drugs
LDL cholesterol (Friedewald formula) (mg/dL)	Calculated the equation below if the patient is fasting at the time of blood collection for laboratory testing with triglyceride 400 mg/dL or over. Indicated by rounding off to an integer alone. Total cholesterol - HDL cholesterol - triglyceride / 5
Non-HDL cholesterol (mg/dL)	Calculated by the equation below if triglyceride is 400 mg/dL or over. Indicated by rounding off to an integer alone.

Item	Definition
	Total cholesterol - HDL cholesterol
TC/LDL-C ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. Total cholesterol / LDL cholesterol (Friedewald formula)
LDL-C/HDL-C ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. LDL cholesterol (Friedewald formula) / HDL cholesterol
LDL-C/Apo-B ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. LDL cholesterol (Friedewald formula) / Apo-B
Summary statistics	Mean value, standard deviation, minimum value, first quartile, median, third quartile, maximum value

1.2 Number of Display Digits

Item	Definition
Percentage (%)	Rate of patients with ADRs: Indicated by rounding off to the second decimal place. Other than above: Indicated by rounding off to the first decimal place.
Summary statistics	Mean value: Indicated by rounding off to the first digit below the raw numerical data. Standard deviation: Indicated by rounding off to the second digit below the raw numerical data. First quartile, median, third quartile: Indicated by rounding off to the first digit below the raw numerical data. Minimum value, maximum value: Indicated at the same digits of the raw numerical data.
Confidence interval	Indicated by rounding off to the second digit below the raw numerical data.
p value	Indicated by rounding down to the third decimal place. Expressed as $p<0.001$ when rounding down at the forth decimal place makes the figure below 0.001.

1.3 Level of Significance

Two-sided 5%

1.4 Handling of Evaluation Timepoint Data

The evaluation timepoints are the start of treatment with the Drug (baseline), Month 3, Month 6, Month 9, Month 12, and final evaluation timepoint.

If multiple data exist within each evaluation timepoint, calculate absolute values of difference in measurement intervals from the basic day count and adopt the minimum absolute value as date for that evaluation timepoint. If all the absolute values are the same, adopt one for the latest date of testing/measurement. Test/Measurement values should not be adopted that have been obtained after completion of treatment with the Drug. The final evaluation timepoint test/measurement should be one taken on the latest date within 405 days elapsed since the start date (including values tested/measured during washout period). Note that the number days elapsed since the start date should be counted with the start date as day 0 and the previous day as day -1.

Evaluation Timepoint	Tolerance (Number of Days Since Baseline)	Basic Day Count
Baseline	-90 to 0	0
Month 3	1 to 135	90
Month 6	136 to 225	180
Month 9	226 to 315	270
Month 12	316 to 405	360
Final evaluation timepoint	1 to 405	–

2.0 Results of Special Drug Use Surveillance (Survey 1)

<Lotriga Granular Capsules Special Drug Use Surveillance [long-term use survey]>

2.1 Patient Breakdown (Patient Disposition)

Statistical Analysis Set	Enrolled patients in this special drug use surveillance
Details of Statistical Analysis	Number of enrolled patients, number of patient enrollment sites, number of patients with eCRFs collected, number of patients with eCRFs uncollected, number of locked patients, number of unlocked patients, number of safety-evaluable patients, number of safety-unevaluable patients, number of efficacy-evaluable patients, number of efficacy-unevaluable patients Do not double-count the same medical institution with different participating clinical departments when counting the number of patient enrollment sites. Count the number of patients per reason below for not collecting and total the numbers when the number of patients with eCRFs uncollected. <Reasons for not collecting> • Survey under way • eCRFs uncollectable • Investigator transferred • Investigator's health reasons • Patients enrolled 15 days after Drug prescription [before eCRF collection] • Others Count the number of patients per reason below for exclusion and total the numbers when counting the numbers of safety- and efficacy-unevaluable patients. If the same patient falls under multiple reasons for exclusion, they should be counted separately. <Reasons for exclusion from safety evaluation> • Drug administered before contract period • Patient enrolled 15 days after Drug prescription • No data available after Drug administration • Drug not administered <Reasons for exclusion from efficacy evaluation> • Pre- or post-administration lipid-related values (fasting or random) unavailable No output needs to be generated for items for which the number of patients is zero. For periodic safety reports, the numbers of efficacy-evaluable and unevaluable patients should not be counted.
Figure/Table No.	Figure 2.1, Table 2.1

2.2 Patient Demographics

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize the patient population by the following categories for each item and compile the number of patients and incidence.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Summary statistics</td></tr>
<tr><td></td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>Treatment category</td><td>Outpatient, inpatient</td></tr>
<tr><td>BMI</td><td>Summary statistics</td></tr>
<tr><td></td><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Complications</td><td>No, Yes</td></tr>
<tr><td>Complication breakdown</td><td>Hypertension, Diabetic, Liver disorder, Kidney disorder, Cardiac disorders [myocardial infarction, angina pectoris, atrial fibrillation, others], Cerebrovascular diseases [hemorrhagic cerebrovascular disease, ischemic cerebrovascular disease, others], Bleeding-related event, Others</td></tr>
<tr><td>Drinking history (Does the patient drink alcoholic beverages nearly every day?)</td><td>Yes, No, Unknown</td></tr>
<tr><td rowspan="2">Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
<tr><td rowspan="2">Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
</table></td></tr>
</table>

	Smoking history	Never, Current, Former, Unknown
	Hypersensitivity disposition	No, Yes, Unknown
	Disease duration	Summary statistics
		Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
	Presence or absence of surgery within one month before baseline	No, Yes
	Pregnancy status during treatment (only for female)	No, Yes
Figure/Table No.	Table 2.2	

2.3 Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize the patient population by the following categories for each item and compile the number of patients and incidence.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, Other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Concomitant medications (during observation period)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant medications (during observation period)</td><td>Antihyperlipidemic drugs [statins drugs, fibrate drugs, intestinal transporter inhibitors, anion-exchange resin, nicotinic acid derivatives, probucol, ethyl icosapentate (EPA), others], Anticoagulant/antiplatelet drugs [anticoagulant drugs, antiplatelet drugs]</td></tr>
<tr><td>Completion of treatment with the Drug</td><td>No, Yes, Unknown</td></tr>
<tr><td>Reason for treatment completion</td><td>Treatment goal achieved, AE developing, Patient no longer visiting hospital due to hospital transfer or otherwise, Insufficient effect, Other</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.3</td></tr>
</table>

