A POST-MARKETING DATABASE SURVEILLANCE TO INVESTIGATE THE RISK OF HEPATIC EVENTS IN HYPERCHOLESTEROLEMIC PATIENTS TREATED WITH ATOZET OR EZETIMIBE ATORVASTATIN COADMINISTRATION IN JAPAN

PASS INFORMATION

Title	A Post-marketing Database Surveillance to Investigate the Risk of Hepatic Events in Hypercholesterolemic Patients Treated with ATOZET or Ezetimibe Atorvastatin coadministration in Japan
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Medicinal product(s)	ATOZET® Combination Tablets LD/HD, ezetimibe / atorvastatin calcium
Product reference	N.A.
Procedure number	N.A.
Marketing authorisation holder(s) (MAH)	Organon K.K.
Joint PASS	No
Research question and objectives	Research question To investigate hepatic 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 hepatic HOI between those taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin. Abnormal liver function includes incidences of hepatic diagnoses (e.g., hepatitis, liver inflammation, jaundice), and the elevations of ALT and AST. Secondary objectives: - To describe the incidence rates of hepatic HOI for patients with and without hepatic impairment among those treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin. - To describe compliance with liver blood tests after administration of ATOZET or 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.
Country(-ies) of surveillance	Japan

EU PAS Register：The European Union electronic Register of Post-Authorisation Studies、HD：高用量、
HOI: Health Outcome of Interest; LD: Low dose; PASS: Post-Authorisation Safety Study

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Organon K.K. WeWork Nogizaka, 1-24-3, Minamiaoyama, Minato-ku, Tokyo 107-0062

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1 ABSTRACT

Title

A Post-marketing Database Surveillance to Investigate the Risk of Hepatic Events in Hypercholesterolemic Patients Treated with ATOZET or Ezetimibe Atorvastatin coadministration in Japan

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 limited. Hepatic events are known to be associated with lipid lowering therapies, 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 surveillance1 as a regulatory requirement to characterize the hepatic risks 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

Important identified risks:

- Hepatic function abnormal, liver inflammation, hepatitis, jaundice

Important missing information:

- Patients with hepatic impairment

Research Question(s) & Objective(s)

Research Question:

To investigate hepatic 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 hepatic HOI between those taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin. Abnormal liver function includes incidences of hepatic diagnoses (e.g., hepatitis, liver inflammation, jaundice), and the elevations of ALT and AST.

Secondary objectives:

- To describe the incidence rates of hepatic HOI for patients with and without hepatic impairment among those treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin.
- To describe compliance with liver blood tests after administration of ATOZET or 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.

Setting

Data Period is from OCT-2017 to MAR-2021 in order to gain 6 months of lookback period for all included patients.

Surveillance subjects and size, including dropouts

Subjects:

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).

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.

Variables and Data sources

Variables:

Outcomes:

For primary objective and secondary objective:

AST, ALT: A number of patients with test value as follow.

- AST > 3 × upper limit of normal（ULN）
- ALT > 3 × ULN

AND Diagnosis code (ICD-10) of hepatic health outcome of interest (hepatitis, fulminant hepatitis, jaundice) among those who do not have prior history of the HOI.

For secondary objective for compliance with liver blood tests:

Proportion of patients for whom AST and ALT laboratory tests were performed per the JPC recommendations.

Covariates:

Sex, age, comorbidities

Data source

Medical Information Database Network (MID-NET)

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).

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 EZEATV-group after adjusting for covariates.

The proportion of patients who have a lab test will be calculated for compliance with laboratory test utilization: 1) baseline, 2) all follow up, 3) every 3 months. To check the number of lab tests per patient per month (per-patient-per-month: PPPM), the total number of lab tests per patient will be divided by the follow-up period (months) to calculate the mean. Basic statistics on the surveillance population will be presented as n (%), mean ± standard deviation (SD), or median (interquartile range [IQR]), as appropriate.

Results

The number of patients extracted from MID-NET who were prescribed ATOZET or coadministration of ezetimibe and atorvastatin during the selection period was 515 and 852, respectively. Among them, 45 patients were included in the ATZ group and 70 patients were included in the EZE-ATV group based on the inclusion/exclusion criteria. There were 8 patients included who were prescribed both ATOZET and coadministration of ezetimibe and atorvastatin (i.e., switched from one treatment to the other) during the selection period. Such patients were included in the ATZ group but not in the EZE-ATV group in the analyses described in sections 10.2 to 10.5. Therefore, the EZE-ATV group in the analyses consisted of 60 patients, excluding two patients for whom the follow-up period could not be confirmed.

Primary objective:

For the comparison of the IR of hepatic HOI between the patients taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin, IRR and adjusted IRR were not calculated because no hepatic HOI event occurred in either group.

Secondary objectives:

In the evaluation of the IR of hepatic HOI for patients with and without hepatic impairment among those treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin, IRR and adjusted IRR were not calculated because no hepatic HOI event occurred in either the ATZ-group or EZE-ATV-group.

In the evaluation of compliance with liver blood tests after administration of ATOZET or coadministration of ezetimibe and atorvastatin, in the analysis by 6-month period, patients with an index date within the categorized periods were included. In the analysis by the follow-up period, blood tests were conducted in more than 80% of the patients in ATZ-group for all categorized periods, except for 2018 Q1-Q2 during which there were no applicable patients. In EZE-ATV-group, blood tests were carried out in ≥ 75% of the patients for all categorized periods. The number of tests per patient per month (PPPM, mean± SD) during the follow-up period for each categorized period ranged from 0.5 ± 0.2 to 1.7 ± 2.3 in ATZ-group, except for 2018 Q1-Q2 during which there were no applicable patients, and ranged from 1.3 ± 1.2 to 3.8 ± 4.7 in EZE-ATV-group. While the number of patients in each categorized period was small in both groups, the compliance appeared to be generally favorable.

In the evaluation of the demographic and clinical characteristics of the patients treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin, 66.7% (30/45) of the patients in ATZ-group and 59.7% (37/62) of the patients in EZE-ATV-group were male. Mean age ± SD was 66.3 ± 11.8 years in ATZ-group and 63.1 ± 14.0 years in EZE-ATV-group. It was found that the male and female ratio and mean age between the groups were similar. It was also considered that the distribution of age groups and the distributions of each category of comorbidities and pre-treatment drugs were generally similar.

Discussion

In this surveillance, no hepatic HOI events occurred in a small population of patients taking ATZ or EZE-ATV. Overall, the surveillance revealed no results regarding hepatic diagnoses or laboratory tests that might affect the benefit-risk balance of ATOZET or concerns requiring safety measures.

The compliance with liver blood tests appeared to be generally favorable.

Marketing authorization holder

Organon K.K.

WeWork Nogizaka, 1-24-3, Minamiaoyama, Minato-ku, Tokyo 107-0062

*The marketing authorization holder of ATOZET® LD/HD was taken over from MSD K.K. on October 1, 2021.

Names and affiliations of principal investigators

N.A.

