PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

A POST-MARKETING DATABASE SURVEILLANCE TO INVESTIGATE THE RISK OF RHABDMYOLYSIS AND MYOPATHY IN HYPERCHOLESTEROLEMIC PATIENTS TREATED WITH ATOZET OR EZETIMEBE ATORVASTATIN COADMINISTRATION IN JAPAN

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

PASS INFORMATION

Title	A Post-marketing Database Surveillance to Investigate the Risk of Rhabdomyolysis and Myopathy in Hypercholesterolemic Patients Treated with ATOZET or Ezetimibe Atorvastatin coadministration in Japan
Protocol Version identifier	2.0
Date of last version of protocol	05-APR-2021
EU PAS Register No.	N.A.
Active substance	C10BA05, ezetimibe, atorvastatin calcium hydrate
Medicinal product(s)	ATOZET® Combination Tablets LD/HD, ezetimibe / atorvastatin calcium
Product reference	N.A.
Procedure number	N.A.
Marketing authorisation holder(s) (MAH)	MSD K.K.
Joint PASS	NO
Research question and objectives	To investigate health outcomes of interest (HOI) related to the identified risks and missing information for ATOZET compared to coadministration of ezetimibe and atorvastatin from APR-2018 to MAR-2021
Country(-ies) of surveillance	Japan
Author	PPD PPD MSD K.K.

	1-13-12 Kudan-kita, Chiyoda-ku, Tokyo, Japan
Marketing authorisation holder(s) including MAH Contact Person	MSD K.K.
Merck Final Repository (RCAM) Date	20-May-2021
Date of Health Authority Approval of Protocol	This protocol will be reviewed and approved by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) prior to conduct of surveillance activities. HA Approval Date: 19-May-2021

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

VERSION HISTORY

Version	*Date*		*Changes*
1	05-NOV-2020	Original	
2	05-APR-2021	Version 2.0	Details of the method of adjusting for covariates are added. (7.1.1, 7.7.2) The minimum follow-up period (6 Months) was removed from the exclusion criteria. (7.2.3) Another pattern of sensitivity analysis is added. (7.7.4) The details of the definition and output diagram were added. (7.1.4, 7.3.2, Attachment 1 (Table layout sample)

Comparative Table

Section	v1.0	V2.0
2 ABSTRACT	Sex, age, comorbidities (myocardial infarction, angina, congestive heart failure, ischemic heart disease)	Sex, age, comorbidities
2 ABSTRACT	The incidence rates of events (rhabdomyolysis and myopathy) will be calculated as the number of events per 1,000 person-years along with the 95% CI. The IRR and 95% CI will be calculated if more than 1 outcome is observed in both ATOZET and coadministration of ezetimibe and atorvastatin groups.	To compare the incidence of HOI, the incidence rates of HOI events will be calculated as the number of events per 1,000 person-years for ATOZET group (ATZ-group) and Atorvastatin/Ezetimibe coadministration group (EZE-ATV-group). Incidence rate ratio (IRR) will be calculated if more than 1 outcome is observed in both ATZ-group and EZE-ATV groups. Incidence rate ratio (IRR) will also be calculated using Poisson regression analysis to compare the incidence of HOI between ATZ-group and EZE-ATV-group after adjusting for covariates.
7.1.1 Brief Summary	-	To compare the incidence of HOI, the incidence rates of HOI events will be calculated as the number of events per 1,000 person-years for ATOZET group (ATZ-group) and Atorvastatin/Ezetimibe coadministration group (EZE-ATV-group). Incidence rate ratio (IRR) will be calculated if more than 1 outcome is observed in both ATZ-group and EZE-ATV-groups. Incidence rate ratio (IRR) will also be

Section	v1.0	V2.0
		calculated using Poisson regression analysis to compare the incidence of HOI between ATZ-group and EZE-ATV-group after adjusting for covariates.
7.1.4 Surveillance data period	The overall surveillance data period ensures that all patients will have a 6-month (180 days) lookback period and at least a 6-month (180 days) follow-up period.	The overall surveillance data period ensures that all patients will have a 6-month lookback period.
7.1.4 Surveillance data period	The treatment period consists of the period from the index date to the last prescription date plus the days' supply plus gap period. (see sections 7.2.2, 7.2.4.1).	The treatment period for the ATZ-group is defined as from the index date to the last prescription date + number of days' supply at the last prescription + a gap period. The treatment period for the EZE-ATV-group is defined as from the index-date (start date of coadministration which is based on the date when the second drug is prescribed) to the last prescription date + number of days' supply + a gap period. (see sections 7.2.2, 7.2.4.1).
7.2.2 Inclusion criteria	EZE-ATV-group is defined as the start date of coadministration.	EZE-ATV-group is defined as the start date of coadministration which is based on the date when the second drug is prescribed.
7.2.3 Exclusion Criteria • For the ATZ-group	Patients who do not have at least a 6-month follow-up period, OR	*Exclusion criterion removed*
7.2.3 Exclusion Criteria • For the EZE-ATV-group	Patients who had treatment before April 2018, OR	Patients who had Ezetimibe/Atorvastatin coadministration treatment before April 2018, OR
7.2.3 Exclusion Criteria • For the EZE-ATV-group	Patients who do not have at least a 6-month follow-up period, OR	*Exclusion criterion removed*
7.2.3 Exclusion Criteria Figure 2 ATZ-group	Patients who do not have at least a 6-month follow-up period	*Exclusion criterion removed*
7.2.3 Exclusion Criteria Figure 2 EZE-ATV-group	Patients who do not have at least a 6-month follow-up period	*Exclusion criterion removed*
7.2.4.1Longitudinality	When assessing the rate of laboratory testing, patients must have at least 6-months of follow-up.	*Removed*
7.2.4.1 Longitudinality	(start date of coadministration)	(start date of coadministration which is based on the date when the second drug is prescribed)

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

Section	v1.0	V2.0
7.3.2 Outcomes	To describe the incidence of HOI, the outcomes targeted in this surveillance are as follows: rhabdomyolysis and myopathy. Lab services are counted according to SS-MIX2. MID-NET records lab services orders and the record format is JLAC10 (19). The target codes are shown in Table 4.	To describe the incidence of HOI, the outcomes targeted in this surveillance are as follows: rhabdomyolysis and myopathy (see Table 5). Lab services are counted according to SS-MIX2. MID-NET records lab services orders and the record format is JLAC10 (19). The target codes are shown in Table 4. Upper Limit of Normal (ULN) is referred to the reference range in the SS-MIX2 data, which is standardized among medical facilities. If an abnormal test value and any of diagnostic codes of rhabdomyolysis or myopathy diagnosis are recorded in the same month, the HOI is defined to occur. The day on which the laboratory test is examined is defined as the day on which the HOI occurs.
7.3.3.2 Comorbidities	The comorbidities used in this surveillance will be "Ischemic heart disease, Myocardial infarction", "Congestive heart failure", "Peripheral vascular disease", "Cerebrovascular disease", "Mild liver disease", "Hypertension", "Diabetes (mild to moderate)", "Diabetes with chronic complications" and "Renal disease".	The comorbidities used in this surveillance will be "Ischemic heart disease, Myocardial infarction", "Congestive heart failure", "Peripheral vascular disease", "Cerebrovascular disease", "Mild liver disease", "Hypertension", "Diabetes (mild to moderate)", "Diabetes with chronic complications", "Renal disease", and “Moderate or severe liver disease”.
7.7.2Primary objective:	To compare the incidence rates of HOI of rhabdomyolysis and myopathy, the incidence rates of events (rhabdomyolysis and myopathy) will be calculated as the number of events per 1,000 person-years along with the 95% CI. For all patients, the exposure time starts at the initiation of treatment. Patients with a prior history of the HOI during the lookback period will be excluded from these analyses. The IRR and 95% confidence interval will be calculated if more than 1 outcome is observed in both ATZ-group and EZE-ATV groups.	To compare the incidence of HOI, the incidence rates of HOI events will be calculated as the number of events per 1,000 person-years for ATZ-group and for EZE-ATV-group. For all patients, the exposure time starts at the initiation of treatment of each patient. Patients with a prior history of the HOI during the lookback period will be excluded from these analyses. The IRR will be calculated if more than 1 outcome is observed in both ATZ-group and EZE-ATV groups. Incidence rate ratio (IRR) will also be calculated using Poisson regression analysis to compare the incidence of HOI between ATZ-group and EZE-ATV-group after adjusting for covariates that differ between ATZ-group and EZE-ATV-group. Covariates will include age, since this variable is often associated with risk of AEs, and may include sex and individual comorbidities (“Ischemic heart disease, Myocardial infarction”, “Congestive heart failure”, “Peripheral vascular

Section	v1.0	V2.0
		disease", "Cerebrovascular disease", "Mild liver disease", "Hypertension", "Diabetes (mild to moderate)", "Diabetes with chronic complications", "Renal disease", and "Moderate or severe liver disease") if there are differences in the distributions of these variables between treatment groups. Because of the low number of events expected, a limited number of covariates will be included.
7.7.4 Sensitivity analysis	The sensitivity analysis is evaluated by an alternative outcome definition. The analyses for the alternative outcome definitions will follow the methods for the primary outcome above.	The sensitivity analysis is evaluated by alternative outcome definitions which are described in section 7.3.2.1. The analyses for the alternative outcome definitions will follow the methods for the primary outcome above. The sensitivity analysis will also be performed limiting ATZ-group to the subjects who are switched from Atorvastatin monotherapy, not including patients switched from coadministration of Atorvastatin and Ezetimibe. The same analytical procedures will be performed for the sensitivity analysis as are performed for primary analysis.