2.4 Safety Statistical Analysis

2.4.1 Onset Status of Adverse Drug Reactions or Infections (Exhibit 2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items for the prior-approval status and per survey unit period of the special drug use surveillance.
Statistical analysis of ‘number of study sites,’ ‘number of surveyed patients,’ ‘number of patients with ADRs,’ and ‘number of ADRs’ should cover safety-evaluable patients locked during each survey unit period.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients with ADRs</td><td>Number of patients in which ADRs occurred.</td></tr>
<tr><td>Number of ADRs</td><td>Number of ADRs that occurred.
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients with ADRs</td><td>Calculated by the following equation: [Number of Patients with ADRs] / [Number of Safety-Evaluable Patients] × 100</td></tr>
<tr><td>ADR type</td><td>Categorize by SOC and compile ADRs by PT in each category.
In the case of laboratory testing, categorize by SOC, summarize by HLGT, and compile ADRs by PT.
At SOC level, the numbers and rates of patients with ADRs should be presented by SOC internationally agreed order.
At PT level, the numbers of ADRs should be presented by PT code in ascending order. If adverse drug reactions (LLTs) under the same PT occur more than once in the same patient, they should be counted as one PT.</td></tr>
<tr><td>Cumulative total for special drug use surveillance</td><td>A respective total of the numbers of study sites and patients per survey unit period.
Do not double-count the same medical institution when counting the number of study sites.</td></tr>
</table>
</td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.1</td></tr>
</table>

2.4.2 Onset Status of Adverse Drug Reactions/Infections in Safety-Unevaluable Patients

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-unevaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this specified drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-unevaluable patients.</td></tr>
<tr><td>Number of patients with ADRs</td><td>Number of patients in which ADRs occurred.</td></tr>
<tr><td>Number of ADRs</td><td>Number of ADRs that have occurred.
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients with ADRs</td><td>Calculated by the following equation: [Number of Patients with ADRs] / [Number of Safety-Unevaluable Patients] × 100</td></tr>
<tr><td>ADR type</td><td>Categorize by SOC and compile ADRs by PT in each category.
In the case of laboratory testing, categorize by SOC, summarize by HLGT, and compile ADRs by PT.
At SOC level, the numbers and rates of patients with ADRs should be presented by SOC internationally agreed order.
At PT level, the numbers of ADRs should be presented by PT code in ascending order. If adverse drug reactions (LLTs) under the same PT occur more than once in the same patient, they should be counted as one PT.</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.2</td></tr>
</table>

2.4.3 Onset Status of AE

Statistical Analysis Set	Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance
Details of Statistical Analysis	The compilation method is the same as described in section 2.4.1. However, adverse drug reactions should be replaced by adverse events.
Figure/Table No.	Table 2.4.3

2.4.4 Onset Status of Adverse Events in Safety-Unevaluable Patients

Statistical Analysis Set	Safety-unevaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this specified drug use surveillance
Details of Statistical Analysis	Compilation method is the same as described in section 2.4.2. However, adverse drug reactions should be replaced by adverse events.
Figure/Table No.	Table 2.4.4

2.4.5 Onset Status of Adverse Drug Reactions or Infections by Seriousness, Onset Time, and Outcome

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Categorize ADRs by the following categories for each item and compile ADR types.
Figure/Table No.	Table 2.4.5

Item Name	Details of Statistical Analysis
Number of patients	Compile the number of patients with ADRs.
Number of ADRs	At SOC, the number of ADRs should be compiled by totaling associated PTs that occurred. At PT level, every PT occurring should be counted as one event.

Item Name	Category
Seriousness	Serious, Not serious
Onset time	1 to 15 days, 16 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over, Unknown
Outcome	Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown

2.4.6 Onset Status of Adverse Events by Seriousness, Onset Time, and Outcome

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize AEs by the following categories for each item and compile AE types.
The compilation method of AE types is the same as described in section 2.4.5. However, adverse drug reactions should be replaced by adverse events.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Seriousness</td><td>Serious, Not serious</td></tr>
<tr><td>Onset time</td><td>1 to 15 days, 16 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over, Unknown</td></tr>
<tr><td>Outcome</td><td>Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown</td></tr>
<tr><td>Causal relationship with the Drug</td><td>Related, Not related, Unevaluable
If AEs (LLTs) occur more than once in the same patient, they should be counted as one event in the following order of priority:
(1) Related, (2) Unevaluable, (3) Not related</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.6</td></tr>
</table>

2.4.7 Onset Status of Adverse Drug Reactions (Bleeding-Related Events) by Seriousness, Onset Time, and Outcome

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Categorize adverse drug reactions (bleeding-related events) by the following categories for each item, and count the types of adverse drug reactions (bleeding-related events). The categories and the compilation method of adverse drug reactions are the same as described in section 2.4.5.
Figure/Table No.	Table 2.4.7

2.4.8 Rate of Patients of Adverse Drug Reactions or Infections by Factor of Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize ADRs by the following categories for each item and compile the rate of patients with ADRs (point estimate and 95% confidence interval).
Perform Fisher’s exact test for items having categories without rank order, and Mann-Whitney U test for items having categories with rank order.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>BMI</td><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Complications</td><td>No, Yes</td></tr>
<tr><td>Complication breakdown</td><td>Hypertension, Diabetic, Liver disorder, Kidney disorder, Cardiac disorders [myocardial infarction, angina pectoris, atrial fibrillation, others], Cerebrovascular diseases [hemorrhagic cerebrovascular disease, ischaemic cerebrovascular disease, others], Bleeding-related event, Others</td></tr>
<tr><td>Drinking history (Does the patient drink alcoholic beverages nearly every day?)</td><td>Yes, No, Unknown</td></tr>
<tr><td rowspan="2">Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
<tr><td rowspan="2">Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
</table></td></tr>
</table>

	Smoking history	Never, Current, Former, Unknown
	Hypersensitivity disposition	No, Yes, Unknown
	Disease duration	Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
	Presence or absence of surgery within one month before baseline	No, Yes
	Pregnancy status during treatment (only for female)	No, Yes
	Initial dose	2 g, 4 g, other
	Change in daily dose	No, Yes
	Breakdown of change in daily dose	2 g → 4 g, 4 g → 2 g, Other
	Mean daily dose	Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over
	Treatment duration	1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over
	Concomitant medications (during observation period)	No, Yes
	Breakdown of concomitant medications (during observation period)	Antihyperlipidemic drugs [statins drugs, fibrate drugs, intestinal transporter inhibitors, anion-exchange resin, nicotinic acid derivatives, probucol, ethyl icosapentate (EPA), others], Anticoagulant/antiplatelet drugs [anticoagulant drugs, antiplatelet drugs]
Figure/Table No.	Table 2.4.8	

