Statistical Analysis Plan

NCT Number: NCT05932407

Title: A Cohort Study to Compare the Risk of Hemorrhage (Serious Intracranial Hemorrhage Such as Cerebral Hemorrhage and Subarachnoid Hemorrhage) Between Trintellix Tablets and SSRIs in Patients With Depression Using JMDC Claims Database

Study Number: Vortioxetine-4005

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Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

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

statistical analysis plan

Patients with depression using the medical information database, **JMDC claims database** and patients with depression

A Cohort Study to Compare the Risk of Haemorrhage (Serious Intracranial Haemorrhage Such as Cerebral Haemorrhage and Subarachnoid Haemorrhage) between Trintellix Tablets, **SSRI** and in Japan

Vortioxetine-4005

Ver. 2.0

Takeda Pharmaceutical Company Limited.

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. Preparation/Revision Record

Version [VERSION DATE]	Key Changes	Reason for change
1.0 [2024/3/25]	New document	-
2.0	6.5 Sensitivity analysis 2) page 48), sensitivity [2024/8/28] was determined. underlined.	Based on the agreements from the PMDA consultation (PMDA The conditions for analysis were changed as follows. Changes are < Before change > 2) GRACE PERIOD CHANGE After changing Grace Period to up to 90 days, the analysis set (analysis set [sensitivity analysis 2)) will be reorganized, and the same analyses as the case composition diagram, patient background, and primary analysis will be performed. < After change > 2) Changes to the Gap Period and the Grace Period Change Gap Period and Graee Period to "Up to 90 Days. " and changed to the analysis population (analysis population) (Sensitivity analysis, 2) and will be reorganized, and the same analyses as the case composition diagram, patient background, and primary analysis will be performed.

. Summary of the survey and summary of the statistical analysis plan

Product name	TRINTELLIX Tablets 10 mg, 20 mg
Survey title	Haemorrhages associated with TRINTELLIX Tablets and SSRIs in patients with depression using the medical information database JMDC claims database (serious headache including cerebral haemorrhage and subarachnoid haemorrhage) Cohort study to compare the risk of intradermal bleeding
Type of investigation	Post-marketing database survey
Purpose of inspection	To evaluate the relative risk of serious intracranial hemorrhage requiring hospitalization in patients with depression treated with TRINTELLIX Tablets compared to SSRI in approximately 3 years from the launch date of TRINTELLIX Tablets (November 2019 to November 2022).
Medical information data used for survey *Tano* t '—	JMDC Claims Database will be used. This database has receipt data and health checkup data provided by multiple health insurance societies. The cumulative population is approximately 14 million (as of May 2022).
Survey period (data period)	Data period: November 1, 2018 to November 30, 2023 Enrollment period: November 27, 2019 to November 30, 2022
Study design	Cohort design
Scope of patients to be surveyed	Patients with depression
Definitions of Exposure and Control Groups	Among the subjects selected according to the inclusion/exclusion criteria, the group of patients who were prescribed TRINTELLIX Tablets on the first day of prescription is defined as the exposure group, and the group of patients who were prescribed SSRI is defined as the control group.
Outcome	Regarding serious intracranial hemorrhage requiring hospitalization, there are 3 definitions combining injury/disease code (ICD-10 code), therapeutic drug (drug code based on medical service fee points), and medical practice (Hospitalization record, classification code).
Analysis Items and Methods	For the primary analysis, incidence rates (per 10,000 person-years) of the outcome during the follow-up period will be estimated in the exposure and control groups, and hazard ratios (crude and adjusted) with reference to the control group will be calculated using Cox proportional hazards models. The following analyses will be performed for secondary analyses: ・ Kaplan-Meier Time to Outcome Measures ・ Estimated Incidence Rates (/ 10,000 PY) of Outcomes by SSRI Components in the Control Group ・ Analysis similar to the primary analysis with alternative definition of outcome The following analyses will be performed as sensitivity analyses: ・ Look back period. Analysis similar to the primary analysis with different definitions of gap period, grace period, and outcome ・ The propensity score for each patient will be estimated using a logistic regression model with cohort as an objective variable and all covariates as explanatory variables, and the hazard ratio relative to the control group will be calculated using a Cox proportional hazards model with cohort and propensity score as two variables in the model.

