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A POST-MARKETING DATABASE SURVEILLANCE TO INVESTIGATE THE RISK OF HYPERGLYCEMIA AND DIABETES MELLITUS 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 Hyperglycemia and Diabetes Mellitus in Hypercholesterolemic Patients Treated with ATOZET or Ezetimibe Atorvastatin coadministration in Japan
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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 the health outcome of interest (HOI) related to the important identified risks and important missing information for ATOZET in patients with no past history of diabetes mellitus compared to the coadministration of ezetimibe and atorvastatin from APR-2018 to MAR-2021. Primary objective: • To compare the incidence rates of HOI related to hyperglycemia and diabetes mellitus between those taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin. The HOI will be hyperglycemia, as well as the occurrence of diabetes mellitus based on blood glucose level, hemoglobin A1c (HbA1c), and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Secondary objectives: • To examine the incidence rates of HOI related to hyperglycemia and diabetes mellitus with and without hepatic impairment among patients prescribed with ATOZET and patients prescribed 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.
Country(-ies) of surveillance	Japan

EU PAS Register: The European Union electronic Register of Post-Authorisation Studies; HD: High dose;

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 Hyperglycemia and Diabetes Mellitus 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.

Hyperglycemia and diabetes mellitus are known to be associated with lipid-lowering therapies, but were not well characterized during the ATOZET clinical development program, and the use of ATOZET in patients with hepatic impairment has not been studied in detail. The Japan Package Circular includes recommendations for careful monitoring of hyperglycemia and diabetes mellitus in patients treated with ATOZET.

The Pharmaceuticals and Medical Devices Agency (PMDA) has requested that the Market Authorization Holder should conduct a post-marketing database surveillance as a regulatory requirement to characterize the risk of hyperglycemia and diabetes mellitus, 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:

- Hyperglycemia, and diabetes mellitus

Important missing information:

- Patients with hepatic impairment

Research Question(s) & Objective(s)

Research Question:

To investigate the health outcome of interest (HOI) related to the important identified risks and important missing information for ATOZET in patients with no past history of diabetes mellitus compared to the coadministration of ezetimibe and atorvastatin from APR-2018 to MAR-2021.

Primary objective:

- To compare the incidence rates of HOI related to hyperglycemia and diabetes mellitus between those taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin. The HOI will be hyperglycemia, as well as the occurrence of diabetes mellitus based on blood glucose level, hemoglobin A1c (HbA1c), and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-

10).

Secondary objectives:

- To examine the incidence rates of HOI related to hyperglycemia and diabetes mellitus with and without hepatic impairment among patients prescribed with ATOZET and patients prescribed 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, the incidence rates of HOI related to hyperglycemia and diabetes mellitus will be compared between ATOZET (ATZ group) and ezetimibe-atorvastatin coadministration (EZE-ATV group).

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 with no past history of diabetes mellitus who are prescribed 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:

Blood glucose, HbA1c: Number of patients whose laboratory values meet the following criteria:

- Blood glucose level > 200 mg/dL and HbA1c > 6.5%, OR

- Blood glucose levels measured twice on different days > 200 mg/dL

AND Diagnosis code (ICD-10) of HOI (hyperglycemia and diabetes mellitus) among the patients with no past history of the HOI.

Covariates:

Sex, age, comorbidities

Data source

Medical Information Database Network (MID-NET)

Data analysis

To compare the incidence rates of HOI related to hyperglycemia and diabetes mellitus, the incidence rates of relevant HOI events will be calculated as the number of events per 1,000 person-years for the ATZ group and the 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.

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. Of these patients, 7 patients were included in ATZ-group and 9 patients were included in EZE-ATV-group based on the inclusion/exclusion criteria. Furthermore, the EZE-ATV group in the analyses consisted of 8 patients, excluding one patients for whom the follow-up period could not be confirmed.

Primary objective:

With respect to comparison of incidence rates of HOI related to hyperglycemia and diabetes mellitus between patients taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin, neither IRR nor adjusted IRR was calculated, because no HOI events related to hyperglycemia and diabetes mellitus occurred in either group.

Secondary objectives:

With respect to comparison of incidence rates of HOI related to hyperglycemia and diabetes mellitus with and without hepatic impairment among patients treated with ATOZET and patients treated with coadministration of ezetimibe and atorvastatin, neither IRR nor adjusted

IRR was calculated, because no HOI events related to hyperglycemia and diabetes mellitus occurred in either ATZ-group or EZE-ATV-group.

Demographic and clinical characteristics of patients treated with ATOZET and those treated with coadministration of ezetimibe and atorvastatin were as follows: The percentage of male patients was 71.4% (5 of 7 patients) in ATZ-group and 55.6% (5 of 9 patients) in EZE-ATV-group; and the mean ± SD age was 67.7 ± 10.6 years in ATZ-group and 58.2 ± 13.8 years in EZE-ATV-group. Due to the small number of patients studied, it was not possible to provide any interpretation of the similarities or differences between the groups.