2.4.9 Onset Status of Adverse Drug Reactions or Infections by Age Group

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Classify the patient population into 64 years or below, 65 to 74 years, and 75 years or over, and compile ADR types. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.9

2.4.10 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Liver Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of liver complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.10

2.4.11 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Kidney Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of kidney complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.11

2.4.12 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Anticoagulant and/or Antiplatelet Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant anticoagulant and/or antiplatelet drugs (Both, Anticoagulant only, Antiplatelet only, Neither). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.12

2.4.13 Onset Status of Adverse Drug Reactions (Bleeding-Related Events) by Presence or Absence of Concomitant Anticoagulant and/or Antiplatelet Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile the types of adverse drug reactions (bleeding-related events) by presence or absence of concomitant anticoagulant and/or antiplatelet drugs (Both, Anticoagulant only, Antiplatelet only, Neither). The compilation method of the types of adverse drug reactions is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.13

2.4.14 Onset Status of Adverse Drug Reactions or Infections by Baseline Fasting Triglyceride Level

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance whose fasting triglyceride levels were measured at baseline
Details of Statistical Analysis	Compile ADR types by baseline fasting triglyceride level (Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.14

2.4.15 Onset Status of Adverse Drug Reactions or Infections by Baseline Random Triglyceride Level

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance whose random triglyceride levels were measured at baseline
Details of Statistical Analysis	Compile ADR types by baseline random triglyceride level (Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.15

2.4.16 Changes in Laboratory Test Values (Glucose Metabolism)

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline. Also perform the corresponding t-test.
Figure/Table No.	Table 2.4.16

2.4.17 Changes in Laboratory Test Values (Glucose Metabolism) <With Diabetic Complications>

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline. Also perform the corresponding t-test.
Remarks	Stratification factor: With diabetic complications
Figure/Table No.	Table 2.4.17

2.4.18 Changes in Laboratory Test Values (Glucose Metabolism) <Without Diabetic Complications>

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline. Also perform the corresponding t-test.
Remarks	Stratification factor: Without diabetic complications
Figure/Table No.	Table 2.4.18

2.5 Efficacy Statistical Analysis

2.5.1 Changes in Laboratory Test Values (Fasting Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting measurements and rates of change from baseline (%) of triglyceride (mg/dL), total cholesterol (mg/dL), LDL cholesterol (direct measurement) (mg/dL), LDL cholesterol (Friedewald formula) (mg/dL), HDL cholesterol (mg/dL), non-HDL cholesterol (mg/dL), VLDL cholesterol (mg/dL), Apo-AI (mg/dL), Apo-B (mg/dL), Apo-CIII (mg/dL), lipoprotein(a) (mg/dL), and remnant lipoprotein cholesterol (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%). Also perform the corresponding t-test.
Figure/Table No.	Table 2.5.1

2.5.2 Changes in Laboratory Test Values (Random Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom random blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for random measurements and rates of change from baseline (%) of triglyceride (mg/dL), total cholesterol (mg/dL), LDL cholesterol (direct measurement) (mg/dL), HDL cholesterol (mg/dL), non-HDL cholesterol (mg/dL), VLDL cholesterol, Apo-AI (mg/dL), Apo-B (mg/dL), Apo-CIII (mg/dL), lipoprotein(a) (mg/dL), and remnant lipoprotein cholesterol (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%). Also perform the corresponding t-test.
Figure/Table No.	Table 2.5.2

2.5.3 Changes in Fasting Lipid-Related Ratio

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for TC/LDL-C, LDL-C/HDL-C, and LDL-C/Apo-B.
Figure/Table No.	Table 2.5.3

2.5.4 Changes in Fasting Triglyceride by Factor of Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Calculate summary statistics by stratification for each item for baseline and final evaluation timepoint measurements and rates of change from baseline (%) of fasting triglyceride.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>BMI</td><td>Less than 18.5kg/m^2, 18.5 to less than 25kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Unknown</td></tr>
<tr><td>Disease duration</td><td>Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown</td></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Concomitant medications (during observation period) (antihyperlipidemic drugs)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant medications (during observation period) (antihyperlipidemic drugs)</td><td>Statins drugs, Fibrate drugs, Intestinal transporter inhibitors, Anion-exchange resin, Nicotinic acid derivatives, Probucol, Ethyl icosapentate (EPA), Others</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.5.4</td></tr>
</table>

2.5.5 Changes in Random Triglyceride by Factor of Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Efficacy-evaluable patients in this special drug use surveillance for whom random blood collection was performed at baseline</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Calculate summary statistics by stratification for each item for baseline and final evaluation timepoint measurements and rates of change from baseline (%) of random triglyceride.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>BMI</td><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Unknown</td></tr>
<tr><td>Disease duration</td><td>Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown</td></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Concomitant medications (during observation period) (antihyperlipidemic drugs)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant medications (during observation period) (antihyperlipidemic drugs)</td><td>Statins drugs, Fibrate drugs, Intestinal transporter inhibitors, Anion-exchange resin, Nicotinic acid derivatives, Probucol, Ethyl icosapentate (EPA), Others</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.5.5</td></tr>
</table>

3.0 Summary of Onset Status of Serious Adverse Events (Exhibit 2-2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items per survey unit period of the prior-approval status and of the special drug use surveillance.
Statistical analysis of ‘number of study sites,’ ‘number of surveyed patients,’ ‘number of patients,’ and ‘number of SAEs’ should cover safety-evaluable patients locked during each survey unit period.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients</td><td>Number of patients with SAEs</td></tr>
<tr><td>Number of SAEs</td><td>Number of SAEs
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients</td><td>Calculated by the following equation: [Number of Patients with SAEs] / [Number of Safety-Evaluable Patients] × 100.</td></tr>
<tr><td>SAE type</td><td>Categorize by SOC and compile ADRs by PT in each category.
In the case of laboratory testing, categorize by SOC, summarize by HLGT, and compile ADRs by PT.
At SOC level, the numbers and rates of patients with SAEs should be presented by SOC internationally agreed order.
At PT level, the numbers of SAEs should be presented by PT code in ascending order. If SAEs (LLTs) under the same PT occur more than once in the same patient, they should be counted as one PT.
The number of SAEs of which causal relationship to the Drug has been denied should be entered in the [ ] brackets.</td></tr>
<tr><td>Cumulative total of special drug use surveillance</td><td>A respective total of the numbers of study sites and patients per survey unit period.
Do not double-count the same medical institution when counting the number of study sites.</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 3.0</td></tr>
</table>