TABLE OF CONTENTS

LIST OF TABLES

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

LIST OF FIGURES

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

LIST OF ABBREVATIONS

AE	Adverse Event
ALT	Alanine transaminase
ARB	Angiotensin II Receptor Blocker
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification System
CCI	Charlson Comorbidity Index
CK	Creatine Kinase
CKP	Creatine Kinase Protein
CPK	Creatine Phosphokinase
CSRM	Clinical Safety Risk Manager
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular Disease
DPC	Diagnosis Procedure Combination
DSUR	Development Safety Update Reports
GPP	Good Pharmacoepidemiology Practice
GPSP	Good Post-marketing Study Practice
HDL-C	High Density Lipoprotein Cholesterol
HMG-CoA	hydroxymethylglutaryl-CoA reductase
HOI	Health Outcomes of Interest
HbA1c	Hemoglobin A1c
ICD	International Classification of Diseases
JAS	Japan Atherosclerosis Society
JLAC10	Japanese Laboratory Code Version 10
JMDC	JMDC Claims Database
JPC	Japan Package Circular
LDL-C	Low-density Lipoprotein Cholesterol
MDV	Medical Data Vision
MID-NET	Medical Information Database Network
NIS	Non-Interventional Study
PBRER	Periodic Benefit Risk Evaluation Report
PMDA	Pharmaceuticals and Medical Devices Agency
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RMST	Risk Management Subteam
SOP	Standard Operating Procedures
SQI	Significant Quality Issue
SS-MIX2	Standardized Structured Medical Information eXchange 2
TG	Triglycerides
ULN	Upper Limit of Normal

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

PRODUCT INFORMATION (SPECIFIC COLUMN FOR PMDA)

Outline of the product			
Approval date	27SEPT2017	Therapeutic class	872189
Reexamination period	4 years	Approval No.	22900AMX00965000 22900AMX00966000
International birth date	03MAY2013		
Brand name	ATOZET® Combination Tablets LD ATOZET® Combination Tablets HD		
Active ingredient	Ezetimibe/JP Atorvastatin Calcium Hydrate		
Content and formulation	[ATOZET® Combination Tablets LD] Content: Each tablet contains 10 mg of ezetimibe and 10.8 mg of atorvastatin calcium hydrate (10 mg as atorvastatin). Dosage form: Film-coated tablets [ATOZET® Combination Tablets HD] Content: Each tablet contains 10 mg of ezetimibe and 21.7 mg of atorvastatin calcium hydrate (20 mg as atorvastatin). Dosage form: Film-coated tablets		
Dosage and administration	The usual dosage for adults is 1 tablet (10 mg/10 mg or 10 mg/20 mg of ezetimibe/atorvastatin) taken orally once daily after meal.		
Indication and effect	Hypercholesterolemia, Familial hypercholesterolemia		
Approval conditions	Formulate the pharmaceuticals risk management plan, and properly implement it.		
Remarks			

1 RESPONSIBLE PARTIES

Principal investigator	PPD
Coordinating investigator for each country in which the study is to be performed	N.A.
Sponsor contacts	Kitanomaru Square, 1-13-12, Kudan−kita, Chiyoda-ku, Tokyo 102-8667
Other contacts	N.A.
Supplier/Collaborator	IQVIA Services Japan K.K. IQVIA Solutions Japan K.K.
Shared responsibilities	N.A.

2 ABSTRACT

Title	A Post-marketing Database Surveillance to Investigate the Risk of Rhabdomyolysis and Myopathy in Hypercholesterolemic Patients Treated with ATOZET or Ezetimibe Atorvastatin coadministration in Japan
Protocol Number / Version	0854 / 2.0
Date	05-APR-2021
Applicant's organization	MSD K.K.
Rationale & Background	ATOZET is a fixed dose combination of two well-established, widely used medications. Because ATOZET is bioequivalent to the coadministration of ezetimibe and atorvastatin, the clinical development program for ATOZET was very limited. Rhabdomyolysis and myopathy are well characterized with individual monotherapy, atorvastatin but were not well-characterized during the ATOZET clinical development program. Use of ATOZET in patients with hepatic impairment was also not well-characterized. The Japan Package Circular includes recommendations for monitoring various liver function tests in patients treated with ATOZET. PMDA has requested that the Market Authorization Holder conduct a post-marketing database surveillance[1] as a regulatory requirement to characterize the risk of rhabdomyolysis and myopathy and missing information on patients with hepatic impairment compared to the coadministration of ezetimibe and atorvastatin.
Safety Specifications for this activity on Japan Risk Management Plan (specific column for PMDA)	Important identified risks: - Rhabdomyolysis, myopathy Important missing information: - Patients with hepatic impairment
Research Question(s) & Objective(s)	Research question

[1] The term “database surveillance” is based on Japanese terminology. This is the same as a secondary database *study*.

	To investigate health outcomes of interest (HOI) related to the identified risks and missing information for ATOZET compared to coadministration of ezetimibe and atorvastatin from APR-2018 to MAR-2021. Primary objective: - To compare the incidence rates of rhabdomyolysis and myopathy (HOI) between those taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin. Secondary objectives: - To describe the incidence rates of rhabdomyolysis and myopathy (HOI) for patients with and without hepatic impairment among those treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin. - To describe demographic and clinical characteristics of the surveillance patients treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin.
Surveillance Design	The surveillance will be primarily descriptive; however, comparison of rates of HOI between ATOZET and Atorvastatin/Ezetimibe coadministration will be performed.
Data Period (specific column for PMDA)	Data Period is from OCT-2017 to MAR-2021 in order to gain 180 days of lookback period for all included patients.
Population	The surveillance population is hypercholesterolemic patients who are treated with ATOZET or coadministration of ezetimibe and atorvastatin between 1-APR-2018 and 30-SEP-2020, (selection period)
Variables	<u>Outcomes:</u> For primary objective and secondary objective: Rhabdomyolysis: Definition 1: Laboratory test value (CK > 10 × upper limit of normal (ULN)),

	AND diagnosis codes (ICD-10) for rhabdomyolysis Definition 2: Laboratory test value (CK > 5 × ULN), AND Diagnosis codes (ICD-10) for rhabdomyolysis. Myopathy: Definition 1: Laboratory test values (CK > 10 × ULN, AND diagnosis codes (ICD-10) for myopathy Definition 2: Laboratory test value (CK >5 × ULN), AND diagnosis codes (ICD-10) for myopathy <u>Covariates:</u> Sex, age, comorbidities
Data Sources	MID-NET
Surveillance Size	The surveillance will use all subjects that meet the inclusion/exclusion criteria with hypercholesterolemia treated with ATOZET or coadministration of ezetimibe and atorvastatin. If the incidence rate in the exposed group is 0.01 and in the non-exposed group is 0.005 and there are 1,000 ATOZET patients and 1,000 coadministration patients, the 95% confidence intervals (CI) of incidence rate ratio (IRR) is 0.68-5.85.
Data Analysis	To compare the incidence of HOI, the incidence rates of HOI events will be calculated as the number of events per 1,000 person-years for ATOZET group (ATZ-group) and Atorvastatin/Ezetimibe coadministration group (EZE-ATV-group). Incidence rate ratio (IRR) will be calculated if more than 1 outcome is observed in both ATZ-group and EZE-ATV-groups. Incidence rate ratio (IRR) will also be calculated using Poisson regression analysis to compare the incidence of HOI between ATZ-group and EZE-ATV-group after adjusting for covariates. Basic statistics on the surveillance population will be presented as n (%), mean ± standard deviation

	(SD), or median (interquartile range [IQR]), as appropriate.

3 AMENDMENTS AND UPDATES

Amendment or Update No.	Date	Section of surveillance Protocol	Amendment or Update	Reason
-	-	-	-	-

4 MILESTONES

Milestone	**Planned Date**
Start of data collection	APR-2021
End of data collection	JUN-2021
Interim report(s) of surveillance results	N.A.
Surveillance progress report(s)	N.A.
Final report of surveillance results	DEC-2021
Submit final report of surveillance results to PMDA	DEC-2021

5 RATIONALE AND BACKGROUND

5.1 Background

Hypercholesterolemia refers to high blood cholesterol levels. Cholesterol is a waxy, fatty substance (also known as lipid) that the body needs the appropriate amounts of to work properly. It comes from food and is also made by the liver. There are a few different types of cholesterol, including:

- Total cholesterol: all the different types of cholesterol combined.
- Low-density lipoprotein cholesterol (LDL-C): also called “bad” cholesterol because it is the main source of cholesterol build-up and blockage in the blood vessels.
- High-density lipoprotein cholesterol (HDL-C): also called “good” cholesterol because it helps keep cholesterol from building up in the blood vessels.

- Triglycerides (TG): are types of fat found in blood. The body uses them for energy.

Hypercholesterolemia is elevation of plasma cholesterol, that may contribute to the development of atherosclerosis. Causes may be primary (genetic) or secondary (1). Diagnosis is made by measuring plasma levels of total cholesterol, LDL-C, or non-HDL-C (2). Treatment includes dietary changes, exercise, and lipid-lowering drugs (2). According to the "Summary of Patient Survey, 2017", the total number of patients with Hypercholesterolemia was 2,205,000 (639,000 males and 1,565,000 females) in Japan (3). An observational study of Japanese hypercholesterolemia patients (24,893 patients, aged 65.8±10.5 years) showed high rates of hypertension (59.4%), and diabetes mellitus and/or impaired glucose tolerance (26.4%) (3). Reduction of plasma LDL-C is crucial for preventing Cardiovascular Disease (CVD) events, and 1.0 mmol/L reduction in LDL-C is associated with reductions of ~10% in all-cause death, ~24% in major coronary events and ~15% in stroke events.