Discussion

In this surveillance, since the extremely small number of patients was included, no conclusion can be made regarding the effects of ATOZET on hyperglycemia or diabetes mellitus.
Because the results from this surveillance were limited, there were no factors that could affect the benefit-risk balance of ATOZET or concerns requiring safety measures.

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
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
HbA1c	Hemoglobin A1c
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
PY	Person-Year
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

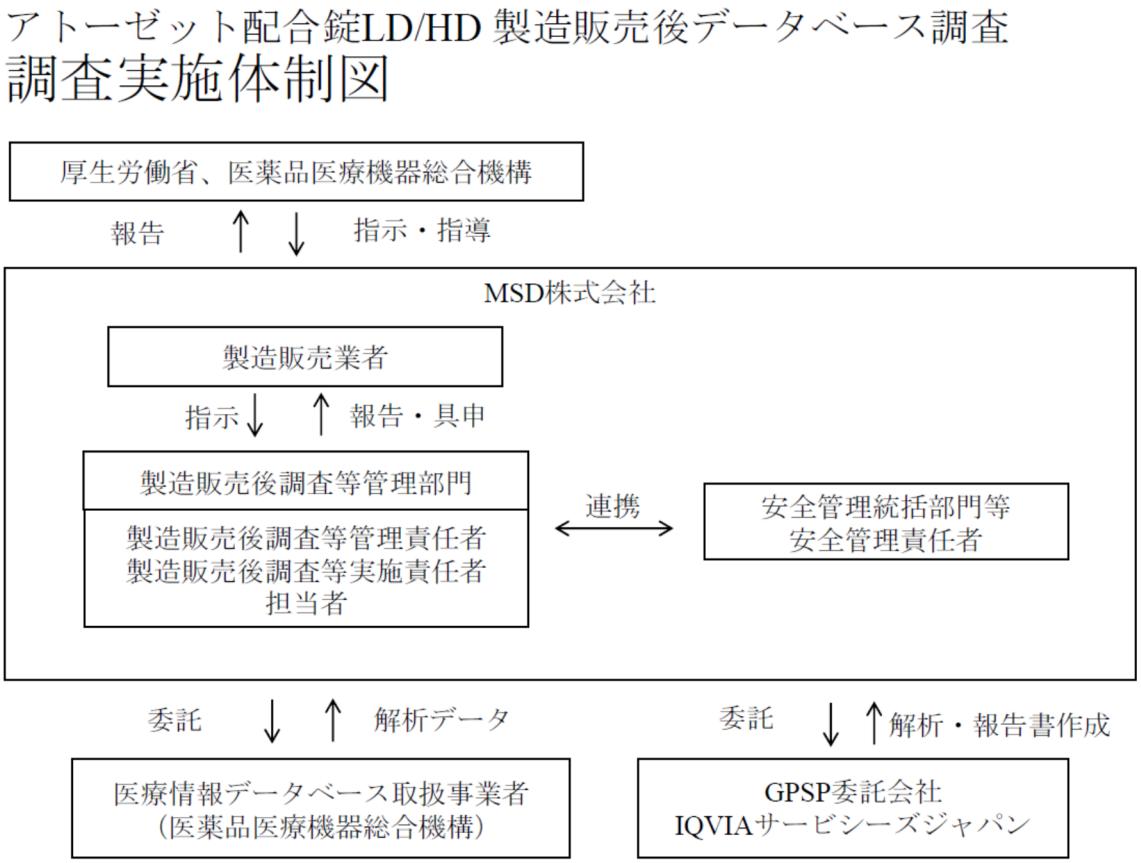
3 RESPONSIBLE PARTIES

N.A.