Statistical Analysis Plan

(for Periodic Safety Reporting/Reexamination Application)

<Lotriga Granular Capsules>

Takeda Pharmaceutical Company Limited

Pharmacovigilance Department, Pharmaceutical Development Division

Postmarketing Surveillance Group Manager

PPD

Statistical Analysis Contractor

PPD

Ver. 1.0: Prepared on February 7, 2014

Table of Contents

1.0 Definitions of Terms

1.1 Definitions

Item	Definition
Survey unit period (periodic safety report)	Periodic Safety Report 3: July 22, 2013 to January 21, 2014 Periodic Safety Report 4: January 22, 2014 to July 21, 2014 Periodic Safety Report 5: July 22, 2014 to July 21, 2015 Periodic Safety Report 6: July 22, 2015 to July 21, 2016 Periodic Safety Report 7: July 22, 2016 to July 21, 2017
Drug	Lotriga Granular Capsules
SOC	System organ class of MedDRA.
HLGT	High level group term of MedDRA.
PT	Preferred term of MedDRA.
LLT	Lowest level term of MedDRA.
Enrolled patient	A patient approved for enrollment in the Study.
Patient with eCRF collected	A patient finalized in CCI [redacted].
Patient with eCRF uncollected	An enrolled patient other than a patient with eCRF collected.
Locked patient	A patient who has completed the approval process in the PMS system.
Unlocked patient	A patient with eCRF collected other than a locked patient.
Safety-evaluable patient	A patient listed as ‘evaluable’ for safety in the evaluability sheet.
Safety-unevaluable patient	A patient listed as ‘unevaluable’ for safety in the evaluability sheet.
Efficacy-evaluable patient	A safety-evaluable patient listed as ‘evaluable’ for efficacy in the evaluability sheet.
Efficacy-unevaluable patient	A safety-evaluable patient listed as ‘unevaluable’ for efficacy in the evaluability sheet.
ADR	An abbreviated form of the term ‘adverse drug reaction or infection.’ Refers to an adverse event other than those judged by the investigator as ‘not related’ in causality to the Drug. In this plan, ‘adverse drug reactions or infections’ is used in headings, and ‘ADRs’ is used in the text and tables.
Serious adverse event (SAE)	An adverse event (AE) judged as ‘serious’ by the investigator. Note that events listed in the separate MedDRA code list of the Takeda Medically Significant AE List should be treated as serious even if judged as ‘not serious’ by the investigator.
Bleeding-related event	An event falling under Standardized MedDRA Query (SMQ) code 20000038 (hemorrhagic SMQ [narrow scope]).
Rate of patients	Calculated by the following equation: [Number of Patients] / [Number of Safety-Evaluable Patients] × 100.

Item	Definition
Incidence	Calculated by the following equation: [Number of Events] / [Number of Safety-Evaluable Patients] × 100.
Onset time	Calculated by the following equation: [Onset Date] - [Start Date] + 1. If the onset date is unknown, use the first day of the month instead in this equation. However, use the start date if [Start Year & Month] = [Onset Year & Month].
Liver patient	A patient with 'fatty liver,' 'alcoholic fatty liver,' 'chronic hepatitis' or 'hepatic cirrhosis' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000005 (hepatic SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Kidney patient	A patient with 'diabetic nephropathy,' 'glomerulonephritis' or 'chronic kidney disease (CKD)' check-marked in the Complication Details field. Or a patient with a complication falling under the Takeda MedDRA query (TMQ) (Renal Disease) in the Complication Details (Other Diseases) field.
Heart patient	A patient with 'myocardial infarction,' 'angina pectoris' or 'atrial fibrillation' check-marked in the Complication Details field. Or a patient with a complication falling under the SOC code 10007541 (cardiac disorders) in the Complication Details (Other Diseases) field.
Cerebrovascular patient	A patient with 'cerebral infarction' or 'cerebral hemorrhage' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000060 (cerebrovascular SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Diabetic patient	A patient with 'diabetes' check-marked in the Complication Details field. Or a patient with a complication falling under the TMQ code (Diabetes Mellitus Confirmed diagnosis, excl diagnostics) in the Complication Details (Other Diseases) field.
Hypertensive patient	A patient with 'hypertension' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000147 (hypertensive SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Myocardial infarction patient	A patient with 'myocardial infarction' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000047 (myocardial infarction SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Anginal patient	A patient with 'angina pectoris' check-marked in the Complication Details field. Or a patient with a complication falling under the MedDRA PT code 10002383 (angina pectoris), 10002388 (unstable angina pectoris), 10036759 (Prinzmetal angina), or 10058144 (postinfarction angina) in the Complication

Item	Definition
	Details (Other Diseases) field.
Atrial fibrillation patient	A patient with 'atrial fibrillation' check-marked in the Complication Details field. Or a patient with a complication falling under the MedDRA PT code 10003658 (atrial fibrillation) in the Complication Details (Other Diseases) field.
Ischemic cerebrovascular patient	A patient with 'cerebral infarction' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000063 (ischemic cerebrovascular disease SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Hemorrhagic cerebrovascular patient	A patient with 'cerebral hemorrhage' check-marked in the Complication Details field. Or a patient with a complication falling under the SMQ code 20000064 (hemorrhagic cerebrovascular disease SMQ [narrow scope]) in the Complication Details (Other Diseases) field.
Age	Calculated by the following equation: [Start Year] - [Birth Year] - 1 if [Start Month & Day] < [Birth Month & Day]. Calculated by the following equation: [Start Year] - [Birth Year] if [Start Month & Day] ≥ [Birth Month & Day]. If the birth day is unknown, use the first day of the month instead in this equation.
BMI	Calculated by the following equation: [Weight (kg)] / (0.0001 × [Height (cm)] × [Height (cm)]). Indicated by rounding off to the first decimal place.
Disease duration (in years)	Calculated by the following equation: ([Start Year & Month] - [Year & Month of Hyperlipidemia Diagnosis] + 1) / 12. Indicated by rounding off to the first decimal place.
Start date	The start date of first administration of the Drug stated in the Treatment Duration field of the eCRF.
End date	The end date of last administration of the Drug stated in the Treatment Duration field of the eCRF. However, if the end date of last administration is in 'ongoing 12 months after baseline,' the end date should be the start date plus 360 days.
Observation period (in days)	Calculated by the following equation: [End Date] - [Start Date] + 1.
Treatment duration (in days)	A total of ([End Date] - [Start Date] + 1) in the number of actual administration days, excluding washout period.
Mean daily dose	Calculated by the following equation: Total of ([Daily Dose] × [Total Period of Treatment with the Dose]) / [Observation Period]. See the above for calculation of observation period.
Concomitant medication	A drug used during the surveillance period. However, concomitant medications