Hydroxymethylglutaryl-CoA reductase (HMG-CoA) reductase inhibitor monotherapy is the recommended first-line treatment for controlling LDL-C, followed by coadministration therapy of a HMG-CoA reductase inhibitor with other lipid-lowering medicines such as ezetimibe or colestimide. This is well documented in the Japan Atherosclerosis Society (JAS) guidelines, as well as in the United States and European guidelines (2, 4, 5). Ezetimibe, Atorvastatin and their coadministration have been widely used for over 10 years in Japan and the coadministration therapy is recommended in the Treatment Guide for Hyperlipidemia published in 2013 by JAS (6). ATOZET is a fixed dose combination drug containing the active ingredients of atorvastatin and ezetimibe, which has been shown in studies to be bioequivalent to the coadministration (7). Atorvastatin belongs to a class of medicines called HMG-CoA reductase inhibitors which work by slowing down the production of cholesterol in the liver. Ezetimibe works by preventing the absorption of cholesterol in the small intestine (7).

Rhabdomyolysis and Myopathy

HMG-CoA reductase inhibitors (i.e. statins) have been associated with myopathy and rarely, rhabdomyolysis. The rate of hospitalization because of HMG-CoA reductase inhibitor-induced rhabdomyolysis was estimated as 0.44 per 10,000 patient-years in a cohort study (8). The risk of developing rhabdomyolysis is expected to be greatest during the first year of therapy (9). A study reviewing randomized controlled studies in 2006 reported that the combination therapy of HMG-CoA reductase inhibitor and ezetimibe did not increase the risk of elevation of CK and rhabdomyolysis compared to the HMG-CoA reductase inhibitor monotherapy (10). No cases of rhabdomyolysis and myopathy were reported in ATOZET's Phase-3 clinical study in Japan (the P383 study and the P384 study) (11) or in 8 double-blind studies outside Japan, but cases of myalgia, muscle weakness, and elevation of CK were reported (11).

As a routine risk minimization practice, rhabdomyolysis and myopathy are described in the "Contraindications", "Careful Administration" and "Clinically significant adverse reactions" sections in the Japan Package Circular (JPC) (7).

Pharmacovigilance activity and risk minimization practice are regulatory requirements for re-examination; therefore, the Market Authorization Holder will conduct a database surveillance for rhabdomyolysis and myopathy of the important identified risks, and important missing information described in the Japanese Risk Management Plan (RMP) for ATOZET (11). Throughout the discussion with PMDA, we focus on disease code and CK values in this surveillance, considering that there are no validation studies for rhabdomyolysis in Japan. Therefore, we used recommendation in ACC/AHA/NHLBI Clinical Advisory (12) and CTCAE grades (13) as definitions of rhabdomyolysis and myopathy.

5.2 Rationale

Because ATOZET is a fixed dose combination of two well-established medications, the clinical development program for ATOZET was limited. Rhabdomyolysis and myopathy events and use of ATOZET in patients with hepatic impairment were not well-characterized during the ATOZET clinical development program, and therefore, post-marketing surveillance was considered important by the PMDA based on JNDA review by the Agency.

PMDA has requested that the Market Authorization Holder conduct a post-marketing database surveillance as a regulatory requirement to characterize the risk of rhabdomyolysis and myopathy and missing information on patients with hepatic impairment comparing ATOZET and EZE/ATV coadministration even though the two drug regimens are bioequivalent.

6 RESEARCH QUESTION AND OBJECTIVES

6.1 Research Question

To investigate HOI related to the identified risks and missing information for ATOZET compared to coadministration of ezetimibe and atorvastatin from APR-2018 to MAR-2021.

6.2 Research Objectives

6.2.1 Primary objectives

- To compare the incidence rates of HOI between those taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin. HOI includes incidences of rhabdomyolysis and/or myopathy with elevation of CK.

6.2.2 Secondary objectives

- To describe the incidence rates of HOI for patients with and without hepatic impairment among those treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin.

- To describe demographic and clinical characteristics of the surveillance patients treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin.

7 RESEARCH METHODS

7.1 Surveillance Design

7.1.1 Brief Summary

This is a non-interventional post-marketing database surveillance (PMS) to investigate the safety of ATOZET administered in hypercholesterolemia patients in a real-world setting. The surveillance type is primarily descriptive; however, despite the expected small sample size and likelihood of inconclusive results, comparison of rates of HOI between ATOZET and Atorvastatin/Ezetimibe coadministration will be performed at the request of PMDA. To compare the incidence of HOI, the incidence rates of HOI events will be calculated as the number of events per 1,000 person-years for ATOZET group (ATZ-group) and Atorvastatin/Ezetimibe coadministration group (EZE-ATV-group). Incidence rate ratio (IRR) will be calculated if more than 1 outcome is observed in both ATZ-group and EZE-ATV groups. Incidence rate ratio (IRR) will also be calculated using Poisson regression analysis to compare the incidence of HOI between ATZ-group and EZE-ATV-group after adjusting for covariates. The study will use the MID-NET database in Japan. It will use data extracted from Standardized Structured Medical Information eXchange 2 (SS-MIX2) data, administrative claims data and Diagnosis Procedure Combination (DPC) data for the period from 01-OCT-2017 to 31-MAR-2021.

7.1.2 Assessment methodology summary

This surveillance calculates the incidence rate for each population group excluding those with a prior history of the HOI. The incidence rate ratio (IRR) will be calculated. There is no minimum follow-up required for assessment of the HOI. The IRR and 95% confidence interval will be calculated if more than 1 outcome is observed in each population group.

7.1.3 Surveillance population

The surveillance populations will include patients with hypercholesterolemia who are: 1) undergoing treatment with ATOZET, or 2) undergoing treatment with coadministration of

ezetimibe and atorvastatin, between 1-APR-2018, and 30-SEP-2020, (selection period) in the MID-NET database (see, section 7.2.2 and 7.2.3).

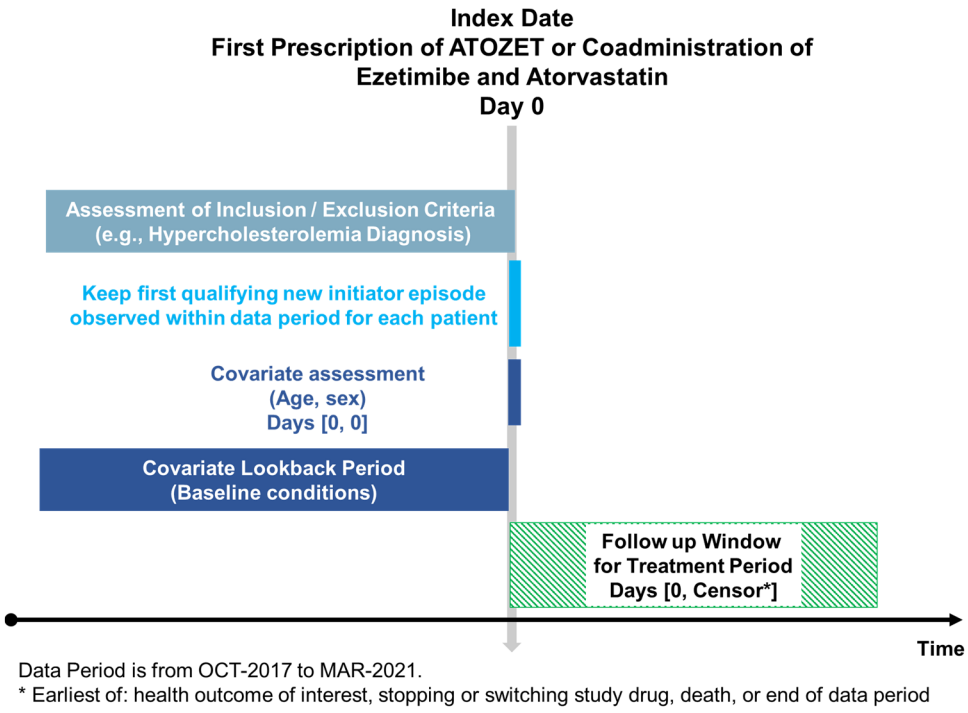
The anti-hypercholesterolemic drug being evaluated is exposure to ATOZET (ATZ-group). The comparison is coadministration of ezetimibe and atorvastatin (EZE-ATV-group). All ATOZET-treated patients will be assigned to the ATZ-group (see, section 7.2.2 for detail). EZE-ATV-group patients who already received coadministration of ezetimibe and atorvastatin treatment before the selection period will be excluded from the cohort. This surveillance will evaluate both doses combined because the safety profiles of 10 mg and 20 mg of Atorvastatin were similar in the Atorvastatin re-examination report (14) and we do not expect sufficient sample size to evaluate the doses separately. Dose will be analyzed descriptively for both groups.

7.1.4 Surveillance data period

The overall surveillance data period will be from 01-OCT-2017 to 31-MAR-2021. The selection period within the overall surveillance data period will be between 01-APR-2018 and 30-SEP-2020. The overall surveillance data period ensures that all patients will have a 6-month lookback period. Baseline characteristics will be summarized during the 6-month lookback period. Therefore, the beginning of the surveillance data period starts 6 months prior to the ATOZET launch date (23-APR-2018).