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List of Abbreviations

Abbreviation	Official name	Japanese name
SSRI	Selective Serotonin Reuptake Inhibitor	selective serotonin reuptake inhibitor
NSAID	Non-Steroidal Anti-Inflammatory Drug	Non-Steroidal Anti-Inflammatory Drugs
DB	Database	Database
ICD	International Statistical Classification of Diseases and Related Health Problems	International Statistical Classification of Diseases and Related Health Problems
CT	Computed Tomography	computed tomography
MRI	Magnetic Resonance Imagin	magnetic resonance imaging
MRA	Magnetic Resonance Angiography	magnetic resonance angiography

Definitions of Terms

Term	Definition
Index date	Date of first prescription within enrollment period
Look back period	Period of Measurement of Each Covariate, etc.
Observation period	Period during which each subject will be observed (look back period+ follow-up period)
Prescription period	Period from the date of each prescription to the date of completion of prescription (date of prescription + number of days of prescription -1)
Duration of prescription	How long the prescription is considered to be ongoing
Gap Period	The period between consecutive prescribed periods
Grace Period	Additional period to be added as the prescription continuation period after the end of the prescription period in consideration of missed doses and persistent effects of discontinued drugs
Follow-up period	Period during which each subject will be followed up to confirm the presence or absence of occurrence of outcomes (from the day after the Index Date to the day of completing the observation period)
Data period	Period during which target data for this survey are extracted from the database
Launch Date	This drug launched on November 27, 2019
This DB	JMDC Claims Database
This drug	TRINTELLIX Tablets 10 mg and TRINTELLIX Tablets 20 mg
Health insurance claims	Medical hospitalization receipt or DPC receipt (inpatient), medical non-hospitalization receipt (outpatient), dispensing receipt (dispensing)

1. Purpose and Scope

This study will evaluate the relative risk of this drug serious intracranial hemorrhage requiring hospitalization during 3 years from the launch date of this drug (2019, November, until 2022, and November) in patients with depression compared with during SSRI treatment.

2. Sample Size and Rationale

As a result of the feasibility survey conducted using this DB prior to this survey, * the number of patients with depression requiring medication in 2019, November (launch date), - 2022 and January was approximately 172,000, and the number of patients in the exposure and control groups to whom the inclusion/exclusion criteria were applied was approximately 11,000 and 76,000, respectively. Considering that the enrollment period in this survey will be up to 2022 or November, approximately 14,000 and 101,000 subjects are expected to be enrolled in this drug and control groups, respectively.

According to a report by Renoux et al., using the Clinical Practice Research Datalink in the UK, over 1.36 million adults who first started taking an SSRI or tricyclic antidepressant between January 1 and June 30, 2014 1995 were followed up for an average of 5.8 years. During the follow-up period, 3,036 patients were diagnosed with intracranial hemorrhage (3.8 cases per 10,000 people per year, or an incidence rate of 0.00038 per 1 year), and it was reported that the risk of intracranial hemorrhage in SSR1 was increased by 17% compared to tricyclic antidepressants 1]. Since the incidence of cerebral haemorrhage is 2.4 times higher in Asians than in non-Asians, the incidence of intracranial haemorrhage per 1 year in SSRI estimated in the Japanese survey was assumed to be 0.0009.

In contrast, using the sample size calculation formula 6.9 proposed for comparative studies in post-marketing surveillance in Sample Size Design for Medicine, a sample size of 13,242 exposed (this drug) and 92,694 unexposed (control) patients can be calculated to detect a 2 -fold increase in the rate of intracranial hemorrhage with TRINTELLIX compared to an SSRI (i.e., a further 0.0009 increase in the rate per 1 year of intracranial hemorrhage), assuming a randomization ratio of 7: 1 for the control group versus this drug group, a two-sided significance level of (4) 0.05, and a power of (1 -8) 0.8 (When the one-sided significance level was 0.05, the sample sizes were 10,644 and 74,508 subjects, respectively.).

Thus, taking into account the accumulation of data, etc. in the future, it is considered that this study can be sufficiently conducted using this study, DB, and MT-MD001.

*1: Protocol Appendix 4 Information on the number of patients, etc. subject to the survey that can be obtained from the medical information database

(that) and 2)

3. Study population

Patients with depression registered in JMDC Claims Database

4. Definition of analysis sets and variables

4.1. Study Population Definitions

1.1 .1. Period covered

Data period: November 1, 2018 to November 30, 2023

Enrollment period: November 27, 2019 (date of launch) to November 30, 2022

4.12 Population Entry Criteria

Patients must meet all of the following criteria to be eligible for enrollment in the study:

1) Diagnosed with depression and prescribed this drug or SSRI during the enrollment period (Index date: Date of first prescription during enrollment period).

