Clinical Study Protocol

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

Post-Marketing Database Study Protocol
< Trintellix Tablets 10 mg and 20 mg>

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

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**Vortioxetine-4005**
Version No.	**Ver. 1.3**
Date of preparation	**6 September 2024**

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1. Study Protocol Update History

Ver	Date of finalization/ Date of update	Description of change	Reason for change
1.0	3 April 2023	Newly prepared	-
1.1	1 September 2023	Minor change	Addition of milestones, addition of contractors, and adjustment of descriptions
1.2	3 June 2024	Minor change	Change in the organizational chart for the study, change in the scope of operations commissioned to the epidemiological and medical advisor, addition of medical advisor, change in the company name of the contractor and addition of operations, "updates of information of Appendices 1, 2 and 3," and adjustment of descriptions
1.3	6 September 2024	Minor change	Update of re-examination period and completion time, correction of error in writing and description adjustment for sensitivity analysis

2. Outline of the Product

Outline of the Product			
Date of market authorization	20 September 2019	Therapeutic category	87117
Re-examination period	10 years	Approval number	[1] 30100AMX00246000 [2] 30100AMX00247000
International birth date	30 September 2013		
Brand name	[1] Trintellix Tablets 10 mg [2] Trintellix Tablets 20 mg		
Active ingredient	Vortioxetine hydrobromide		
Strength and dosage form	[1] Film-coated tablets, each containing 10 mg of vortioxetine (12.71 mg of vortioxetine hydrobromide) [2] Film-coated tablets, each containing 20 mg of vortioxetine (25.42 mg of vortioxetine hydrobromide)		
Dosage and administration	The usual adult dosage for oral use is 10 mg of vortioxetine once daily. The dose may be adjusted as appropriate within the range not exceeding 20 mg per day according to the patient's condition. The dose should be increased at intervals of at least 1 week.		
Indications	Depression/depressive state		
Conditions for approval	Develop a risk management plan and implement it appropriately.		

3. Items to be Discussed in the Study

The risk management plan for Trintellix Tablets (hereinafter referred to as "Trintellix") has selected "hemorrhage" as an important potential risk. Of the hemorrhage events, this study targeted serious intracranial hemorrhages, such as cerebral and subarachnoid hemorrhages. Hereafter, serious intracranial hemorrhages, such as cerebral and subarachnoid hemorrhages, are referred to as "intracranial hemorrhage."

(Excerpted from the Trintellix risk management plan)

Important potential risks (only hemorrhage extracted)
Hemorrhage
Reason why it is identified as an important potential risk: Serotonin is involved in platelet aggregation. Trintellix not only acts on multiple 5-hydroxytryptamine (5-HT) receptors, but also inhibits serotonin transporter (SERT). Therefore, Trintellix inhibits reuptake of serotonin, presumably inhibiting platelet aggregation and causing bleeding. A combined summary of the phase 2/3 global study, including Japan (Study CCT-002), and Japanese phase 3 controlled studies (Studies CCT-003 and CCT-004) in patients with major depressive disorder revealed that the incidence of hemorrhage-related adverse events* was 1.1% (5/436 patients) in the placebo group, 0.9% (4/435 patients) in the Trintellix 10 mg group, and 1.0% (3/313 patients) in the Trintellix 20 mg group. In Study OCT-001, a long-term study, the incidence was 3.6% (10/280 participants). Among these events, the outcome of death was reported in the 20 mg group in one patient with subarachnoid hemorrhage, which was not related to Trintellix, and one patient with cerebral hemorrhage related to Trintellix. Hemorrhage-related adverse events* (including serious cases) have been reported in the post-marketing setting in foreign countries. However, there is no evidence strongly suggesting a relationship between Trintellix administration and serious intracranial hemorrhages including cerebral and subarachnoid hemorrhages. As described above, the results of clinical studies and overseas post-marketing reports have demonstrated no clear relationship between Trintellix and hemorrhage-related adverse events. However, the possibility of hemorrhage occurring in patients receiving Trintellix cannot be ruled out. Therefore, hemorrhage is listed as an important potential risk of this drug. *: Events (Preferred Terms) included in narrow scope of "haemorrhage terms (excl laboratory terms)" in standardized MedDRA queries (SMQ)
Contents of pharmacovigilance activities and reasons for selecting them: [Contents] • Routine pharmacovigilance activities • As an additional pharmacovigilance activity, a post-marketing database study (hemorrhage) will be conducted. [Reason for selection] Hemorrhage is an adverse reaction reported with some drugs that inhibit serotonin-reuptake. However, there is no evidence strongly suggesting the relationship between Trintellix administration and serious intracranial hemorrhages including cerebral and subarachnoid hemorrhages. Therefore, a post-marketing database study with a control group will be conducted to evaluate the relative risks of Trintellix therapy to SSRI treatment with respect to serious intracranial hemorrhage requiring hospitalization.
Contents of risk minimization activities and reasons for selecting them: [Contents] Describe hemorrhage in the package insert sections, "9.1 Patients with Complication or History of Diseases," "10.2 Precautions for Co-administration," and "11.2 Other Adverse Reactions," and in the patient medication guide as routine risk minimization activities for calling attention. [Reason for selection]

