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

NCT Number: NCT02153073

Protocol Approve Date: 02-Apr-2018

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

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

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

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

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

Special Drug Use Surveillance Protocol

Lotriga Granular Capsules Special Drug Use Surveillance

[Long-term use survey]

Version No.	**7th Version**
Date Prepared	**April 2, 2018**
Study Sponsor	**Takeda Pharmaceutical Company Limited**

Table of Contents

1.0 Background

Lotriga Granular Capsules (the “Drug”) is an oral capsule formulation containing the active ingredient omega-3 fatty acid ethyl esters (principally EPA-E and DHA-E). The Drug differs from general marine oil products, such as supplements, in containing a high concentration of omega-3 fatty acid ethyl esters. Since first approved in Norway in September 1994, the Drug has been in extensive use overseas, sold in more than 60 countries. In the clinical study of the Drug conducted in Japan in patients with hypertriglyceridemia, adverse drug reactions (ADRs) including ‘laboratory test abnormal’ were observed in 91 (9.6%) of the 948 patients administered at 2 g or 4 g of omega-3 fatty acid ethyl esters, and the major ADR was Diarrhea (2.5%).

Despite the proven track record of extensive use overseas and the fact that the safety of long-term use was already evaluated during the clinical study, it is important to evaluate the safety of long-term use of the Drug in the general patient population in Japan.

Special drug use surveillance (hereinafter the "Study") has been therefore designed to evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

2.0 Objective

To evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

3.0 Target Sample Size and Rationale for Sample Size Setting

3.1 Target Sample Size

3,000 patients

3.2 Rationale for Sample Size Setting

Bleeding-related events are set as a priority survey item for the Drug. As postmarketing surveillance of EPA products in antihyperlipidemic therapy has reported that the incidence of bleeding-related ADRs was 0.4% and that the percentage of anticoagulant and antiplatelet concomitant use was about 10%, the Study sets a target of 3,000 patients so that anticoagulant and antiplatelet concomitant use can be assessed to some degree, in addition to bleeding-related ADRs.

Note that this rationale for the sample size is not based on statistical evidence.

4.0 Study Population

Patients with hyperlipidemia will be eligible for this study; however, those who meet the following exclusion criteria were excluded from the study.

Exclusion criteria:

(1) Patients with hemorrhage (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, or vitreous hemorrhage)

(2) Patients with a history of hypersensitivity to ingredients in the Drug

5.0 Dosage and Administration for Study Population

The usual adult dosage is 2 g of omega-3 fatty acid ethyl esters administered orally once daily after meals. However, the dosage can be increased up to twice daily (at a dose of 2 g) depending on the patient's triglyceride level.

6.0 Number of Study Sites by Clinical Department

About 200 sites (clinical departments not specified)

7.0 Study Method

7.1 Observation Period

12 months

7.2 Request and Contract to Study Sites

The Study will be requested and contracted using a web-based electronic data collection system CCI. Takeda Pharmaceutical's staffs (hereinafter "Takeda staffs") will adequately explain to investigators about the purpose and description of the Study, CCI's operating procedure, electronic signature, and user ID and password handling for request for the Study, based on the Letter of Request for Cooperation in Special Drug Use Surveillance, the Implementation Guidance, data input screen images, and the abbreviated CCI Operating Manual. Takeda MRs will then conclude a contract in writing with study sites to perform the Study within the specified surveillance period.

7.3 Patient Enrollment Method

Patients will be "centrally" enrolled using CCI. The investigator will enter into CCI patient enrollment information (see Section 9.1) of patients for whom the Drug has been prescribed since the start date of the period of contract with the study site, within 14 days after the prescription date of the Drug (the prescription date is defined as "Day 0"; the day following the prescription date is defined as "Day 1").

7.4 Data Entry and Electronic Signature to Electronic Case Report Form (eCRF)

The investigator will enter patient data including demographics and treatment into CCI and electronically sign the eCRF in 12 months after the start of treatment with the Drug (baseline).

If a patient discontinues the treatment with the Drug for some reason during the observation period, the investigator will be expected to enter their information including demographics and treatment into CCI and electronically sign the eCRF within one month after the completion of necessary observations. However, if the patient discontinues the treatment with the Drug due to the occurrence of an adverse event (AE), the investigator should continue to observe them after discontinuation, as long as possible until the AE is resolved or resolving. The investigator should then enter the result of the observation into CCI and

electronically sign the eCRF.

After review of the information, Takeda Pharmaceutical may request for re-survey, if deemed necessary, via [redacted] The investigator will, upon checking, perform the details of the requested re-survey and enter the result of the re-survey into [redacted] and electronically sign the eCRF.

7.5 Action Taken at Onset of Serious Adverse Event

The investigator will immediately contact the Takeda staff if a serious AE occurs during the observation period. The investigator will also separately provide detailed information thereof upon request, if any, from the Takeda staff.

8.0 Expected Duration of Study

Surveillance period: May 2013 to May 31, 2017

Patient enrollment period: May 2013 to May 31, 2015*

*Enrollment may be closed before the end of the enrollment period if the total number of patients enrolled in the Study reaches the target sample size.

9.0 Survey Items

The investigator will enter the information of the following items into [redacted]. The schedule for the Study is provided in the Appendix.

9.1 Patient Enrollment

1) Survey items

Prescription date of the Date, patient ID number, patient initials, sex, birth date, determination with inclusion criteria, and determination with exclusion criteria

2) Survey timing

The time of patient enrollment

9.2 Patient Demographics

1) Survey items

Height, weight, time of hyperlipidemia diagnosis, treatment category, menopausal status (only for female), complications (presence or absence and details), medical history (presence or absence and details), hypersensitivity disposition (presence or absence and details), drinking history, smoking history, presence or absence of surgery within one month before baseline, and presence or absence of healthier lifestyle education (diet and exercise therapies)

2) Survey time

Baseline

9.3 Treatment Information

1) Survey items

Administration of the Drug (daily dose, treatment duration, and status of completion of treatment with the Drug), administration of antihyperlipidemic drugs other than the Drug* (presence or absence, drug name, daily dose, and treatment duration), and administration of concomitant medications (other than antihyperlipidemic drugs) (presence or absence, drug name, and purpose of administration)

*: Including antihyperlipidemic drugs with which treatment is discontinued within two months before baseline.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.4 Testing/Observation Items

1) Survey items

Triglyceride (TG), total cholesterol (TC), LDL cholesterol* (LDL-C), HDL cholesterol (HDL-C), VLDL cholesterol (VLDL-C), Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), remnant lipoprotein cholesterol (RLP-C), fasting blood glucose (FBG), HbA1c

*: When tested by direct measurement

2) Survey timing

Baseline, Month 3, Month 6, Month 9, and Month 12 (or discontinuation of treatment) test timepoints

9.5 Other Observation Items

1) Survey items

Pregnancy status

If the patient is found to be pregnant during the observation period, the investigator will report the Takeda staff. The investigator will, upon request from the Takeda staff, use a sheet for pregnant women to provide detailed information (including information available up to childbirth, including premature birth or other pregnancy results, if possible).

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.6 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (see Table 1), AE name, date of onset, seriousness and reason for seriousness (see Table 2), action taken to the Drug, date of determination of outcome, outcome, and causal relationship to the Drug* (see Table 3)

If the outcome is not resolved or unknown and the casual relationship is determined as unevaluable, follow-up survey should be conducted to some extent possible.

*If causal relationship to the Drug is determined as not related, reasons that may constitute the rationale for determination should be collected if it is unevaluable.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

3) Priority survey item

Bleeding-related events occurring after baseline are set as a priority survey item. If any bleeding-related event is reported as an AE, laboratory test values related to bleeding should be separately collected.

Table 1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
The following should be also handled as an AE:

- A symptoms or other problem occurring in an infant breastfed from a mother taking the medicinal product
- A symptom or other problem occurring in a child administered the medicinal product
- A symptom or other problem occurring in a patient administered or taking more than the approved dose of the medicinal product

Table 2 Seriousness Criteria

An event is classified as serious if:

1. resulting in death (death),
2. being life-threatening (at risk of death),
3. requiring inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization),
4. resulting in persistent or significant disability/incapacity (disorder),
5. being a congenital anomaly/birth defect (birth defect), or
6. being any other medically serious condition that does not fall under any of 1 to 5 above. Note that all those listed in the Takeda Medically Significant AE List are included in this criterion. (Examples include bronchospasm, which requires short-term intensive care in emergency room settings.)

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/acute respiratory distress syndrome (ARDS)
- Torsade de pointes/ventricular fibrillation/ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including spasm and epilepsy)
- Agranulocytosis
- Aplastic anaemia
- Toxic epidermal necrolysis/muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial lung disease)
- Neuroleptic malignant syndrome/malignant hyperthermia
- Spontaneous abortion/stillbirth and foetal death
- Confirmed or suspected transmission of infection by a medicinal product
- Confirmed or suspected endotoxin shock

Table 3 Criteria for Casual Relationship between Adverse Event and the Drug

Determination	Criteria
Related	There is temporal correlation between the Drug and the event (including results from discontinuation of treatment). Or the event is an AE considered likely to have been caused by the Drug although it is presumed to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Not related	There is no temporal correlation between the Drug and the event. Or the event is adequately considered to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Unevaluable	There is lack of information necessary for evaluation of the event, including temporal correlation (including results from discontinuation of treatment), primary disease, complications, concomitant medications, and combined treatments.

10.0 Analysis Items and Method

10.1 Patient Disposition Items

Compile information including the number of enrolled patients, number of patients with eCRFs collected, numbers of safety- and efficacy-evaluable patients, and the number of patients excluded from analysis and reasons for exclusion.

10.2 Patient Demographics

Compile patient demographic information including sex, age, hypersensitivity disposition, and complications.

10.3 Treatment Details

Compile information on administration of the Drug and of concomitant medications.

10.4 Safety Items

Compile the following regarding the safety-evaluable population. AEs, coded using MedDRA, will be summarized by preferred term (PT) and by system organ class (SOC).

10.4.1 Onset Status of Adverse Events

Compile the incidence of AEs occurring during the observation period, in terms of, e.g., causal relationship with the Drug, type, seriousness. Note that bleeding-related events should be separately compiled because such events are set as a priority survey item.

10.4.2 Factors Likely to Affect Safety

Compile the incidence of ADRs occurring during the observation period, by stratification variables: patient baseline characteristics (sex, age, presence or absence of renal

dysfunction, presence or absence of hepatic dysfunction, etc.) and treatment regimen (administration of the Drug, administration of concomitant medications such as anticoagulant drugs, antiplatelet drugs).

10.5 Efficacy Items

Compile the following regarding the efficacy-evaluable population.

10.5.1 Changes in Lipid Parameters: TG, TC, LDL-C, HDL-C, Non-HDL-C, etc.

Tabulate observed values and changes (observed value at each observational timepoint after baseline minus observed value at baseline) at each observational timepoint for TG, TC, LDL-C (by converted value calculated by direct measurement, Friedewald formula*), HDL-C, Non-HDL-C (converted value**), VLDL cholesterol, Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), and RLP-C.

*: LDL-C = TC-HDL-C - TG / 5

**: Non-HDL-C = TC-HDL-C

Note that LDL-C, Non-HDL-C, TC/LDL-C ratio, LDL-C/HDL-C ratio, and LDL-C/Apo-B ratio should be calculated from test results.

10.5.2 Factors Likely to Affect Efficacy

Compile TG values by stratification variables: patient baseline characteristics (sex and age) and treatment regimen (administration of the Drug, administration of concomitant medications, etc.).

11.0 Organizational Structure for Conducting the Study

Study Chair

Takeda Pharmaceutical Co., Ltd.

Post Marketing Surveillance Manager

12.0 Service Contractor's Name and Address and Scope of Contract Work

(1) PPD

Scope of work: Data management

(2) PPD

Scope of work: Data management and statistical analysis

(3) PPD

Scope of work: Storage of relevant records, PDF preparation of adverse events and other relevant information, and support services related to provision of information

(4) PPD

Scope of work: Formulation of CCI and its technical operations

(5) PPD

Scope of work: Medical writing

13.0 Other Necessary Items

13.1 Protocol Revision

During the surveillance period, keep track of, e.g., the progress of the Study, the onset of unexpected ADRs or serious ADRs based on the precautions, presence or absence of increased incidence of specified ADRs, the appropriateness of survey items. If needed, review and revise this protocol. If partial change approval is obtained for dosage and administration or indications during the surveillance period, examine whether to revise this protocol if necessary and revise it if necessary.