4 ORGANIZATION TO CONDUCT THE POST-MARKETING DATABASE SURVEILLANCE

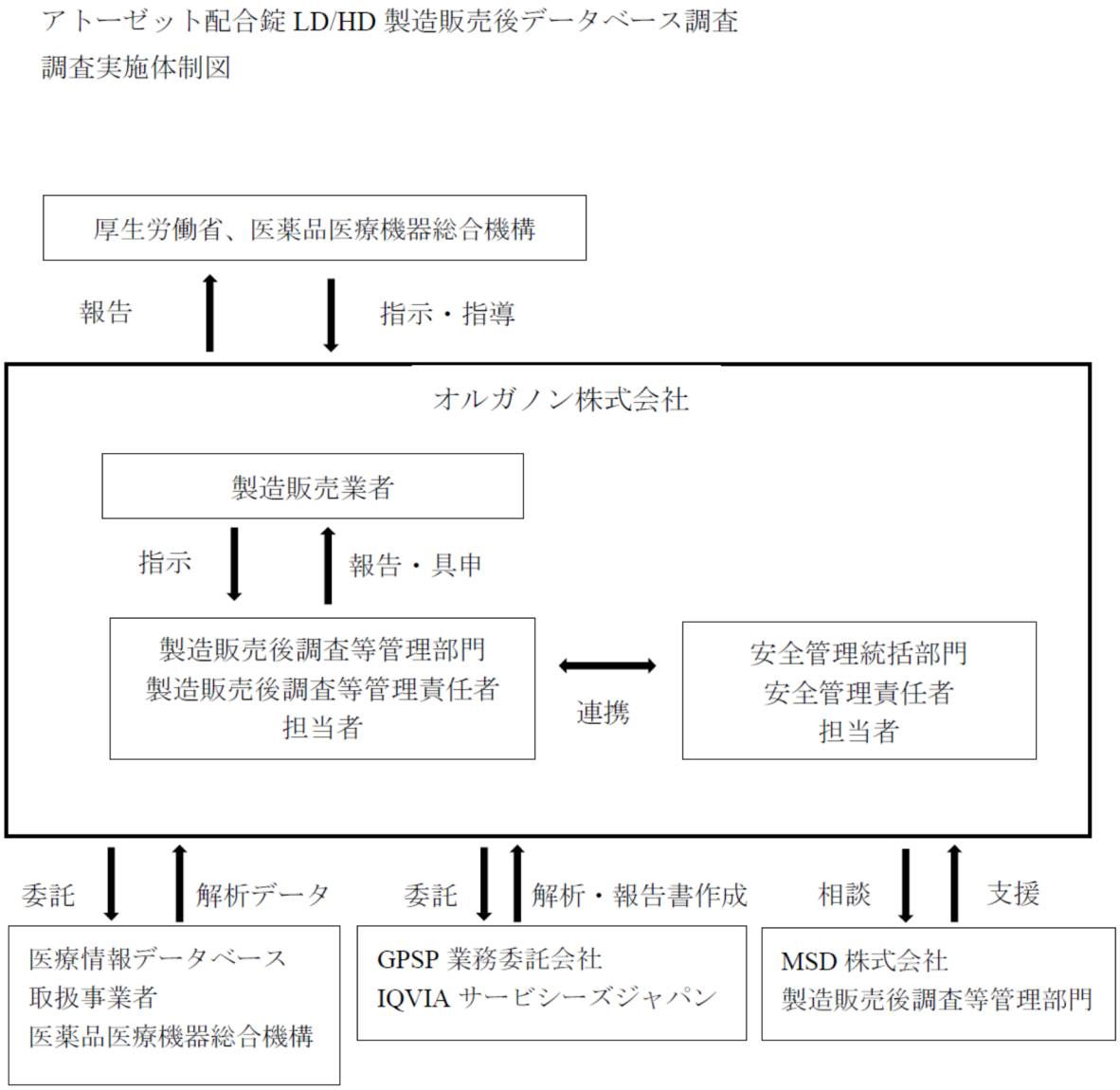
The marketing authorization holder of ATOZET® LD/HD was taken over from MSD K.K. by Organon K.K. on October 1, 2021. Thus, organization to conduct this surveillance by MSD K.K. and that by Organon K.K. are shown in Figure 4.1-1 and Figure 4.1-2, respectively.

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、
PMDA: Pharmaceuticals and Medical Devices Agency

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).

Hyperglycemia and diabetes mellitus

Administration of HMG-CoA reductase inhibitors provides a variety of beneficial effects on cardiovascular events, but HMG-CoA reductase inhibitors, including atorvastatin, have been reported to increase HbA1c levels and fasting serum glucose levels. Results of a meta-analysis demonstrated that treatment with HMG-CoA reductase inhibitors slightly increases the risk of developing diabetes mellitus (2-4). In a pooled analysis on the five studies using statins, it was demonstrated that high-dose statin increases the risk of new onset of diabetes mellitus compared with moderate-dose statin (5). In a research, it was demonstrated that coadministration of HMG-CoA reductase inhibitors and ezetimibe does not increase the risk of developing diabetes mellitus compared with the monotherapy with HMG-CoA reductase inhibitors (6). In the Phase III clinical studies (P383 and P384) of ATOZET in 272 Japanese patients, there were no patients with hyperglycemia or diabetes mellitus (7). In the P384 study, the mean HbA1c level increased by 0.4% at Week 24 after the start of treatment with ATOZET in 44 patients with type 2 diabetes mellitus (7). Diabetes mellitus, increased HbA1c levels, and increased blood glucose levels were reported in the overseas post-marketing surveillance (7). The Japan Package Circular includes recommendations for monitoring hyperglycemia and diabetes mellitus in patients treated with ATOZET (1). The definition of

diabetes mellitus by the Japan Diabetes Society (8) was used in this surveillance.