	To provide information on the event to healthcare professionals to promote their understanding of proper use of Trintellix, considering the importance of the event, although the relationship between Trintellix and hemorrhage is unclear.

4. Outline of the Study Protocol

Section	Summary
Items to be discussed in the study	Hemorrhage (important potential risk)
Study objective (research question)	To evaluate the relative risks of Trintellix therapy to SSRI treatment with respect to serious intracranial hemorrhage requiring hospitalization in patients with depression for a period of approximately 3 years after the launch of Trintellix (November 2019 to November 2022).
Summary of the medical information database used for the study	JMDC Claims Database will be used. The database accumulates health insurance claims data and medical checkup data from multiple health insurance societies. The cumulative population is approximately 14 million (as of May 2022).
Study period (data period)	Data period: November 2018 to November 2023 Enrollment period: November 2019 (launch date) to November 2022
Study design	Cohort design
Scope of study subjects	Patients with depression
Definition of exposure/control and matters used for them	Prescribing information
Outcome definitions and matters used for them	Injury/disease code for intracranial hemorrhage, therapeutic drugs, and medical practice, among others.
Items to be analyzed and methods	Primary analysis: • Using the outcome Definition 2*, the incidence rate of intracranial hemorrhage (per 10,000 person-years) in the Trintellix and control groups will be estimated, and the hazard ratio of Trintellix relative to the control will be calculated (crude and adjusted). Covariates: Covariance 1 [COV1] age and sex; and covariance 2 [COV2] antithrombotic drug administration, non-steroidal anti-inflammatory drug (NSAID) administration, and hypertension Secondary analysis: • The survival function will be graphically presented using the Kaplan–Meier method, and the time to onset of intracranial hemorrhage will be evaluated. • Using the outcome Definition 2*, the incidence rate of intracranial hemorrhage (per 10,000 person-years) with each SSRI* will be estimated in the control group. If there is a large difference in the incidence rate of outcomes between SSRIs, an additional analysis with an appropriate control group will be performed to appropriately interpret the relative risks of Trintellix to SSRIs for intracranial hemorrhage. • Using the outcome Definition 3*, the incidence rate of serious hemorrhage requiring hospitalization (intracranial or gastrointestinal hemorrhage) (per 10,000 person-years) in the Trintellix and control groups will be estimated, and the hazard ratio of Trintellix relative to the control will be calculated (crude and adjusted). Covariates: [COV1] age and sex; and [COV2] antithrombotic