2 LIST OF ABBREVATIONS

Abbrevations	Representation
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical Classification System
ATV	Atorvastatin
ATZ	ATOZET
ATZ group	ATOZET Group
AUC	Area Under the Concentration-Time Curve
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CSRM	Clinical Safety Risk Manager
DPC	Diagnosis Procedure Combination
EU PAS Register	The European Union electronic Register of Post-Authorisation Studies
EZE	Ezetimibe
EZE-ATV group	Ezetimibe/Atorvastatin Coadministration Group
GPP	Good Pharmacoepidemiology Practice
GPSP ordinance	Good Post-marketing Study Practice
γ-GTP	γ-Glutamyl TransPeptidase
HD	High Dose
HMG-CoA	Hydroxymethylglutaryl-CoA
HOI	Health Outcomes of Interest
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
IQR	Inter-Quartile Range
IR	Incidence Rate
IRR	Incidence Rate Ratio
JLAC10	Japanese Laboratory Code Version 10
JMDC	JMDC Claims Database
LD	Low Dose
MDV	Medical Data Vision
MID-NET	Medical Information Database Network
PASS	Post-Authorisation Safety Study
PPPM	Per-Patient-per-Month
PY	Person-Year
Q1	First Quarter
Q2	Second Quarter
Q3	Third Quarter
Q4	Fourth Quarter
RMST	Risk Management Subteam
SD	Standard Deviation
SOP	Standard Operating Procedures
SQI	Significant Quality Issue
SS-MIX2	Standardized Structured Medical Information eXchange 2
ULN	Upper Limit of Normal
PMDA	Pharmaceuticals and Medical Devices Agency

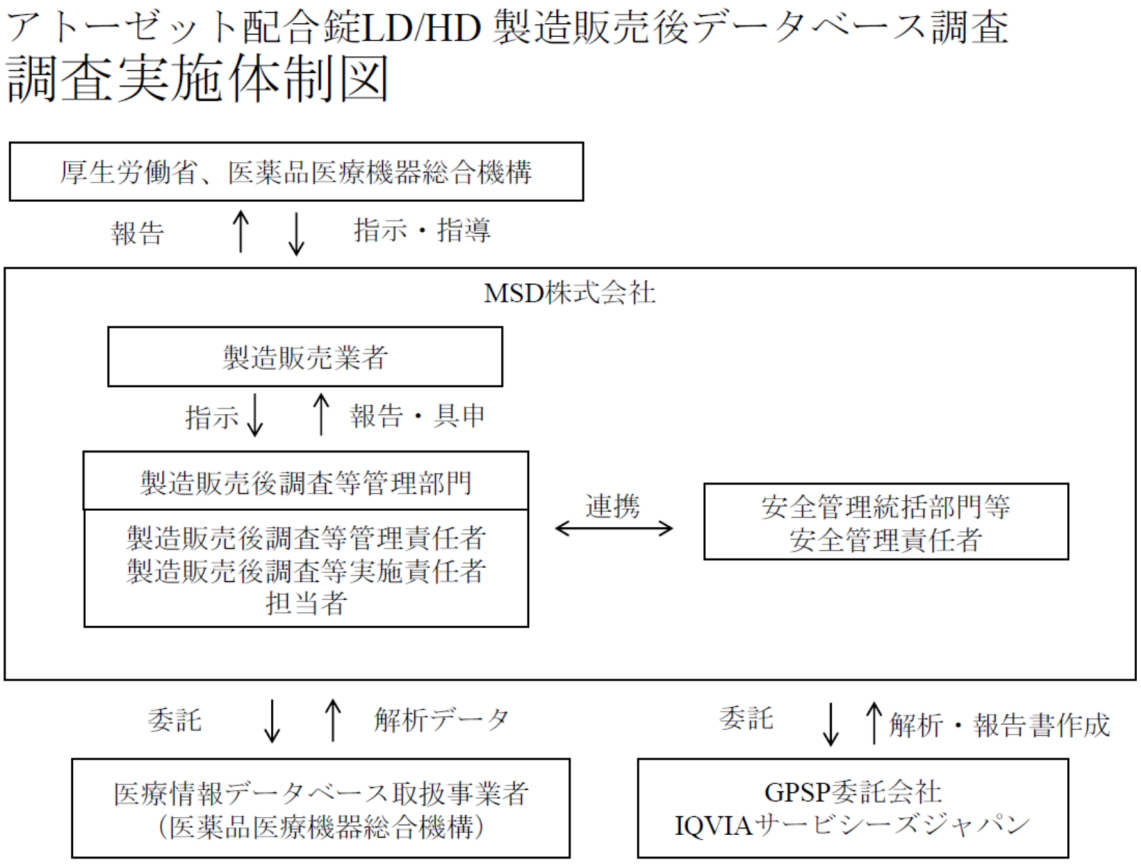
3 RESPONSIBLE PARTIES

N.A.

4 ORGANIZATION TO CONDUCT THE POST-MARKETING DATABASE SURVEILLANCE

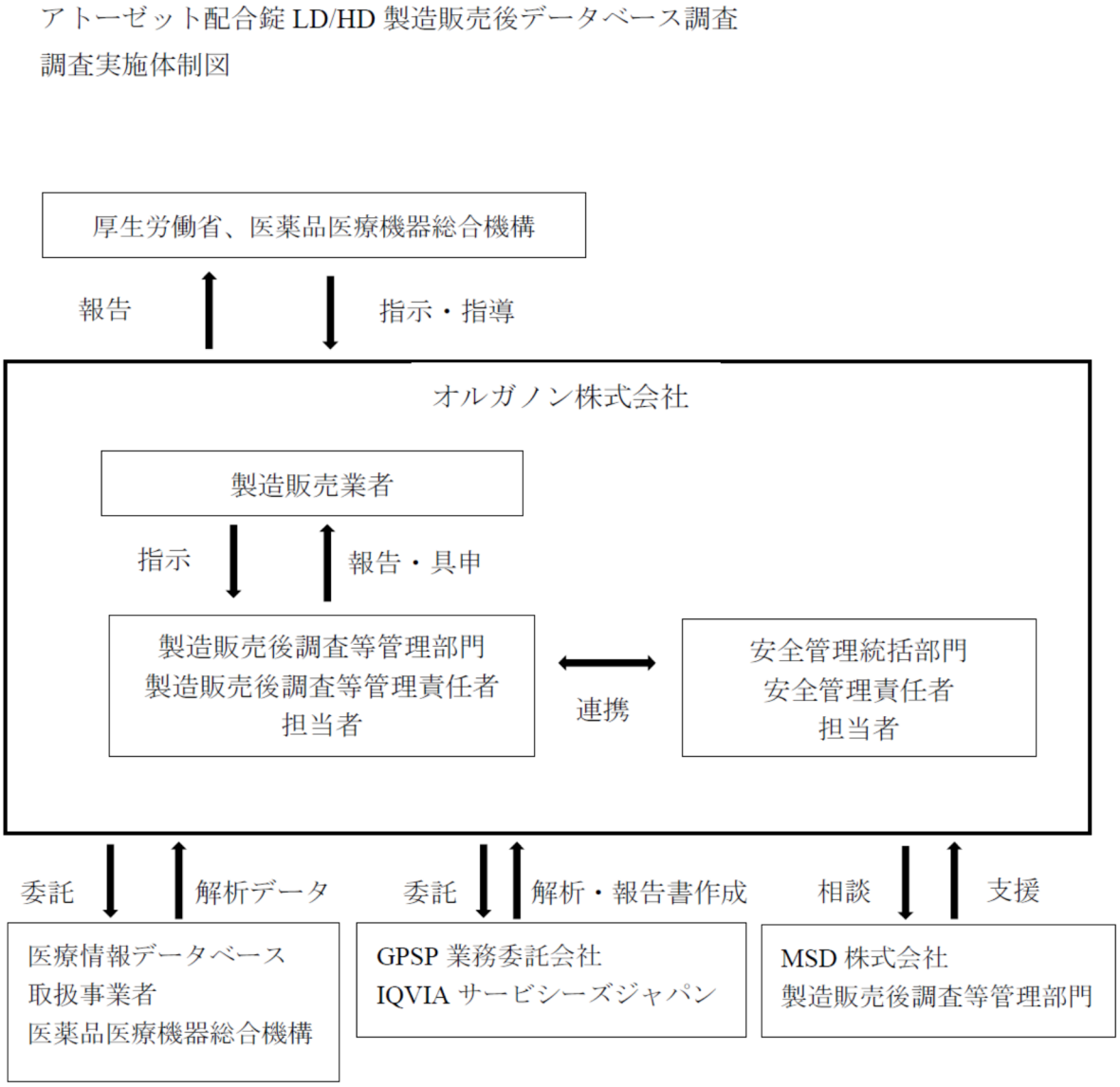
The marketing authorization holder of ATOZET® LD/HD was taken over from MSD K.K. by Organon K.K. on October 1, 2021. Thus, organization to conduct this surveillance by MSD K.K. and that by Organon K.K. are shown in Figure 4.1-1 and Figure 4.1-2, respectively.