Item	Definition
	exclude drugs used for adverse events occurring during the period.
Antihyperlipidemic drug	A drug starting with any of the following drug codes: 218, 2190006, 2190101, 2190102, 2190103, 2190104, 290006, 3133001, 3133400, 3399004.
Statins drug	A drug starting with any of the following drug codes: 2189010, 2189011, 2189012, 2189015, 2189016, 2189017.
Fibrate drug	A drug starting with drug code: 2183.
Intestinal transporter inhibitor	A drug starting with drug code: 2189018.
Anion-exchange resin	A drug starting with any of the following drug codes: 2189009, 2189014.
Nicotinic acid derivative	A drug starting with any of the following drug codes: 2189004, 2189005, 2190006.
Probucol	A drug starting with drug code: 2189008.
Ethyl icosapentate (EPA)	A drug starting with drug code: 3399004.
Cardiovascular drug	A drug starting with drug code: 21.
Antidiabetic drug	A drug starting with any of the following drug codes: 396, 2492, 249941.
Anticoagulant drug	A drug starting with any of the following drug codes: 333, 2190408, 6343424.
Antiplatelet drug	A drug starting with any of the following drug codes: 3399 (excluding 3399004), 2171010, 2171402.
LDL cholesterol (Friedewald formula) (mg/dL)	Calculated the equation below if the patient is fasting at the time of blood collection for laboratory testing with triglyceride 400 mg/dL or over. Indicated by rounding off to an integer alone. Total cholesterol - HDL cholesterol - triglyceride / 5
Non-HDL cholesterol (mg/dL)	Calculated by the equation below if triglyceride is 400 mg/dL or over. Indicated by rounding off to an integer alone. Total cholesterol - HDL cholesterol
TC/LDL-C ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. Total cholesterol / LDL cholesterol (Friedewald formula)
LDL-C/HDL-C ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. LDL cholesterol (Friedewald formula) / HDL cholesterol
LDL-C/Apo-B ratio	Calculated by the equation below. Indicated by rounding off to the first decimal place. LDL cholesterol (Friedewald formula) / Apo-B
Summary statistics	Mean value, standard deviation, minimum value, first quartile, median, third quartile, maximum value

1.2 Number of Display Digits

Item	Definition
Percentage (%)	Rate of patients with ADRs: Indicated by rounding off to the second decimal place. Other than above: Indicated by rounding off to the first decimal place.
Summary statistics (Mean value/standard deviation)	Mean value: Indicated by rounding off to the first digit below the raw numerical data. Standard deviation: Indicated by rounding off to the second digit below the raw numerical data.
p value	Indicated by rounding down to the third decimal place. Expressed as $p<0.001$ when rounding down at the forth decimal place makes the figure below 0.001.

1.3 Level of Significance

Two-sided 5%

1.4 Handling of Evaluation Timepoint Data

The evaluation timepoints are the start of treatment with the Drug (baseline), Month 3, Month 6, Month 9, Month 12, and final evaluation timepoint.

If multiple data exist within each evaluation timepoint, calculate absolute values of difference in measurement intervals from the basic day count and adopt the minimum absolute value as date for that evaluation timepoint. If all the absolute values are the same, adopt one for the latest date of measurement. Measurements should not be adopted that have been obtained after completion of treatment with the Drug. The final evaluation timepoint measurement should be one taken on the latest date within 405 days elapsed since the start date (including values measured during washout period). Note that the number days elapsed since the start date should be counted with the start date as day 0 and the previous day as day -1.

Evaluation Timepoint	Tolerance (Number of Days Since Baseline)	Basic Day Count
Baseline	-90 to 0	0
Month 3	1 to 135	90
Month 6	136 to 225	180
Month 9	226 to 315	270
Month 12	316 to 405	360
Final evaluation timepoint	1 to 405	–

2.0 Results of Special Drug Use Surveillance (Survey 1)

<Lotriga Granular Capsules Special Drug Use Surveillance [long-term use survey]>

2.1 Patient Breakdown (Patient Disposition)

Statistical Analysis Set	Enrolled patients in this special drug use surveillance
Details of Statistical Analysis	Number of enrolled patients, number of patient enrollment sites, number of patients with eCRFs collected, number of patients with eCRFs uncollected, number of locked patients, number of unlocked patients, number of safety-evaluable patients, number of safety-unevaluable patients, number of efficacy-evaluable patients, number of efficacy-unevaluable patients Do not double-count the same medical institution with different participating clinical departments when counting the number of patient enrollment sites. Count the number of patients per reason for not collecting and total the numbers when the number of patients with eCRFs uncollected. Count the number of patients per reason for exclusion and total the numbers when counting the numbers of safety- and efficacy-unevaluable patients.
Figure/Table No.	Figure 2.1, Table 2.1

2.2 Patient Demographics

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance

<table>
<tr><td>Details of Statistical Analysis</td><td>Categorize the patient population by the following categories for each item and compile the number of patients and incidence.

<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td rowspan="2">Age</td><td>Summary statistics</td></tr>
<tr><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>Treatment category</td><td>Outpatient, inpatient</td></tr>
<tr><td rowspan="2">Weight</td><td>Summary statistics</td></tr>
<tr><td>Less than 40 kg, 40 to less than 50 kg, 50 to less than 60 kg, 60 to less than 70 kg, 70 to less than 80 kg, 80 to less than 90 kg, 90 kg or over, Not measured</td></tr>
<tr><td rowspan="2">BMI</td><td>Summary statistics</td></tr>
<tr><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Complications</td><td>No, Yes</td></tr>
<tr><td>Complication breakdown</td><td>Hypertension, Diabetic, Liver disorder, Kidney disorder, Cardiac disorders [myocardial infarction, angina pectoris, atrial fibrillation, others], Cerebrovascular diseases [hemorrhagic cerebrovascular disease, ischemic cerebrovascular disease, others], Bleeding-related event, Others</td></tr>
<tr><td>Drinking history (Does the patient drink alcoholic beverages nearly every day?)</td><td>Yes, No, Unknown</td></tr>
<tr><td rowspan="2">Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
</table>
</td></tr>
</table>