The treatment period for the ATZ-group is defined from the index date to the last prescription date + number of days' supply at the last prescription + a gap period. The treatment period for the EZE-ATV-group is defined from the index-date (start date of coadministration which is based on the date when the second drug is prescribed (i.e., data when EZE is added to ATV)) to the last prescription date + number of days' supply + a gap period. The start dates of EZE and ATV do not need to be the same. (see sections 7.2.2, 7.2.4.1).

Figure 1: Surveillance Design



7.1.5 Surveillance subgroup summary

To characterize missing information in the RMP about the patients with hepatic impairment in the RMP, additional subgroup analyses will be conducted by dividing the patients into two subgroups according to their AST and ALT levels. Patients whose ALT or AST levels exceed twice the upper limit of normal (ULN) level during the lookback period will be included in the hepatic impairment subgroup. Patients whose ALT or AST levels do not exceed twice the ULN level will be included in the non-hepatic impairment subgroup.

Reasons for setting:

The subgroup setting criteria will be the same as those set for exclusion in clinical trials (11).

7.2 Setting

7.2.1 Database

This surveillance will be analyzed using a database provided by MID-NET. MID-NET is a medical information platform developed by the Pharmaceuticals and Medical Devices Agency (PMDA) (15).

The Medical Information Database NETwork (MID-NET) was built to facilitate pharmacoepidemiological assessments of drug safety. This database consists of electronic

medical records from 23 hospitals and contains information about procedures, medications, clinical test results and insurance claim data that result from inpatient hospitalizations and outpatient consultations (primarily with specialists) (15). The advantages of MID-NET are as follows;

1. Standardized clinical laboratory data are available.

2. MID-NET captures data for both non-elderly and elderly patients, especially compared to the JMDC Claims Database (JMDC), which basically captures only data for non-elderly patients.

3. Compared to other databases (JMDC: about every 5 months, Medical Data Vision (MDV): every 2 months), the data is updated almost in real time (Every 1 week to 1 month).

By considering these advantages, this surveillance will be conducted by using MID-NET to investigate HOI.

To utilize MID-NET, we will send a data extraction script set from the MID-NET data center to the 23 participating institutions (15). Each institution accepts the script set and sends the anonymized output raw data set back to the central data center, which will then combine the data so it can be analyzed by MSD. The script is based on the combination of SS-MIX2, Administrative claims and DPC data. The script is composed of two settings, “Setting extraction” and “Setting output”. Appendices A and B show the code listings.

Setting extraction conditions:

The extraction condition matches any one of SS-MIX2, Administrative claims or DPC.

- SS-MIX2
  The prescription / injection (order), YJ code matches one of C10BA05, C10AX09 or C10AA05, AND
  Disease name order, International Classification of Diseases (ICD)10 code matches E78.5.

- Administrative claims
  Drug information, receipt code matches one of C10BA05, C10AX09 or C10AA05, AND
  Disease name order, diagnosis code matches E78.5.

- DPC
  Drug information, receipt code matches one of C10BA05, C10AX09 or C10AA05, AND
  Disease name order, diagnosis code match E78.5.

Setting output conditions:

Table 1 shows the settings of the data tables belonging to each data type. Appendix C shows the set-code listing.

Table 1: Data tables

Output period	Data types	Table name
Oct 01, 2017 to Mar 30, 2021	SS-MIX2	Visit information
		Diagnostic information (illness order)
		Diagnostic information (discharge summary)
		Prescription / injection order
		Prescription / injection
		Specimen test information
	DPC	DPC patient information
		DPC admission and discharge information
		DPC diagnostic information
		DPC drug information
		DPC medical practice information
	Administrative claims	Receipt diagnostic information
		Receipt drug information
		Receipt medical care information

7.2.2 Inclusion Criteria

1. Patients who have a hypercholesterolemia diagnosis (ICD code: E78.5) during the selection period, AND

2. Patients who have received ATOZET (ATC code: C10BA05) or coadministration of ezetimibe and atorvastatin (ATC code: C10AX09 and C10AA05) during the selection period.

   The ATZ-group will be new ATOZET prescription patients. The EZE-ATV-group will be new users of ezetimibe and atorvastatin coadministration.

Table 2: The expected treatment patterns in the ATZ-group

Pre-treatment*	At index date	Inclusion
Atorvastatin (C10AA05)	ATOZET (C10BA05)	Inclusion
Ezetimibe (C10AA05) and Atorvastatin (C10AX09)**	ATOZET (C10BA05)	Inclusion

* Pre-treatment means the medication prescribed just before the index date.
** Started coadministration during the selection period.

Table 3: The expected treatment patterns in the EZE-ATV-group

Pre-treatment*	At index date	Inclusion

Atorvastatin (C10AA05)	Ezetimibe (C10AA05) and Atorvastatin (C10AX09)	Inclusion

* Pre-treatment means the medication prescribed just before the index date.

The index date is the first prescription date of ATOZET in patients in the exposure group. The index date for the EZE-ATV-group is defined as the start date of coadministration which is based on the date when the second drug is prescribed. For the coadministration group, the EZE and ATV prescriptions do not have to be on the same day; an EZE prescription can be added to existing ATZ treatment. The index date is defined as the date when any of the following events occur: prescription order, Administrative claims order, or DPC order in the SS-MIX2 data of the MID-NET dataset.

7.2.3 Exclusion Criteria

The exclusion criteria are as follows:

- For the ATZ-group

    1. Patients given ezetimibe monotherapy (C10AX09) as a pre-treatment drug, OR
    2. Patients given other lipid modifying agents (C10) as a pre-treatment drug except atorvastatin (C10AX05), OR
    3. Patients who were not given any pre-treatment drug, OR
    4. Patients who had ATOZET treatment before April 2018, OR
    5. Patients who do not have a 6-month lookback period prior to the index date, OR
    6. Patients who have any missing information on critical variables (e.g., gender, age), OR
    7. Patients who have severe liver dysfunction considered as the contraindication for the use of ATOZET, OR
    8. Patients whose CK level during the 6 months (180 days) before the index date exceeds ULN, OR
    9. Patients who have any of the following diagnoses of rhabdomyolysis and myopathy (see Table 5) during the 6 months before the index date.

- For the EZE-ATV-group

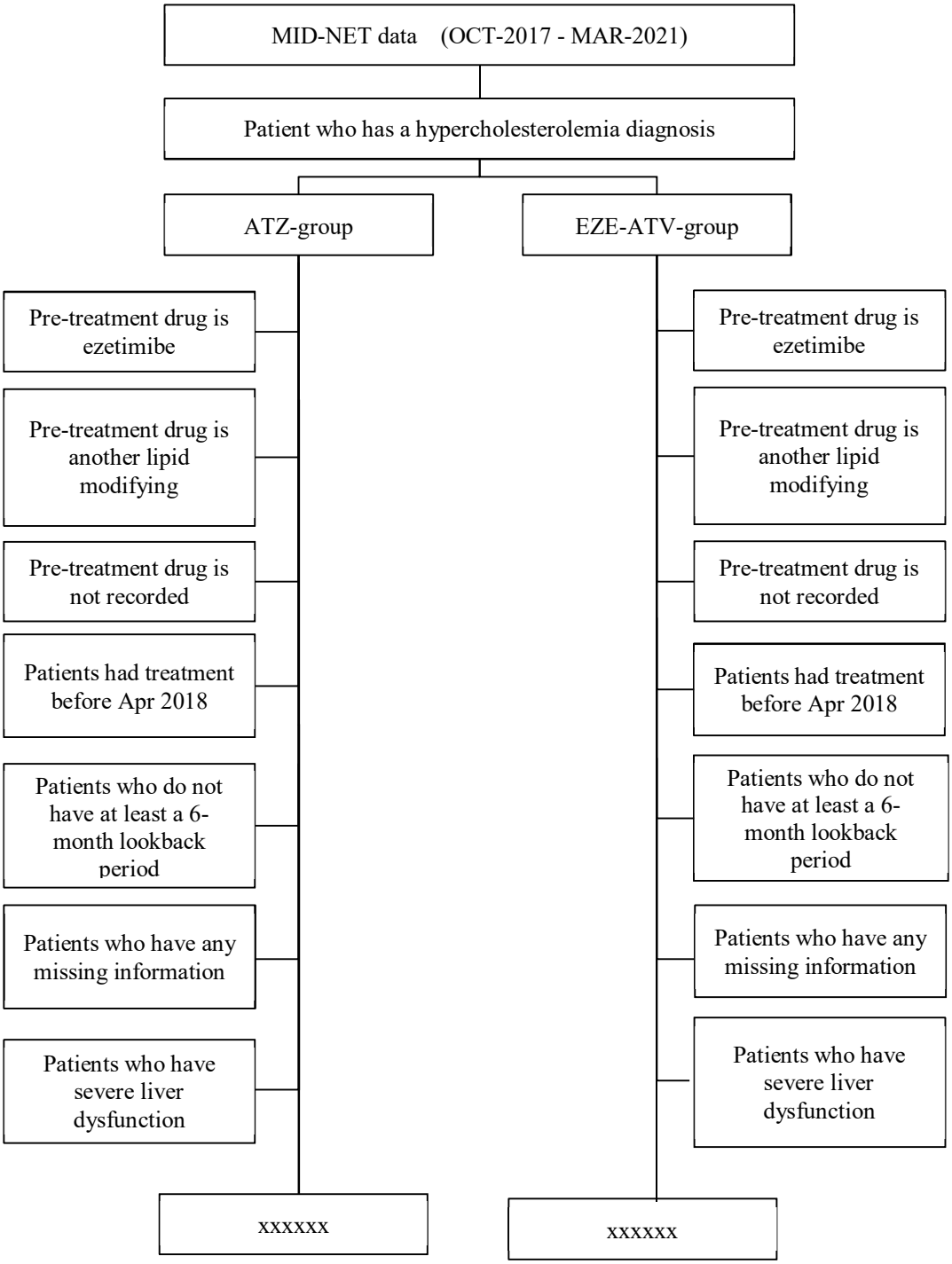
    1. Patients given ezetimibe (C10AX09) as a pre-treatment drug, OR
    2. Patients given other lipid modifying agents (C10) as a pre-treatment drug except atorvastatin (C10AX05), OR

3. Patients who were not given any pre-treatment drug, OR
4. Patients who had Ezetimibe/Atorvastatin coadministration treatment before April 2018, OR
5. Patients who do not have a 6-month lookback period prior to the index date, OR
6. Patients who have any missing information (e.g., gender, age), OR
7. Patients who have severe liver dysfunction considered as the contraindication for the use of Ezetimibe or Atorvastatin, OR
8. Patients whose CK level during the 6 months (180 days) before the index date exceeds ULN, OR
9. Patients who have any of the following diagnoses of rhabdomyolysis and myopathy (see Table 5) during the 6 months before the index date.