Figure 4.1-1 Organization to conduct the post-marketing database surveillance by MSD K.K. (in Japanese)



GPSP: Good Post-marketing Study Practice; HD: High dose; LD: Low dose

Figure 4.1-2 Organization to conduct the post-marketing database surveillance by Organon K.K.



GPSP: Good Post-marketing Study Practice; HD: High dose; LD: Low dose

4.1 INFORMATION OF OUTSOURCED VENDOR AND SCOPE OF OUTSOURCE

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 1st Building, 4-10-8 Takanawa, Minato-ku, Tokyo

Business scope: Dataset analysis

4.2 OTHER RESPONSIBLE PARTIES

N.A.

5 MILESTONES

Milestone	Planned date	Actual date
Start of data collection	Apr., 2021	
End of data collection	Jun., 2021	
Registration in the EU PAS register	Jun., 2021	June, 2021
Interim report of the surveillance	N.A.	N.A.
Progress report of the surveillance	N.A.	N.A.
Reanalysis of data		Dec., 2021
Final report of the surveillance	Dec., 2021	Dec., 2021
Submission of the final report to the PMDA	Dec., 2021	Dec., 2021

EU PAS Register：The European Union electronic Register of Post-Authorisation Studies、
機構：独立行政法人医薬品医療機器総合機構

6 RATIONALE AND BACKGROUND

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 (1). 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 (1).

Hepatotoxicity and Transaminase Elevations

Serious hepatotoxicity based on specific hepatic diagnoses (e.g., fulminant hepatitis, hepatitis) is very rare with statin use. Statin-induced hepatotoxicity most commonly occurs within the first 3 to 4 months of therapy (2), but cases with prolonged latency for up to 10 years have been reported (3). There were no cases of fulminant hepatitis, hepatitis and jaundice in two Phase-3 clinical trials (the P383 study and the P384 study) of coadministration of ezetimibe and atorvastatin including 272 patients conducted in Japan (4, 5).

Rates of transaminase elevations have not been higher with ezetimibe monotherapy compared with placebo.

When used in combination with statin, the rates of transaminase elevations have been slightly elevated. In the two trials using coadministration of ezetimibe and atorvastatin, alanine transaminase (ALT) increase was reported in 3 cases (1.1%) and aspartate transaminase (AST) increase was reported in 1 case (0.4%) in ezetimibe and atorvastatin coadministration group. Cases exceeding 5 times and 10 times the upper limit of normal, respectively, have also been reported (5).

As a routine risk minimization practice, hepatic risks (hepatotoxicity and transaminase elevations) are described in the "Contraindications", "Careful Administration", "Important Basic Precautions" and "Clinically significant adverse reactions" sections in the Japan Package Circular (JPC) and in the Medication Guide for Patients in order to promote awareness (1, 6).

The contraindications describe that HMG-CoA reductase inhibiting activity level in plasma was elevated in patients with liver cirrhosis as compared with the level in healthy adults (4.4–9.8 fold area under the curve) based on the results of clinical trials for atorvastatin. Therefore, the plasma concentration of atorvastatin may be increased in such patients resulting in an increased frequency of adverse reactions. The careful administration section describes that in patients with current or previous hepatic impairment and alcoholics treated with ezetimibe, an increase in plasma concentrations was observed corresponding to the degree of severity of hepatic dysfunction. The important Basic Precautions section also describes that periodic liver function tests should be performed because hepatitis may occur during the treatment of this drug.

Because ATOZET is a fixed dose combination of two well-established medications, the clinical development program for ATOZET was limited. Hepatic events and use of ATOZET in patients with hepatic impairment were not well-characterized during the ATOZET clinical development program. Compliance with the Japan Package Circular recommendations for monitoring various liver function tests in patients treated with ATOZET is not known. Furthermore, according to the discussion during the JNDA review, it was stated from PMDA that it is considered important in post-marketing use to confirm that there are no safety problems.

PMDA has requested that the Market Authorization Holder conduct a post-marketing database surveillance as a regulatory requirement to characterize the hepatic risks and missing information on patients with hepatic impairment and to determine how well the guidance on liver function testing is followed comparing ATOZET and EZE/ATV coadministration even though the two drug regimens are bioequivalent.

Pharmacovigilance activity and risk minimization practice are regulatory requirements for reexamination; therefore, the Market Authorization Holder will conduct a database surveillance for three important identified risks, and important missing information described in the Japanese Risk Management Plan (RMP) for ATOZET (7).

7 RESEARCH QUESTION AND OBJECTIVES

7.1 Research Question

To investigate hepatic 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.

7.2 Research Objectives

7.2.1 Primary objectives

To compare the incidence rates of hepatic health outcomes of interest (HOI) between those taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin. Hepatic HOI includes incidences of hepatic diagnoses (e.g., hepatitis, liver inflammation, jaundice), and elevations of ALT and/or AST among those without a prior history of the HOI.

7.2.2 Secondary objectives

- To describe the incidence rates of hepatic HOI for patients with and without hepatic impairment among those treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin.
- To describe compliance with liver blood tests after administration of ATOZET or 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.

8 AMENDMENTS AND UPDATES

N.A.