	drug administration, NSAID administration, and hypertension • Using the outcome Definition 3*, the incidence rate of serious hemorrhage (intracranial or gastrointestinal hemorrhage) (per 10,000 person-years) with each SSRI* will be estimated in the control group. If there is a large difference in the incidence rate of outcomes between SSRIs, an additional analysis with an appropriate control group will be performed to appropriately interpret the relative risks of Trintellix to SSRIs for serious hemorrhage (intracranial or gastrointestinal hemorrhage). * Classify by the name of the ingredient administered at the index date Sensitivity analysis: • The robustness of the primary analysis will be confirmed by observing how much the results of the primary analysis is changed by each of the following changes: change of the look-back period (changed to a period of 1 year [360 days] prior to the day before the index date), change of the prescription continuation period (the gap period and the grace period are changed to 90 days), and change of the definition of outcome (changed to Definition 1*; for Definition 2*, "within the same hospitalization" is defined as "the same claim ID or the hospitalization claim ID in the following month after the start of hospitalization," the drug is changed to injection only, and the suspect flag is changed to "not considered"). • In addition to [COV1] and [COV2], to adjust approximately 20 covariates (covariance 3 [COV3]) that are suggested to possibly affect the outcome in the preceding research and the Trintellix package insert, the covariates of COV1 to COV3 will be combined in one propensity score, which will be added to the models (adjustment). Then, the adjusted hazard ratio of Trintellix relative to the control group will be calculated. *See "13.6. Outcome Definitions and Matters Used for Them."

5. Definition of Terms

(Alphabetical/Japanese alphabetical order)

Term	Definition
Gap period	Period between consecutive prescription periods
Grace period	The period to be added following the end of the prescription period, considering leftover drugs or persistent effects of the discontinued drug
Index date	Date of first prescription within the enrollment period
Look back period	Period to measure each covariate
New user	New prescription recipient
Observation period	Period to observe each patient (look-back period + follow-up period)
Date of approval	20 September 2019 when Trintellix was approved
Prescription period	Period from each prescription date to prescription end date (prescription date + prescription days - 1 day)
Prescription continuation period	Period during which the prescription is deemed to be continued
Follow-up period	Period to follow up each patient to confirm the onset (Yes/No) of outcome (from the following day of the index date to the end day of the observation period)
Data period	Period to extract data targeted in this study from the database
Launch date	27 November 2019 when Trintellix was launched
The DB	JMDC Claims Database
Trintellix	Trintellix Tablets 10 mg and 20 mg
Health insurance claim	Medical hospitalization claims or DPC claims (inpatient), medical non-hospitalization claims (outpatient), and dispensing claims (dispensing)

6. Definition of Abbreviations

(Alphabetical/Japanese alphabetical order)

Abbreviations	Formal name
SSRI	Selective Serotonin Reuptake Inhibitor
5-HT	5-hydroxytryptamine
SERT	Serotonin transporter
SMQ	Standardized MedDRA Queries
NSAID	Non-Steroidal Anti-Inflammatory Drug
DB	Database
RMP	Risk Management Plan
ICD	International Statistical Classification of Diseases and Related Health Problems
ATC classification	Anatomical Therapeutic Chemical Classification
PMDA	Pharmaceuticals and Medical Devices Agency
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography

7. Study Process

7.1. Study Process Chart

Milestones	Scheduled time
Finalization of the study protocol	April 2023
Data collection completed	November 2023
Analysis data set lock	July 2024
Analysis completed (study completed)	July 2024
Evaluation of analysis results and finalization of study results report	January 2025
End of re-examination period	September 2029

7.2. Scheduled Milestones to Evaluate the Study Progress and Obtained Results, or Make a Report to the Pharmaceuticals and Medical Devices Agency, and Their Rationale

Time to prepare the report: A report will be prepared at the end of the study period.

7.3. Additional Measures That May Be Taken Based on the Results of the Study and the Decision Criteria for Its Initiation

Review the risk management plan, including the following information, at the scheduled milestones.

- The necessity of changing the contents of the study plan, including the addition of new safety specifications, will be examined.
- The necessity of developing a risk-minimization plan for new safety specifications will be examined.

7.4. Publication of Results

The results of this study will be published in a research paper.

8. Organizational Structure for Conducting the Study

8.1. Organizational Chart for the Study

See Attachment.