The exclusion criteria are based on the “Careful Administration” section of the JPC. The exclusion criteria are in accordance with the “Precautions regarding dosage and administration” section of the Japanese package insert. In this section it indicates: ”As a general rule, administration of ATOZET should be considered when ezetimibe and atorvastatin is co-administered, or if the effect is insufficient with the use of atorvastatin”.

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

Figure 2: Flow chart



PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

7.2.4 Participant Follow-up

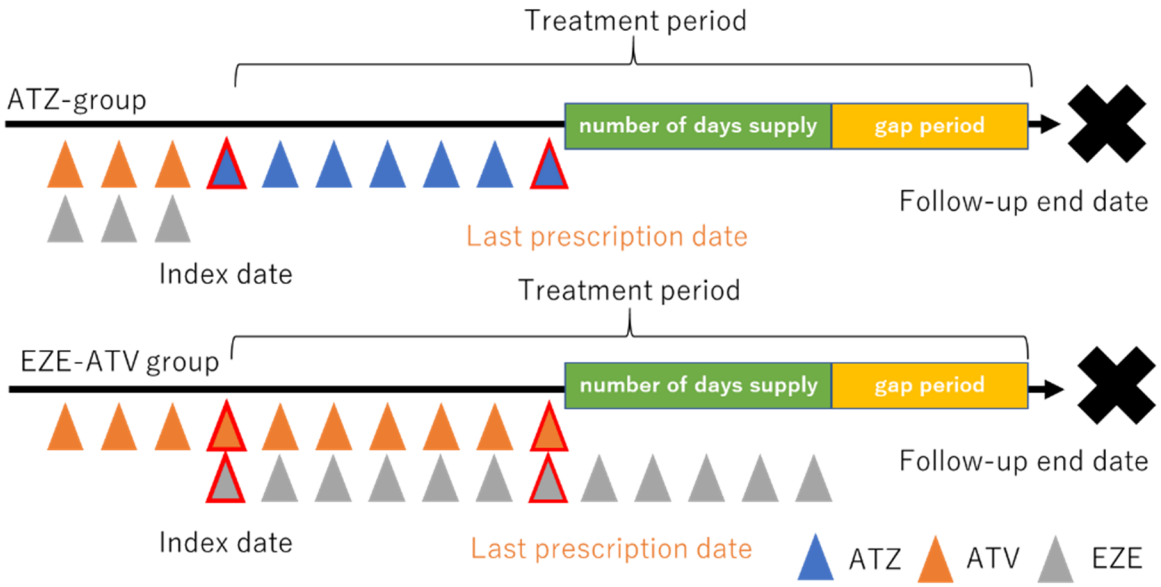
The follow-up end date will be defined as the date of loss to follow-up, the treatment period end, date of death, or the end of surveillance period, whichever comes first. Loss to follow-up means the loss of all data from SS-MIX2, Administrative claims and DPC. The date of death means recorded in SS-MIX2 as "date of death" or "death" in the hospital visit information summary or recorded in the DPC file as "death" in the discharge summary.

The treatment period for the ATZ-group is defined as from the index date to the last prescription date + number of days' supply at the last prescription + a gap period. The ATZ-group will be considered as censored when they change to coadministration of ezetimibe and atorvastatin. The treatment period for the EZE-ATV-group is defined as from the index date (start date of coadministration) to the last prescription date + number of days' supply + a gap period. EZE and ATV do not need to be on the same prescription or prescribed the same day. Coadministration was defined as the period of overlapping treatment periods for each drug. The EZE-ATV-group will be considered as censored when they stop either of ezetimibe or atorvastatin, or they change to ATOZET.

The gap period is the average number of days prescribed for the last prescription of SS-MIX2 for all patients. The gap period will be calculated after the data extraction (see section 7.2.4.1).

The index date is the first prescription date of ATOZET in patients in the exposure group. The index date for the EZE-ATV-group is defined as the start date of coadministration. The index date is defined as the date when any of following events occur: prescription order, Administrative claims order, or DPC order in the SS-MIX2 data of the MID-NET dataset

Figure 3: Participant Follow-up (example)



7.2.4.1 Longitudinality

This is a longitudinal surveillance. Factors to be considered in describing the clinical course of each patient are as follows:

- All patients must have 6 months (180 days) before the index date.
- The treatment period for the ATZ-group is defined as from the index date to the last prescription date + number of days' supply at the last prescription + a gap period. The treatment period for the EZE-ATV-group is defined as from the index-date (start date of coadministration which is based on the date when the second drug is prescribed) to the last prescription date + number of days' supply + a gap period. The EZE-ATV-group will be considered as censored when they stop either of ezetimibe or atorvastatin.

7.3 Variables

7.3.1 Exposure

The group of patients who are newly exposed to ATOZET during the selection period will be considered as the ATZ-group. The start date of the selection period coincides with the date ATOZET was placed on the market, so the index date corresponds to the new incident use of ATZ in the database. The group of patients who newly start coadministration of ezetimibe and atorvastatin during the selection period will be considered as the EZE-ATV-group. Given the limited number of patients exposed to ATOZET and EZE-ATV, the HOI analysis will not be conducted by ATOZET dose or by the dose of the ATV component for the EZE-ATV group. Dose will be analyzed descriptively for the 2 treatment groups.

7.3.2 Outcomes

To describe the incidence of HOI, the outcomes targeted in this surveillance are as follows: rhabdomyolysis and myopathy (see Table 5). Lab services are counted according to SS-MIX2. MID-NET records lab services orders and the record format is JLAC10 (19). The target codes are shown in Table 4. Upper Limit of Normal (ULN) is referred to the reference range in the SS-MIX2 data, which is standardized among medical facilities. If an abnormal test value and any of diagnostic codes of rhabdomyolysis or myopathy diagnosis are recorded in the same month, the HOI is defined to occur. The day that the laboratory test is performed is defined as the day on which the HOI occurs.

Table 4: Target codes

Target	Item	JLAC10
creatine kinase	creatine kinase	3B0100000023***01

7.3.2.1 Abnormal liver blood tests and diagnoses

For primary analysis of rhabdomyolysis and myopathy, definitions are used a relevant diagnosis code plus CK >10 × ULN according to recommendation in ACC/AHA/NHLBI Clinical Advisory (12) and Grade 4 of Common Terminology Criteria for Adverse Events (CTCAE) (13).

Rhabdomyolysis:

Laboratory test value: CK > 10 × ULN,
AND
Any of the following diagnosis codes (ICD-10) for rhabdomyolysis which are shown as (R) in Table 5.

Myopathy:

Laboratory test values: CK >10 × ULN,
AND
Any of the following diagnosis codes (ICD-10) for myopathy which are shown as (M) in Table 5.

Table 5: List of rhabdomyolysis and myopathy diagnostic codes

G72 Other myopathy --- (M)
G72.0 Drug-induced myopathy --- (M)
G72.8 Other specified myopathies --- (M)
G72.9 Myopathy, unspecified ---(M)
M62.89 Other specified disorders of muscle
Rhabdomyolysis --- (R)
Drug-induced rhabdomyolysis --- (R)
M62.99 Myopathy ---(M)
Y579 Drug-induced rhabdomyolysis --- (R)
Receipt Code: 20084821 * Myopathy --- (M)

Note: Diagnosis is defined as applicable if there is a diagnosis in SS-MIX2, administrative claims, or DPC. A diagnosis in the same month is allowed along with the claims and DPC. (R) is diagnosis codes for rhabdomyolysis, and (M) is diagnosis codes for myopathy.

Reasons for setting:

For the definition of the incidence of rhabdomyolysis and myopathy, the target values in both patterns defined above are as follows. The target values defined in the primary

analysis were recommended in ACC/AHA/NHLBI Clinical Advisory (12) for rhabdomyolysis and Grade 4 of CTCAE (13) for myopathy. The diagnosis codes for the primary analysis are also set according to a preceding study which assessed the incidence of HMG-CoA reductase inhibitor-associated myopathy in a database (17). The abnormal test values and diagnosis are essential, and SS-MIX2 can capture all diagnostic and recorded events.

- Sensitivity analysis

For the sensitivity analysis, the definition of the incidence of rhabdomyolysis and myopathy are set as following 4 patterns. The target values defined in the sensitivity analysis used Grade 3 of CTCAE.

Sensitivity analysis 1:

Rhabdomyolysis:

Laboratory test value: CK > 5 × ULN,
AND
Any of the following diagnosis codes (ICD-10) for rhabdomyolysis which are shown as (R) in Table 5.