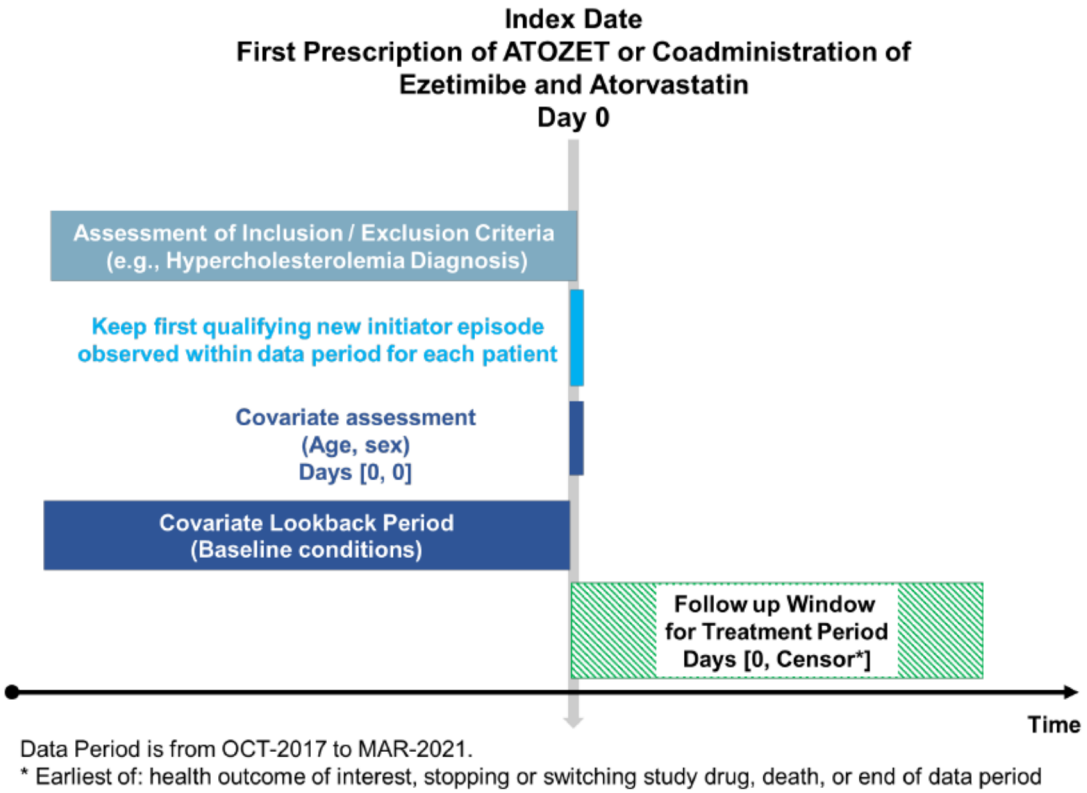
9 RESEARCH METHODS

9.1 Study design

This surveillance was a post-marketing database surveillance with a cohort design using the Medical Information Database Network (MID-NET).

Outline of the surveillance design was shown in Figure 9.1-1.

Figure 9.1-1 Study design



9.1.1 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. 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.

9.1.2 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.

To describe compliance with liver blood tests after administration of ATOZET, the proportion of patients who have a lab test for the following three points will be calculated for compliance of laboratory test implementation: 1) baseline, 2) all follow-up, 3) every 3 months. The reason for checking compliance at 3 months and for all follow-up is based on the section on "Important Basic Precautions" in JPC which states that liver function tests should be performed at least once during 12 weeks after the treatment initiation of ATOZET.

To take into account the varying duration of follow-up, the mean (the total number of lab tests per patient divided by the follow-up period (months)) will be calculated. This analysis will only be performed on patients who have been undergoing treatment more than 180 days (6 months). A minimum of 180 days of follow-up is being used for this analysis because long-term prescriptions may be for 90 days and this will allow assessment for lab tests which occur after the second prescription.

9.2 Setting

9.2.1 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) (8) (see section 9.5).

9.2.2 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 section 9.2.3.1, 9.3.1).

9.2.3 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.

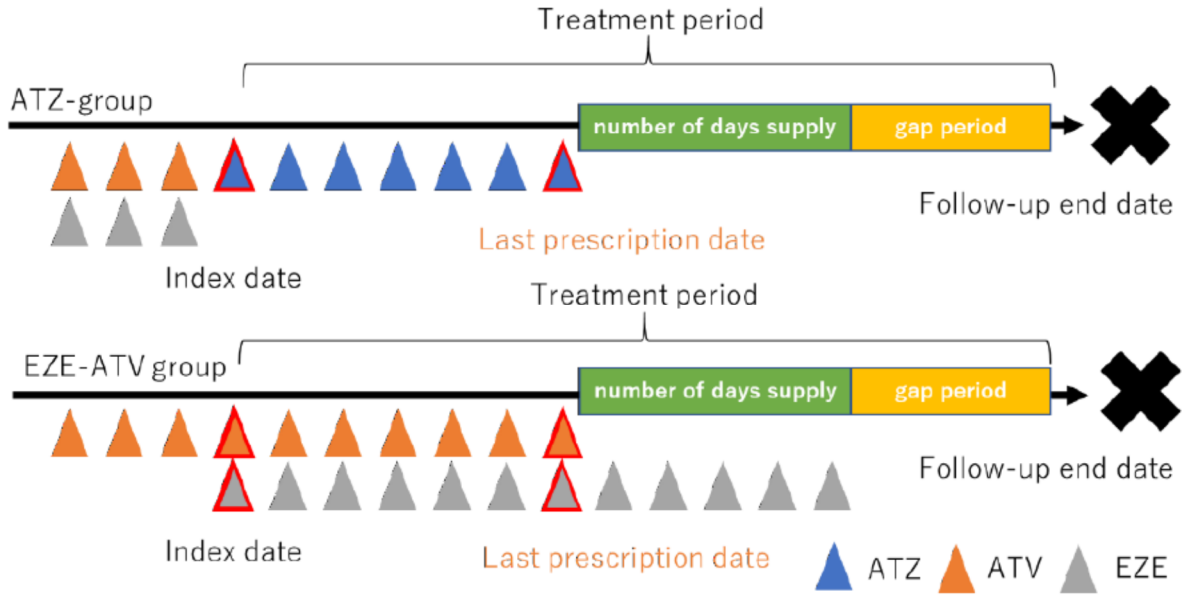
The treatment period for the ATZ-group is defined as from the index date to the last prescription date + number of days' supply at the last prescription + a gap period. The ATZgroup will be considered as censored when they change to coadministration of ezetimibe and atorvastatin. The treatment period 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 9.2.3.1)

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

Example of participant follow-up was shown in Figure 9.2-1.

Figure 9.2-1 Participant Follow-up (example)



ATV：アトルバスタチン、ATZ：アトーゼット、EZE：エゼチミブ

9.2.3.1 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 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.
- When assessing the rate of laboratory testing, patients must have at least 6-months of follow-up.

9.3 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 9.3.1 and 9.3.2).

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 9.3.1 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 (9) and we do not expect sufficient sample size to evaluate the doses separately. Dose will be analyzed descriptively for both treatment groups.

9.3.1 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.

The expected treatment patterns in the ATZ-group and EZE-AT-group were shown in Table 9.3-1 and Table 9.3-2.

Table 9.3-1 The expected treatment patterns in the ATZ-group

Pre-treatment† (ATC code)	At index date (ATC code)	Inclusion
Atorvastatin (C10AA05)	ATOZET (C10BA05)	Inclusion
Ezetimibe (C10AX09) and Atorvastatin (C10AA05)‡	ATOZET (C10BA05)	Inclusion

ATC：解剖治療化学分類法
† Pre-treatment means the medication prescribed just before the index date.
‡ Started coadministration during the selection period.

Table 9.3-2 The expected treatment patterns in the EZE-ATV-group

Pre-treatment† (ATC code)	At index date (ATC code)	Inclusion
Atorvastatin (C10AA05)	Ezetimibe (C10AX09) and Atorvastatin (C10AA05)	Inclusion

ATC：解剖治療化学分類法
† 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.

9.3.2 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 (C10AA05), 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 will be excluded

- 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

(C10AX09), 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 will be excluded.

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”.

9.4 Variables

9.4.1 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 EZEATV-group. Dose will be analyzed descriptively for the 2 treatment groups.