8.2. Medical Expert

Epidemiological and medical advisor

[redacted],

[redacted]

[Scope of commissioned operations]

- Advice on the preparation and revision of the protocol for this post-marketing database study
- Advice on the preparation and revision of the statistical analysis plan of this study
- Other advice that requires various medical judgments to conduct this post-marketing database study

*Contract terminated on 30 April 2024

Medical advisor

[redacted],

[redacted]

[Scope of commissioned operations]

- Advice on the preparation and revision of the clinical study report of this study
- Other advice that requires various medical judgments to conduct this post-marketing database study

*Contract started on 17 May 2024

8.3. Name and Address of the Contractor and the Scope of the Outsourced Operations

Contractor

[redacted].

[redacted]

Details of operations: Support for preparing the study plan, data extraction, and other associated operations

Contractor

[redacted]

Details of operations: Statistical analysis (preparation of the dataset for analysis) and other associated operations

Contractor

[redacted]

[redacted]

Details of operations: Storage of records and medical writing

9. Study Objective (Research Question)

To evaluate the relative risks of Trintellix therapy to SSRI treatment with respect to serious intracranial hemorrhage requiring hospitalization in patients with depression for approximately 3 years after the launch of Trintellix (November 2019 to November 2022).

10. Background of the Study

Trintellix is indicated for “depression and depressive state,” and as with other approved antidepressants, this drug can be a new treatment option for depression.

Trintellix-related hemorrhage has been identified as an important potential risk factor for the risk management plan (RMP). Serotonin is involved in platelet aggregation. Trintellix not only acts on multiple 5-HT receptors, but also inhibits SERT. Therefore, Trintellix inhibits the reuptake of serotonin, thereby presumably inhibiting platelet aggregation and causing bleeding. A combined summary of the phase 2/3 global study including Japan (Study CCT-002) and Japanese phase 3 controlled studies (Studies CCT-003 and CCT-004) in patients with major depressive disorder revealed that the incidence rate of hemorrhage-related adverse events* was 1.1% (5/436 patients) in the placebo group, 0.9% (4/435 patients) in the Trintellix 10 mg group, and 1.0% (3/313 patients) in the Trintellix 20 mg group. In Study OCT-001, a long-term study, the incidence rate was 3.6% (10/280 patients). Among these events, death was reported in one patient with cerebral hemorrhage, which was related to Trintellix, and one patient with subarachnoid hemorrhage, which unrelated to Trintellix. Hemorrhage-related adverse events* (including serious cases) have been reported in the post-marketing setting in foreign countries. However, there is no evidence strongly suggesting a relationship between Trintellix administration and serious intracranial hemorrhages, such as cerebral and subarachnoid hemorrhages. Therefore, we decided to investigate the onset of hemorrhage in patients with depression who use Trintellix in a post-marketing setting.

*: Events (Preferred Terms) included in narrow scope of “haemorrhage terms (excl laboratory terms)” in SMQ

11. Summary of the Medical Information Database Used for the Study

In this study, the JMDC Claims Database (hereinafter referred to as the DB) provided by JMDC Inc. (hereinafter referred to as JMDC) will be used. The DB promotes health services in health insurance societies. JMDC Inc. has accumulated data as anonymized personal information after obtaining permission for third-party use of the medical care provided in January 2005. The number of health insurance societies contracted with JMDC is annually increasing, and the cumulative number of participants in the DB is approximately 14 million as of February 2022.

The DB consists of members (insured persons and their dependents) of health insurance societies and includes member information (such as age, sex, and insurance coverage period) and health insurance claims information (such as name of injury/disease, prescribed drugs, and medical treatment). The names of injuries/diseases are coded using the International Statistical Classification of Diseases and Related Health Problems (ICD)-10, and prescribed drugs are coded using the Anatomical Therapeutic Chemical (ATC) classification. It is possible to track the behavior of visiting hospitals, even if the medical institution or dispensing pharmacy changes or multiple visits are made unless a member withdraws from the health insurance society after the health insurance society starts a contract with JMDC. However, as the DB is derived from health insurance societies, it does not include information on older adults aged 75 years or older, or information from the National Health Insurance, Mutual Aid Association, and other insurers not contracted by JMDC. Additionally, the DB includes a few older adults aged 65 years or older and has no test values other than the results of medical checkups.