Random triglyceride at baseline (mg/dL)	Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured
	Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured
Smoking history	Never, Current, Former, Unknown
Menopausal status (only for female)	No, Yes
Hypersensitivity disposition	No, Yes, Unknown
Disease duration	Summary statistics
	Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
Presence or absence of surgery within one month before baseline	No, Yes
Pregnancy status during treatment (only for female)	No, Yes

Figure/Table No.	Table 2.2

2.3 Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize the patient population by the following categories for each item and compile the number of patients and incidence.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, Other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Concomitant medications (during observation period)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant medications (during observation period)</td><td>Antihyperlipidemic drugs [statins drugs, fibrate drugs, intestinal transporter inhibitors, anion-exchange resin, nicotinic acid derivatives, probucol, ethyl icosapentate (EPA), others], Cardiovascular drugs, Antidiabetic drugs, Anticoagulant/antiplatelet drugs [anticoagulant drugs, antiplatelet drugs]</td></tr>
<tr><td>Completion of treatment with the Drug</td><td>No, Yes, Unknown</td></tr>
<tr><td>Reason for treatment completion</td><td>Treatment goal achieved, AE developing, Patient no longer visiting hospital due to hospital transfer or otherwise, Insufficient effect, Other</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.3</td></tr>
</table>

2.4 Safety Statistical Analysis

2.4.1 Onset Status of Adverse Drug Reactions or Infections (Exhibit 2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items for the prior-approval status and per survey unit period of the special drug use surveillance.
Statistical analysis of ‘number of study sites,’ ‘number of surveyed patients,’ ‘number of patients with ADRs,’ and ‘number of ADRs’ should cover safety-evaluable patients locked during each survey unit period.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients with ADRs</td><td>Number of patients in which ADRs occurred.</td></tr>
<tr><td>Number of ADRs</td><td>Number of ADRs that occurred.
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients with ADRs</td><td>Described in section 1.1.</td></tr>
<tr><td>ADR type</td><td>Categorize by SOC and compile ADRs by PT in each category.
In the case of laboratory testing, categorize by SOC, summarize by HLGT, and compile ADRs by PT.
At SOC level, the numbers and rates of patients with ADRs should be presented by SOC internationally agreed order.
At PT level, the numbers of ADRs should be presented by PT code in ascending order. If adverse drug reactions (LLTs) under the same PT occur more than once in the same patient, they should be counted as one PT.</td></tr>
<tr><td>Cumulative total for special drug use surveillance</td><td>A respective total of the numbers of study sites and patients per survey unit period.
Do not double-count the same medical institution when counting the number of study sites.</td></tr>
<tr><td>Combined total</td><td>A combination of the total for the prior-approval status and the cumulative total for the special drug use surveillance.
Do not double-count the same medical institution when counting the number of study sites.</td></tr>
</table>
</td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.1</td></tr>
</table>

2.4.2 Onset Status of Adverse Drug Reactions/Infections in Safety-Unevaluable Patients (Exhibit 2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-unevaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this specified drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-unevaluable patients.</td></tr>
<tr><td>Number of patients with ADRs</td><td>Number of patients in which ADRs occurred.</td></tr>
<tr><td>Number of ADRs</td><td>Number of ADRs that have occurred.
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients with ADRs</td><td>Described in section 1.1.</td></tr>
<tr><td>ADR type</td><td>Categorize by SOC and compile ADRs by PT in each category.
In the case of laboratory testing, categorize by SOC, summarize by HLGT, and compile ADRs by PT.
At SOC level, the numbers and rates of patients with ADRs should be presented by SOC internationally agreed order.
At PT level, the numbers of ADRs should be presented by PT code in ascending order. If adverse drug reactions (LLTs) under the same PT occur more than once in the same patient, they should be counted as one PT.</td></tr>
<tr><td>Combined total</td><td>A combination of the totals for the prior-approval status and for the special drug use surveillance.
Do not double-count the same medical institution when counting the number of study sites.</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.2</td></tr>
</table>

2.4.3 Onset Status of AE

Statistical Analysis Set	Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance
Details of Statistical Analysis	The compilation method is the same as described in section 2.4.1. However, adverse drug reactions should be replaced by adverse events.
Figure/Table No.	Table 2.4.3

2.4.4 Onset Status of Adverse Events in Safety-Unevaluable Patients

Statistical Analysis Set	Safety-unevaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this specified drug use surveillance
Details of Statistical Analysis	Compilation method is the same as described in section 2.4.2. However, adverse drug reactions should be replaced by adverse events.
Figure/Table No.	Table 2.4.4

2.4.5 Onset Status of Adverse Drug Reactions or Infections by Seriousness, Onset Time, and Outcome

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Categorize ADRs by the following categories for each item and compile ADR types.

Item Name	Details of Statistical Analysis
Number of patients	Compile the number of patients with ADRs.
Number of ADRs	At SOC, the number of ADRs should be compiled by totaling associated PTs that occurred. At PT level, every PT occurring should be counted as one event.
Item Name	Category
Seriousness	Serious, Not serious, N/A
Onset time	1 to 15 days, 16 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over, Unknown
Outcome	Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown

Figure/Table No.	Table 2.4.5

2.4.6 Onset Status of Adverse Events by Seriousness, Onset Time, and Outcome

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize AEs by the following categories for each item and compile AE types.
The compilation method of ADR types is the same as described in section 2.4.5. However, adverse drug reactions should be replaced by adverse events.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Seriousness</td><td>Serious, Not serious, N/A</td></tr>
<tr><td>Onset time</td><td>1 to 15 days, 16 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over, Unknown</td></tr>
<tr><td>Outcome</td><td>Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown</td></tr>
<tr><td>Causal relationship with the Drug</td><td>Related, Not related, Unevaluable
If adverse drug reactions (LLTs) occur more than once in the same patient, they should be counted as one event in the following order of priority:
(1) Related, (2) Unevaluable, (3) Not related</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.4.6</td></tr>
</table>

2.4.7 Onset Status of Adverse Drug Reactions (Bleeding-Related Events) by Seriousness, Onset Time, and Outcome

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Categorize adverse drug reactions (bleeding-related events) by the following categories for each item, and count the types of adverse drug reactions (bleeding-related events). The categories and the compilation method of adverse drug reactions are the same as described in section 2.4.5.
Figure/Table No.	Table 2.4.7