9.4.2 Outcomes

To describe the incidence of abnormal liver function, the outcomes targeted in this surveillance are as follows: fulminant hepatitis, hepatitis, jaundice. Lab services are counted according to SS-MIX2. MID-NET records lab services orders and the record format is JLAC10 (10). The target codes are shown in Appendix C of Appendix 1 “Appendix 1_List of Diagnosis Codes.” 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 hepatic 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.

9.4.2.1 Abnormal liver blood tests and hepatic diagnoses

- For primary analysis for abnormal liver function

Laboratory test value: AST > 3 × ULN or ALT > 3 × ULN AND
Diagnosis code (ICD-10) of hepatic diagnoses.

Hepatic diagnoses (diagnosis codes) were listed in Appendix A of Appendix 1 “Appendix 1 List of Diagnosis Codes.”
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.

Reasons for setting:

For the definition of liver dysfunction, the definition above is set with reference to definition in the Phase-3 clinical trials of ezetimibe / atorvastatin (4, 5). The combination of abnormal test values and diagnosis is essential because SS-MIX2 can capture all diagnostic and recorded events. In this study, γ-GTP was not used to define the outcomes, because The Common Technical Document assessed that there was no significant difference in the proportion of subjects with abnormal γ-GTP between the groups in both the P383 and the P384 trials for γ-GTP (11).

9.4.2.2 Compliance with liver blood tests

The proportion of patients who have a lab test for the following three points will be calculated for compliance of laboratory test implementation: 1) baseline, 2) all follow-up, 3) every 3 months. To check the number of lab tests per patient per month (PPPM), the total number of lab tests per patient will be divided by the follow-up period (months) to calculate the mean.. This analysis will only be performed on patients who have been undergoing treatment more than 180 days (6 months). A minimum of 180 days of follow-up is being used for this analysis because long-term prescriptions may be for 90 days and this will allow assessment for lab tests which occur after the second prescription.

9.4.3 Covariates

9.4.3.1 Gender / Age

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

9.4.3.2 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".

Target codes of the comorbidities were listed in Appendix A of Appendix 1 “Appendix 1 List of Diagnosis Codes.”

The comorbidities were defined according to the Charlson Comorbidity Index (CCI) (12). 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.

9.4.3.3 Pre-treatment drugs

Pre-treatment drugs associated with Hypercholesterolemia are shown in Appendix B1 and Appendix B2 of Appendix 1 “Appendix 1 List of Diagnosis Codes” and the ATC codes of pre-treatment drugs are listed in Table 9.4-1. 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 9.4-1 Pre-treatment drugs

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

ATC：解剖治療化学分類法、DPC：診断群分類包括評価、
HMG CoA：ヒドロキシメチルグルタリルコエンザイム A、SS-MIX2：厚生労働省電子的診療情報交換推進事業2
The co-treatment definition is recorded in SS-MIX2, Administrative claims, or DPC.

9.5 Data source and Measurement

This surveillance will be analyzed using a database provided by MID-NET.

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) (8). 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 nonelderly 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 and compliance with laboratory tests.

To utilize MID-NET, we will send a data extraction script set from the MID-NET data center to the 23 participating institutions (8). 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 MID-NET user.

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”.

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:

The settings of the data tables belonging to each data type were listed in Table 9.5-1.

Table 9.5-1 Data table

Output period	Data types	Table name
Oct 01, 2017 to Mar 31, 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

DPC: Diagnosis Procedure Combination; SS-MIX2: Standardized Structured Medical Information eXchange Version 2 by the Ministry of Health, Labour and Welfare

9.5.1 Surveillance Procedures

See section 9.2.2, 9.4.2, 9.4.3, and 9.2.3 for Surveillance data period, Outcomes, Covariates, Participant follow-up, respectively.

9.6 Bias

Age, some comorbidities, some prior/concomitant drugs, etc. could affect risk of HOI which is why 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).

In this surveillance, IRR will also be calculated using Poisson regression analysis to compare the incidence of HOI between ATZ-group and EZEATV-group after adjusting for covariates. For the adjusting, see section 9.9.2, and 9.9.4 for main statistical methods and sensitivity analyses.

9.7 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.

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:

Increased ALT: 3 cases (1.1%)

Increased AST: 1 case (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 9.7-1. 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 9.7-1 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

ATZ group: Atozet group; CI: Confidence interval; EZE-ATV group: Ezetimibe-Atorvastatin group; IRR: Incidence rate ratio
The expected incidence risk of the outcome in the exposed group is 0.01. The expected incidence risk of the outcome in the non-exposed group is 0.005. IRR=2, Alpha=0.05.

9.8 Data Transformation

9.8.1 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 (13).

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. Organon K.K., MSD K.K. 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.

9.9 Statistical Methods

9.9.1 Main summary measures

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

9.9.2 Main statistical methods

9.9.2.1 Patient characteristics

To facilitate interpretation of the surveillance results regarding incidence of hepatic 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).

9.9.2.2 Primary objective

To compare the incidence of HOI, incidence rates of HOI events will be calculated as the number of events per 1,000 person-years for ATZ-group and EZE-ATV-group. 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 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" and "Renal disease") if there are large 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.

9.9.2.3 Subgroup analysis

To characterize missing information in the RMP about the patients with hepatic impairment, 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 (the elevation of ALT and AST, the incident of hepatitis, fulminant hepatitis, and jaundice) 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 9.9.2.2.

Possible contraindications to treatment with ATZ was listed in Table 9.9-1.

Table 9.9-1 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	Unspecified jaundice

9.9.2.4 To describe compliance with liver function blood tests

The proportion of patients who have a lab test at the three time points will be calculated for the compliance of laboratory test implementation: 1) baseline, 2) all follow up, 3) every 3 months.

In order to evaluate the number of tests per patient per month, for the number of tests per patient per month (PPPM), the total number of tests per patient was divided by the length of follow-up (the number of months), and its mean number was calculated. Tests will be calculated for the follow-up period and censored on the date of discontinuation.

The measurement points shall be set for the following time points ;

Baseline: to check whether inspections have been performed in the previous 90 days as a basis for deciding to switch.

All follow up: to check that inspections are conducted throughout the entire period.

Every 3 months: to check that regular examinations are conducted.

9.9.3 Missing information

In this surveillance, no measures were taken for the missing information since patients who have any missing information were excluded from surveillance population.

9.9.4 Sensitivity analysis

The sensitivity analysis will be performed using an alternative outcome definition. The analyses for the alternative outcome definitions will follow the methods for the primary analysis above (section 9.9.2.2).

The definition for sensitivity analysis of the incidence of hepatic impairment is as follows: laboratory test value used for primary objects and according to “Severity classification criteria for adverse drug reaction (Ministry of Health, Labor and Welfare)” (14)

The sensitivity analysis will be also 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.

1) AST > 3 × ULN or ALT > 3 × ULN
2) AST 100 ≤ x < 500 or ALT 100 ≤ x < 500 AND Diagnosis code (ICD-10) of hepatic diagnoses
3) AST 100 ≤ x < 500 or ALT 100 ≤ x < 500
4) AST ≥ 500 or ALT ≥ 500 AND Diagnosis code (ICD-10) of hepatic diagnoses
5) AST ≥ 500 or ALT ≥ 500
6) Diagnosis code (ICD-10) of hepatic diagnoses

9.9.5 Amendments and updates of statistical analysis plan

以下に統計解析計画書（図表形式）の作成・改訂経緯を示す。

版番号	作成日	改訂理由
01.00	2021年7月20日	初版
02.00	2021年7月30日	誤記修正 Compliance of test の出力項目修正 Follow-up period の出力項目修正
03.00	2021年8月19日	誤記修正

9.10 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 (13).