Because ATOZET is a fixed dose combination of two well-established medications, the clinical development program for ATOZET was limited. Events associated with HOI related to hyperglycemia and diabetes mellitus and the use of ATOZET in patients with hepatic impairment were not well-characterized during the ATOZET clinical development program; therefore, based on the discussion during the JNDA review, PMDA expressed its view that it is important to confirm that there are no safety problems in post-marketing use.

PMDA has requested that the Market Authorization Holder should conduct a post-marketing database surveillance as a regulatory requirement to characterize the risk of relevant HOI in patients with hepatic impairment and missing information on patients with hepatic impairment 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 post-marketing database surveillance for hyperglycemia and diabetes mellitus among the important identified risks described in the Japanese Risk Management Plan (RMP) for ATOZET, and important missing information (patients with hepatic impairment) (7).

7 RESEARCH QUESTION AND OBJECTIVES

7.1 Research Question

To investigate the HOI related to the important identified risks and important missing information for ATOZET in patients with no past history of diabetes mellitus compared to the 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 HOI related to hyperglycemia and diabetes mellitus between those taking ATOZET and those taking the coadministration of ezetimibe and atorvastatin. The HOI will be hyperglycemia, as well as the occurrence of diabetes mellitus based on blood glucose level, hemoglobin A1c (HbA1c), and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).

7.2.2 Secondary objectives

- To examine the incidence rates of HOI related to hyperglycemia and diabetes mellitus with and without hepatic impairment among patients prescribed with ATOZET and patients prescribed 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.

8 AMENDMENTS AND UPDATES

N.A.

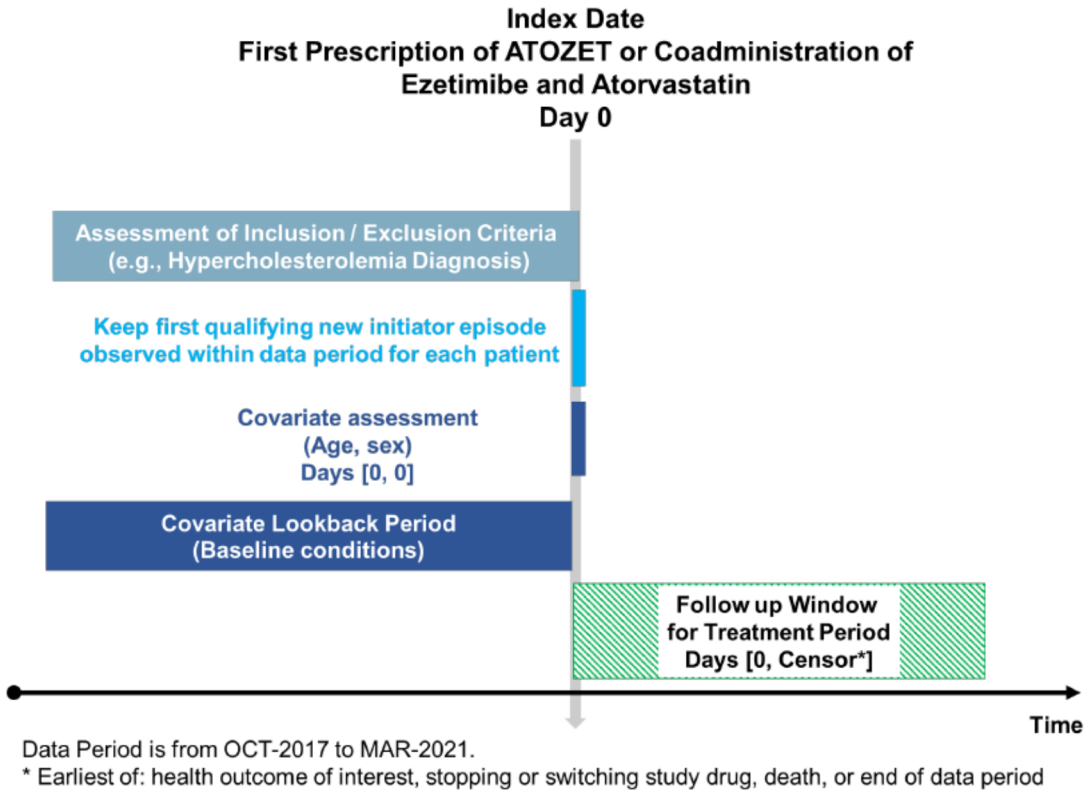
9 RESEARCH METHODS

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, the incidence rates of HOI related to hyperglycemia and diabetes mellitus will be compared between the ATZ group and EZE-ATV group at the request of PMDA.