2.4.8 Rate of Patients of Adverse Drug Reactions or Infections by Factor of Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Categorize ADRs by the following categories for each item and compile the rate of patients with ADRs (point estimate and 95% confidence interval).
Perform Fisher’s exact test for items having categories without rank order, and Mann-Whitney U test for items having categories with rank order.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>Weight</td><td>Less than 40 kg, 40 to less than 50 kg, 50 to less than 60 kg, 60 to less than 70 kg, 70 to less than 80 kg, 80 to less than 90 kg, 90 kg or over, not measured</td></tr>
<tr><td>BMI</td><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Complications</td><td>No, Yes</td></tr>
<tr><td>Complication breakdown</td><td>Hypertension, Diabetic, Liver disorder, Kidney disorder, Cardiac disorders [myocardial infarction, angina pectoris, atrial fibrillation, others], Cerebrovascular diseases [hemorrhagic cerebrovascular disease, ischaemic cerebrovascular disease, others], Bleeding-related event, Others</td></tr>
<tr><td>Drinking history (Does the patient drink alcoholic beverages nearly every day?)</td><td>Yes, No, Unknown</td></tr>
<tr><td rowspan="2">Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured</td></tr>
<tr><td>Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured</td></tr>
</table></td></tr>
</table>

Item Name	Category
Random triglyceride at baseline (mg/dL)	Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500mg/dL or over, Not measured
	Less than 150 mg/dL, 150 to less than 400mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over, Not measured
Smoking history	Never, Current, Former, Unknown
Menopausal status (only for female)	No, Yes
Hypersensitivity disposition	No, Yes, Unknown
Disease duration	Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown
Presence or absence of surgery within one month before baseline	No, Yes
Pregnancy status during treatment (only for female)	No, Yes
Initial dose	2 g, 4 g, other
Change in daily dose	No, Yes
Breakdown of change in daily dose	2 g → 4 g, 4 g → 2 g, Other
Mean daily dose	Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over
Treatment duration	1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over
Concomitant medications (during observation period)	No, Yes
Breakdown of concomitant medications (during observation period)	Antihyperlipidemic drugs [statins drugs, fibrate drugs, intestinal transporter inhibitors, anion-exchange resin, nicotinic acid derivatives, probucol, ethyl icosapentate (EPA), others], Cardiovascular drugs, Antidiabetic drugs, Anticoagulant/antiplatelet drugs [anticoagulant drugs, antiplatelet drugs]

Figure/Table No.	Table 2.4.8

2.4.9 Onset Status of Adverse Drug Reactions or Infections by Age Group

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Classify the patient population into 64 years or below, 65 to 74 years, and 75 years or over, and compile ADR types. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.9

2.4.10 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Liver Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of liver complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.10

2.4.11 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Kidney Complications

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of kidney complications. The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.11

2.4.12 Onset Status of Adverse Drug Reactions or Infections by Presence or Absence of Concomitant Anticoagulant and/or Antiplatelet Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile ADR types by presence or absence of concomitant anticoagulant and/or antiplatelet drugs (Both, Anticoagulant only, Antiplatelet only, Neither). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.12

2.4.13 Onset Status of Adverse Drug Reactions (Bleeding-Related Events) by Presence or Absence of Concomitant Anticoagulant and/or Antiplatelet Drugs

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Compile the types of adverse drug reactions (bleeding-related events) by presence or absence of concomitant anticoagulant and/or antiplatelet drugs (Both, Anticoagulant only, Antiplatelet only, Neither). The compilation method of the types of adverse drug reactions is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.13

2.4.14 Onset Status of Adverse Drug Reactions or Infections by Baseline Fasting Triglyceride Level

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance whose fasting triglyceride levels were measured at baseline
Details of Statistical Analysis	Compile ADR types by baseline fasting triglyceride level (Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.14

2.4.15 Onset Status of Adverse Drug Reactions or Infections by Baseline Random Triglyceride Level

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance whose random triglyceride levels were measured at baseline
Details of Statistical Analysis	Compile ADR types by baseline random triglyceride level (Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over). The compilation method of ADR types is the same as described in section 2.4.1.
Figure/Table No.	Table 2.4.15

2.4.16 Changes in Laboratory Test Values (Glucose Metabolism)

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline. Also perform the corresponding t-test.
Figure/Table No.	Table 2.4.16

2.4.17 Changes in Laboratory Test Values (Glucose Metabolism) <With Diabetic Complications>

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline. Also perform the corresponding t-test.
Remarks	Stratification factor: With diabetic complications
Figure/Table No.	Table 2.4.17

2.4.18 Changes in Laboratory Test Values (Glucose Metabolism) <Without Diabetic Complications>

Statistical Analysis Set	Safety-evaluable patients in this special drug use surveillance
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting blood glucose (mg/dL) and HbA1c (NGSP value) (%) measurements and variations from baseline. In addition, calculate the 95% confidence interval for the mean value for variations from baseline. Also perform the corresponding t-test.
Remarks	Stratification factor: Without diabetic complications
Figure/Table No.	Table 2.4.18

2.5 Efficacy Statistical Analysis

2.5.1 Changes in Laboratory Test Values (Fasting Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for fasting measurements and rates of change from baseline (%) of triglyceride (mg/dL), total cholesterol (mg/dL), LDL cholesterol (direct measurement) (mg/dL), LDL cholesterol (Friedewald formula) (mg/dL), HDL cholesterol (mg/dL), non-HDL cholesterol (mg/dL), VLDL cholesterol (mg/dL), Apo-AI (mg/dL), Apo-B (mg/dL), Apo-CIII (mg/dL), lipoprotein(a) (mg/dL), and remnant lipoprotein cholesterol (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%). Also perform the corresponding t-test.
Figure/Table No.	Table 2.5.1

2.5.2 Changes in Laboratory Test Values (Random Lipid)

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom random blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for random measurements and rates of change from baseline (%) of triglyceride (mg/dL), total cholesterol (mg/dL), LDL cholesterol (direct measurement) (mg/dL), HDL cholesterol (mg/dL), non-HDL cholesterol (mg/dL), VLDL cholesterol, Apo-AI (mg/dL), Apo-B (mg/dL), Apo-CIII (mg/dL), lipoprotein(a) (mg/dL), and remnant lipoprotein cholesterol (mg/dL). In addition, calculate the 95% confidence interval for the mean value for rates of change from baseline (%). Also perform the corresponding t-test.
Figure/Table No.	Table 2.5.2