For the reliability of the DB, the procedures are audited in accordance with the “DB Study Management Tool” released by the Pharmaceuticals and Medical Devices Agency (PMDA).

In a feasibility study conducted prior to the study, the number of patients with depression requiring drug therapy from November 2019 (launch date) to January 2022 was approximately 172,000. The number of patients in the Trintellix and control groups satisfying the inclusion/exclusion criteria was approximately 11,000 and 76,000, respectively.

The study period (data period) was from November 2018 to November 2023.

The start of the data period was decided as November 2018, the month obtained by going back 1 year (360 days) from the date of launch as the look-back period, and the end of the data period was decided as November 2023.

12. Items to Be Investigated

Attached in Appendix 1.

13. Method of Study

13.1. Study Period (Data Period)

Data period: November 2018 to November 2023

Enrollment period: November 2019 (launch date) to November 2022

13.2. Study Design

The study employed a cohort design.

A cohort design was used to estimate the incidence rate of hemorrhage in the exposure and control groups. The risk of intracranial hemorrhage will be assessed, including the effects of Trintellix exposure duration. The exposure and control groups will include new users of Trintellix or other antidepressant SSRIs (hereinafter referred to as SSRIs).

13.3. Scope of Study Participants

Based on the inclusion and exclusion criteria and observation period, the study participants are defined below. The disease and drug codes are presented in Appendix 2.

13.3.1. Inclusion Criteria

1) Patients diagnosed with depression and prescribed Trintellix or an SSRI during the enrollment period (index date: date of first prescription during the enrollment period).
2) Patients who can be observed for 6 months (180 days) prior to the day before the index date (look-back period).
3) No prescription of Trintellix or an SSRI during the look-back period.

Rationale:

1) This criterion is specified to enroll patients with depression requiring Trintellix or an SSRI.
2) If there are multiple prescriptions within this period, the earliest prescription will be adopted as the first.
3) This criterion is specified as the period for obtaining the covariates. The look-back period is specified as a period of 6 months (180 days) prior to the day before the index date based on the following: the prescription period of SSRIs for one prescription is assumed to be up to 3 months, and such patients could have visited the hospital twice during this period.
4) This criterion is specified to include patients who have not been prescribed Trintellix or SSRIs during the look-back period as new users.

13.3.2. Exclusion Criteria

1) A diagnosis of intracranial hemorrhage during the look-back period.
   For the diagnosis of intracranial hemorrhage, see "13.6. Outcome Definitions and Matters Used for Them."
2) Concomitant use of Trintellix and SSRIs on the index date.

Rationale:

1) and 2) These criteria are specified to understand the relationship of the onset of new events after prescription of Trintellix or an SSRI.

The inclusion of patients with recurrent intracranial hemorrhage in the primary analysis cannot be ruled out. Therefore, a sensitivity analysis will be performed with a look-back period set as 1 year (360 days) prior to the day before the index date, to confirm whether new events are

appropriately captured.

13.3.3. Definition of Observation Period

The observation period for each patient is defined as follows.
Starting date of the observation period: 6 months (180 days) before the index date
End date of the observation period: Earliest date among the following:

1) Onset of outcome (intracranial hemorrhage)
2) End of Trintellix or SSRI prescription continuation period
3) Switching to other drugs (Trintellix or SSRIs)
4) Combined use of Trintellix and SSRIs
5) Death
6) Withdrawal from health insurance societies or termination of a contract between health insurance societies and JMDC
7) 360 days following the day after the index date (completion of follow-up period)

Rationale:

5) The Treatment Guidelines by the Japanese Society of Mood Disorders describes the principle of depression treatment as follows: "The length of the observation period, which is set up to determine whether the patient responds to the first-line drug, should also be determined on a case-by-case basis. It is often difficult to determine the presence of a response at 3–4 weeks, although sometimes the assessment can be made slightly earlier (e.g., 2 weeks). We often experience antidepressant effects emerging over a period of 4 to 6 weeks or 8 weeks in some cases.[1)]" For maintenance therapy, the Guidelines states as follows: "There is an opinion that in patients in the first episode achieving remission with a combination of an antipsychotic and an antidepressant, the antipsychotic and the antidepressant should be continued for several months and at least 1 year, respectively.[1) 2)]" According to an article by Christel et al, the risk of intracranial hemorrhage associated with SSRIs is the highest during the first 30 days following the start of treatment, and almost no events have been observed thereafter.[3)] Therefore, the follow-up period in this study is set as 360 days.
6) For the health insurance claims data, the chronological order cannot be determined for data on the same day. The start of the follow-up period is defined as the day after the index date.

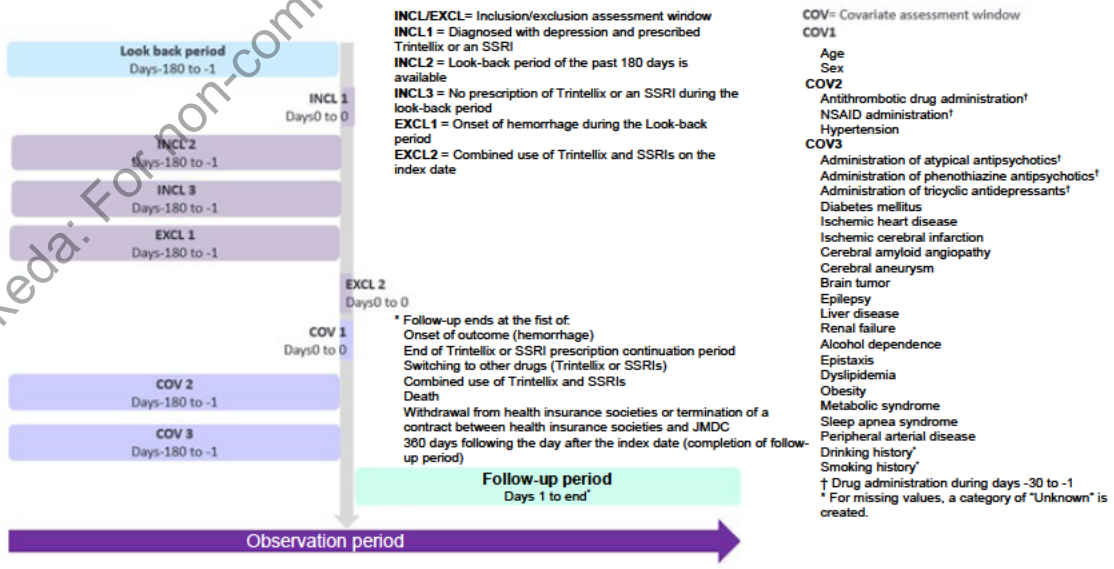


Fig. 1: Outline of the Study Design

13.4. Definition of Exposure and Control and Matters Used for Them

Exposure is defined as the prescription of Trintellix and SSRIs for the controls. Drug codes are provided in Appendix 2.

The prescription continuation period is defined as the period from the day after the index date to 30 days after the last prescription end date (grace period). If the interval (gap period) between consecutive prescription periods is within 30 days, the prescription will be considered to be continued. If the interval (gap period) between consecutive prescription periods is 31 days or longer, the prescription will be considered to be discontinued.

Rationale:

1) SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), or noradrenergic and specific serotonergic antidepressants (NaSSAs) are often used as first-line antidepressants for moderate depression, and all antidepressants can be candidates as first-line drugs for severe depression.[1)] Moreover, because Trintellix has an inhibitory effect on SERT, the drug may cause bleeding owing to mechanism of action. Similarly, SSRIs have been reported to inhibit platelet aggregation via SERT inhibitory action, potentially resulting in bleeding. SSRIs were selected as controls.
2) The Japanese medical fee system advises careful consideration for prescriptions exceeding 30 days. Depression treatment appropriately provided by monitoring the clinical course, including the dosing regimen and treatment period of the drug,[1)] is also desirable. The standard prescription period is considered to be 30 days, and the gap and grace periods are set to 30 days, considering the possibility of delayed visits and missed doses.