2) It is possible to observe the (180 days) or (look back period) for the past 6 months from the day before the Index date.

3) No this drug or SSRI or was prescribed during the look back period.

4.13 Population Exclusion Criteria

Patients meeting any of the following criteria will be excluded.

1) Look back period Intracranial hemorrhage was diagnosed.

See "4.4. Outcome Definition (Definition 2)" for the diagnosis of intracranial hemorrhage.

2) Index date, this drug, SSRI, and are used concomitantly.

4.2. Study Population Definitions

4.2.1. Exposure

Of patients in the target population, patients for whom this drug was prescribed on the Index date and patients

4.2.2. Control group

Patients in the target population who are given a prescription of SSRI on the Index date

4.3. Observation period

4.3.1. Duration of prescription

Prescription continuation period is the period from the day after the Index Date to (Grace Period) after 30 days from the final prescription completion date. In addition,

If the interval (Gap Period) between consecutive prescription periods is within 30 days, the prescription is considered to be continued. If the interval (Gap Period) between consecutive prescription periods is 31 days or more, the prescription is considered to be discontinued.

4.3.2. Start date and end date of observation period

First day of observation period: The day before 6 months in the past (180 days) from the day before Index Date

End date of observation period: among the following, Index date, the earliest date after

① Onset of outcome (intracranial hemorrhage)

(2)End of prescription period for this drug or SSRI End of prescription period for

(3)Switching to other drugs (this drug or), SSRI, and switching to

(4)With this drug, SSRI and combination

⑤ Death

(6)Withdrawal from health insurance society or termination of the agreement between health insurance society and the stock company, JMDC and JMDC

⑦ From the day after Index Date to Day 360 (end of follow-up period)

4.3.3. Follow-up period

First day of the follow-up period: Index date the day after

End date of follow-up period: End date of observation period

Follow-up period: the end date of follow-up period - the start date of follow-up period + 1

4.4. Outcome definitions

Outcome is defined as intracranial haemorrhage such as serious cerebral haemorrhage and subarachnoid haemorrhage requiring inpatient treatment that meets all of the conditions in the following definitions.

Definition 1:

1) ICD-10 code: 4) 5) with a record of ICD -10 code for any of 160 subarachnoid hemorrhage, 161 intracerebral hemorrhage, or 162 other nontraumatic intracranial hemorrhage. (excluding those with suspicion flag)

2) There is a record of hospitalization ("hospitalization or DPC in" receipt type ") in the same month as the diagnosis of intracranial haemorrhage such as cerebral haemorrhage and subarachnoid haemorrhage in 1) above.

3) A record of any of CT, MRI, or MRA tests (Category code: E 200, computed tomography (CT) imaging (per series), E 202, magnetic resonance computed tomography (MRI) imaging (per series), E 203, computed tomography) is present within the same hospitalization (the same "Receipt ID) for intracranial haemorrhage such as cerebral haemorrhage and subarachnoid haemorrhage mentioned in 2) above.
(date of outcome onset)

Definition 2:

1) In addition to the above definition for Definition 1, any of the following records (1) to (6) is present within the same hospitalization (the same receipt) for intracranial hemorrhage such as cerebral hemorrhage and subarachnoid hemorrhage according to Definition 12).

(1)Anti-edema agents: Drug Code K01F1 (for osmotherapy) 6)

(2)Nitrite and Nitrate: Drug Code C01E6)

(3)Calcium antagonists: Drug code C [086])

(4)Hemostatic agent: Active ingredient name [Tranexamic Acid] (B02A1) 1.

⑤ Preventive agent for cerebrovascular spasm: Ingredient name [Ozagrel Sodium (B01C9), fasudil hydrochloride hydrate (C04A1), clazosentan sodium (C04A1)].