9.11 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 reexamination. The number of the patients and their % will be redacted if there are less than 5 cases according to the MID-NET publication rules.

10 Results

10.1 Participants

Patients included in ATZ-group and EZE-ATV-group are shown in Table 10.1-1 and Table 10.1-2, respectively. During the selection period, ATOZET was prescribed to 515 patients (Table 10.1-1) and coadministration of ezetimibe and atorvastatin was prescribed to 852 patients (Table 10.1-2) in MID-NET. Of these, 45 patients were included in ATZ-group (Table 10.1-1) and 70 patients were included in EZE-ATV-group (Table 10.1-2) based on the inclusion/ exclusion criteria.

The numbers of patients in ATZ-group (45 patients) and EZE-ATV-group (70 patients) listed in Table 10.1-1 and Table 10.1-2 include 8 patients who were prescribed with both ATOZET and coadministration of ezetimibe and atorvastatin during the selection period (switched prescription during the selection period). These patients were included in ATZ-group and not in EZE-ATV-group for analyses presented in sections 10.2 to 10.5. Therefore, the EZE-ATV group in the analyses consisted of 60 patients, excluding two patients for whom the follow-up period could not be confirmed.

Table 10.1-1 Patients in ATZ-group

ATZ-group				
	Cases Excluded		**Cases remaining**	
	N	**%**	**N**	**%**
MID-NET data	-	-	515	100.0
Patient who has a hypercholesterolemia diagnosis	54	10.5	461	89.5
Pre-treatment drug is ezetimibe	16	3.1	445	86.4
Pre-treatment drug is another lipid modifying	108	21.0	337	65.4
Pre-treatment drug is not recorded	245	47.6	92	17.9
Patients had treatment before April 2018	0	0.0	92	17.9
Patients who do not have at least a 6-month lookback period	46	8.9	46	8.9
Patients who have any missing information	0	0.0	46	8.9
Patients who have severe liver dysfunction	1	0.2	45	8.7

Table 10.1-2 Patients in EZE-ATV-group

EZE-ATV-group				
	Cases Excluded		**Cases remaining**	
	N	**%**	**N**	**%**
MID-NET data	-	-	852	100.0
Patient who has a hypercholesterolemia diagnosis	131	15.4	721	84.6
Pre-treatment drug is ezetimibe	3	0.4	718	84.3
Pre-treatment drug is another lipid modifying	67	7.9	651	76.4
Pre-treatment drug is not recorded	491	57.6	160	18.8
Patients had treatment before Jan 2018	0	0.0	160	18.8
Patients who do not have at least a 6-month lookback period	80	9.4	80	9.4
Patients who have any missing information	0	0.0	80	9.4
Patients who have severe liver dysfunction	10	1.2	70	8.2

10.1.1 Protection of human subjects

10.1.1.1 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.

10.2 Descriptive data

10.2.1 Demographics & Clinical Characteristics

The aggregate results of demographic and clinical characteristics of the patients included in this surveillance are shown in Table 10.2-1.

A total of 66.7% (30/45) of the patients in ATZ-group and 59.7% (37/62) of the patients in EZE-ATV-group were male. Mean age ± SD was 66.3 ± 11.8 years in ATZ-group and 63.1 ± 14.0 years in EZE-ATV-group. It was found that the male and female ratio and the mean age were similar between the groups.

It was also considered that the distribution of age groups and the distributions of comorbidities and pre-treatment drugs were generally similar.

Table 10.2-1 Demographic and clinical characteristics of the patients by treatment group

		ATZ-group		EZE-ATV-group	
		No.	%	No.	%
Number of Cases		45	100.0	62	100.0
Sex	Male	30	66.7	37	59.7
	Female	15	33.3	25	40.3
Age	mean	66.3	-	63.1	-
	SD	11.8	-	14.0	-
	<20	0	0.0	0	0.0
	20-29	0	0.0	1	1.6
	30-39	2	4.4	2	3.2
	40-49	2	4.4	7	11.3
	50-59	7	15.6	14	22.6
	60-69	12	26.7	17	27.4
	70-79	16	35.6	14	22.6
	80-89	6	13.3	7	11.3
	90-99	0	0.0	0	0.0
	≧100	0	0.0	0	0.0
Comorbidities					
Ischemic heart disease, Myocardial infarction		33	73.3	33	53.2
Congestive heart failure		22	48.9	28	45.2
Peripheral vascular disease		8	17.8	12	19.4
Cerebrovascular disease		6	13.3	9	14.5
Mild liver disease		1	2.2	7	11.3

	ATZ-group		EZE-ATV-group	
	No.	%	No.	%
Hypertension	18	40.0	30	48.4
Diabetes (mild to moderate)	16	35.6	19	30.6
Diabetes with chronic complications	6	13.3	5	8.1
Renal disease	3	6.7	3	4.8
Moderate or severe liver disease	0	0.0	0	0.0
Pre-treatment drugs				
HMG CoA reductase inhibitors	0	0.0	7	11.3
Fibrates	1	2.2	3	4.8
Bile acid sequestrants	0	0.0	0	0.0
Nicotinic acid and derivatives	0	0.0	0	0.0
Other lipid modifying agents	0	0.0	0	0.0

10.2.2 Prescription status

Prescription of drugs contraindicated in coadministration with atorvastatin, ATOZET and atorvastatin in this surveillance is shown in Table 10.2-2.

Pre-index shows the past prescription status including the index date. Post-index shows the prescription status on and after the next day of the index date. Patients without visit record are not included in the data.

For either Pre-Index or Post-Index, telaprevir, ombitasvir/paritaprevir/ritonavir, or glecaprevir/pibrentasvir, which were contraindicated in coadministration with atorvastatin, were not prescribed.

Low-dose (LD) ATOZET was prescribed in 51.1% of the patients in ATZ-group, and atorvastatin 10 mg was prescribed in 45.2% of the patients in EZE-ATV-group.

High-dose (HD) ATOZET was prescribed in 40.0% of the patients in ATZ-group, and atorvastatin 20 mg was not prescribed in EZE-ATV-group. During the surveillance data period, atorvastatin 20 mg was distributed as a generic drug by only one company, and atorvastatin 5 mg should be considered, which we did not in the analysis.

Table 10.2-2 Prescription status by treatment group

	ATZ-group		EZE-ATV-group	
	No.	%	No.	%
Pre-Index				
Telaprevir	0	0.0	0	0.0
Ombitasvir/paritaprevir/ritonavir	0	0.0	0	0.0
Glecaprevir/pibrentasvir	0	0.0	0	0.0
Post-Index				
Telaprevir	0	0.0	0	0.0
Ombitasvir/paritaprevir/ritonavir	0	0.0	0	0.0
Glecaprevir/pibrentasvir	0	0.0	0	0.0
ATZ LD	23	51.1		
ATZ HD	18	40.0		
Atorvastatin 10 mg			28	45.2
Atorvastatin 20 mg			0	0.0

10.2.3 Follow-up period

Basic statistics of follow-up period are shown in Table 10.2-3.

The mean ± SD follow-up period was 1.05 ± 0.64 years in ATZ-group and 0.85 ± 0.77 years in EZE-ATV-group.

The total number of patient years of follow- up period was 47.1 for ATZ-group and 50.7 person-years for EZE-ATV-group.