To compare the incidence rates of HOI related to hyperglycemia and diabetes mellitus, the

incidence rates of relevant HOI events will be calculated as the number of events per 1,000 person-years for the ATZ group and 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

In this surveillance, the incidence rate will be calculated for each patient group excluding those with a past history of HOI related to hyperglycemia and diabetes mellitus. 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.

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) (9) (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

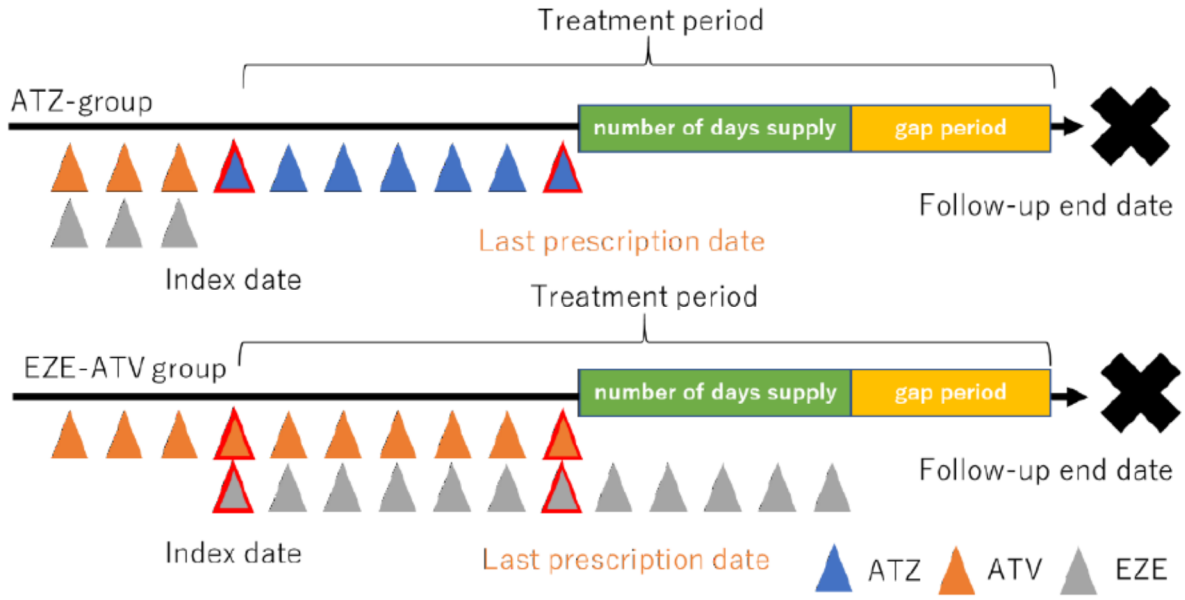
prescription date + number of days' supply at the last prescription + a gap period. The ATZ group will be considered as censored when they change to coadministration of ezetimibe and atorvastatin. The treatment period for the EZE-ATV-group is defined as from the index date (start date of coadministration) 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 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: Atorvastatin; ATZ: Atozet; EZE: Ezetimibe

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.

9.3 Surveillance population

The surveillance populations will be hypercholesterolemic patients with no past history of diabetes mellitus 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 sections 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 (10) 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-ATV-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: Anatomical Therapeutic Chemical Classification
† 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: Anatomical Therapeutic Chemical Classification
† 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, OR
  8) Patients who were diagnosed with diabetes mellitus (ICD-10 codes: E10-E14) or were using antidiabetic drugs (A10) during the lookback period, OR
  9) Patients whose blood glucose level was >200 mg/dL during the 6-month lookback period prior to the index date, OR
  10) Patients whose HbA1c level was >6.5% during the 6-month lookback period before the index date 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, OR
8) Patients who were diagnosed with diabetes mellitus (ICD-10 codes: E10-E14) or were using antidiabetic drugs (A10) during the lookback period, OR
9) Patients whose blood glucose level was >200 mg/dL during the 6-month lookback period prior to the index date, OR
10) Patients whose HbA1c level was >6.5% during the 6-month lookback period before the index date 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 analysis of HOI related to hyperglycemia and diabetes mellitus 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.

9.4.2 Outcomes

To describe the incidence of HOI related to hyperglycemia and diabetes mellitus, the outcomes targeted in this surveillance are defined as hyperglycemia and diabetes mellitus events that occur earliest during the follow-up period. Lab services are counted according to SS-MIX2. MID-NET records lab services orders and the record format is JLAC10 (11). 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 any of the diagnostic codes of hyperglycemia or diabetes mellitus are recorded in the same month, or in consecutive two months, it will be considered as an occurrence of HOI. The day of the laboratory test when any abnormal value is found is defined as the day on which the HOI occurs.