13.2 Action Taken in Case of Problem or Question

If any problem is found in the safety or efficacy of the Drug, carefully review the data and examine what needs to be done.

Appendix Study Schedule

Survey Item \ Survey and Data Entry Timing		Observation Period						
		Patient enrollment	Baseline	Month 3	Month 6	Month 9	Month 12	Discontinuation
Patient Enrollment	Prescription date of the Drug	○						
	Patient ID number	○						
	Patient initials	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria/exclusion criteria	○						
Patient demographics	Height, Weight		○					
	Time of hyperlipidemia diagnosis		○					
	Treatment category		○					
	Menopausal status (only for female)		○					
	Complications		○					
	Medical history		○					
	Hypersensitivity disposition		○					
	Drinking history, smoking history		○					
	Presence or absence of surgery before baseline		○					
	Presence or absence of healthier lifestyle education (diet and exercise therapies)		○					
Treatment Information	Administration of the Drug		← ○ →					○
	Administration of other antihyperlipidemic drugs		← ○ →					○
	Administration of concomitant medications (other than antihyperlipidemic drug)		← ○ →					○
Testing /Observation Items	TG		○	○	○	○	○	○
	TC		○	○	○	○	○	○
	LDL-C (direct measurement)		○	○	○	○	○	○
	HDL-C		○	○	○	○	○	○
	VLDL-C		○	○	○	○	○	○
	Apo-AI		○	○	○	○	○	○
	Apo-B		○	○	○	○	○	○
	Apo-CIII		○	○	○	○	○	○
	Lipoprotein (a)		○	○	○	○	○	○
	RLP-C		○	○	○	○	○	○
	FBG		○	○	○	○	○	○
	HbA1c		○	○	○	○	○	○
	Pregnancy status (only for female)		← ○ →					○
	AE		← ○ →					○

○: Surveyed, tested, or observed ← ○: → Surveyed, tested, or observed throughout the period

Special Drug Use Surveillance Protocol

Lotriga Granular Capsules Special Drug Use Surveillance

[Long-term use survey]

Version No.	**6th Version**
Date Prepared	**June 2, 2017**
Study Sponsor	**Takeda Pharmaceutical Company Limited**

Table of Contents

1.0 Background

Lotriga Granular Capsules (the “Drug”) is an oral capsule formulation containing the active ingredient omega-3 fatty acid ethyl esters (principally EPA-E and DHA-E). The Drug differs from general marine oil products, such as supplements, in containing a high concentration of omega-3 fatty acid ethyl esters. Since first approved in Norway in September 1994, the Drug has been in extensive use overseas, sold in more than 60 countries. In the clinical study of the Drug conducted in Japan in patients with hypertriglyceridemia, adverse drug reactions (ADRs) including ‘laboratory test abnormal’ were observed in 91 (9.6%) of the 948 patients administered at 2 g or 4 g of omega-3 fatty acid ethyl esters, and the major ADR was Diarrhea (2.5%).

Despite the proven track record of extensive use overseas and the fact that the safety of long-term use was already evaluated during the clinical study, it is important to evaluate the safety of long-term use of the Drug in the general patient population in Japan.

Special drug use surveillance (hereinafter the "Study") has been therefore designed to evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

2.0 Objective

To evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

3.0 Target Sample Size and Rationale for Sample Size Setting

3.1 Target Sample Size

3,000 patients

3.2 Rationale for Sample Size Setting

Bleeding-related events are set as a priority survey item for the Drug. As postmarketing surveillance of EPA products in antihyperlipidemic therapy has reported that the incidence of bleeding-related ADRs was 0.4% and that the percentage of anticoagulant and antiplatelet concomitant use was about 10%, the Study sets a target of 3,000 patients so that anticoagulant and antiplatelet concomitant use can be assessed to some degree, in addition to bleeding-related ADRs.

Note that this rationale for the sample size is not based on statistical evidence.

4.0 Study Population

Patients with hyperlipidemia will be eligible for this study; however, those who meet the following exclusion criteria were excluded from the study.

Exclusion criteria:

(1) Patients with hemorrhage (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, or vitreous hemorrhage)

(2) Patients with a history of hypersensitivity to ingredients in the Drug

5.0 Dosage and Administration for Study Population

The usual adult dosage is 2 g of omega-3 fatty acid ethyl esters administered orally once daily after meals. However, the dosage can be increased up to twice daily (at a dose of 2 g) depending on the patient's triglyceride level.

6.0 Number of Study Sites by Clinical Department

About 200 sites (clinical departments not specified)

7.0 Study Method

7.1 Observation Period

12 months

7.2 Request and Contract to Study Sites

The Study will be requested and contracted using a web-based electronic data collection system CCI. Takeda Pharmaceutical's staffs (hereinafter "Takeda staffs") will adequately explain to investigators about the purpose and description of the Study, CCI's operating procedure, electronic signature, and user ID and password handling for request for the Study, based on the Letter of Request for Cooperation in Special Drug Use Surveillance, the Implementation Guidance, data input screen images, and the abbreviated CCI Operating Manual. Takeda MRs will then conclude a contract in writing with study sites to perform the Study within the specified surveillance period.

7.3 Patient Enrollment Method

Patients will be "centrally" enrolled using CCI. The investigator will enter into CCI patient enrollment information (see Section 9.1) of patients for whom the Drug has been prescribed since the start date of the period of contract with the study site, within 14 days after the prescription date of the Drug (the prescription date is defined as "Day 0"; the day following the prescription date is defined as "Day 1").

7.4 Data Entry and Electronic Signature to Electronic Case Report Form (eCRF)

The investigator will enter patient data including demographics and treatment into CCI and electronically sign the eCRF in 12 months after the start of treatment with the Drug (baseline).

If a patient discontinues the treatment with the Drug for some reason during the observation period, the investigator will be expected to enter their information including demographics and treatment into CCI and electronically sign the eCRF within one month after the completion of necessary observations. However, if the patient discontinues the treatment with the Drug due to the occurrence of an adverse event (AE), the investigator should continue to observe them after discontinuation, as long as possible until the AE is resolved or resolving. The investigator should then enter the result of the observation into CCI and

electronically sign the eCRF.

After review of the information, Takeda Pharmaceutical may request for re-survey, if deemed necessary, via [redacted]. The investigator will, upon checking, perform the details of the requested re-survey and enter the result of the re-survey into [redacted] and electronically sign the eCRF.

7.5 Action Taken at Onset of Serious Adverse Event

The investigator will immediately contact the Takeda staff if a serious AE occurs during the observation period. The investigator will also separately provide detailed information thereof upon request, if any, from the Takeda staff.

8.0 Expected Duration of Study

Surveillance period: May 2013 to May 31, 2017

Patient enrollment period: May 2013 to May 31, 2015*

*Enrollment may be closed before the end of the enrollment period if the total number of patients enrolled in the Study reaches the target sample size.

9.0 Survey Items

The investigator will enter the information of the following items into [redacted]. The schedule for the Study is provided in the Appendix.

9.1 Patient Enrollment

1) Survey items

Prescription date of the Date, patient ID number, patient initials, sex, birth date, determination with inclusion criteria, and determination with exclusion criteria

2) Survey timing

The time of patient enrollment

9.2 Patient Demographics

1) Survey items

Height, weight, time of hyperlipidemia diagnosis, treatment category, menopausal status (only for female), complications (presence or absence and details), medical history (presence or absence and details), hypersensitivity disposition (presence or absence and details), drinking history, smoking history, presence or absence of surgery within one month before baseline, and presence or absence of healthier lifestyle education (diet and exercise therapies)

2) Survey time

Baseline

9.3 Treatment Information

1) Survey items

Administration of the Drug (daily dose, treatment duration, and status of completion of treatment with the Drug), administration of antihyperlipidemic drugs other than the Drug* (presence or absence, drug name, daily dose, and treatment duration), and administration of concomitant medications (other than antihyperlipidemic drugs) (presence or absence, drug name, and purpose of administration)

*: Including antihyperlipidemic drugs with which treatment is discontinued within two months before baseline.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.4 Testing/Observation Items

1) Survey items

Triglyceride (TG), total cholesterol (TC), LDL cholesterol* (LDL-C), HDL cholesterol (HDL-C), VLDL cholesterol (VLDL-C), Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), remnant lipoprotein cholesterol (RLP-C), fasting blood glucose (FBG), HbA1c

*: When tested by direct measurement

2) Survey timing

Baseline, Month 3, Month 6, Month 9, and Month 12 (or discontinuation of treatment) test timepoints

9.5 Other Observation Items

1) Survey items

Pregnancy status

If the patient is found to be pregnant during the observation period, the investigator will report the Takeda staff. The investigator will, upon request from the Takeda staff, use a sheet for pregnant women to provide detailed information (including information available up to childbirth, including premature birth or other pregnancy results, if possible).

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.6 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (see Table 1), AE name, date of onset, seriousness and reason for seriousness (see Table 2), action taken to the Drug, date of determination of outcome, outcome, and causal relationship to the Drug* (see Table 3)

If the outcome is not resolved or unknown and the casual relationship is determined as unevaluable, follow-up survey should be conducted to some extent possible.

*If causal relationship to the Drug is determined as not related, reasons that may constitute the rationale for determination should be collected if it is unevaluable.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

3) Priority survey item

Bleeding-related events occurring after baseline are set as a priority survey item. If any bleeding-related event is reported as an AE, laboratory test values related to bleeding should be separately collected.

Table 1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
The following should be also handled as an AE:

- A symptoms or other problem occurring in an infant breastfed from a mother taking the medicinal product
- A symptom or other problem occurring in a child administered the medicinal product
- A symptom or other problem occurring in a patient administered or taking more than the approved dose of the medicinal product

Table 2 Seriousness Criteria

An event is classified as serious if:

1. resulting in death (death),
2. being life-threatening (at risk of death),
3. requiring inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization),
4. resulting in persistent or significant disability/incapacity (disorder),
5. being a congenital anomaly/birth defect (birth defect), or
6. being any other medically serious condition that does not fall under any of 1 to 5 above. Note that all those listed in the Takeda Medically Significant AE List are included in this criterion. (Examples include bronchospasm, which requires short-term intensive care in emergency room settings.)

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/acute respiratory distress syndrome (ARDS)
- Torsade de pointes/ventricular fibrillation/ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including spasm and epilepsy)
- Agranulocytosis
- Aplastic anaemia
- Toxic epidermal necrolysis/muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial lung disease)
- Neuroleptic malignant syndrome/malignant hyperthermia
- Spontaneous abortion/stillbirth and foetal death
- Confirmed or suspected transmission of infection by a medicinal product
- Confirmed or suspected endotoxin shock

Table 3 Criteria for Casual Relationship between Adverse Event and the Drug

Determination	Criteria
Related	There is temporal correlation between the Drug and the event (including results from discontinuation of treatment). Or the event is an AE considered likely to have been caused by the Drug although it is presumed to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Not related	There is no temporal correlation between the Drug and the event. Or the event is adequately considered to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Unevaluable	There is lack of information necessary for evaluation of the event, including temporal correlation (including results from discontinuation of treatment), primary disease, complications, concomitant medications, and combined treatments.

10.0 Analysis Items and Method

10.1 Patient Disposition Items

Compile information including the number of enrolled patients, number of patients with eCRFs collected, numbers of safety- and efficacy-evaluable patients, and the number of patients excluded from analysis and reasons for exclusion.

10.2 Patient Demographics

Compile patient demographic information including sex, age, hypersensitivity disposition, and complications.

10.3 Treatment Details

Compile information on administration of the Drug and of concomitant medications.

10.4 Safety Items

Compile the following regarding the safety-evaluable population. AEs, coded using MedDRA, will be summarized by preferred term (PT) and by system organ class (SOC).

10.4.1 Onset Status of Adverse Events

Compile the incidence of AEs occurring during the observation period, in terms of, e.g., causal relationship with the Drug, type, seriousness. Note that bleeding-related events should be separately compiled because such events are set as a priority survey item.

10.4.2 Factors Likely to Affect Safety

Compile the incidence of ADRs occurring during the observation period, by stratification variables: patient baseline characteristics (sex, age, presence or absence of renal

dysfunction, presence or absence of hepatic dysfunction, etc.) and treatment regimen (administration of the Drug, administration of concomitant medications such as anticoagulant drugs, antiplatelet drugs).

10.5 Efficacy Items

Compile the following regarding the efficacy-evaluable population.