⑥ Intracranial haemorrhage procedure: (Category code: K 145 Craniotomy (Trepanathion), K 147 Craniectomy (Trepanathion), K 149 Decompressive craniectomy, K 164 intracranial hematoma evacuation (Craniotomy, K 176 Cerebral aneurysm inflow vessel clipping (Performed through craniotomy, K 178, cerebrovascular procedure)) 5) 6)

Definition 3:

2) ICD-10 code: documented ICD -10 code for either intracranial hemorrhage (160 Subarachnoid haemorrhage, 161 Intracerebral haemorrhage 162 Other non-traumatic intracranial haemorrhage) or gastrointestinal hemorrhage (1850 Esophageal varices with hemorrhage, K 226 Esophagogastric junction laceration bleeding syndrome, K 250 Gastric ulcer/acute with hemorrhage, K 251 Gastric ulcer/acute with hemorrhage and perforation, K 252 Gastric ulcer/acute with both hemorrhage and perforation, K 253 Gastric ulcer/acute without hemorrhage or perforation, K 254 Gastric ulcer/chronic or unspecified with hemorrhage, K 255 Gastric ulcer/chronic or unspecified with perforation, K 256 Gastric ulcer/chronic or unspecified with both hemorrhage and perforation, K 260 Duodenal ulcer/acute with hemorrhage, K 261 Duodenal ulcer/acute with perforation, K 262 Duodenal ulcer/acute with both hemorrhage and perforation, K 250 Duodenal ulcer/acute, without hemorrhage or perforation, K 251 Duodenal ulcer/chronic or unspecified, with hemorrhage, K 252 Duodenal ulcer/chronic or unspecified, with perforation, K 253 Duodenal ulcer/chronic or unspecified, with both hemorrhage and perforation, K 254 Peptic ulcer of unspecified site/acute, with hemorrhage, K 255 Gastrojejunal ulcer/chronic or unspecified, with hemorrhage, K 256 Gastrojejunal ulcer/chronic or unspecified, with perforation, K 260 Acute hemorrhagic gastritis, K 1850 Hematemesis, K 226 Melaena, K 263 Gastrointestinal hemorrhage, unspecified). (excluding those with suspicion flag)

2)There is a record of hospitalization ("hospitalization or DPC in" receipt type) in the same month as the diagnosis of intracranial haemorrhage or gastrointestinal haemorrhage such as cerebral haemorrhage and subarachnoid haemorrhage in 1) above.

4.5. Covariates

The following covariates will be used to adjust the background of the exposure and control groups (COV 1 and 2 will be used for multivariate analysis, and COV 1~ 3 will be used for propensity score analysis.).

Table (4) -1 Covariates

Covariate Name	Time of adoption/method of derivation
COV1	
Age (continuous variable) patient data.	Age as of the Index Date is calculated from the month and year of birth of the Participant in the
Gender (Male, Female)	Obtained from the sex of subscribers in patient data
COV2	
Prescription of administration of antithrombotic drug (Yes, No)	If there is at least 1 relevant prescription information on [Index date-30] to [Index date-1], Yes. None if there is no applicable data.
Prescribed NSAID use (Yes, No)	[! ^ Early -30] If there is at least 1 relevant prescription information in 10 [-1 in 1 year], Yes. None if there is no applicable data.
Hypertension (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
COV3	
Atypical antipsychotic prescription (Yes, No)	If there is at least 1 relevant prescription information on [Index date-30] to [Index date-1], Yes. None if there is no applicable data.
Prescription of administration of phenothiazine antipsychotics (Yes, No)	If there is at least 1 relevant prescription information on [Index date-30] to [Index date-1], Yes. None if there is no applicable data.
Tricyclic antidepressant prescription (Yes, No)	If there is at least 1 relevant prescription information on [Index date-30] to [Index date-1], Yes. None if there is no applicable data.
Diabetes mellitus (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
Ischaemic heart disease (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
Ischemic cerebral infarction (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
Cerebral amyloid angiopathy (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
Cerebral aneurysm (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
Brain tumor (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
Epilepsy (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
Hepatic disease (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.

Renal failure (Yes, No)	Yes, if at least one diagnosis of the disease is available during the look back period. 1 None if there is no applicable data.
Alcoholism (Yes, No)	Yes, if at least one diagnosis of the disease is available during the look back period. 1 None if there is no applicable data.
Bleeding from the nose (Yes, No)	Yes, if at least one diagnosis of the disease is available during the look back period. 1 None if there is no applicable data.
Dyslipidemia (Yes, No)	Yes, if at least one diagnosis of the disease is available during the look back period. 1 None if there is no applicable data.
Obesity (Yes, No)	Yes, if at least one diagnosis of the disease is available during the look back period. 1 None if there is no applicable data.
Metabolic syndrome (Yes, No)	Yes, if at least one diagnosis of the disease is available during the look back period. 1 None if there is no applicable data.
Sleep apnoea syndrome (Yes, No)	Yes, if there is at least one diagnosis of the disease in the look back period. 1 None if there is no applicable data.
Peripheral Arterial Disease (Yes, No)	Yes, if at least one diagnosis of the disease is available during the look back period. 1 None if there is no applicable data.
Drinking history (Present, absent, unknown)	In the health checkup data during the look back period, ・If there is a description of “Drinking alcohol: every day ” or“ Drinking alcohol: at least 1Gou ” in at least one case Yes, Yes - "Drink: sometimes 0r, hardly drink" and "Drink amount: less than 1Gou" None if there is only description ・Otherwise, unknown
Smoking history (Present, absent, unknown)	In the health checkup data during the lookback period, ・Yes if smoking is described in at least one case. ・Absent if there is only a description of no smoking ・Otherwise, unknown