9.4.2.1 Definitions of HOI related to hyperglycemia and diabetes mellitus

- The definitions of hyperglycemia and diabetes mellitus in the primary analysis of hyperglycemia and diabetes mellitus are as follows:

Laboratory test values: [(Blood glucose level > 200 mg/dL and HbA1c > 6.5%) OR
Blood glucose levels measured twice on different days > 200 mg/dL]
AND
diagnosis code for hyperglycemia or diabetes mellitus (ICD-10)

The list of diagnosis codes for diabetes mellitus is shown 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:

The blood glucose and HbA1c levels included in the definitions of cases with hyperglycemia and diabetes mellitus in this surveillance are the same as those specified in the report of Japanese Clinical Practice Guideline for Diabetes 2019 published by the Japan Diabetes Society (8). Fasting blood glucose was not included in the diagnostic criteria because it is not determined by SS-MIX2. Laboratory abnormalities were required, and all diagnostic events and recorded events were collected by SS-MIX2.

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," "Renal disease," and "Moderate or severe liver 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: Anatomical Therapeutic Chemical Classification; DPC: Diagnosis Procedure Combination; HMG CoA: Hydroxymethylglutaryl coenzyme A; SS-MIX2: Standardized Structured Medical Information eXchange Version 2 by the Ministry of Health, Labour and Welfare
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) (9). 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 using MID-NET to investigate HOI related to hyperglycemia and diabetes mellitus.

To utilize MID-NET, we will send a data extraction script set from the MID-NET data center to the 23 participating institutions (9). 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 the risk of HOI related to hyperglycemia and diabetes mellitus 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:

Hyperglycemia: 0 case (0%)

Diabetes mellitus: 0 case (0%)

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 the incidence of HOI related to hyperglycemia and diabetes mellitus, 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 rates of HOI related to hyperglycemia and diabetes mellitus, the incidence rates of relevant HOI events will be calculated as the number of events per 1,000 person-years for the ATZ group and EZE-ATV group. For all patients, the exposure time starts at the initiation of treatment. 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," “Renal disease,” and “Moderate or severe liver disease”) if there are large differences in the distributions of these variables between the 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 related to hyperglycemia and diabetes mellitus will be calculated also in the subgroup analysis if more than 1 outcome is observed in each subgroup of the ATZ group and EZE-ATV group. 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

9.9.3 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 definitions for sensitivity analysis on the incidence of HOI related to hyperglycemia and diabetes mellitus are as mentioned below.

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.

Sensitivity analysis 1:

Definition for sensitivity analysis on the incidence of the relevant HOI using laboratory test:

(Blood glucose level > 200 mg/dL AND HbA1c > 6.5%) OR blood glucose levels measured twice on different days > 200 mg/dL

Sensitivity analysis 2:

Definition for sensitivity analysis on the incidence of the relevant HOI using another combination of laboratory test and diagnosis code:

Blood glucose level measured once or twice or more > 200 mg/dL
AND
diagnosis code for hyperglycemia or diabetes mellitus (ICD-10)

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

† 肝関連事象の発生リスクを検討する製造販売後データベース調査の評価項目に関する修正である。
Because a common statistical analysis plan has been prepared for the post-marketing database surveillance to investigate the risk of rhabdomyolysis and myopathy and that to investigate the risk of hepatic events, the abovementioned revision history is presented.

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.

In the MID-NET, during a selection period, 515 patients were prescribed ATOZET (Table 10.1-1) and 852 patients were prescribed the combination of ezetimibe and atorvastatin (Table 10.1-2). Of these patients, 7 patients were included in ATZ-group (Table 10.1-1) and 9 patients were included in EZE-ATV-group (Table 10.1-2) based on the inclusion/exclusion criteria. In addition to the exclusions because of lack of a hypercholesterolemia diagnosis and non-permitted pre-treatments, most of the remaining patients in each group were excluded because they had a history of diabetes or an elevated baseline blood glucose or HbA1c so were not eligible for analysis of the incidence of these conditions. Therefore, only 7 patients met all of the criteria for inclusion in the ATZ-group and only 9 patients met all of the criteria for inclusion in the EZE-ATV-group. Because of the extremely low number of patients and exposure time included, all analyses of patient characteristics and health outcomes of interest should be considered purely exploratory and interpreted with extreme caution. These patients are not likely to be representative and one or two values can have a large effect on the group characteristics.

The numbers of patients presented in ATZ-group and EZE-ATV-group, before application of the inclusion/exclusion criteria, in Table 10.1-1 and Table 10.1-2, include patients prescribed both ATOZET and the combination of ezetimibe and atorvastatin during the selection period (prescription was switched during the selection period).