10.5.1 Changes in Lipid Parameters: TG, TC, LDL-C, HDL-C, Non-HDL-C, etc.

Tabulate observed values and changes (observed value at each observational timepoint after baseline minus observed value at baseline) at each observational timepoint for TG, TC, LDL-C (by converted value calculated by direct measurement, Friedewald formula*), HDL-C, Non-HDL-C (converted value**), VLDL cholesterol, Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), and RLP-C.

*: LDL-C = TC-HDL-C - TG / 5

**: Non-HDL-C = TC-HDL-C

Note that LDL-C, Non-HDL-C, TC/LDL-C ratio, LDL-C/HDL-C ratio, and LDL-C/Apo-B ratio should be calculated from test results.

10.5.2 Factors Likely to Affect Efficacy

Compile TG values by stratification variables: patient baseline characteristics (sex and age) and treatment regimen (administration of the Drug, administration of concomitant medications, etc.).

11.0 Organizational Structure for Conducting the Study

Study Chair

Takeda Pharmaceutical Co., Ltd.

Post Marketing Surveillance Manager

12.0 Service Contractor's Name and Address and Scope of Contract Work

(1) PPD

Scope of work: Data management

(2) PPD

Scope of work: Data management and statistical analysis

(3) PPD

Scope of work: Storage of relevant records, PDF preparation of adverse events and other relevant information, and support services related to provision of information

(4) PPD

Scope of work: Formulation of CCI and its technical operations

13.0 Other Necessary Items

13.1 Protocol Revision

During the surveillance period, keep track of, e.g., the progress of the Study, the onset of unexpected ADRs or serious ADRs based on the precautions, presence or absence of increased incidence of specified ADRs, the appropriateness of survey items. If needed, review and revise this protocol. If partial change approval is obtained for dosage and administration or indications during the surveillance period, examine whether to revise this protocol if necessary and revise it if necessary.

13.2 Action Taken in Case of Problem or Question

If any problem is found in the safety or efficacy of the Drug, carefully review the data and examine what needs to be done.

Appendix Study Schedule

Survey Item \ Survey and Data Entry Timing		Observation Period						
		Patient enrollment	Baseline	Month 3	Month 6	Month 9	Month 12	Discontinuation
Patient Enrollment	Prescription date of the Drug	○						
	Patient ID number	○						
	Patient initials	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria/exclusion criteria	○						
Patient demographics	Height, Weight		○					
	Time of hyperlipidemia diagnosis		○					
	Treatment category		○					
	Menopausal status (only for female)		○					
	Complications		○					
	Medical history		○					
	Hypersensitivity disposition		○					
	Drinking history, smoking history		○					
	Presence or absence of surgery before baseline		○					
	Presence or absence of healthier lifestyle education (diet and exercise therapies)		○					
Treatment Information	Administration of the Drug		← ○ →					○
	Administration of other antihyperlipidemic drugs		← ○ →					○
	Administration of concomitant medications (other than antihyperlipidemic drug)		← ○ →					○
Testing /Observation Items	TG		○	○	○	○	○	○
	TC		○	○	○	○	○	○
	LDL-C (direct measurement)		○	○	○	○	○	○
	HDL-C		○	○	○	○	○	○
	VLDL-C		○	○	○	○	○	○
	Apo-AI		○	○	○	○	○	○
	Apo-B		○	○	○	○	○	○
	Apo-CIII		○	○	○	○	○	○
	Lipoprotein (a)		○	○	○	○	○	○
	RLP-C		○	○	○	○	○	○
	FBG		○	○	○	○	○	○
	HbA1c		○	○	○	○	○	○
	Pregnancy status (only for female)		← ○ →					○
	AE		← ○ →					○

○: Surveyed, tested, or observed ← ○: → Surveyed, tested, or observed throughout the period

Special Drug Use Surveillance Protocol

Lotriga Granular Capsules Special Drug Use Surveillance

[Long-term use survey]

Version No.	**5th Version**
Date Prepared	**March 2, 2017**
Study Sponsor	**Takeda Pharmaceutical Company Limited**

Table of Contents

1.0 Background

Lotriga Granular Capsules (the “Drug”) is an oral capsule formulation containing the active ingredient omega-3 fatty acid ethyl esters (principally EPA-E and DHA-E). The Drug differs from general marine oil products, such as supplements, in containing a high concentration of omega-3 fatty acid ethyl esters. Since first approved in Norway in September 1994, the Drug has been in extensive use overseas, sold in more than 60 countries. In the clinical study of the Drug conducted in Japan in patients with hypertriglyceridemia, adverse drug reactions (ADRs) including ‘laboratory test abnormal’ were observed in 91 (9.6%) of the 948 patients administered at 2 g or 4 g of omega-3 fatty acid ethyl esters, and the major ADR was Diarrhea (2.5%).

Despite the proven track record of extensive use overseas and the fact that the safety of long-term use was already evaluated during the clinical study, it is important to evaluate the safety of long-term use of the Drug in the general patient population in Japan.

Special drug use surveillance (hereinafter the "Study") has been therefore designed to evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

2.0 Objective

To evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

3.0 Target Sample Size and Rationale for Sample Size Setting

3.1 Target Sample Size

3,000 patients

3.2 Rationale for Sample Size Setting

Bleeding-related events are set as a priority survey item for the Drug. As postmarketing surveillance of EPA products in antihyperlipidemic therapy has reported that the incidence of bleeding-related ADRs was 0.4% and that the percentage of anticoagulant and antiplatelet concomitant use was about 10%, the Study sets a target of 3,000 patients so that anticoagulant and antiplatelet concomitant use can be assessed to some degree, in addition to bleeding-related ADRs.

Note that this rationale for the sample size is not based on statistical evidence.

4.0 Study Population

Patients with hyperlipidemia will be eligible for this study; however, those who meet the following exclusion criteria were excluded from the study.

Exclusion criteria:

(1) Patients with hemorrhage (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, or vitreous hemorrhage)

(2) Patients with a history of hypersensitivity to ingredients in the Drug

5.0 Dosage and Administration for Study Population

The usual adult dosage is 2 g of omega-3 fatty acid ethyl esters administered orally once daily after meals. However, the dosage can be increased up to twice daily (at a dose of 2 g) depending on the patient's triglyceride level.

6.0 Number of Study Sites by Clinical Department

About 200 sites (clinical departments not specified)

7.0 Study Method

7.1 Observation Period

12 months

7.2 Request and Contract to Study Sites

The Study will be requested and contracted using a web-based electronic data collection system (CCI [redacted]). Takeda Pharmaceutical's staffs (hereinafter "Takeda staffs") will adequately explain to investigators about the purpose and description of the Study, CCI [redacted]'s operating procedure, electronic signature, and user ID and password handling for request for the Study, based on the Letter of Request for Cooperation in Special Drug Use Surveillance, the Implementation Guidance, data input screen images, and the abbreviated CCI [redacted] Operating Manual. Takeda MRs will then conclude a contract in writing with study sites to perform the Study within the specified surveillance period.

7.3 Patient Enrollment Method

Patients will be "centrally" enrolled using CCI [redacted]. The investigator will enter into CCI [redacted] patient enrollment information (see Section 9.1) of patients for whom the Drug has been prescribed since the start date of the period of contract with the study site, within 14 days after the prescription date of the Drug (the prescription date is defined as "Day 0"; the day following the prescription date is defined as "Day 1").

7.4 Data Entry and Electronic Signature to Electronic Case Report Form (eCRF)

The investigator will enter patient data including demographics and treatment into CCI [redacted] and electronically sign the eCRF in 12 months after the start of treatment with the Drug (baseline).

If a patient discontinues the treatment with the Drug for some reason during the observation period, the investigator will be expected to enter their information including demographics and treatment into CCI [redacted] and electronically sign the eCRF within one month after the completion of necessary observations. However, if the patient discontinues the treatment with the Drug due to the occurrence of an adverse event (AE), the investigator should continue to observe them after discontinuation, as long as possible until the AE is resolved or resolving. The investigator should then enter the result of the observation into CCI [redacted] and

electronically sign the eCRF.

After review of the information, Takeda Pharmaceutical may request for re-survey, if deemed necessary, via [redacted]. The investigator will, upon checking, perform the details of the requested re-survey and enter the result of the re-survey into [redacted] and electronically sign the eCRF.

7.5 Action Taken at Onset of Serious Adverse Event

The investigator will immediately contact the Takeda staff if a serious AE occurs during the observation period. The investigator will also separately provide detailed information thereof upon request, if any, from the Takeda staff.

8.0 Expected Duration of Study

Surveillance period: May 2013 to May 31, 2017

Patient enrollment period: May 2013 to May 31, 2015*

*Enrollment may be closed before the end of the enrollment period if the total number of patients enrolled in the Study reaches the target sample size.

9.0 Survey Items

The investigator will enter the information of the following items into [redacted]. The schedule for the Study is provided in the Appendix.

9.1 Patient Enrollment

1) Survey items

Prescription date of the Date, patient ID number, patient initials, sex, birth date, determination with inclusion criteria, and determination with exclusion criteria

2) Survey timing

The time of patient enrollment

9.2 Patient Demographics

1) Survey items

Height, weight, time of hyperlipidemia diagnosis, treatment category, menopausal status (only for female), complications (presence or absence and details), medical history (presence or absence and details), hypersensitivity disposition (presence or absence and details), drinking history, smoking history, presence or absence of surgery within one month before baseline, and presence or absence of healthier lifestyle education (diet and exercise therapies)

2) Survey time

Baseline

9.3 Treatment Information

1) Survey items

Administration of the Drug (daily dose, treatment duration, and status of completion of treatment with the Drug), administration of antihyperlipidemic drugs other than the Drug* (presence or absence, drug name, daily dose, and treatment duration), and administration of concomitant medications (other than antihyperlipidemic drugs) (presence or absence, drug name, and purpose of administration)

*: Including antihyperlipidemic drugs with which treatment is discontinued within two months before baseline.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.4 Testing/Observation Items

1) Survey items

Triglyceride (TG), total cholesterol (TC), LDL cholesterol* (LDL-C), HDL cholesterol (HDL-C), VLDL cholesterol (VLDL-C), Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), remnant lipoprotein cholesterol (RLP-C), fasting blood glucose (FBG), HbA1c

*: When tested by direct measurement

2) Survey timing

Baseline, Month 3, Month 6, Month 9, and Month 12 (or discontinuation of treatment) test timepoints

9.5 Other Observation Items

1) Survey items

Pregnancy status

If the patient is found to be pregnant during the observation period, the investigator will report the Takeda staff. The investigator will, upon request from the Takeda staff, use a sheet for pregnant women to provide detailed information (including information available up to childbirth, including premature birth or other pregnancy results, if possible).

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.6 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (see Table 1), AE name, date of onset, seriousness and reason for seriousness (see Table 2), action taken to the Drug, date of determination of outcome, outcome, and causal relationship to the Drug* (see Table 3)

If the outcome is not resolved or unknown and the casual relationship is determined as unevaluable, follow-up survey should be conducted to some extent possible.

*If causal relationship to the Drug is determined as not related, reasons that may constitute the rationale for determination should be collected if it is unevaluable.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

3) Priority survey item

Bleeding-related events occurring after baseline are set as a priority survey item. If any bleeding-related event is reported as an AE, laboratory test values related to bleeding should be separately collected.

Table 1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
The following should be also handled as an AE:

- A symptoms or other problem occurring in an infant breastfed from a mother taking the medicinal product
- A symptom or other problem occurring in a child administered the medicinal product
- A symptom or other problem occurring in a patient administered or taking more than the approved dose of the medicinal product

Table 2 Seriousness Criteria

An event is classified as serious if:

1. resulting in death (death),
2. being life-threatening (at risk of death),
3. requiring inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization),
4. resulting in persistent or significant disability/incapacity (disorder),
5. being a congenital anomaly/birth defect (birth defect), or
6. being any other medically serious condition that does not fall under any of 1 to 5 above. Note that all those listed in the Takeda Medically Significant AE List are included in this criterion. (Examples include bronchospasm, which requires short-term intensive care in emergency room settings.)

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/acute respiratory distress syndrome (ARDS)
- Torsade de pointes/ventricular fibrillation/ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including spasm and epilepsy)
- Agranulocytosis
- Aplastic anaemia
- Toxic epidermal necrolysis/muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial lung disease)
- Neuroleptic malignant syndrome/malignant hyperthermia
- Spontaneous abortion/stillbirth and foetal death
- Confirmed or suspected transmission of infection by a medicinal product
- Confirmed or suspected endotoxin shock

Table 3 Criteria for Casual Relationship between Adverse Event and the Drug

Determination	Criteria
Related	There is temporal correlation between the Drug and the event (including results from discontinuation of treatment). Or the event is an AE considered likely to have been caused by the Drug although it is presumed to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Not related	There is no temporal correlation between the Drug and the event. Or the event is adequately considered to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Unevaluable	There is lack of information necessary for evaluation of the event, including temporal correlation (including results from discontinuation of treatment), primary disease, complications, concomitant medications, and combined treatments.