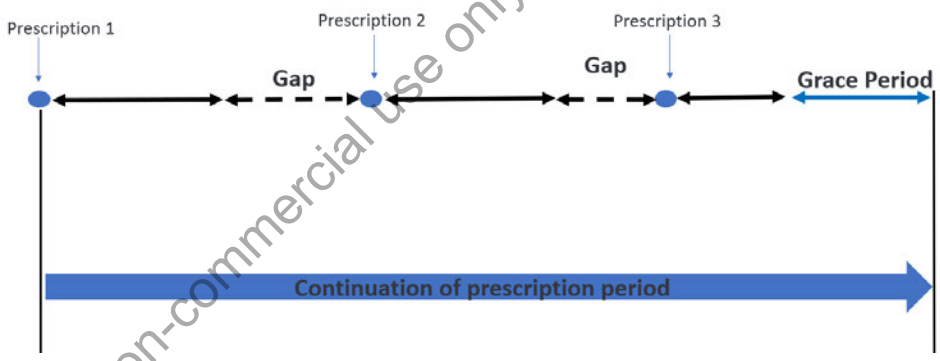
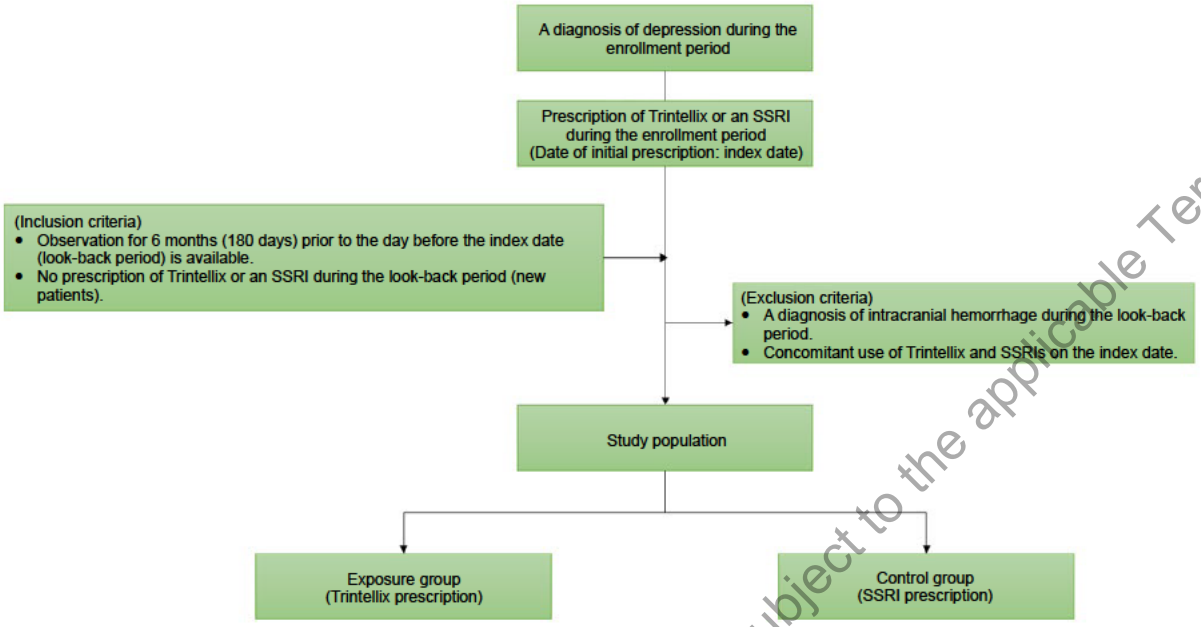


Fig. 2: Prescription Continuation Period

In this study, for the prescription continuation period, a sensitivity analysis will be performed with the gap and grace periods of 90 days as the case for the longest prescription days to capture outcomes more broadly.