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 Jan 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
Patients who have a history of a diagnosis of diabetes mellitus (ICD-10 code: E10-E14) or take anti-diabetic agent (A10) during the lookback period	37	7.2	8	1.6
Patients whose glucose level during the 6-month lookback period before the index date > 200 mg/dL	0	0.0	8	1.6
Patients whose HbA1c level during the 6-month lookback period before the index date > 6.5%	1	0.2	7	1.4

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
Patients who have a history of a diagnosis of diabetes mellitus (ICD-10 code: E10-E14) or take anti-diabetic agent (A10) during the lookback period	57	6.7	13	1.5
Patients whose glucose level during the 6-month lookback period before the index date > 200 mg/dL	2	0.2	11	1.3
Patients whose HbA1c level during the 6-month lookback period before the index date > 6.5%	2	0.2	9	1.1

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

Demographic and clinical characteristics of the patients included in this surveillance are shown in Table 10.2-1.

The percentage of male patients was 71.4% (5 of 7 patients) in ATZ-group and 55.6% (5 of 9 patients) in EZE-ATV-group. The age (mean ± SD) was 67.7 ± 10.6 years in ATZ-group and 58.2 ± 13.8 years in EZE-ATV-group. Since the number of the target patients was small, it appears that no interpretation could be made for similarity or difference between the two groups.

Table 10.2-1 Demographic and clinical characteristics of the patients

		ATZ-group		EZE-ATV-group	
		No.	%	No.	%
Number of Cases		7	100.0	9	100.0
Sex	Male	5	71.4	5	55.6
	Female	2	28.6	4	44.4
Age	mean	67.7	-	58.2	-
	SD	10.6	-	13.8	-
	<20	0	0.0	0	0.0
	20-29	0	0.0	0	0.0
	30-39	0	0.0	1	11.1
	40-49	0	0.0	1	11.1
	50-59	1	14.3	3	33.3
	60-69	3	42.9	2	22.2
	70-79	2	28.6	2	22.2
	80-89	1	14.3	0	0.0
	90-99	0	0.0	0	0.0
	≧100	0	0.0	0	0.0
Comorbidities					
Ischemic heart disease, Myocardial infarction		6	85.7	2	22.2
Congestive heart failure		1	14.3	4	44.4
Peripheral vascular disease		2	28.6	0	0.0
Cerebrovascular disease		0	0.0	0	0.0
Mild liver disease		1	14.3	1	11.1
Hypertension		2	28.6	3	33.3
Renal disease		0	0.0	0	0.0
Moderate or severe liver disease		0	0.0	0	0.0
Pre-treatment drugs					
HMG CoA reductase inhibitors		0	0.0	2	22.2
Fibrates		0	0.0	1	11.1
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 status of drugs contraindicated for use 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.

In both Pre- and Post-index data, no patients were prescribed any of the following drugs contraindicated for use with ATOZET: telaprevir, ombitasvir/paritaprevir/ritonavir, and glecaprevir/ribrentasvir.

ATOZET low dose (LD) was prescribed to 42.9% of patients in ATZ-group, and atorvastatin 10 mg was prescribed to 33.3% of patients in EZE-ATV-group.

ATOZET high dose (HD) was prescribed to 28.6% of patients in ATZ-group, and atorvastatin 20 mg was prescribed to none of patients in EZE-ATV-group. Atorvastatin 20 mg was marketed as a generic drug only from one pharmaceutical company, and atorvastatin 5mg 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	3	42.9		
ATZ HD	2	28.6		
Atorvastatin 10 mg			3	33.3
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 follow-up period (mean ± SD) was 0.92 ± 0.52 year in ATZ-group and 0.45 ± 0.49 year in EZE-ATV-group.

The number of patient years in the follow-up period was 6.5 for the ATZ-group and 3.6 for the EZE-ATV-group.

Table 10.2-3 Follow-up period by treatment group

		ATZ-group	EZE-ATV-group
Number of patients		7	9
Follow-up period (years)	N	7	8
	Mean	0.92	0.45
	SD	0.52	0.49
Person-years		6.5	3.6

Note: Follow-up period was confirmed using the SS-MIX2 data. In EZE-ATV-group, if a patient's follow-up period could not be confirmed by the SS-MIX2 data, the follow-up period of the patient was not calculated even if DPC data and administrative claims data of the patient were available.

10.3 Outcome data

10.3.1 Incidence of HOI related to hyperglycemia and diabetes mellitus

The incidence status of HOI related to hyperglycemia and diabetes mellitus is shown in section 10.4.1.

10.4 Main results

10.4.1 IRR of HOI related to hyperglycemia and diabetes mellitus

10.4.1.1 Main analysis

The results of analysis on the incidence of HOI related to hyperglycemia and diabetes mellitus are shown in Table 10.4-1.

No HOI events related to hyperglycemia and diabetes mellitus occurred in either group; therefore, neither IRR nor adjusted IRR was calculated.

Table 10.4-1 The incidence of HOI related to hyperglycemia and diabetes mellitus 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
7	6	0	0.00	8	3	0	0.00	-	-	-

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

10.5 Other analyses

10.5.1 Subgroup analysis on the incidence of HOI related to hyperglycemia and diabetes mellitus

Results of subgroup analysis on the incidence of HOI related to hyperglycemia and diabetes mellitus for patients with or without hepatic impairment are shown in Table 10.5-1.