10.0 Analysis Items and Method

10.1 Patient Disposition Items

Compile information including the number of enrolled patients, number of patients with eCRFs collected, numbers of safety- and efficacy-evaluable patients, and the number of patients excluded from analysis and reasons for exclusion.

10.2 Patient Demographics

Compile patient demographic information including sex, age, hypersensitivity disposition, and complications.

10.3 Treatment Details

Compile information on administration of the Drug and of concomitant medications.

10.4 Safety Items

Compile the following regarding the safety-evaluable population. AEs, coded using MedDRA, will be summarized by preferred term (PT) and by system organ class (SOC).

10.4.1 Onset Status of Adverse Events

Compile the incidence of AEs occurring during the observation period, in terms of, e.g., causal relationship with the Drug, type, seriousness. Note that bleeding-related events should be separately compiled because such events are set as a priority survey item.

10.4.2 Factors Likely to Affect Safety

Compile the incidence of ADRs occurring during the observation period, by stratification variables: patient baseline characteristics (sex, age, presence or absence of renal

dysfunction, presence or absence of hepatic dysfunction, etc.) and treatment regimen (administration of the Drug, administration of concomitant medications such as anticoagulant drugs, antiplatelet drugs).

10.5 Efficacy Items

Compile the following regarding the efficacy-evaluable population.

10.5.1 Changes in Lipid Parameters: TG, TC, LDL-C, HDL-C, Non-HDL-C, etc.

Tabulate observed values and changes (observed value at each observational timepoint after baseline minus observed value at baseline) at each observational timepoint for TG, TC, LDL-C (by converted value calculated by direct measurement, Friedewald formula*), HDL-C, Non-HDL-C (converted value**), VLDL cholesterol, Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), and RLP-C.

*: LDL-C = TC-HDL-C - TG / 5

**: Non-HDL-C = TC-HDL-C

Note that LDL-C, Non-HDL-C, TC/LDL-C ratio, LDL-C/HDL-C ratio, and LDL-C/Apo-B ratio should be calculated from test results.

10.5.2 Factors Likely to Affect Efficacy

Compile TG values by stratification variables: patient baseline characteristics (sex and age) and treatment regimen (administration of the Drug, administration of concomitant medications, etc.).

11.0 Organizational Structure for Conducting the Study

Study Chair

Takeda Pharmaceutical Co., Ltd.

Post Marketing Surveillance Manager

12.0 Service Contractor's Name and Address and Scope of Contract Work

Contractor: PPD

Scope of contract work: Data management and statistical analysis

Contractor: PPD

Scope of contract work: Storage of relevant records

13.0 Other Necessary Items

13.1 Protocol Revision

During the surveillance period, keep track of, e.g., the progress of the Study, the onset of unexpected ADRs or serious ADRs based on the precautions, presence or absence of increased incidence of specified ADRs, the appropriateness of survey items. If needed, review and revise

this protocol. If partial change approval is obtained for dosage and administration or indications during the surveillance period, examine whether to revise this protocol if necessary and revise it if necessary.

13.2 Action Taken in Case of Problem or Question

If any problem is found in the safety or efficacy of the Drug, carefully review the data and examine what needs to be done.

Appendix Study Schedule

Survey Item \ Survey and Data Entry Timing		Observation Period						
		Patient enrollment	Baseline	Month 3	Month 6	Month 9	Month 12	Discontinuation
Patient Enrollment	Prescription date of the Drug	○						
	Patient ID number	○						
	Patient initials	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria/exclusion criteria	○						
Patient demographics	Height, Weight		○					
	Time of hyperlipidemia diagnosis		○					
	Treatment category		○					
	Menopausal status (only for female)		○					
	Complications		○					
	Medical history		○					
	Hypersensitivity disposition		○					
	Drinking history, smoking history		○					
	Presence or absence of surgery before baseline		○					
	Presence or absence of healthier lifestyle education (diet and exercise therapies)		○					
Treatment Information	Administration of the Drug		←——— ○ ———→					○
	Administration of other antihyperlipidemic drugs		←——— ○ ———→					○
	Administration of concomitant medications (other than antihyperlipidemic drug)		←——— ○ ———→					○
Testing /Observation Items	TG		○	○	○	○	○	○
	TC		○	○	○	○	○	○
	LDL-C (direct measurement)		○	○	○	○	○	○
	HDL-C		○	○	○	○	○	○
	VLDL-C		○	○	○	○	○	○
	Apo-AI		○	○	○	○	○	○
	Apo-B		○	○	○	○	○	○
	Apo-CIII		○	○	○	○	○	○
	Lipoprotein (a)		○	○	○	○	○	○
	RLP-C		○	○	○	○	○	○
	FBG		○	○	○	○	○	○
	HbA1c		○	○	○	○	○	○
	Pregnancy status (only for female)		←——— ○ ———→					○
	AE		←——— ○ ———→					○

○: Surveyed, tested, or observed ←— ○: —→ Surveyed, tested, or observed throughout the period

Special Drug Use Surveillance Protocol

Lotriga Granular Capsules Special Drug Use Surveillance

[Long-term use survey]

Version No.	**4th Version**
Date Prepared	**June 14, 2016**
Study Sponsor	**Takeda Pharmaceutical Company Limited**

Table of Contents

1.0 Background

Lotriga Granular Capsules (the “Drug”) is an oral capsule formulation containing the active ingredient omega-3 fatty acid ethyl esters (principally EPA-E and DHA-E). The Drug differs from general marine oil products, such as supplements, in containing a high concentration of omega-3 fatty acid ethyl esters. Since first approved in Norway in September 1994, the Drug has been in extensive use overseas, sold in more than 60 countries. In the clinical study of the Drug conducted in Japan in patients with hypertriglyceridemia, adverse drug reactions (ADRs) including ‘laboratory test abnormal’ were observed in 91 (9.6%) of the 948 patients administered at 2 g or 4 g of omega-3 fatty acid ethyl esters, and the major ADR was Diarrhea (2.5%).

Despite the proven track record of extensive use overseas and the fact that the safety of long-term use was already evaluated during the clinical study, it is important to evaluate the safety of long-term use of the Drug in the general patient population in Japan.

Special drug use surveillance (hereinafter the "Study") has been therefore designed to evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

2.0 Objective

To evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

3.0 Target Sample Size and Rationale for Sample Size Setting

3.1 Target Sample Size

3,000 patients

3.2 Rationale for Sample Size Setting

Bleeding-related events are set as a priority survey item for the Drug. As postmarketing surveillance of EPA products in antihyperlipidemic therapy has reported that the incidence of bleeding-related ADRs was 0.4% and that the percentage of anticoagulant and antiplatelet concomitant use was about 10%, the Study sets a target of 3,000 patients so that anticoagulant and antiplatelet concomitant use can be assessed to some degree, in addition to bleeding-related ADRs.

Note that this rationale for the sample size is not based on statistical evidence.

4.0 Study Population

Patients with hyperlipidemia will be eligible for this study; however, those who meet the following exclusion criteria were excluded from the study.

Exclusion criteria:

(1) Patients with hemorrhage (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, or vitreous hemorrhage)

(2) Patients with a history of hypersensitivity to ingredients in the Drug

5.0 Dosage and Administration for Study Population

The usual adult dosage is 2 g of omega-3 fatty acid ethyl esters administered orally once daily after meals. However, the dosage can be increased up to twice daily (at a dose of 2 g) depending on the patient's triglyceride level.

6.0 Number of Study Sites by Clinical Department

About 200 sites (clinical departments not specified)

7.0 Study Method

7.1 Observation Period

12 months

7.2 Request and Contract to Study Sites

The Study will be requested and contracted using a web-based electronic data collection system (CCI [redacted]. Takeda Pharmaceutical's staffs (hereinafter "Takeda staffs") will adequately explain to investigators about the purpose and description of the Study, CCI [redacted]'s operating procedure, electronic signature, and user ID and password handling for request for the Study, based on the Letter of Request for Cooperation in Special Drug Use Surveillance, the Implementation Guidance, data input screen images, and the abbreviated CCI [redacted] Operating Manual. Takeda MRs will then conclude a contract in writing with study sites to perform the Study within the specified surveillance period.

7.3 Patient Enrollment Method

Patients will be "centrally" enrolled using CCI [redacted]. The investigator will enter into CCI [redacted] patient enrollment information (see Section 9.1) of patients for whom the Drug has been prescribed since the start date of the period of contract with the study site, within 14 days after the prescription date of the Drug (the prescription date is defined as "Day 0"; the day following the prescription date is defined as "Day 1").

7.4 Data Entry and Electronic Signature to Electronic Case Report Form (eCRF)

The investigator will enter patient data including demographics and treatment into CCI [redacted] and electronically sign the eCRF in 12 months after the start of treatment with the Drug (baseline).

If a patient discontinues the treatment with the Drug for some reason during the observation period, the investigator will be expected to enter their information including demographics and treatment into CCI [redacted] and electronically sign the eCRF within one month after the completion of necessary observations. However, if the patient discontinues the treatment with the Drug due to the occurrence of an adverse event (AE), the investigator should continue to observe them after discontinuation, as long as possible until the AE is resolved or resolving. The investigator should then enter the result of the observation into CCI [redacted] and

electronically sign the eCRF.

After review of the information, Takeda Pharmaceutical may request for re-survey, if deemed necessary, via [redacted]. The investigator will, upon checking, perform the details of the requested re-survey and enter the result of the re-survey into [redacted] and electronically sign the eCRF.

7.5 Action Taken at Onset of Serious Adverse Event

The investigator will immediately contact the Takeda staff if a serious AE occurs during the observation period. The investigator will also separately provide detailed information thereof upon request, if any, from the Takeda staff.

8.0 Expected Duration of Study

Surveillance period: May 2013 to March 31, 2017

Patient enrollment period: May 2013 to May 31, 2015*

*Enrollment may be closed before the end of the enrollment period if the total number of patients enrolled in the Study reaches the target sample size.

9.0 Survey Items

The investigator will enter the information of the following items into [redacted]. The schedule for the Study is provided in the Appendix.

9.1 Patient Enrollment

1) Survey items

Prescription date of the Date, patient ID number, patient initials, sex, birth date, determination with inclusion criteria, and determination with exclusion criteria

2) Survey timing

The time of patient enrollment

9.2 Patient Demographics

1) Survey items

Height, weight, time of hyperlipidemia diagnosis, treatment category, menopausal status (only for female), complications (presence or absence and details), medical history (presence or absence and details), hypersensitivity disposition (presence or absence and details), drinking history, smoking history, presence or absence of surgery within one month before baseline, and presence or absence of healthier lifestyle education (diet and exercise therapies)

2) Survey time

Baseline

9.3 Treatment Information

1) Survey items

Administration of the Drug (daily dose, treatment duration, and status of completion of treatment with the Drug), administration of antihyperlipidemic drugs other than the Drug* (presence or absence, drug name, daily dose, and treatment duration), and administration of concomitant medications (other than antihyperlipidemic drugs) (presence or absence, drug name, and purpose of administration)

*: Including antihyperlipidemic drugs with which treatment is discontinued within two months before baseline.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.4 Testing/Observation Items

1) Survey items

Triglyceride (TG), total cholesterol (TC), LDL cholesterol* (LDL-C), HDL cholesterol (HDL-C), VLDL cholesterol (VLDL-C), Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), remnant lipoprotein cholesterol (RLP-C), fasting blood glucose (FBG), HbA1c

*: When tested by direct measurement

2) Survey timing

Baseline, Month 3, Month 6, Month 9, and Month 12 (or discontinuation of treatment) test timepoints

9.5 Other Observation Items

1) Survey items

Pregnancy status

If the patient is found to be pregnant during the observation period, the investigator will report the Takeda staff. The investigator will, upon request from the Takeda staff, use a sheet for pregnant women to provide detailed information (including information available up to childbirth, including premature birth or other pregnancy results, if possible).

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.6 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (see Table 1), AE name, date of onset, seriousness and reason for seriousness (see Table 2), action taken to the Drug, date of determination of outcome, outcome, and causal relationship to the Drug* (see Table 3)

If the outcome is not resolved or unknown and the casual relationship is determined as unevaluable, follow-up survey should be conducted to some extent possible.