5. GENERAL STUDY CONSIDERATIONS

5.1. Descriptive statistics

For categorical and quantitative data, descriptive statistics shown in Table, 5. -1 and will be calculated.

Table (5) -1 Descriptive statistics to be calculated

Data type	Summary Type	Statistics to be calculated
Categorical data	Frequency table	Number and percentage of patients
Quantitative data	Summary statistics	Number of patients, arithmetic mean, standard deviation, Minimum, 14 quantiles, median, 34 quantiles, maximum

5.2. Display of numerical values

Descriptive statistics are presented in a table format 5 -2 according to.

Tables 5 -2 and Presentation of descriptive statistics

Descriptive statistics	Labeling
Number of patients	Display as an integer.
Percentage	Round to one decimal place.
Arithmetic mean, standard deviation, 14 minutes quantiles, median, 34 quantiles	Round up to +2 significant digits of data and present with +1 significant digits of data.
Min, Max	Display the data with the same number of significant digits as the data.
Hazard ratio, confidence interval of hazard ratio Interval	Round off to one decimal place.

5.3. Software Used for Aggregate Analysis

SAS ® System Release 9.4 Use the above.

5.4. Significance level and confidence interval

Unless otherwise specified, the significance level for hypothesis testing will be two-sided 5% and the confidence interval will be two-sided 95%.

5.5. Handling of missing data

Categories of "Unknown/Not specified " should be added as needed.

5.6. Handling of Outliers

Outliers will not be handled in a special way in principle.

6. Analysis Methods

6.1. Patient composition

Analyzed: all patients

Analysis item: Number of patients enrolled in the target population

Patients excluded from study population

Number of patients in exposure and control groups

Analysis procedure: For the above analytical variables, frequencies will be tabulated. The number of patients included and excluded will be tabulated for each reason for inclusion and exclusion.

A Calculation of frequencies

62 Patient characteristics

Analysis population: Analysis population

Analysis item: 4.5 Covariates items

Age (years) (category) 1)	0-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-
Age (years) (category) 2)	0-19, 20-39, 40-59, 60-
Age (years) (category) 3)	0-17, 18-64, 65-

Analysis procedure: For the above analytical variables, frequency tabulation of categorical data and quantitative data

Summary statistics of data will be calculated. At that time, the standardized difference between groups was calculated for each item.

Yes

6.3. Primary Analysis

Analysis population:	Analysis Sets
Outcome:	Outcome (definition) 2)
Period covered:	Follow-up period
Analysis Conventions:	The incidence of outcomes per 10,000 person-years was calculated for each exposure and control group. Also, a Cox proportional hazards model will be used to calculate the hazard ratio with 95% confidence interval referring to the control group.

6.4. Secondary Analyses

1) Kaplan-Meier curve

Analysis population:	Analysis Sets
Outcome:	Outcome (definition) 2)
Period covered:	Follow-up period
Analysis Conventions:	Cumulative Incidence of Outcomes by Exposure and Control Group, Kaplan-Meier, and Plot curves. N

The number of risk groups, the number of outcomes, and the number of censored subjects will be calculated by exposure and control group.

(a)

2) SSRI and other risks

Analysis population:	Analysis Set (Control Group)
	Outcome (Definition) 2)
Outcome:	
Period covered:	Follow-up period
Stratification factors:	SSRI • Escitalopram Oxalate • Sertraline Hydrochloride • Paroxetine Hydrochloride • Fluvoxamine Maleate • Above, 2, and Use of more than one type
Analysis Conventions:	Incidence of outcome by stratification factor Estimate (/ 10,000 person-years)

3) Outcome (definition) 3)

Analysis population:	Analysis Sets
	Outcome (definition) 3)
Outcome:	
Period covered:	Follow-up period
Analysis Conventions:	The incidence of outcomes per 10,000 person-years was calculated for each exposure and control group. Also, a Cox proportional hazards model will be used to calculate the hazard ratio with 95% confidence interval referring to the control group.