Myopathy:

Laboratory test value: CK > 5 × ULN,
AND
Any of the following diagnosis codes (ICD-10) for myopathy which are shown as (M) in Table 5.

Sensitivity analysis 2:

Laboratory test value: CK > 10 × ULN

Sensitivity analysis 3:

Laboratory test value: CK > 5 × ULN

Sensitivity analysis 4:

For rhabdomyolysis:
Any of the diagnosis codes (ICD-10) for rhabdomyolysis which are shown as (R) in Table 5

For myopathy:
Any of the diagnosis codes (ICD-10) for myopathy which are shown as (M) in Table 5

7.3.3 Covariates (Demographics & Clinical Characteristics)

7.3.3.1 Gender / Age

The gender and age will be determined as of the index date.

7.3.3.2 Comorbidities

The comorbidities used in this surveillance will be “Ischemic heart disease, Myocardial infarction”, “Congestive heart failure”, “Peripheral vascular disease”, “Cerebrovascular disease”, “Mild liver disease”, “Hypertension”, “Diabetes (mild to moderate)”, “Diabetes with chronic complications”, “Renal disease”, and “Moderate or severe liver disease”.

The comorbidities were defined according to the Charlson Comorbidity Index (CCI) (18). The CCI score will not be calculated.

The comorbidities refer to medical records in the lookback period (including the index date). The granularity of the Administrative claims data is on a monthly basis, so there may be discrepancies with the actual date of diagnosis.

Table 6: Target codes

Comorbidities	Definition
Ischemic heart disease, Myocardial infarction	I20.x, I21.x, I22.x, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	G45.x, G46.x: H34.0, I60.x-I69.x
Mild liver disease	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73x, K74x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Hypertension	I10.x, I15.x
Diabetes (mild to moderate)	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complications	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5,

	E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7

The diagnostic definition is recorded in SS-MIX2, Administrative claims, or DPC.

7.3.3.3 Pre-treatment drugs

Pre-treatment drugs associated with Hypercholesterolemia are shown in Table 7. Each drug is defined by an ATC code and further converted into specific corresponding codes according to the files, SS-MIX2 or Administrative claims, used for analysis.

Table 7: Pre-treatment drugs

Covariates	Definition
HMG CoA* reductase inhibitors	C10AA
Fibrates	C10AB
Bile acid sequestrants	C10AC
Nicotinic acid and derivatives	C10AD
Other lipid modifying agents (excluding ezetimibe)	C10AX

*HMG CoA: hydroxymethylglutaryl-CoA

The pre-treatment definition is recorded in SS-MIX2, Administrative claims, or DPC.

7.4 Data Sources

Establishment of the MID-NET medical data platform provided a reliable and valuable resource for drug safety assessments in Japan. This platform is designed and developed by the Ministry of Health, Labour and Welfare and includes the prescription drugs from the Medical Devices Agency as well as 23 hospitals from 10 healthcare organizations across Japan. MID-NET is a distributed and closed platform system that connects all collaborative organizations through a central data center. MID-NET has three types of datasets: SS-MIX2 data such as electronic medical records, administrative claims data, and DPC data. Several coding standards are used to standardize the data stored in MID-NET to allow the integration of information originating from different hospitals. A rigorous and consistent quality management system was implemented to ensure that MID-NET data are of high quality and meet Good Post-marketing Study Practices (GPSP). A major advantage of MID-NET is that approximately 260 standardized clinical laboratory test values are available for analysis.

7.4.1 Surveillance Procedures (specific requirement for PMDA)

7.4.1.1 Forecasted schedule

Date	Activity
27-SEP-2017	ATOZET Approval date
23-APR-2018	ATOZET Launch date
26-JUN-2019	MID-NET utilization approval and contract
JAN-2021	Epidemiological consultation by PMDA
APR-2021	MID-NET data analysis
JUL-2021	Finalization of research results
DEC-2021	Submission of research results

7.4.1.2 Schedule and rationale for the progress of the surveillance and the milestones for evaluating the obtained results or reporting to PMDA

If necessary, consider further activities and measures based on the results of this surveillance.

7.4.1.3 Additional measures that may be implemented based on the results of the drug safety monitoring activities and criteria for starting them

If necessary, consider further activities and measures based on the results of this surveillance.

7.4.1.4 Responsible person

Title	Department	Name
PPD	Pharmacovigilance	PPD

7.4.1.5 Organizational structure

The organization is shown in Appendix D.

7.4.1.6 Supplier's name, address and business scope

Database vendor: Pharmaceuticals and Medical Devices Agency (PMDA)

Address: Shin-Kasumigaseki Building, 3-3-2 Kasumigaseki Chiyoda-ku, Tokyo

Business scope: dataset creation from the 23 collaborating hospitals.

Data analysis

Supplier: IQVIA Solutions Japan K.K.

Address: Keikyu 7th Building, 4-10-8 Takanawa, Minato-ku, Tokyo

Business scope: Dataset analysis

7.4.1.7 Record keeping

Appropriate documents shall be saved in accordance with the MSD GPSP SOP and various guidance related to MID-NET.

7.5 Surveillance Size

From preliminary assessment of MID-NET data (data period from JUL-2017 to JUN-2019), there were 843 patients treated with ATOZET.

From the open data of MID-NET in 2019, the number of patients treated with ezetimibe was 1,038 and those treated with atorvastatin was 26,660. The number of patients treated with coadministration of ezetimibe and atorvastatin was unknown. While the number of patients treated with ATOZET will be greater over the entire surveillance period, the number who will be included in the ATOZET treatment group will be reduced when applying the inclusion /exclusion criteria (which require a diagnosis of hypercholesterolemia and specific prior therapies) and requiring sufficient lookback and follow-up periods. In this situation, the number of patients treated with ATOZET is not expected to reach these sample sizes, but the power of the comparisons based on various sample sizes is shown as follows.

The incidences in the domestic phase 3 trial are as follows:

Rhabdomyolysis: 0 cases (0.0%)

Myopathy: 0 cases (0.0%)

Elevation of CK >3 times the ULN: 11 cases (0.4%)

If IRR was 2 (IR in the ATZ group of 0.01 and IR in the EZE-ATZ group of 0.005), with similar numbers of ATZ and EZE/ATV patients, the 95% CI and Power are shown in Table 8. This shows that with 1000 – 3,500 patients per group, the power ranges from 0.29 – 0.76 and the confidence intervals are quite wide (especially for the lower numbers of patients that are likely to be observed) and if there are 2,000 or fewer patients per group, the CI would

include 1. Therefore, it is likely that the results of the assessment of IRR will be inconclusive.

Table 8: Calculate 95% confidence intervals (95% CI) for IRR and Power of Poisson regression analysis

ATZ-group	1,000	1,500	2,000	2,500	3,000	3,500
EZE/ATV-group	1,000	1,500	2,000	2,500	3,000	3,500
95% CI	0.68-5.85	0.83-4.81	0.94-4.27	1.01-3.94	1.08-3.72	1.13-3.55
Power	0.29	0.41	0.52	0.61	0.69	0.76

For these calculations, the expected incidence risk of the outcome in ATZ-group is 0.01. The expected incidence risk of the outcome in EZE-ATV-group is 0.005. IRR=2, Alpha= 0.05.

7.6 Data Management

This surveillance will utilize post-marketing database studies that must comply with the quality standards stipulated in the ministerial ordinance for good post-marketing study practices (GPSP) and their related guidelines (19).

Data management for this surveillance will be conducted using standard MID-NET processes. The processes will take into consideration any data governance imposed on the data source. MSD and IQVIA will adhere to all local and regional laws on data protection and privacy.

Data management and analyses will be performed using SAS 9.04.01.M3 or R 4.0.2.

7.7 Data Analysis

7.7.1 Patient characteristics

Basic statistics on the surveillance populations will be presented as n (%), mean ± SD, or median (interquartile range [IQR]), as appropriate.

- To facilitate interpretation of the surveillance results regarding incidence of HOI, it is important to understand whether the two treatment groups are comparable. Therefore, the following descriptive analyses will be done to characterize the ATZ and EZE/ATV groups: Demographic and clinical characteristics and patterns of utilization of ATZ and EZE/ATV (e.g., dose, year of entry into cohort, duration of follow-up period, duration of treatment, number of patients censored for various reasons).

7.7.2 Primary Objective

To compare the incidence of HOI, the incidence rates of HOI events will be calculated as the number of events per 1,000 person-years for ATZ-group and for EZE-ATV-group. For all patients, the exposure time starts at the initiation of treatment of each patient. Patients with a prior history of the HOI during the lookback period will be excluded from these analyses. The IRR will be calculated if more than 1 outcome is observed in both ATZ-group and EZE-ATV groups. IRR will also be calculated using Poisson regression analysis to compare the incidence of HOI between ATZ-group and EZE-ATV-group after adjusting for covariates that differ between ATZ group and EZE-ATV group. Covariates will include age, since this variable is often associated with risk of AEs, and may include sex and individual comorbidities ("Ischemic heart disease, Myocardial infarction", "Congestive heart failure", "Peripheral vascular disease", "Cerebrovascular disease", "Mild liver disease", "Hypertension", "Diabetes (mild to moderate)", "Diabetes with chronic complications", "Renal disease", and "Moderate or severe liver disease") if there are differences in the distributions of these variables between treatment groups. Because of the low number of events expected, a limited number of covariates will be included.