Table 10.2-3 Follow-up period by treatment group

		ATZ-group	EZE-ATV-group
Number of patients		45	62
Follow-up period (years)	N	45	60
	Mean	1.05	0.85
	SD	0.64	0.77
Person-years		47.1	50.7

Note: The follow-up period was evaluated using SS-MIX2 data. In EZE-ATV-group, even if DPC and administrative claims data were available, the follow-up period of patients was not calculated if they could not be confirmed with SS-MIX2 data.

10.3 Outcome data

10.3.1 Incidence status of hepatic HOI

The incidence status of hepatic HOI is described in section 10.4.1.

10.4 Main results

10.4.1 IRR of hepatic HOI

10.4.1.1 Main analysis

The incidence of hepatic HOI is shown in Table 10.4-1.

No hepatic HOI events occurred in either group therefore, IRR and adjusted IRR were not calculated.

Table 10.4-1 Incidence of hepatic HOI by treatment group

ATZ-group				EZE-ATV-group						
N (population)	PY*	n (event)	IR (/1000person-years)**	N (population)	PY*	n (event)	IR (/1000person-years)**	IRR*** (crude)	IRR*** (adjusted)	95%CI
45	47	0	0.00	60	50	0	0.00	-	-	-

Note: *person-years; **incidence rate; *** incidence rate ratio

10.4.2 Compliance with liver function blood tests

Compliance with liver function blood tests is shown in Table 10.4-2.

In the analysis by 6-month period, patients with an index date within the categorized periods were included.

Blood tests at baseline were performed in 100.0% of the patients in both groups for all categorized periods, except for 2018 Q1-Q2 during which there were no applicable patients in ATZ-group.

During the follow-up period, blood tests were conducted in more than 80% of the patients in ATZ-group for all categorized periods, except for 2018 Q1-Q2 during which there were no applicable patients. In EZE-ATV-group, blood tests were carried out in ≥ 75% of the patients for all categorized periods.

The proportion of patients who had blood tests for every 3-month period ranged from 66.7% to 90.9% in ATZ-group for each categorized period, except for 2018 Q1-Q2 during which there were no applicable patients, and ranged from 73.3% to 87.5% in EZE-ATV-group.

The number of tests per patient per month (PPPM, mean± SD) during the follow-up period for each categorized period ranged from 0.5 ± 0.2 to 1.7 ± 2.3 in ATZ-group, except for 2018 Q1-Q2 during which there were no applicable patients, and ranged from 1.3 ± 1.2 to 3.8 ± 4.7 in EZE-ATV-group.

Because the number of patients in each categorized period was small, the compliance could not be evaluated in detail, but the compliance with blood tests appeared to be generally favorable.

Table 10.4-2 Compliance with liver function blood tests by treatment group

		2018 Q1-Q2	2018 Q3-Q4	2019 Q1-Q2	2019 Q3-Q4	2020 Q1-Q2	2020 Q3-Q4	All
Baseline								
ATOZET	n	0	11	11	11	9	3	45
	%	0.0	100.0	100.0	100.0	100.0	100.0	100.0
	95%CI	-	71.5 - 100.0	71.5 - 100.0	71.5 - 100.0	66.4 - 100.0	29.2 - 100.0	92.1 - 100.0
EZE-ATV	n	15	5	9	16	13	4	62
	%	100.0	100.0	100.0	100.0	100.0	100.0	100.0
	95%CI	78.2 - 100.0	47.8 - 100.0	66.4 - 100.0	79.4 - 100.0	75.3 - 100.0	39.8 - 100.0	94.2 - 100.0
Follow up								
ATOZET								
All follow up	n	0	11	9	10	8	3	41
	%	0.0	100.0	81.8	90.9	88.9	100.0	91.1
	95%CI	-	71.5 - 100.0	48.2 - 97.7	58.7 - 99.8	51.8 - 99.7	29.2 - 100.0	78.8 - 97.5
Every 3 months	n	0	10	8	8	8	2	36
	%	0.0	90.9	72.7	72.7	88.9	66.7	80.0
	95%CI	-	58.7 - 99.8	39.0 - 94.0	39.0 - 94.0	51.8 - 99.7	9.4 - 99.2	65.4 - 90.4
PPPM, mean SD	mean	-	1.5	1.7	0.5	1.1	1.4	1.2
	SD	-	1.9	2.3	0.2	0.7	1.1	1.5
EZE-ATV								
All follow up	n	13	4	8	14	10	3	52
	%	86.7	80.0	88.9	87.5	76.9	75.0	83.9
	95%CI	59.5 - 98.3	28.4 - 99.5	51.8 - 99.7	61.7 - 98.4	46.2 - 95.0	19.4 - 99.4	72.3 - 92.0
Every 3 months	n	11	4	7	14	10	3	49
	%	73.3	80.0	77.8	87.5	76.9	75.0	79.0
	95%CI	44.9 - 92.2	28.4 - 99.5	40.0 - 97.2	61.7 - 98.4	46.2 - 95.0	19.4 - 99.4	66.8 - 88.3
PPPM, mean SD	mean	2.1	3.3	1.3	1.9	1.6	3.8	2.0

		2018 Q1-Q2	2018 Q3-Q4	2019 Q1-Q2	2019 Q3-Q4	2020 Q1-Q2	2020 Q3-Q4	All
	SD	3.2	4.8	1.2	2.0	0.9	4.7	2.5

per-patient-per-month (PPPM)

10.5 Other analyses

10.5.1.1 Subgroup analysis for the incidence of hepatic HOI

Results of subgroup analysis for the incidence status of hepatic HOI in patients with or without hepatic impairment are shown in Table 10.5-1.

Of the 45 patients in the ATZ-group, 6 patients had hepatic impairment and 39 patients had hepatic impairment. Of the 60 patients in the EZE-ATV-group, 11 patients had hepatic impairment and 49 patients had no hepatic impairment.

As mentioned in section 10.4.1.1, no hepatic HOI events occurred in either group so IRR and adjusted IRR were not calculated in the hepatic impairment subgroups.

Table 10.5-1 Incidence of hepatic HOI in patients with or without hepatic impairment by treatment group

	ATZ-group				EZE-ATV-group						
	N (population)	PY*	n (event)	IR (/1000person-years)**	N (population)	PY*	n (event)	IR (/1000person-years)**	IRR*** (crude)	IRR*** (adjusted)	95%CI
Hepatic impairment group	6	6	0	0.00	11	5	0	0.00	-	-	-
Non-hepatic impairment group	39	40	0	0.00	49	45	0	0.00	-	-	-

Note: *person-years; **incidence rate; *** incidence rate ratio

10.5.1.2 Sensitivity analyses for incidence of hepatic HOI

Results of sensitivity analyses with alternative outcome definitions (laboratory values and diagnosis codes) described in section 9.9.4 are shown in Table 10.5-2.

The IR of hepatic HOI using "AST > 3 × ULN or ALT > 3 × ULN" as an alternative outcome was 21.24/1,000 person-years in ATZ-group and 137.95/1,000 person-years in EZE-ATV group.

The IR of HOI using "AST 100 ≤ x < 500 or ALT 100 ≤ x < 500" as an alternative outcome was 21.24/1,000 person-years in ATZ-group and 157.66/1,000 person-years in EZE-ATV group.

For all alternative outcome definitions, IRR and adjusted IRR and its 95% CI listed in Table 10.5-2 could not be properly calculated because there were no events or a few events.