*If causal relationship to the Drug is determined as not related, reasons that may constitute the rationale for determination should be collected if it is unevaluable.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

3) Priority survey item

Bleeding-related events occurring after baseline are set as a priority survey item. If any bleeding-related event is reported as an AE, laboratory test values related to bleeding should be separately collected.

Table 1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
The following should be also handled as an AE:

- A symptoms or other problem occurring in an infant breastfed from a mother taking the medicinal product
- A symptom or other problem occurring in a child administered the medicinal product
- A symptom or other problem occurring in a patient administered or taking more than the approved dose of the medicinal product

Table 2 Seriousness Criteria

An event is classified as serious if:

1. resulting in death (death),
2. being life-threatening (at risk of death),
3. requiring inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization),
4. resulting in persistent or significant disability/incapacity (disorder),
5. being a congenital anomaly/birth defect (birth defect), or
6. being any other medically serious condition that does not fall under any of 1 to 5 above. Note that all those listed in the Takeda Medically Significant AE List are included in this criterion. (Examples include bronchospasm, which requires short-term intensive care in emergency room settings.)

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/acute respiratory distress syndrome (ARDS)
- Torsade de pointes/ventricular fibrillation/ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including spasm and epilepsy)
- Agranulocytosis
- Aplastic anaemia
- Toxic epidermal necrolysis/muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial lung disease)
- Neuroleptic malignant syndrome/malignant hyperthermia
- Spontaneous abortion/stillbirth and foetal death
- Confirmed or suspected transmission of infection by a medicinal product
- Confirmed or suspected endotoxin shock

Table 3 Criteria for Casual Relationship between Adverse Event and the Drug

Determination	Criteria
Related	There is temporal correlation between the Drug and the event (including results from discontinuation of treatment). Or the event is an AE considered likely to have been caused by the Drug although it is presumed to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Not related	There is no temporal correlation between the Drug and the event. Or the event is adequately considered to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Unevaluable	There is lack of information necessary for evaluation of the event, including temporal correlation (including results from discontinuation of treatment), primary disease, complications, concomitant medications, and combined treatments.

10.0 Analysis Items and Method

10.1 Patient Disposition Items

Compile information including the number of enrolled patients, number of patients with eCRFs collected, numbers of safety- and efficacy-evaluable patients, and the number of patients excluded from analysis and reasons for exclusion.

10.2 Patient Demographics

Compile patient demographic information including sex, age, hypersensitivity disposition, and complications.

10.3 Treatment Details

Compile information on administration of the Drug and of concomitant medications.

10.4 Safety Items

Compile the following regarding the safety-evaluable population. AEs, coded using MedDRA, will be summarized by preferred term (PT) and by system organ class (SOC).

10.4.1 Onset Status of Adverse Events

Compile the incidence of AEs occurring during the observation period, in terms of, e.g., causal relationship with the Drug, type, seriousness. Note that bleeding-related events should be separately compiled because such events are set as a priority survey item.

10.4.2 Factors Likely to Affect Safety

Compile the incidence of ADRs occurring during the observation period, by stratification variables: patient baseline characteristics (sex, age, presence or absence of renal

dysfunction, presence or absence of hepatic dysfunction, etc.) and treatment regimen (administration of the Drug, administration of concomitant medications such as anticoagulant drugs, antiplatelet drugs).

10.5 Efficacy Items

Compile the following regarding the efficacy-evaluable population.

10.5.1 Changes in Lipid Parameters: TG, TC, LDL-C, HDL-C, Non-HDL-C, etc.

Tabulate observed values and changes (observed value at each observational timepoint after baseline minus observed value at baseline) at each observational timepoint for TG, TC, LDL-C (by converted value calculated by direct measurement, Friedewald formula*), HDL-C, Non-HDL-C (converted value**), VLDL cholesterol, Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), and RLP-C.

*: LDL-C = TC-HDL-C - TG / 5

**: Non-HDL-C = TC-HDL-C

Note that LDL-C, Non-HDL-C, TC/LDL-C ratio, LDL-C/HDL-C ratio, and LDL-C/Apo-B ratio should be calculated from test results.

10.5.2 Factors Likely to Affect Efficacy

Compile TG values by stratification variables: patient baseline characteristics (sex and age) and treatment regimen (administration of the Drug, administration of concomitant medications, etc.).

11.0 Organizational Structure for Conducting the Study

Study Chair

Takeda Pharmaceutical Co., Ltd.

Post Marketing Surveillance Manager

12.0 Service Contractor's Name and Address and Scope of Contract Work

Contractor: PPD

Scope of contract work: Data management and statistical analysis

Contractor: PPD

Scope of contract work: Storage of relevant records

13.0 Other Necessary Items

13.1 Protocol Revision

During the surveillance period, keep track of, e.g., the progress of the Study, the onset of unexpected ADRs or serious ADRs based on the precautions, presence or absence of increased incidence of specified ADRs, the appropriateness of survey items. If needed, review and revise

this protocol. If partial change approval is obtained for dosage and administration or indications during the surveillance period, examine whether to revise this protocol if necessary and revise it if necessary.

13.2 Action Taken in Case of Problem or Question

If any problem is found in the safety or efficacy of the Drug, carefully review the data and examine what needs to be done.

Appendix Study Schedule

Survey Item \ Survey and Data Entry Timing		Observation Period						
		Patient enrollment	Baseline	Month 3	Month 6	Month 9	Month 12	Discontinuation
Patient Enrollment	Prescription date of the Drug	○						
	Patient ID number	○						
	Patient initials	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria/exclusion criteria	○						
Patient demographics	Height, Weight		○					
	Time of hyperlipidemia diagnosis		○					
	Treatment category		○					
	Menopausal status (only for female)		○					
	Complications		○					
	Medical history		○					
	Hypersensitivity disposition		○					
	Drinking history, smoking history		○					
	Presence or absence of surgery before baseline		○					
	Presence or absence of healthier lifestyle education (diet and exercise therapies)		○					
Treatment Information	Administration of the Drug		←——— ○ ———→					○
	Administration of other antihyperlipidemic drugs		←——— ○ ———→					○
	Administration of concomitant medications (other than antihyperlipidemic drug)		←——— ○ ———→					○
Testing /Observation Items	TG		○	○	○	○	○	○
	TC		○	○	○	○	○	○
	LDL-C (direct measurement)		○	○	○	○	○	○
	HDL-C		○	○	○	○	○	○
	VLDL-C		○	○	○	○	○	○
	Apo-AI		○	○	○	○	○	○
	Apo-B		○	○	○	○	○	○
	Apo-CIII		○	○	○	○	○	○
	Lipoprotein (a)		○	○	○	○	○	○
	RLP-C		○	○	○	○	○	○
	FBG		○	○	○	○	○	○
	HbA1c		○	○	○	○	○	○
	Pregnancy status (only for female)		←——— ○ ———→					○
	AE		←——— ○ ———→					○

○: Surveyed, tested, or observed ←— ○: —→ Surveyed, tested, or observed throughout the period

Special Drug Use Surveillance Protocol

Lotriga Granular Capsules Special Drug Use Surveillance

[Long-term use survey]

Version No.	**3rd Version**
Date Prepared	**April 1, 2015**
Study Sponsor	**Takeda Pharmaceutical Company Limited**

Table of Contents

1.0 Background

Lotriga Granular Capsules (the “Drug”) is an oral capsule formulation containing the active ingredient omega-3 fatty acid ethyl esters (principally EPA-E and DHA-E). The Drug differs from general marine oil products, such as supplements, in containing a high concentration of omega-3 fatty acid ethyl esters. Since first approved in Norway in September 1994, the Drug has been in extensive use overseas, sold in more than 60 countries. In the clinical study of the Drug conducted in Japan in patients with hypertriglyceridemia, adverse drug reactions (ADRs) including ‘laboratory test abnormal’ were observed in 91 (9.6%) of the 948 patients administered at 2 g or 4 g of omega-3 fatty acid ethyl esters, and the major ADR was Diarrhea (2.5%).

Despite the proven track record of extensive use overseas and the fact that the safety of long-term use was already evaluated during the clinical study, it is important to evaluate the safety of long-term use of the Drug in the general patient population in Japan.

Special drug use surveillance (hereinafter the "Study") has been therefore designed to evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

2.0 Objective

To evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

3.0 Target Sample Size and Rationale for Sample Size Setting

3.1 Target Sample Size

3,000 patients

3.2 Rationale for Sample Size Setting

Bleeding-related events are set as a priority survey item for the Drug. As postmarketing surveillance of EPA products in antihyperlipidemic therapy has reported that the incidence of bleeding-related ADRs was 0.4% and that the percentage of anticoagulant and antiplatelet concomitant use was about 10%, the Study sets a target of 3,000 patients so that anticoagulant and antiplatelet concomitant use can be assessed to some degree, in addition to bleeding-related ADRs.

Note that this rationale for the sample size is not based on statistical evidence.

4.0 Study Population

Patients with hyperlipidemia will be eligible for this study; however, those who meet the following exclusion criteria were excluded from the study.

Exclusion criteria:

(1) Patients with hemorrhage (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, or vitreous hemorrhage)

(2) Patients with a history of hypersensitivity to ingredients in the Drug

5.0 Dosage and Administration for Study Population

The usual adult dosage is 2 g of omega-3 fatty acid ethyl esters administered orally once daily after meals. However, the dosage can be increased up to twice daily (at a dose of 2 g) depending on the patient's triglyceride level.

6.0 Number of Study Sites by Clinical Department

About 200 sites (clinical departments not specified)

7.0 Study Method

7.1 Observation Period

12 months

7.2 Request and Contract to Study Sites

The Study will be requested and contracted using a web-based electronic data collection system (CCI [redacted]). Takeda Pharmaceutical's staffs (hereinafter "Takeda staffs") will adequately explain to investigators about the purpose and description of the Study, CCI [redacted]'s operating procedure, electronic signature, and user ID and password handling for request for the Study, based on the Letter of Request for Cooperation in Special Drug Use Surveillance, the Implementation Guidance, data input screen images, and the abbreviated CCI [redacted] Operating Manual. Takeda MRs will then conclude a contract in writing with study sites to perform the Study within the specified surveillance period.

7.3 Patient Enrollment Method

Patients will be "centrally" enrolled using CCI [redacted]. The investigator will enter into CCI [redacted] patient enrollment information (see Section 9.1) of patients for whom the Drug has been prescribed since the start date of the period of contract with the study site, within 14 days after the prescription date of the Drug (the prescription date is defined as "Day 0"; the day following the prescription date is defined as "Day 1").

7.4 Data Entry and Electronic Signature to Electronic Case Report Form (eCRF)

The investigator will enter patient data including demographics and treatment into CCI [redacted] and electronically sign the eCRF in 12 months after the start of treatment with the Drug (baseline).

If a patient discontinues the treatment with the Drug for some reason during the observation period, the investigator will be expected to enter their information including demographics and treatment into CCI [redacted] and electronically sign the eCRF within one month after the completion of necessary observations. However, if the patient discontinues the treatment with the Drug due to the occurrence of an adverse event (AE), the investigator should continue to observe them after discontinuation, as long as possible until the AE is resolved or resolving. The investigator should then enter the result of the observation into CCI [redacted] and

electronically sign the eCRF.

After review of the information, Takeda Pharmaceutical may request for re-survey, if deemed necessary, via [redacted]. The investigator will, upon checking, perform the details of the requested re-survey and enter the result of the re-survey into [redacted] and electronically sign the eCRF.

7.5 Action Taken at Onset of Serious Adverse Event

The investigator will immediately contact the Takeda staff if a serious AE occurs during the observation period. The investigator will also separately provide detailed information thereof upon request, if any, from the Takeda staff.

8.0 Expected Duration of Study

Surveillance period: May 2013 to September 30, 2016

Patient enrollment period: May 2013 to May 31, 2015*

*Enrollment may be closed before the end of the enrollment period if the total number of patients enrolled in the Study reaches the target sample size.

9.0 Survey Items

The investigator will enter the information of the following items into [redacted]. The schedule for the Study is provided in the Appendix.