4) SSRI, different risk (definition), 3)

Analysis population:	Analysis Set (Control Group)
	Outcome (Definition) 3)
Outcome:	
Period covered:	Follow-up period
Stratification factors:	SSRI • Escitalopram Oxalate • Sertraline Hydrochloride • Paroxetine Hydrochloride • Fluvoxamine Maleate • Above, 2, and Use of more than one type
Analysis Conventions:	Incidence of outcome by stratification factor Estimate (/ 10,000 person-years)

6.5. Sensitivity analyses

The same analysis as the primary analysis will be performed with the following conditions.

1) Change of the look back period and Change of

After changing the look back period to 1 year and (days) from the day before the Index Date to the past 1 year and (360 days), the analysis set (analysis set [sensitivity analysis 1]) will be reorganized, and the same analyses as the figure of patient composition, patient background, and primary analysis will be performed.

2) Changes in Gap Period and Grace Period and

After changing the Gap Period and Grace Period to up to 90 days, the analysis set (analysis set [sensitivity analysis 2)) will be reorganized, and the same analyses as the figure of patient composition, patient background, and primary analysis will be performed.

3) Change in outcome definition

The same analysis as the primary analysis will be performed for the outcome (definition 1) and outcome (modified definition 2 *).

*Definition, 2 and were changed to (1) to (3) below.

① The definition of the same hospitalization is "the same ' Receipt ID or hospitalization in the month following the start of hospitalization ' Receipt ID. "

② For drugs, only injections are applicable.

③ Suspect flag is not considered for injuries/diseases

4) Adjustments for propensity score

Analyzed:	Analysis Sets
Outcome: Outcome (definition) 2)	
Period covered:	Follow-up period
Analysis Conventions:	Logistic regression with the cohort as an objective variable, COV 1~ 3 and covariates of COV as explanatory variables
	The propensity score will be estimated for each patient using the model, and the hazard ratio for this drug to the control group will be calculated using the Cox proportional hazards model with the exposure and 2 variables for propensity score in the model.

7. APPENDICES

7.1. References

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4) Sacco R, et al. An updated definition of stroke for the 21st Century. A statement for healthcare professionals fromthe American Heart Association/American Stroke Association. Strok Epi 2013; 44: 2064 -2089.

5) Kazuya F, et al., Accuracy of Japanese claims data in identifying diabetes-related complications.Pharmacoepidemio1 Drug Saf. 2021;30:594-601.

6) Guidelines for the Treatment of Stroke 2021 The Committee for Guidelines for the Treatment of Stroke of the Japan Stroke Society

7) Masao I, et al., Gastrointestinal bleeding risk of selective serotonin reuptake inhibitors by level of kidney function:A population-based cohort study. Br J Clin Pharmacol 2018; 84:2142-2151.

7.2. Induction rules, statistical methods

Tables 7 -1 and Analytical Handling

Item	Definition
Look back period	From Day – 180 to 1 Day Before Index Date Injuries and illnesses are judged "on a monthly basis." Specifically, the 6 months before the month to which the Index Date belongs - the month to which the Index Date belongs - will be considered as the target period. .
Look back period (sensitivity analysis 1): Period from day − 360 to the day before the index date	Injuries and illnesses are judged "on a monthly basis." Specifically, the target period is determined to be the month to which the Index Date belongs, which is 12 months before the month to which the Index Date belongs. Yes.
Duration of prescription completion date (grace period).	Prescription continuation period is the period from the day after the Index Date to 30 days after the final prescription Yes. If the interval (gap period) between consecutive prescription periods is ≤ 30 days, it will be considered as prescription continued. If the interval (gap period) between consecutive prescription periods is ≥ 31 days, it will be
Age calculated in the following manner.	The first day of the month of birth of an enrollee will be considered as the birth date, and the age on the Index Date will be . ■Index if the birth date of the year has passed (Date of birth (month and day), Index date Date of birth (month and day)) Index date, Year of year of 1 year of birth ■Index If the birth date in the year has not passed (month and day of birth) > Index date month and day of Index Date Year of – Year of Birth Date -1
Incidence (person-year method)	Incidence rate (/ 10,000 patient-years) = (Number of patients/Total follow-up period of target patients) X10000 * The total follow-up period of target patients should be summed up by the number of days and then divided by 365.25.