Of the 7 patients in the ATZ-group, 7 patients had hepatic impairment and no patients had hepatic impairment. Of the 8 patients in the EZE-ATV-group, 2 patients had hepatic impairment and 6 patients had no hepatic impairment.

As shown in section 10.4.1.1, no HOI events related to hyperglycemia and diabetes mellitus occurred in either group; therefore, neither IRR nor adjusted IRR was calculated in subgroup analysis for hepatic impairment.

Table 10.5-1 The incidence of HOI related to hyperglycemia and diabetes mellitus for patients with or without hepatic impairment by treatment group

	ATZ-group				EZE-ATV-group				IRR*** (crude)	IRR*** (adjusted)	95%CI
	N (population)	PY*	n (event)	IR**	N (population)	PY*	n (event)	IR**			
Hepatic impairment group	0	--	0	-	2	0	0	0.00	-	-	-
Non-hepatic impairment group	7	6	0	0.00	6	3	0	0.00	-	-	-

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

10.5.2 Sensitivity analysis on the incidence of HOI related to hyperglycemia and diabetes mellitus

Table 10.5-2 shows the results of sensitivity analyses with alternative outcome definitions (laboratory values and diagnosis codes) presented in section 9.9.4 and the results of sensitivity analysis performed limiting ATZ-group to the 4 patients who were switched from atorvastatin monotherapy.

In sensitivity analyses with alternative outcome definitions, since no HOI events related to hyperglycemia and diabetes mellitus occurred in either group, neither IRR nor adjusted IRR was calculated.

In the sensitivity analysis performed limiting ATZ-group to the 4 patients who were switched from atorvastatin monotherapy, since no HOI events related to hyperglycemia and diabetes mellitus occurred in either group as shown in section 10.4.1.1, neither IRR nor adjusted IRR was calculated.

Table 10.5-2 The incidence of HOI related to hyperglycemia and diabetes mellitus by treatment group using the alternative outcome definitions

	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
other outcome definitions: (blood glucose > 200 mg/dL AND HbA1c > 6.5 %) OR blood glucose > 200 mg/dL two times on different days	7	6	0	0.00	8	3	0	0.00	-	-	-
other outcome definitions: blood glucose > 200 mg/dL once or more than once AND diagnostic codes (ICD-10) for hyperglycemia or diabetes mellitus	7	6	0	0.00	8	3	0	0.00	-	-	-
limiting ATZ-group to subjects who does not switch from coadministration of Ezetimibe and Atorvastatin	4	4	0	0.00	8	3	0	0.00	-	-	-

Note: *person-year **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

Because of the short identification period and the strict exclusion criteria for this study which eliminated patients who had specific prior drugs or no information on prior drugs as well as any patient with a history of DM or without blood glucose or HbA1c data, this study included an extremely small number of patients who were prescribed ATZ (7 patients) or coadministration of EZE and ATV (9 patients). Therefore, this study is only able to provide very limited insight into diabetes and hyperglycemia.

The analysis by hepatic impairment or the sensitivity analyses based on alternative definitions revealed no HOI related to hyperglycemia and diabetes mellitus. In this surveillance, there was no concern about hyperglycemia and diabetes mellitus associated with ATZ.

11.2 Limitations

At the time of planning this surveillance, it was estimated that there would be very few patients treated with ATOZET or combination of ezetimibe and atorvastatin even before selection of patients based on the inclusion/exclusion criteria (diagnosis of hypercholesterolemia and specific prior therapies) because of low frequency of use of these drugs. The duration of treatment in these cohorts was estimated to be relatively short. The number of patients used for analysis of HOI related to hyperglycemia and diabetes mellitus in this surveillance was small in both groups. No HOI related to hyperglycemia and diabetes mellitus was detected 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 outcome definitions:

There is no consistent view on the best algorithm for defining 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 HOI related to hyperglycemia and diabetes mellitus (e.g., laboratory values, occurrence of events such as diabetes mellitus) 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 HOI events related to hyperglycemia and diabetes mellitus occurred. The same results were obtained when sensitivity analyses with alternative outcome definitions were performed. However, because of the extremely small number of patients included in this study, no conclusion can be made regarding the effects of ATOZET on diabetes or hyperglycemia.

11.4 Generalisability

See section 11.2.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

Because of the extremely small number of patients included in this surveillance, no conclusion can be made regarding the effects of ATOZET on hyperglycemia or diabetes. The benefit-risk balance of ATOZET remains positive, and there was no concern requiring safety measures based on the limited results of this surveillance.

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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 Study Protocol

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

Annex 3 Additional Information

N.A.