9.1 Patient Enrollment

1) Survey items

Prescription date of the Date, patient ID number, patient initials, sex, birth date, determination with inclusion criteria, and determination with exclusion criteria

2) Survey timing

The time of patient enrollment

9.2 Patient Demographics

1) Survey items

Height, weight, time of hyperlipidemia diagnosis, treatment category, menopausal status (only for female), complications (presence or absence and details), medical history (presence or absence and details), hypersensitivity disposition (presence or absence and details), drinking history, smoking history, presence or absence of surgery within one month before baseline, and presence or absence of healthier lifestyle education (diet and exercise therapies)

2) Survey time

Baseline

9.3 Treatment Information

1) Survey items

Administration of the Drug (daily dose, treatment duration, and status of completion of treatment with the Drug), administration of antihyperlipidemic drugs other than the Drug* (presence or absence, drug name, daily dose, and treatment duration), and administration of concomitant medications (other than antihyperlipidemic drugs) (presence or absence, drug name, and purpose of administration)

*: Including antihyperlipidemic drugs with which treatment is discontinued within two months before baseline.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.4 Testing/Observation Items

1) Survey items

Triglyceride (TG), total cholesterol (TC), LDL cholesterol* (LDL-C), HDL cholesterol (HDL-C), VLDL cholesterol (VLDL-C), Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), remnant lipoprotein cholesterol (RLP-C), fasting blood glucose (FBG), HbA1c *: When tested by direct measurement

2) Survey timing

Baseline, Month 3, Month 6, Month 9, and Month 12 (or discontinuation of treatment) test timepoints

9.5 Other Observation Items

1) Survey items

Pregnancy status

If the patient is found to be pregnant during the observation period, the investigator will report the Takeda staff. The investigator will, upon request from the Takeda staff, use a sheet for pregnant women to provide detailed information (including information available up to childbirth, including premature birth or other pregnancy results, if possible).

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.6 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (see Table 1), AE name, date of onset, seriousness and reason for seriousness (see Table 2), action taken to the Drug, date of determination of outcome, outcome, and causal relationship to the Drug* (see Table 3)

If the outcome is not resolved or unknown and the casual relationship is determined as unevaluable, follow-up survey should be conducted to some extent possible.

*If causal relationship to the Drug is determined as not related, reasons that may constitute the rationale for determination should be collected if it is unevaluable.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

3) Priority survey item

Bleeding-related events occurring after baseline are set as a priority survey item. If any bleeding-related event is reported as an AE, laboratory test values related to bleeding should be separately collected.

Table 1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
The following should be also handled as an AE:

- A symptoms or other problem occurring in an infant breastfed from a mother taking the medicinal product
- A symptom or other problem occurring in a child administered the medicinal product
- A symptom or other problem occurring in a patient administered or taking more than the approved dose of the medicinal product

Table 2 Seriousness Criteria

An event is classified as serious if:

1. resulting in death (death),
2. being life-threatening (at risk of death),
3. requiring inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization),
4. resulting in persistent or significant disability/incapacity (disorder),
5. being a congenital anomaly/birth defect (birth defect), or
6. being any other medically serious condition that does not fall under any of 1 to 5 above. Note that all those listed in the Takeda Medically Significant AE List are included in this criterion. (Examples include bronchospasm, which requires short-term intensive care in emergency room settings.)

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/acute respiratory distress syndrome (ARDS)
- Torsade de pointes/ventricular fibrillation/ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including spasm and epilepsy)
- Agranulocytosis
- Aplastic anaemia
- Toxic epidermal necrolysis/muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial lung disease)
- Neuroleptic malignant syndrome/malignant hyperthermia
- Spontaneous abortion/stillbirth and foetal death
- Confirmed or suspected transmission of infection by a medicinal product
- Confirmed or suspected endotoxin shock

Table 3 Criteria for Casual Relationship between Adverse Event and the Drug

Determination	Criteria
Related	There is temporal correlation between the Drug and the event (including results from discontinuation of treatment). Or the event is an AE considered likely to have been caused by the Drug although it is presumed to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Not related	There is no temporal correlation between the Drug and the event. Or the event is adequately considered to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Unevaluable	There is lack of information necessary for evaluation of the event, including temporal correlation (including results from discontinuation of treatment), primary disease, complications, concomitant medications, and combined treatments.

10.0 Analysis Items and Method

10.1 Patient Disposition Items

Compile information including the number of enrolled patients, number of patients with eCRFs collected, numbers of safety- and efficacy-evaluable patients, and the number of patients excluded from analysis and reasons for exclusion.

10.2 Patient Demographics

Compile patient demographic information including sex, age, hypersensitivity disposition, and complications.

10.3 Treatment Details

Compile information on administration of the Drug and of concomitant medications.

10.4 Safety Items

Compile the following regarding the safety-evaluable population. AEs, coded using MedDRA, will be summarized by preferred term (PT) and by system organ class (SOC).

10.4.1 Onset Status of Adverse Events

Compile the incidence of AEs occurring during the observation period, in terms of, e.g., causal relationship with the Drug, type, seriousness. Note that bleeding-related events should be separately compiled because such events are set as a priority survey item.

10.4.2 Factors Likely to Affect Safety

Compile the incidence of ADRs occurring during the observation period, by stratification variables: patient baseline characteristics (sex, age, presence or absence of renal

dysfunction, presence or absence of hepatic dysfunction, etc.) and treatment regimen (administration of the Drug, administration of concomitant medications such as anticoagulant drugs, antiplatelet drugs).

10.5 Efficacy Items

Compile the following regarding the efficacy-evaluable population.

10.5.1 Changes in Lipid Parameters: TG, TC, LDL-C, HDL-C, Non-HDL-C, etc.

Tabulate observed values and changes (observed value at each observational timepoint after baseline minus observed value at baseline) at each observational timepoint for TG, TC, LDL-C (by converted value calculated by direct measurement, Friedewald formula*), HDL-C, Non-HDL-C (converted value**), VLDL cholesterol, Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), and RLP-C.

*: LDL-C = TC-HDL-C - TG / 5

**: Non-HDL-C = TC-HDL-C

Note that LDL-C, Non-HDL-C, TC/LDL-C ratio, LDL-C/HDL-C ratio, and LDL-C/Apo-B ratio should be calculated from test results.

10.5.2 Factors Likely to Affect Efficacy

Compile TG values by stratification variables: patient baseline characteristics (sex and age) and treatment regimen (administration of the Drug, administration of concomitant medications, etc.).

11.0 Organizational Structure for Conducting the Study

Study Chair

Takeda Pharmaceutical Co., Ltd.

Post Marketing Surveillance Manager

12.0 Service Contractor's Name and Address and Scope of Contract Work

Contractor: PPD

Scope of contract work: Data management and statistical analysis

Contractor: PPD

Scope of contract work: Storage of relevant records

13.0 Other Necessary Items

13.1 Protocol Revision

During the surveillance period, keep track of, e.g., the progress of the Study, the onset of unexpected ADRs or serious ADRs based on the precautions, presence or absence of increased incidence of specified ADRs, the appropriateness of survey items. If needed, review and revise

this protocol. If partial change approval is obtained for dosage and administration or indications during the surveillance period, examine whether to revise this protocol if necessary and revise it if necessary.

13.2 Action Taken in Case of Problem or Question

If any problem is found in the safety or efficacy of the Drug, carefully review the data and examine what needs to be done.

Appendix Study Schedule

Survey Item \ Survey and Data Entry Timing		Observation Period						
		Patient enrollment	Baseline	Month 3	Month 6	Month 9	Month 12	Discontinuation
Patient Enrollment	Prescription date of the Drug	○						
	Patient ID number	○						
	Patient initials	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria/exclusion criteria	○						
Patient demographics	Height, Weight		○					
	Time of hyperlipidemia diagnosis		○					
	Treatment category		○					
	Menopausal status (only for female)		○					
	Complications		○					
	Medical history		○					
	Hypersensitivity disposition		○					
	Drinking history, smoking history		○					
	Presence or absence of surgery before baseline		○					
	Presence or absence of healthier lifestyle education (diet and exercise therapies)		○					
Treatment Information	Administration of the Drug		←——— ○ ———→					○
	Administration of other antihyperlipidemic drugs		←——— ○ ———→					○
	Administration of concomitant medications (other than antihyperlipidemic drug)		←——— ○ ———→					○
Testing /Observation Items	TG		○	○	○	○	○	○
	TC		○	○	○	○	○	○
	LDL-C (direct measurement)		○	○	○	○	○	○
	HDL-C		○	○	○	○	○	○
	VLDL-C		○	○	○	○	○	○
	Apo-AI		○	○	○	○	○	○
	Apo-B		○	○	○	○	○	○
	Apo-CIII		○	○	○	○	○	○
	Lipoprotein (a)		○	○	○	○	○	○
	RLP-C		○	○	○	○	○	○
	FBG		○	○	○	○	○	○
	HbA1c		○	○	○	○	○	○
	Pregnancy status (only for female)		←——— ○ ———→					○
	AE		←——— ○ ———→					○

○: Surveyed, tested, or observed ←— ○: —→ Surveyed, tested, or observed throughout the period

Special Drug Use Surveillance Protocol

Lotriga Granular Capsules Special Drug Use Surveillance

[Long-term use survey]

Version No.	**2nd Version**
Date Prepared	**April 3, 2013**
Study Sponsor	**Takeda Pharmaceutical Company Limited**

Table of Contents

1.0 Background

Lotriga Granular Capsules (the “Drug”) is an oral capsule formulation containing the active ingredient omega-3 fatty acid ethyl esters (principally EPA-E and DHA-E). The Drug differs from general marine oil products, such as supplements, in containing a high concentration of omega-3 fatty acid ethyl esters. Since first approved in Norway in September 1994, the Drug has been in extensive use overseas, sold in more than 60 countries. In the clinical study of the Drug conducted in Japan in patients with hypertriglyceridemia, adverse drug reactions (ADRs) including ‘laboratory test abnormal’ were observed in 91 (9.6%) of the 948 patients administered at 2 g or 4 g of omega-3 fatty acid ethyl esters, and the major ADR was Diarrhea (2.5%).

Despite the proven track record of extensive use overseas and the fact that the safety of long-term use was already evaluated during the clinical study, it is important to evaluate the safety of long-term use of the Drug in the general patient population in Japan.

Special drug use surveillance (hereinafter the "Study") has been therefore designed to evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

2.0 Objective

To evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

3.0 Target Sample Size and Rationale for Sample Size Setting

3.1 Target Sample Size

3,000 patients

3.2 Rationale for Sample Size Setting

Bleeding-related events are set as a priority survey item for the Drug. As postmarketing surveillance of EPA products in antihyperlipidemic therapy has reported that the incidence of bleeding-related ADRs was 0.4% and that the percentage of anticoagulant and antiplatelet concomitant use was about 10%, the Study sets a target of 3,000 patients so that anticoagulant and antiplatelet concomitant use can be assessed to some degree, in addition to bleeding-related ADRs.

Note that this rationale for the sample size is not based on statistical evidence.

4.0 Study Population

Patients with hyperlipidemia will be eligible for this study; however, those who meet the following exclusion criteria were excluded from the study.

Exclusion criteria:

(1) Patients with hemorrhage (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, or vitreous hemorrhage)

(2) Patients with a history of hypersensitivity to ingredients in the Drug

5.0 Dosage and Administration for Study Population

The usual adult dosage is 2 g of omega-3 fatty acid ethyl esters administered orally once daily after meals. However, the dosage can be increased up to twice daily (at a dose of 2 g) depending on the patient's triglyceride level.

6.0 Number of Study Sites by Clinical Department

About 200 sites (clinical departments not specified)

7.0 Study Method

7.1 Observation Period

12 months

7.2 Request and Contract to Study Sites

The Study will be requested and contracted using a web-based electronic data collection system (CCI [redacted]). Takeda Pharmaceutical's MRs (hereinafter "Takeda MRs") will adequately explain to investigators about the purpose and description of the Study, CCI [redacted]'s operating procedure, electronic signature, and user ID and password handling for request for the Study, based on the Letter of Request for Cooperation in Special Drug Use Surveillance, the Implementation Guidance, data input screen images, and the abbreviated CCI [redacted] Operating Manual. Takeda MRs will then conclude a contract in writing with study sites to perform the Study within the specified surveillance period.

7.3 Patient Enrollment Method

Patients will be "centrally" enrolled using CCI [redacted]. The investigator will enter into CCI [redacted] patient enrollment information (see Section 9.1) of patients for whom the Drug has been prescribed since the start date of the period of contract with the study site, within 14 days after the prescription date of the Drug (the prescription date is defined as "Day 0"; the day following the prescription date is defined as "Day 1").

7.4 Data Entry and Electronic Signature to Electronic Case Report Form (eCRF)

The investigator will enter patient data including demographics and treatment into CCI [redacted] and electronically sign the eCRF in 12 months after the start of treatment with the Drug (baseline).