Table 10.5-3 shows results of the sensitivity analysis which was performed limiting ATZ-group to 29 subjects who were switched from Atorvastatin monotherapy.

As mentioned in section 10.4.1.1, no hepatic HOI event occurred in either treatment group so IRR and adjusted IRR were not calculated.

Table 10.5-2 Incidence of hepatic HOI with alternative outcome definitions by treatment group

	ATZ-group				EZE-ATV-group						
	N (population)	PY*	n (event)	IR (/1000person-years)**	N (population)	PY*	n (event)	IR (/1000person-years)**	IRR*** (crude)	IRR*** (adjusted)	95%CI
AST > 3 × ULN or ALT > 3 × ULN	45	47	1	21.24	60	50	7	137.95	-	-	-
(100 ≤ AST < 500 or 100 ≤ ALT < 500) and Diagnosis code	45	47	0	0.00	60	50	0	0.00	-	-	-
100 ≤ AST < 500 or 100 ≤ ALT < 500	45	47	1	21.24	60	50	8	157.66	-	-	-
(AST ≥ 500 or ALT ≥ 500) and Diagnosis code	45	47	0	0.00	60	50	0	0.00	-	-	-
AST ≥ 500 or ALT ≥ 500	45	47	1	21.24	60	50	0	0.00	-	-	-
Diagnosis code	45	47	0	0.00	60	50	0	0.00	-	-	-

Note: *person-years; **incidence rate; *** incidence rate ratio

Table 10.5-3 Incidence of hepatic HOI limiting ATZ-group to patients switching from Atorvastatin monotherapy

ATZ-group				EZE-ATV-group						
N (population)	PY*	n (event)	IR (/1000person-years)**	N (population)	PY*	n (event)	IR (/1000person-years)**	IRR*** (crude)	IRR*** (adjusted)	95%CI
29	33	0	0.00	60	50	0	0.00	-	-	-

Note: *person-years; **incidence rate; *** incidence rate ratio

10.6 Adverse events/ Adverse reactions

This is non-interventional post-marketing database surveillance based on secondary use of data collected for other purposes. No reporting of individual adverse events or product quality complaints to the regulatory authorities was possible for this database surveillance because no access to individual patient records could be made. Likewise, it was not possible to assess the causality of individual cases. HOI is to be summarized in this report.

11 DISCUSSION

11.1 Key results

Hepatic HOI:

Because of the short identification period and the strict exclusion criteria for this surveillance which eliminated patients who had specific prior drugs or no information on prior drugs, this study included a very small number of patients who were prescribed ATZ or coadministration of EZE and ATV. For the primary endpoint (and the analysis by hepatic impairment), there were no hepatic impairment based on a combination of hepatic diagnosis codes for toxic liver disease, hepatic failure, chronic hepatitis, and jaundice and abnormal liver function test (AST > 3 × ULN or ALT > 3 × ULN). For the sensitivity analyses based on alternative definitions of hepatic HOI, there were a few definitions based on AST and ALT alone which showed lower incidence for ATZ than for EZE-ATV, but these are based on the values from the extremely small number. This surveillance did not raise any concerns about hepatic events for ATZ.

Compliance with liver tests

In the evaluation of compliance with liver blood tests after administration of ATOZET or coadministration of ezetimibe and atorvastatin, all patients received LFT tests at baseline and during follow-up, while the number of patients in each categorized period was small in both groups, the compliance appeared to be generally favorable (at least 75% in each period).

11.2 Limitations

At the time of planning this surveillance, it was already expected that the number of patients treated with ATOZET or coadministration of ezetimibe and atorvastatin would be very small even before selecting patients based on the inclusion and exclusion criteria (diagnosed hyperlipidemia and administration of certain pre-treatment drugs) because these drugs are not frequently used. It was also expected that the treatment duration in these cohorts would be relatively short. With a small number of patients included in the analysis of hepatic HOI in both treatment groups, no hepatic HOI events were observed in this surveillance.

MID-NET data are mainly from secondary medical care hospitals. Therefore, because primary medical care data are limited, selection biases might have occurred, and thus the surveillance results may not be applicable to the general population of hypercholesterolemic patients in Japan.

Another major limitation of MID-NET is that because there are no data on a patient level among hospitals, if patients are treated at medical institutions which are not the MID-NET collaborating hospitals, the patients cannot be followed up. Consequently, information on events (e.g., diagnosis, laboratory tests and death) that occurred outside of the 23 hospitals are not available in MID-NET even if they occurred during the follow-up period.

Since the results of routine periodic laboratory tests in local areas are not available, this may account for the incidence of abnormal values may be overestimated due to reasons such as the low rates of some laboratory tests, the severity of patients who are referred to specialist care being higher, and/or the proportion of patients with comorbidities being high.

Representativeness:

For this surveillance activity, because MID-NET is composed of only 23 hospitals including specialty clinics, it is likely that the population studies included more secondary prevention patients. Therefore, the target population of the surveillance might not be representative of the general population of hypercholesterolemic patients or their medical care in Japan. MID-NET was composed of main hospital groups (the Kitasato Institute Group, NTT Medical Center Group and Tokushukai Group) and university hospitals. Patients, who were prescribed with ATOZET in accordance with the indications presented in the package insert, might not include all patients treated with ATOZET (For example, it has been known that there are patients, who are not diagnosed as having hypercholesterolemia who receive ATOZET or patients who receive ATOZET by switching from drugs that are not specified to be switchable in the package insert.) This definitely occurred in this study where the majority of patients on ATZ had disallowed switches or no prior drug recorded .

Appropriateness of the outcome definitions:

There is no consistent view on the best algorithm for defining hepatic HOI for Japanese databases. In existing algorithms, there was a possibility of a lack of optimal sensitivity, specificity or positive predictive value. Whether the definitions of hepatic HOI (e.g., laboratory test values and the onset of events such as hepatitis) are appropriate for assessing the effect of drugs on liver function has not been evaluated in Japan, particularly for databases. Since medical records were not accessible, the definitions used in this surveillance could not be tested.

Since this surveillance was conducted with the secondary use of medical data, there may be unmeasured confounding factors affecting the results.

11.3 Interpretation

In this surveillance, no hepatic HOI occurred in a small population of patients taking ATZ or EZE-ATV. The surveillance revealed no results regarding hepatic diagnoses or laboratory tests that might affect the

benefit-risk balance of ATOZET or concerns requiring safety measures.

In the analysis of compliance with liver blood tests by 6-month period, while the number of patients in each categorized period was small, the compliance appeared to be generally favorable.

11.4 Generalisability

See section 11.2.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

In this surveillance, no hepatic HOI events occurred in a small population of patients taking ATZ or EZE-ATV. Overall, the surveillance revealed no results regarding hepatic diagnoses or laboratory tests that might affect the benefit-risk balance of ATOZET or concerns requiring safety measures.

The compliance with liver blood tests appeared to be generally favorable.

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14. 「医薬品等の副作用の重篤度分類基準について」（平成4年6月29日薬安第80号）

Annex 1　List of Stand-Alone Documents

番号	文書参照番号	日付	標題
1	該当なし	2021年8月19日	別添1_コードリスト （横紋筋融解症及びミオパチーの製造販売後データベース調査報告書の別添1に添付）

Annex 2 Protocol for the surveillance

The implementation plan for this survey will be submitted separately as a re-examination document.

Annex 3 Additional information

N.A.