2.5.3 Changes in Fasting Lipid-Related Ratio

Statistical Analysis Set	Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline
Details of Statistical Analysis	Calculate summary statistics at each evaluation timepoint for TC/LDL-C, LDL-C/HDL-C, and LDL-C/Apo-B.
Figure/Table No.	Table 2.5.3

2.5.4 Changes in Fasting Triglyceride by Factor of Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Efficacy-evaluable patients in this special drug use surveillance for whom fasting blood collection was performed at baseline</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Calculate summary statistics by stratification for each item for baseline and final evaluation timepoint measurements and rates of change from baseline (%) of fasting triglyceride.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>Weight</td><td>Less than 40 kg, 40 to less than 50 kg, 50 to less than 60 kg, 60 to less than 70 kg, 70 to less than 80 kg, 80 to less than 90 kg, 90 kg or over, not measured</td></tr>
<tr><td>BMI</td><td>Less than 18.5kg/m^2, 18.5 to less than 25kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Fasting triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over</td></tr>
<tr><td>Menopausal status (only for female)</td><td>No, Yes</td></tr>
<tr><td>Disease duration</td><td>Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown</td></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Concomitant medications (during observation period) (antihyperlipidemic drugs)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant medications (during observation period) (antihyperlipidemic drugs)</td><td>Statins drugs, Fibrate drugs, Intestinal transporter inhibitors, Anion-exchange resin, Nicotinic acid derivatives, Probucol, Ethyl icosapentate (EPA), Others</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.5.4</td></tr>
</table>

2.5.5 Changes in Random Triglyceride by Factor of Patient Demographics and Treatment Details

<table>
<tr><td>Statistical Analysis Set</td><td>Efficacy-evaluable patients in this special drug use surveillance for whom random blood collection was performed at baseline</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Calculate summary statistics by stratification for each item for baseline and final evaluation timepoint measurements and rates of change from baseline (%) of random triglyceride.
<table>
<tr><th>Item Name</th><th>Category</th></tr>
<tr><td>Sex</td><td>Male, Female</td></tr>
<tr><td>Age</td><td>Minimum age to 64 years, 65 to 74 years, 75 years to maximum age, Unknown</td></tr>
<tr><td>Weight</td><td>Less than 40 kg, 40 to less than 50 kg, 50 to less than 60 kg, 60 to less than 70 kg, 70 to less than 80 kg, 80 to less than 90 kg, 90 kg or over, not measured</td></tr>
<tr><td>BMI</td><td>Less than 18.5 kg/m^2, 18.5 to less than 25 kg/m^2, 25 to less than 30 kg/m^2, 30 kg/m^2 or over, unknown</td></tr>
<tr><td>Random triglyceride at baseline (mg/dL)</td><td>Less than 150 mg/dL, 150 to less than 400 mg/dL, 400 to less than 500 mg/dL, 500 to less than 750 mg/dL, 750 mg/dL or over</td></tr>
<tr><td>Menopausal status (only for female)</td><td>No, Yes</td></tr>
<tr><td>Disease duration</td><td>Less than 1 year, 1 to less than 3 years, 3 to less than 5 years, 5 years or over, Unknown</td></tr>
<tr><td>Initial dose</td><td>2 g, 4 g, other</td></tr>
<tr><td>Change in daily dose</td><td>No, Yes</td></tr>
<tr><td>Breakdown of change in daily dose</td><td>2 g → 4 g, 4 g → 2 g, Other</td></tr>
<tr><td>Mean daily dose</td><td>Less than 2 g, 2 to less than 4 g, 4 to less than 6 g, 6 g or over</td></tr>
<tr><td>Treatment duration</td><td>1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days, 361 days or over</td></tr>
<tr><td>Concomitant medications (during observation period) (antihyperlipidemic drugs)</td><td>No, Yes</td></tr>
<tr><td>Breakdown of concomitant medications (during observation period) (antihyperlipidemic drugs)</td><td>Statins drugs, Fibrate drugs, Intestinal transporter inhibitors, Anion-exchange resin, Nicotinic acid derivatives, Probucol, Ethyl icosapentate (EPA), Others</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 2.5.5</td></tr>
</table>

3.0 Summary of Onset Status of Serious Adverse Events (Exhibit 2-2)

<table>
<tr><td>Statistical Analysis Set</td><td>Safety-evaluable patients in clinical studies before approval (total of patients in clinical studies inside and outside Japan used for safety evaluation stated in the Adverse Drug Reactions section of the package insert) and this special drug use surveillance</td></tr>
<tr><td>Details of Statistical Analysis</td><td>Compile the following items per survey unit period of the prior-approval status and of the use-results surveillance/special drug use surveillance.
Statistical analysis of ‘number of study sites,’ ‘number of surveyed patients,’ ‘number of patients with AEs,’ and ‘number of AEs’ should cover safety-evaluable patients locked during each survey unit period.
<table>
<tr><th>Item Name</th><th>Details of Statistical Analysis</th></tr>
<tr><td>Number of study sites</td><td>Number of medical institutions that have collected eCRFs</td></tr>
<tr><td>Number of surveyed patients</td><td>Number of safety-evaluable patients.</td></tr>
<tr><td>Number of patients</td><td>Number of patients with SAEs</td></tr>
<tr><td>Number of SAEs</td><td>Number of SAEs
Every PT occurring should be counted as one event.</td></tr>
<tr><td>Rate of patients</td><td>Calculated by the following equation: [Number of Patients with SAEs] / [Number of Safety-Evaluable Patients] × 100.</td></tr>
<tr><td>SAE type</td><td>Categorize by SOC and compile ADRs by PT in each category.
In the case of laboratory testing, categorize by SOC, summarize by HLGT, and compile ADRs by PT.
At SOC level, the numbers and rates of patients with AEs should be presented by SOC internationally agreed order.
At PT level, the numbers of ADRs should be presented by PT code in ascending order. If adverse drug reactions (LLTs) under the same PT occur more than once in the same patient, they should be counted as one PT.
The number of SAEs of which causal relationship to the Drug has been denied should be entered in the [ ] brackets.</td></tr>
<tr><td>Cumulative total</td><td>A respective total of the numbers of study sites and patients per survey unit period.
Do not double-count the same medical institution when counting the number of study sites.</td></tr>
<tr><td>Combined total</td><td>A combination of the total for the prior-approval status and the cumulative total.
Do not double-count the same medical institution when counting the number of study sites.</td></tr>
</table></td></tr>
<tr><td>Figure/Table No.</td><td>Table 3.0</td></tr>
</table>