If a patient discontinues the treatment with the Drug for some reason during the observation period, the investigator will be expected to enter their information including demographics and treatment into CCI [redacted] and electronically sign the eCRF within one month after the completion of necessary observations. However, if the patient discontinues the treatment with the Drug due to the occurrence of an adverse event (AE), the investigator should continue to observe them after discontinuation, as long as possible until the AE is resolved or resolving. The investigator should then enter the result of the observation into CCI [redacted] and

electronically sign the eCRF.

After review of the information, Takeda Pharmaceutical may request for re-survey, if deemed necessary, via [redacted]. The investigator will, upon checking, perform the details of the requested re-survey and enter the result of the re-survey into [redacted] and electronically sign the eCRF.

7.5 Action Taken at Onset of Serious Adverse Event

The investigator will immediately contact the Takeda MR if a serious AE occurs during the observation period. The investigator will also separately provide detailed information thereof upon request, if any, from the Takeda MR.

8.0 Expected Duration of Study

Surveillance period: May 2013 to September 30, 2016

Patient enrollment period: May 2013 to May 31, 2015*

*Enrollment may be closed before the end of the enrollment period if the total number of patients enrolled in the Study reaches the target sample size.

9.0 Survey Items

The investigator will enter the information of the following items into [redacted]. The schedule for the Study is provided in the Appendix.

9.1 Patient Enrollment

1) Survey items

Prescription date of the Date, patient ID number, patient initials, sex, birth date, determination with inclusion criteria, and determination with exclusion criteria

2) Survey timing

The time of patient enrollment

9.2 Patient Demographics

1) Survey items

Height, weight, time of hyperlipidemia diagnosis, treatment category, menopausal status (only for female), complications (presence or absence and details), medical history (presence or absence and details), hypersensitivity disposition (presence or absence and details), drinking history, smoking history, presence or absence of surgery within one month before baseline, and presence or absence of healthier lifestyle education (diet and exercise therapies)

2) Survey time

Baseline

9.3 Treatment Information

1) Survey items

Administration of the Drug (daily dose, treatment duration, and status of completion of treatment with the Drug), administration of antihyperlipidemic drugs other than the Drug* (presence or absence, drug name, daily dose, and treatment duration), and administration of concomitant medications (other than antihyperlipidemic drugs) (presence or absence, drug name, and purpose of administration)

*: Including antihyperlipidemic drugs with which treatment is discontinued within two months before baseline.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.4 Testing/Observation Items

1) Survey items

Triglyceride (TG), total cholesterol (TC), LDL cholesterol* (LDL-C), HDL cholesterol (HDL-C), VLDL cholesterol (VLDL-C), Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), remnant lipoprotein cholesterol (RLP-C), fasting blood glucose (FBG), HbA1c *: When tested by direct measurement

2) Survey timing

Baseline, Month 3, Month 6, Month 9, and Month 12 (or discontinuation of treatment) test timepoints

9.5 Other Observation Items

1) Survey items

Pregnancy status

If the patient is found to be pregnant during the observation period, the investigator will report the Takeda MR. The investigator will, upon request from the Takeda MR, use a sheet for pregnant women to provide detailed information (including information available up to childbirth, including premature birth or other pregnancy results, if possible).

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.6 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (see Table 1), AE name, date of onset, seriousness and reason for seriousness (see Table 2), action taken to the Drug, date of determination of outcome, outcome, and causal relationship to the Drug* (see Table 3)

If the outcome is not resolved or unknown and the casual relationship is determined as unevaluable, follow-up survey should be conducted to some extent possible.

*If causal relationship to the Drug is determined as not related, reasons that may constitute the rationale for determination should be collected if it is unevaluable.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

3) Priority survey item

Bleeding-related events occurring after baseline are set as a priority survey item. If any bleeding-related event is reported as an AE, laboratory test values related to bleeding should be separately collected.

Table 1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
The following should be also handled as an AE:

- A symptoms or other problem occurring in an infant breastfed from a mother taking the medicinal product
- A symptom or other problem occurring in a child administered the medicinal product
- A symptom or other problem occurring in a patient administered or taking more than the approved dose of the medicinal product

Table 2 Seriousness Criteria

An event is classified as serious if:

1. resulting in death (death),
2. being life-threatening (at risk of death),
3. requiring inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization),
4. resulting in persistent or significant disability/incapacity (disorder),
5. being a congenital anomaly/birth defect (birth defect), or
6. being any other medically serious condition that does not fall under any of 1 to 5 above. Note that all those listed in the Takeda Medically Significant AE List are included in this criterion. (Examples include bronchospasm, which requires short-term intensive care in emergency room settings.)

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/acute respiratory distress syndrome (ARDS)
- Torsade de pointes/ventricular fibrillation/ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including spasm and epilepsy)
- Agranulocytosis
- Aplastic anaemia
- Toxic epidermal necrolysis/muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial lung disease)
- Neuroleptic malignant syndrome/malignant hyperthermia
- Spontaneous abortion/stillbirth and foetal death
- Confirmed or suspected transmission of infection by a medicinal product
- Confirmed or suspected endotoxin shock

Table 3 Criteria for Casual Relationship between Adverse Event and the Drug

Determination	Criteria
Related	There is temporal correlation between the Drug and the event (including results from discontinuation of treatment). Or the event is an AE considered likely to have been caused by the Drug although it is presumed to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Not related	There is no temporal correlation between the Drug and the event. Or the event is adequately considered to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Unevaluable	There is lack of information necessary for evaluation of the event, including temporal correlation (including results from discontinuation of treatment), primary disease, complications, concomitant medications, and combined treatments.

10.0 Analysis Items and Method

10.1 Patient Disposition Items

Compile information including the number of enrolled patients, number of patients with eCRFs collected, numbers of safety- and efficacy-evaluable patients, and the number of patients excluded from analysis and reasons for exclusion.

10.2 Patient Demographics

Compile patient demographic information including sex, age, hypersensitivity disposition, and complications.

10.3 Treatment Details

Compile information on administration of the Drug and of concomitant medications.

10.4 Safety Items

Compile the following regarding the safety-evaluable population. AEs, coded using MedDRA, will be summarized by preferred term (PT) and by system organ class (SOC).

10.4.1 Onset Status of Adverse Events

Compile the incidence of AEs occurring during the observation period, in terms of, e.g., causal relationship with the Drug, type, seriousness. Note that bleeding-related events should be separately compiled because such events are set as a priority survey item.

10.4.2 Factors Likely to Affect Safety

Compile the incidence of ADRs occurring during the observation period, by stratification variables: patient baseline characteristics (sex, age, presence or absence of renal

dysfunction, presence or absence of hepatic dysfunction, etc.) and treatment regimen (administration of the Drug, administration of concomitant medications such as anticoagulant drugs, antiplatelet drugs).

10.5 Efficacy Items

Compile the following regarding the efficacy-evaluable population.

10.5.1 Changes in Lipid Parameters: TG, TC, LDL-C, HDL-C, Non-HDL-C, etc.

Tabulate observed values and changes (observed value at each observational timepoint after baseline minus observed value at baseline) at each observational timepoint for TG, TC, LDL-C (by converted value calculated by direct measurement, Friedewald formula*), HDL-C, Non-HDL-C (converted value**), VLDL cholesterol, Apo-AI, Apo-B, Apo-CIII, lipoprotein (a), and RLP-C.

*: LDL-C = TC-HDL-C - TG / 5

**: Non-HDL-C = TC-HDL-C

Note that LDL-C, Non-HDL-C, TC/LDL-C ratio, LDL-C/HDL-C ratio, and LDL-C/Apo-B ratio should be calculated from test results.

10.5.2 Factors Likely to Affect Efficacy

Compile TG values by stratification variables: patient baseline characteristics (sex and age) and treatment regimen (administration of the Drug, administration of concomitant medications, etc.).

11.0 Organizational Structure for Conducting the Study

Study Chair

Pharmacovigilance Department, Pharmaceutical Development Division, Takeda Pharmaceutical Co., Ltd.

PPD

12.0 Service Contractor's Name and Address and Scope of Contract Work

Contractor: PPD

Scope of contract work: Data management and statistical analysis

13.0 Other Necessary Items

13.1 Protocol Revision

During the surveillance period, keep track of, e.g., the progress of the Study, the onset of unexpected ADRs or serious ADRs based on the precautions, presence or absence of increased incidence of specified ADRs, the appropriateness of survey items. If needed, review and revise this protocol. If partial change approval is obtained for dosage and administration or indications during the surveillance period, examine whether to revise this protocol if necessary and revise it if necessary.

13.2 Action Taken in Case of Problem or Question

If any problem is found in the safety or efficacy of the Drug, carefully review the data and examine what needs to be done.

Appendix Study Schedule

Survey Item \ Survey and Data Entry Timing		Observation Period						
		Patient enrollment	Baseline	Month 3	Month 6	Month 9	Month 12	Discontinuation
Patient Enrollment	Prescription date of the Drug	○						
	Patient ID number	○						
	Patient initials	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria/exclusion criteria	○						
Patient demographics	Height, Weight		○					
	Time of hyperlipidemia diagnosis		○					
	Treatment category		○					
	Menopausal status (only for female)		○					
	Complications		○					
	Medical history		○					
	Hypersensitivity disposition		○					
	Drinking history, smoking history		○					
	Presence or absence of surgery before baseline		○					
	Presence or absence of healthier lifestyle education (diet and exercise therapies)		○					
Treatment Information	Administration of the Drug		← ○ →					○
	Administration of other antihyperlipidemic drugs		← ○ →					○
	Administration of concomitant medications (other than antihyperlipidemic drug)		← ○ →					○
Testing /Observation Items	TG		○	○	○	○	○	○
	TC		○	○	○	○	○	○
	LDL-C (direct measurement)		○	○	○	○	○	○
	HDL-C		○	○	○	○	○	○
	VLDL-C		○	○	○	○	○	○
	Apo-AI		○	○	○	○	○	○
	Apo-B		○	○	○	○	○	○
	Apo-CIII		○	○	○	○	○	○
	Lipoprotein (a)		○	○	○	○	○	○
	RLP-C		○	○	○	○	○	○
	FBG		○	○	○	○	○	○
	HbA1c		○	○	○	○	○	○
	Pregnancy status (only for female)		← ○ →					○
	AE		← ○ →					○

○: Surveyed, tested, or observed ← ○: → Surveyed, tested, or observed throughout the period

Special Drug Use Surveillance Protocol

Lotriga Granular Capsules Special Drug Use Surveillance

[Long-term use survey]

Version No.	**First Version**
Date Prepared	**December 7, 2012**
Study Sponsor	**Takeda Pharmaceutical Company Limited**

Table of Contents

1.0 Background

Lotriga Granular Capsules (the “Drug”) is an oral capsule formulation containing the active ingredient omega-3 fatty acid ethyl esters (principally EPA-E and DHA-E). The Drug differs from general marine oil products, such as supplements, in containing a high concentration of omega-3 fatty acid ethyl esters. Since first approved in Norway in September 1994, the Drug has been in extensive use overseas, sold in more than 60 countries. In the clinical study of the Drug conducted in Japan in patients with hypertriglyceridemia, adverse drug reactions (ADRs) including ‘laboratory test abnormal’ were observed in 91 (9.6%) of the 948 patients administered at 2 g or 4 g of omega-3 fatty acid ethyl esters, and the major ADR was Diarrhea (2.5%).

Despite the proven track record of extensive use overseas and the fact that the safety of long-term use was already evaluated during the clinical study, it is important to evaluate the safety of long-term use of the Drug in the general patient population in Japan.

Special drug use surveillance (hereinafter the "Study") has been therefore designed to evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

2.0 Objective

To evaluate the safety and efficacy of long-term use of the Drug in patients with hyperlipidemia in a routine clinical setting.

3.0 Target Sample Size and Rationale for Sample Size Setting

3.1 Target Sample Size

3,000 patients

3.2 Rationale for Sample Size Setting

Bleeding-related events are set as a priority survey item for the Drug. As postmarketing surveillance of EPA products in antihyperlipidemic therapy has reported that the incidence of bleeding-related ADRs was 0.4% and that the percentage of anticoagulant and antiplatelet concomitant use was about 10%, the Study sets a target of 3,000 patients so that anticoagulant and antiplatelet concomitant use can be assessed to some degree, in addition to bleeding-related ADRs.

Note that this rationale for the sample size is not based on statistical evidence.

4.0 Study Population

Patients with hyperlipidemia will be eligible for this study; however, those who meet the following exclusion criteria were excluded from the study.