7.7.3 Subgroup analysis

To characterize missing information in the RMP about the patients with hepatic impairment in the RMP, additional subgroup analyses will be conducted by dividing the patients into two subgroups according to their AST and ALT levels. Patients whose ALT or AST levels exceed twice the ULN level during the lookback period will be included in the hepatic impairment subgroup. Patients whose ALT or AST levels do not exceed twice the ULN level will be included in the non-hepatic impairment subgroup. Patients without AST or ALT value during the lookback period will be excluded. Other inclusion criteria and exclusion criteria for the ATZ-group and EZE-ATV-group in the subgroup analysis are the same as those in the primary analysis. The IRR and 95% confidence interval for the HOI (rhabdomyolysis and myopathy) will be calculated also in the subgroup analysis if more than 1 outcome is observed in both ATZ-group and EZE-ATV-groups of the subgroups. The same analytical procedures will be performed for the subgroup analysis as are performed for primary analysis. The analysis method will be the same as 7.7.2.

Table 9: Possible Contraindications to Treatment with ATZ (to be excluded from subgroup analysis)

B15 Acute hepatitis A
B16 Acute hepatitis B
B17 Other acute viral hepatitis
K712 Toxic liver disease with acute hepatitis
K720 Acute and subacute hepatic failure

K703 Alcoholic cirrhosis of liver
K717 Toxic liver disease with fibrosis and cirrhosis of liver
K743 Primary biliary cirrhosis
K744 Secondary biliary cirrhosis
K745 Biliary cirrhosis, unspecified
K746 Other and unspecified cirrhosis of live
C22 Malignant neoplasm of liver and intrahepatic bile ducts
C787 Secondary malignant neoplasm of liver and intrahepatic bile duct
R17 Hyperbilirubinaemia, with or without jaundice, not elsewhere classified

7.7.4 Sensitivity analysis

The sensitivity analysis is evaluated by alternative outcome definitions which are described in section 7.3.2.1. The analyses for the alternative outcome definitions will follow the methods for the primary outcome above.

The sensitivity analysis will also be performed limiting ATZ-group to the subjects who are switched from Atorvastatin monotherapy, not including patients switched from coadministration of Atorvastatin and Ezetimibe. The same analytical procedures will be performed for the sensitivity analysis as are performed for primary analysis.

7.8 Quality Control

By signing this protocol, all parties agree to follow applicable standard operating procedures (SOPs). All parties also agree to ensure all existing and new surveillance personnel are appropriately trained to ensure the surveillance is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the surveillance and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the surveillance are completed in accordance with the protocol, quality standards (e.g., GPP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the surveillance, it must be escalated to the Sponsor immediately. An SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or surveillance participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

This surveillance will utilize post-marketing database studies that must comply with the quality standards stipulated in the ministerial ordinance for good post-marketing study practices (GPSP) and their related guidelines (19).

7.9 Limitations of the research methods

Overall

The number of patients treated with ATOZET or coadministration of ezetimibe and atorvastatin are likely to be very small because of low use of these medications, even before applying the inclusion and exclusion criteria (which requires a hypercholesterolemia diagnosis and specific prior therapies). In addition, the treatment period for these cohorts will be relatively short. Given very small numbers (patients / patient years), a high-risk population, previous treatment with other lipid-lowering drugs that could be associated with HOI that are diagnosed at a later time, and many concomitant medications that can also be associated with the HOI, it is possible that rates may be higher than observed in clinical trials or that there will appear to be imbalances between the two cohorts (who are actually taking bioequivalent medications), etc. Therefore, assessment of IRR is likely to be inconclusive and care must be taken in interpretation of the data and generalizability of the surveillance results. The sensitivity analysis which further restricts the population is even more likely to be inconclusive. More details on the specific limitations which may affect the surveillance results and their interpretation are described below.

MID-NET contains data mostly from secondary care hospitals. Hence, data from primary care settings is limited, which may cause selection biases and limit generalizability of the results to the general hypercholesterolemic population.

Another major limitation of MID-NET is that patients cannot be followed up if they receive care at other healthcare facilities that do not contribute to MID-NET due to lack of patient-level data linkages among hospitals. Event incidences (e.g., diagnoses, laboratory tests, death, etc.) that occur outside the 23 hospitals are not captured in MID-NET, even during the follow-up period.

The frequency of some laboratory tests may be low and/or the proportion of abnormal values may be overestimated because normal routine lab tests from the community are not captured.

Representativeness – MID-NET in this activity comprises only 23 hospitals. When the 23 hospitals have specific clinical practices or include specific patients, e.g. more secondary prevention patients, the surveillance population or the results may not represent the general hypercholesterolemic patient population or practices in Japan. MID-NET is made up of major hospital groups (Kitasato University, NTT Hospital and Tokushukai Hospital) and university hospitals. The patients prescribed ATOZET per the label may not be representative of all patients who take ATOZET (e.g., we know that some patients will not have a hypercholesterolemia diagnosis or may switch from a drug where switching is not specified in the JPC.

Validity of outcome definitions – there is not a consensus on the best algorithms for defining the HOI overall or specifically in Japanese databases. The algorithms that do exist may not have optimal sensitivity, specificity, and positive predictive value. The definitions of the HOI (laboratory values, occurrence of events such as rhabdomyolysis, etc.) has not previously been validated to be appropriate for assessing the impact of medications, particularly in a database. Because there is no access to medical records, it will not be possible to do any validation of the definitions used in this study.

Selection bias - Some patients would use ezetimibe and atorvastatin coadministration rather than ATOZET because using generic ezetimibe and atorvastatin is less expensive than ATOZET. Selection bias may occur if patients with multiple comorbidities and poly-pharmacy use ATOZET to reduce the total number of medication tablets resulting in the ATOZET population having higher risk of the HOI. Therefore, this selection bias may increase IR for ATOZET relative to coadministration.

The surveillance does not provide an analysis adjusted by risk factors for the HOI. Age, some comorbidities, some prior/concomitant drugs, etc. could affect risk of HOI which is why that we will examine demographic and clinical characteristics of the 2 groups as well as characteristics of drug utilization (e.g., duration of treatment, duration of follow-up, reasons for censoring). If there are differences in compliance / censoring, this could also affect the rates of HOI and limit interpretation of the results. Because of expected small numbers, there are no plans to do any kind of analyses with adjustment / matching. Therefore, a nominal elevation of IRR may be seen due to imbalance of these factors, which needs to be taken into account in interpretation of the results and potentially limits generalizability.

This surveillance will be conducted through secondary use of medical data so not all covariates of interest are measured.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent

MID-NET is operated and managed under the Act on Pharmaceuticals and Medical Devices Agency, Independent Administrative Agency (Act No. 192, 2002), and is exempt from requirements to obtain informed consent from patients in accordance with the Act on the Protection of Personal Information (Act No. 57, 2003), and the PMDA discloses information on the utilization of MID-NET data and provides opportunities for patients to deny the provision of their hospital data to MID-NET.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

ADVERSE EVENT AND PRODUCT QUALITY COMPLIANT REPORTING

This is a non-interventional database surveillance based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. No reporting of individual adverse events or product quality complaints to regulatory agencies is planned for this database surveillance because there is no access to individual patient/subject records, and it is not possible to assess the causality of individual cases. surveillance-specific health outcomes of interest, including any that qualify as adverse events, will be summarized as part of any interim analysis (including safety analysis, if required) and in the final surveillance report, which will be provided to regulatory agencies by the sponsor as required.

Any relevant safety information will be summarized and the Sponsor will include in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

If an investigator elects to spontaneously report any suspected adverse reactions or product quality complaints, they should be reported via fax to Local DPOC PPD (Japan) in English using an AE and PQC report form (see section 13 for form) for reporting to worldwide regulatory agencies as appropriate.

10 PLANS FOR DISSEMINATING AND COMMUNICATING SURVEILLANCE RESULTS

The Risk Management Subteam (RMST) Lead/Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final surveillance report or any interim report. The safety and conclusion sections of the final surveillance report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

The results of the surveillance will be published by the PMDA as the results of the re-examination. The number of the patients and their % will be redacted if there are less than 5 cases according to the MID-NET publication rules.

11 REFERENCES

1. Kolovou GD, Anagnostopoulou KK, Cokkinos DV. Pathophysiology of dyslipidaemia in the metabolic syndrome. Postgrad Med J. 2005;81(956):358-66.
2. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. 2018:GL2017.
3. Mori K. Ministry of Health, Summary of Patient Survey, 2017 Tokyo: Ministry of Health, Labor and Welfare; 2019 [Available from: . https://www.mhlw.go.jp/toukei/saikin/hw/kanja/17/index.html..
4. Stone NJ, Robinson JG, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014;63(25 Part B):2889-934.
5. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. 2016;37(39):2999-3058.
6. Japan Atherosclerosis Society: Treatment Guide for Hyperlipidemia 2013 Q&A.
7. ATOZET Combination Tablets LD/HD Japanese Package Circular (MAR-2019)
8. Newman CB, Preiss D, Tobert JA, et al. Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association [published correction appears in Arterioscler Thromb Vasc Biol. 2019;39(2):e38-e81.
9. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial [published correction appears in Lancet. 2011 Jan 8;377(9760):126]. Lancet. 2010;376(9753):1658-1669.
10. Kashani A, Sallam T, Bheemreddy S, Mann DL, Wang Y, Foody JM. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. Am J Cardiol. 2008;101(11):1606-1613.
11. ATOZET Combination Tablets LD/HD Risk Management Plan
12. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins Circulation. 2002;106:1024
13. Common Terminology Criteria for Adverse Events (CTCAE) v5-JCOG_2017Nov27
14. LIPTOR Tablets 5mg/10fm Re-examination report
15. Yamaguchi M, Inomata S, Harada S, Matsuzaki Y, Kawaguchi M, Ujibe M, et al. Establishment of the MID-NET((R)) medical information database etwork as a reliable and valuable database for drug safety assessments in Japan. Pharmacoepidemiol Drug Saf. 2019;28(10):1395-404.
16. 日本臨床検査医学会 臨床検査項目分類コード第 10 回版 (JLAC10) 1999. 2001;21(1):97-104. https://www.jslm.org/committees/code/.
17. Ihle P, Dippel FW, Schubert I. Statin-associated myopathy. Assessment of frequency based on data of all statutory health insurance funds in Germany. Pharmacol Res Perspect. 2018 May 10;6(3):e00404.