Exclusion criteria:

(1) Patients with hemorrhage (e.g., hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, or vitreous hemorrhage)

(2) Patients with a history of hypersensitivity to ingredients in the Drug

5.0 Dosage and Administration for Study Population

The usual adult dosage is 2 g of omega-3 fatty acid ethyl esters administered orally once daily after meals. However, the dosage can be increased up to twice daily (at a dose of 2 g) depending on the patient's triglyceride level.

6.0 Number of Study Sites by Clinical Department

About 200 sites (clinical departments not specified)

7.0 Study Method

7.1 Observation Period

12 months

7.2 Request and Contract to Study Sites

The Study will be requested and contracted using a web-based electronic data collection system (CCI [redacted]). Takeda Pharmaceutical's MRs (hereinafter "Takeda MRs") will adequately explain to investigators about the purpose and description of the Study, CCI [redacted]'s operating procedure, electronic signature, and user ID and password handling for request for the Study, based on the Letter of Request for Cooperation in Special Drug Use Surveillance, the Implementation Guidance, data input screen images, and the abbreviated CCI [redacted] Operating Manual. Takeda MRs will then conclude a contract in writing with study sites to perform the Study within the specified surveillance period.

7.3 Patient Enrollment Method

Patients will be "centrally" enrolled using CCI [redacted] The investigator will enter into CCI [redacted] patient enrollment information (see Section 9.1) of patients for whom the Drug has been prescribed since the start date of the period of contract with the study site, within 14 days after the prescription date of the Drug (the prescription date is defined as "Day 0"; the day following the prescription date is defined as "Day 1").

7.4 Data Entry and Electronic Signature to Electronic Case Report Form (eCRF)

The investigator will enter patient data including demographics and treatment into CCI [redacted] and electronically sign the eCRF in 12 months after the start of treatment with the Drug (baseline).

If a patient discontinues the treatment with the Drug for some reason during the observation period, the investigator will be expected to enter their information including demographics and treatment into CCI [redacted] and electronically sign the eCRF within one month after the completion of necessary observations. However, if the patient discontinues the treatment with the Drug due to the occurrence of an adverse event (AE), the investigator should continue to observe them after discontinuation, as long as possible until the AE is resolved or resolving. The investigator should then enter the result of the observation into CCI [redacted] and

electronically sign the eCRF.

After review of the information, Takeda Pharmaceutical may request for re-survey, if deemed necessary, via [redacted]. The investigator will, upon checking, perform the details of the requested re-survey and enter the result of the re-survey into [redacted] and electronically sign the eCRF.

7.5 Action Taken at Onset of Serious Adverse Event

The investigator will immediately contact the Takeda MR if a serious AE occurs during the observation period. The investigator will also separately provide detailed information thereof upon request, if any, from the Takeda MR.

8.0 Expected Duration of Study

Surveillance period: May 2013 to September 30, 2016

Patient enrollment period: May 2013 to May 31, 2015*

*Enrollment may be closed before the end of the enrollment period if the total number of patients enrolled in the Study reaches the target sample size.

9.0 Survey Items

The investigator will enter the information of the following items into [redacted]. The schedule for the Study is provided in the Appendix.

9.1 Patient Enrollment

1) Survey items

Prescription date of the Date, patient ID number, patient initials, sex, birth date, determination with inclusion criteria, and determination with exclusion criteria

2) Survey timing

The time of patient enrollment

9.2 Patient Demographics

1) Survey items

Height, weight, time of hyperlipidemia diagnosis, treatment category, menopausal status (only for female), complications (presence or absence and details), medical history (presence or absence and details), hypersensitivity disposition (presence or absence and details), drinking history, smoking history, presence or absence of surgery within one month before baseline, and presence or absence of healthier lifestyle education (diet and exercise therapies)

2) Survey time

Baseline

9.3 Treatment Information

1) Survey items

Administration of the Drug (daily dose, treatment duration, and status of completion of treatment with the Drug), administration of antihyperlipidemic drugs other than the Drug* (presence or absence, drug name, daily dose, and treatment duration), and administration of concomitant medications (other than antihyperlipidemic drugs) (presence or absence, drug name, and purpose of administration)

*: Including antihyperlipidemic drugs with which treatment is discontinued within two months before baseline.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.4 Testing/Observation Items

1) Survey items

Triglyceride (TG), total cholesterol (TC), LDL cholesterol* (LDL-C), HDL cholesterol (HDL-C), VLDL cholesterol (VLDL-C), Apo-AI, Apo-B, Apo-CIII, lipoprotein a, remnant lipoprotein cholesterol (RLP-C), fasting blood glucose (FBG), HbA1c *: When tested by direct measurement

2) Survey timing

Baseline, Month 3, Month 6, Month 9, and Month 12 (or discontinuation of treatment) test timepoints

9.5 Other Observation Items

1) Survey items

Pregnancy status

If the patient is found to be pregnant during the observation period, the investigator will report the Takeda MR. The investigator will, upon request from the Takeda MR, use a sheet for pregnant women to provide detailed information (including information available up to childbirth, including premature birth or other pregnancy results, if possible).

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

9.6 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (see Table 1), AE name, date of onset, seriousness and reason for seriousness (see Table 2), action taken to the Drug, date of determination of outcome, outcome, and causal relationship to the Drug* (see Table 3)

If the outcome is not resolved or unknown and the casual relationship is determined as unevaluable, follow-up survey should be conducted to some extent possible.

*If causal relationship to the Drug is determined as not related, reasons that may constitute the rationale for determination should be collected if it is unevaluable.

2) Survey timing

Period from baseline to Month 12 (or discontinuation of treatment)

3) Priority survey item

Bleeding-related events occurring after baseline are set as a priority survey item. If any bleeding-related event is reported as an AE, laboratory test values related to bleeding should be separately collected.

Table 1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
The following should be also handled as an AE:

- A symptoms or other problem occurring in an infant breastfed from a mother taking the medicinal product
- A symptom or other problem occurring in a child administered the medicinal product
- A symptom or other problem occurring in a patient administered or taking more than the approved dose of the medicinal product

Table 2 Seriousness Criteria

An event is classified as serious if:

1. resulting in death (death),
2. being life-threatening (at risk of death),
3. requiring inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization),
4. resulting in persistent or significant disability/incapacity (disorder),
5. being a congenital anomaly/birth defect (birth defect), or
6. being any other medically serious condition that does not fall under any of 1 to 5 above. Note that all those listed in the Takeda Medically Significant AE List are included in this criterion. (Examples include bronchospasm, which requires short-term intensive care in emergency room settings.)

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/acute respiratory distress syndrome (ARDS)
- Torsade de pointes/ventricular fibrillation/ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including spasm and epilepsy)
- Agranulocytosis
- Aplastic anaemia
- Toxic epidermal necrolysis/muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial lung disease)
- Neuroleptic malignant syndrome/malignant hyperthermia
- Spontaneous abortion/stillbirth and foetal death
- Confirmed or suspected transmission of infection by a medicinal product
- Confirmed or suspected endotoxin shock

Table 3 Criteria for Casual Relationship between Adverse Event and the Drug

Determination	Criteria
Related (if the Drug is suspected to have contributed to the event)	There is temporally evident correlation between the Drug and the event (including results from discontinuation of treatment). Or the event is an AE considered likely to have been caused by the Drug although it is presumed to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Not related (if the Drug is considered unlikely to have contributed to the event)	There is no temporally evident correlation between the Drug and the event. Or the event is adequately considered to have been contributed by other factors, such as primary disease, complications, concomitant medications, or combined treatments.
Unevaluable	There is lack of information necessary for evaluation of the event, including temporal correlation (including results from discontinuation of treatment), primary disease, complications, concomitant medications, and combined treatments.

10.0 Analysis Items and Method

10.1 Patient Disposition Items

Compile information including the number of enrolled patients, number of patients with eCRFs collected, numbers of safety- and efficacy-evaluable patients, and the number of patients excluded from analysis and reasons for exclusion.

10.2 Patient Demographics

Compile patient demographic information including sex, age, hypersensitivity disposition, and complications.

10.3 Treatment Details

Compile information on administration of the Drug and of concomitant medications.

10.4 Safety Items

Compile the following regarding the safety-evaluable population. AEs, coded using MedDRA, will be summarized by preferred term (PT) and by system organ class (SOC).

10.4.1 Onset Status of Adverse Events

Compile the incidence of AEs occurring during the observation period, in terms of, e.g., causal relationship with the Drug, type, seriousness. Note that bleeding-related events should be separately compiled because such events are set as a priority survey item.

10.4.2 Factors Likely to Affect Safety

Compile the incidence of ADRs occurring during the observation period, by stratification variables: patient baseline characteristics (sex, age, presence or absence of renal

dysfunction, presence or absence of hepatic dysfunction, etc.) and treatment regimen (administration of the Drug, administration of concomitant medications such as anticoagulant drugs, antiplatelet drugs).

10.5 Efficacy Items

Compile the following regarding the efficacy-evaluable population.

10.5.1 Changes in Lipid Parameters: TG, TC, LDL-C, HDL-C, Non-HDL-C, etc.

Tabulate observed values and changes (observed value at each observational timepoint after baseline minus observed value at baseline) at each observational timepoint for TG, TC, LDL-C (by converted value calculated by direct measurement, Friedewald formula*), HDL-C, Non-HDL-C (converted value**), VLDL cholesterol, Apo-AI, Apo-B, Apo-CIII, lipoprotein a, and RLP-C.

*: LDL-C = TC-HDL-C - TG / 5

**: Non-HDL-C = TC-HDL-C

Note that LDL-C, Non-HDL-C, TC/LDL-C ratio, LDL-C/HDL-C ratio, and LDL-C/Apo-B ratio should be calculated from test results.

10.5.2 Factors Likely to Affect Efficacy

Compile TG values by stratification variables: patient baseline characteristics (sex and age) and treatment regimen (administration of the Drug, administration of concomitant medications, etc.).

11.0 Organizational Structure for Conducting the Study

Study Chair

Pharmacovigilance Department, Pharmaceutical Development Division, Takeda Pharmaceutical Co., Ltd.

PPD

12.0 Service Contractor's Name and Address and Scope of Contract Work

Contractor: PPD

Scope of contract work: Data management and statistical analysis

13.0 Other Necessary Items

13.1 Protocol Revision

During the surveillance period, keep track of, e.g., the progress of the Study, the onset of unexpected ADRs or serious ADRs based on the precautions, presence or absence of increased incidence of specified ADRs, the appropriateness of survey items. If needed, review and revise this protocol. If partial change approval is obtained for dosage and administration or indications during the surveillance period, examine whether to revise this protocol if necessary and revise it if necessary.

13.2 Action Taken in Case of Problem or Question

If any problem is found in the safety or efficacy of the Drug, carefully review the data and examine what needs to be done.

Appendix Study Schedule

Survey Item \ Survey and Data Entry Timing		Observation Period						
		Patient enrollment	Baseline	Month 3	Month 6	Month 9	Month 12	Discontinuation
Patient Enrollment	Prescription date of the Drug	○						
	Patient ID number	○						
	Patient initials	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria/exclusion criteria	○						
Patient demographics	Height, Weight		○					
	Time of hyperlipidemia diagnosis		○					
	Treatment category		○					
	Menopausal status (only for female)		○					
	Complications		○					
	Medical history		○					
	Hypersensitivity disposition		○					
	Drinking history, smoking history		○					
	Presence or absence of surgery before baseline		○					
	Presence or absence of healthier lifestyle education (diet and exercise therapies)		○					
Treatment Information	Administration of the Drug		← ○ →					○
	Administration of other antihyperlipidemic drugs		← ○ →					○
	Administration of concomitant medications (other than antihyperlipidemic drug)		← ○ →					○
Testing /Observation Items	TG		○	○	○	○	○	○
	TC		○	○	○	○	○	○
	LDL-C (direct measurement)		○	○	○	○	○	○
	HDL-C		○	○	○	○	○	○
	VLDL-C		○	○	○	○	○	○
	Apo-AI		○	○	○	○	○	○
	Apo-B		○	○	○	○	○	○
	Apo-CIII		○	○	○	○	○	○
	Lipoprotein a		○	○	○	○	○	○
	RLP-C		○	○	○	○	○	○
	FBG		○	○	○	○	○	○
	HbA1c		○	○	○	○	○	○
	Pregnancy status (only for female)		← ○ →					○
	AE		← ○ →					○

○: Surveyed, tested, or observed ← ○: → Surveyed, tested, or observed throughout the period