18. Charlson ME, Pompei P, Ales KL, MacKenzie CRJJocd. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40(5):373-83.
19. Pharmaceutical Safety and Environmental Health Bureau, Notification No. 221-1 from Director of Pharmaceutical Evaluation Division, 2018: Points to consider for ensuring data reliability on post-marketing database study of a drug. 2018. https://www.pmda.go.jp/files/000223003.pdf

Annex 1 List of Stand-Alone Documents

No.	Document Reference No.	Date	Title
1.	<No>	<Date>	<Text>
2.	<No>	<Date>	<Text>
N	<No>	<Date>	<text>

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

ANNEX 2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 4)

Adopted by the ENCePP Steering Group on 15 OCT 2018

ANNEX 3 ADMINISTRATIVE AND REGULATORY DETAILS

Confidentiality:

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this surveillance will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative) or Regulatory Agency representatives may consult and/or copy surveillance documents in order to verify worksheet/case report form data.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this surveillance in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. By signing this protocol, the investigator expressly consents to these uses and disclosures. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. The investigator is hereby notified that the collection, processing and sharing of their personal data with respect to adverse event reports to the Sponsor and regulatory agencies occurs on

the basis of performance of a legal obligation, and the investigator expressly consents to these uses and disclosures when reporting such events to other investigators.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

Administrative:

Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the surveillance in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the surveillance.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of surveillance-related documents and procedures and provide for direct access to all surveillance-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the surveillance reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate surveillance documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject

participating in the surveillance, provide all data, and, upon completion or termination of the surveillance, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Surveillance documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the surveillance documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the surveillance in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the surveillance for 5 years after final report or first publication of surveillance results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All surveillance documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding surveillance and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this surveillance.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the surveillance is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center surveillance (including multinational). When more than one surveillance site is open in an EU country, MSD, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center surveillance, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the surveillance report that summarizes the surveillance results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the surveillance in the surveillance's final report. The Sponsor may consider one or more factors in the

selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of surveillance methods, appropriate enrollment of subject cohort, timely achievement of surveillance milestones). The Protocol CI must be a participating surveillance investigator.

Compliance with Surveillance Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the surveillance is solely responsible for determining whether the surveillance and its results are subject to the requirements for submission to the Clinical Trials Data Bank, such as ENCePP. MSD, as Sponsor of this surveillance, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate surveillance locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this surveillance or its results to the Clinical Trials Data Bank.

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT 0854 VERSION 2.0
REV OPS #: NIS009100	CORE DRC APPROVAL DATE: 31-MAR-2021

ANNEX 5 QUALIFIED PERSON FOR PHARMACOVIGILANCE (QPPV)

PPD
EU Qualified Person for Pharmacovigilance
Tel: PPD ; GSM: PPD
Fax: PPD
Email: PPD

MERCK SHARP & DOHME

Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
Telephone PPD

Deputy QPPVs:
PPD

Emergency/Out of Hours: GSM numbers above or via PPD

Dear Sir/Madam

Re: EU QPPV Signature Page for PASS

INN:
Product:
Protocol No.:
Epidemiology No.:
Protocol Date:
MAH:

In line with the Guidelines on Good Pharmacovigilance Practice (GVP), Module VIII – Post-Authorisation Safety Studies (PASS) and according to MSD internal SOPs, this surveillance has been reviewed and approved by the European Qualified Person for Pharmacovigilance.

Yours faithfully

PPD
,
EU Qualified Person for Pharmacovigilance

12 APPENDICES

Appendix A: Code list of drug for setting extraction and setting output

Appendix B: Code list of disease for setting extraction and setting output

Appendix C: Set-code list for setting output condition

Appendix D: Organization to conduct the surveillance (specific material for PMDA)

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT VERSION NO.: 854
VEAP ID NO: 9100	CORE DRC APPROVAL DATE: 31-MAR-2021

13 ATTACHMENTS

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT VERSION NO.: 854
VEAP ID NO: 9100	CORE DRC APPROVAL DATE: 31-MAR-2021

Attachment 1 **Table layout sample**

1-1 Baseline Characteristic

		ATZ		EZE-ATV	
		No.	%	No.	%
Number of subjects					
Sex	Male				
	Female				
Age	mean				
	SD				
	<20				
	20-29				
	30-39				
	40-49				
	50-59				
	60-69				
	70-79				
	80-89				
	90-99				
	≧100				
Comorbidities					
Ischemic heart disease, Myocardial infarction					
Congestive heart failure					
Peripheral vascular disease					
Cerebrovascular disease					
Mild liver disease					
Hypertension					
Diabetes (mild to moderate)					
Diabetes with chronic complications					
Renal disease					
Moderate or severe liver disease					
Concomitant drugs					
HMG CoA reductase inhibitors					
Fibrates					
Bile acid sequestrants					
Nicotinic acid and derivatives					
Other lipid modifying agents					

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT VERSION NO.: 854
VEAP ID NO: 9100	CORE DRC APPROVAL DATE: 31-MAR-2021

1-2 : Prescription status of drugs

	ATZ		EZE-ATV	
	No.	%	No.	%
Pre-Index				
Telaprevir				
Ombitasvir・Paritaprevir・Ritonavir				
Glecaprevir・Pibrentasvir				
Post-Index				
Telaprevir				
Ombitasvir・Paritaprevir・Ritonavir				
Glecaprevir・Pibrentasvir				
ATOZET Combination Tablets LD				
ATOZET Combination Tablets HD				
Atorvastatin 10				
Atorvastatin 20				

1-3 follow-up period

	ATZ		EZE-ATV	
	Mean	SD	Mean	SD
Follow-up period				

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT VERSION NO.: 854
VEAP ID NO: 9100	CORE DRC APPROVAL DATE: 31-MAR-2021

1-4 Incidence for rhabdomyolysis

1) Primary Analysis

	ATZ				EZE-ATV				IRR*** (crude)	IRR*** (adjusted)
	N (pop)	PY*	n (eve)	IR**	N (pop)	PY*	n (eve)	IR**		
Adjustment only for covariates different between 2 groups										

note: *person-year **incidence rate *** incidence rate ratio

2) Subgroup Analysis

Adjustment only for covariates different between 2 groups

	ATZ				EZE-ATV				IRR*** (crude)	IRR*** (adjusted)
	N (pop)	PY*	n (eve)	IR**	N (pop)	PY*	n (eve)	IR**		
Hepatic impairment group										
Hon-hepatic impairment group										

note: *person-year **incidence rate *** incidence rate ratio

3) Sensitivity Analysis

Adjustment only for covariates different between 2 groups

	ATZ				EZE-ATV				IRR*** (crude)	IRR*** (adjusted)
	N (pop)	PY*	n (eve)	IR**	N (pop)	PY*	n (eve)	IR**		
other outcome definitions: Laboratory test value: CK > 5 × ULN, AND Any of the diagnosis codes (ICD-10) for rhabdomyolysis										
other outcome definitions: Laboratory test value: CK > 10 × ULN										

other outcome definitions: Laboratory test value: CK > 5 × ULN										
other outcome definitions: Any of the diagnosis codes (ICD-10) for rhabdomyolysis										
limiting ATZ-group to subjects who does not switch from coadministration of Ezetimibe and Atorvastatin										

note: *person-year **incidence rate *** incidence rate ratio

1-5 Incidence for myopathy

1) Primary Analysis

	ATZ				EZE-ATV				IRR*** (crude)	IRR*** (adjusted)
	N (pop)	PY*	n (eve)	IR**	N (pop)	PY*	n (eve)	IR**		
Adjustment only for covariates different between 2 groups										

note: *person-year **incidence rate *** incidence rate ratio

2) Subgroup Analysis

Adjustment only for covariates different between 2 groups

	ATZ				EZE-ATV				IRR*** (crude)	IRR*** (adjusted)
	N (pop)	PY*	n (eve)	IR**	N (pop)	PY*	n (eve)	IR**		
Hepatic impairment group										
Hon-hepatic impairment group										

note: *person-year **incidence rate *** incidence rate ratio

PRODUCT: MK-0653C	PROTOCOL/AMENDMENT VERSION NO.: 854
VEAP ID NO: 9100	CORE DRC APPROVAL DATE: 31-MAR-2021

3)Sensitivity Analysis

Adjustment only for covariates different between 2 groups

	ATZ				EZE-ATV				IRR*** (crude)	IRR*** (adjusted)
	N (pop)	PY*	n (eve)	IR**	N (pop)	PY*	n (eve)	IR**		
other outcome definitions: Laboratory test value: CK > 5 × ULN, AND Any of the diagnosis codes (ICD-10) for myopathy										
other outcome definitions: Laboratory test value: CK > 10 × ULN										
other outcome definitions: Laboratory test value: CK > 5 × ULN										
other outcome definitions: Any of the diagnosis codes (ICD-10) for myopathy										
limiting ATZ-group to subjects who does not switch from coadministration of Ezetimibe and Atorvastatin										

note: *person-year **incidence rate *** incidence rate ratio