13.5. Flow Chart



13.6. Outcome Definitions and Matters Used for Them

An outcome is defined as serious intracranial hemorrhage, such as cerebral hemorrhage and subarachnoid hemorrhage, that requires inpatient treatment and meets all of the conditions for each definition as follows:

Definition 1:

1) ICD-10 codes: There are records of ICD-10 codes from any of the following: I60 subarachnoid hemorrhage, I61 intracerebral hemorrhage, I62 other nontraumatic intracranial hemorrhage.[4) 5)] (excluding cases with suspect flags)
2) There are records of hospitalization ("hospitalization or diagnosis procedure combination [DPC]" in "claim type") in the same month as the diagnosis of intracranial hemorrhage, such as cerebral hemorrhage and subarachnoid hemorrhage in 1) above.
3) There are records of any of the following tests within the same hospitalization (same "claim identification [ID]") due to intracranial hemorrhage, such as cerebral hemorrhage and subarachnoid hemorrhage in 2) above: computed tomography (CT), magnetic resonance imaging (MRI), or magnetic resonance angiography (MRA) (category code: E200 computed tomography [CT] [per set], E202 magnetic resonance imaging [MRI] [per set], and E203 computed tomography diagnosis).[4)] (Date of onset of outcome)

Definition 2:

1) In addition to Definition 1, any of the following (1) to (6) is recorded within the same hospitalization (same "claim ID") due to intracranial hemorrhage, such as cerebral hemorrhage and subarachnoid hemorrhage in 2) of Definition 1.
    (1) Anti-edema agents: drug code K01F1 (for osmotherapy)[6)]
    (2) Nitrite and nitrate: drug code C01E[6)]
    (3) Calcium antagonist: drug code C08[6)]
    (4) Hemostatic drug: name of ingredient (tranexamic acid [B02A1])[6)]
    (5) Cerebrovascular spasm prophylactic drugs: name of ingredient (ozagrel sodium [B01C9], fasudil hydrochloride hydrate [C04A1], clazosentan sodium [C04A1])[6)]
    (6) Intracranial hemorrhage treatment: (category codes: K145 trepanning ventricular drainage, K147 trepanation, K149 decompressive craniectomy, K164 intracranial hematoma evacuation [performed with craniotomy], K176 cerebral aneurysm inflow vessel clipping [performed with craniotomy], and K178 cerebrovascular surgery)[5) 6)]

Definition 3:

1) ICD-10 codes: There are records of ICD-10 codes from any of the following (excluding cases with suspect flags): intracranial hemorrhage (I60 subarachnoid hemorrhage, I61 intracerebral hemorrhage, I62 other nontraumatic intracranial hemorrhage); or gastrointestinal hemorrhage[7)] (I850 esophageal varices with bleeding, K226 gastro-esophageal laceration-hemorrhage syndrome, K250 gastric ulcer/acute with hemorrhage, K251 gastric ulcer/acute with perforation, K252 gastric ulcer/acute with both hemorrhage and perforation, K253 gastric ulcer/acute without hemorrhage or perforation, K254 gastric ulcer/chronic or unspecified with hemorrhage, K255 gastric ulcer/chronic or unspecified with perforation, K256 gastric ulcer/chronic or unspecified with both hemorrhage and perforation, K260 duodenal ulcer/acute with hemorrhage, K261 duodenal ulcer/acute with perforation, K262 duodenal ulcer/acute with both hemorrhage and perforation, K263 duodenal ulcer/acute without hemorrhage or perforation, K264 duodenal ulcer/chronic or unspecified with hemorrhage, K265 duodenal ulcer/chronic or unspecified with perforation, K266 duodenal ulcer/chronic or unspecified with both hemorrhage and perforation, K270 peptic ulcer, site unspecified/acute with hemorrhage, K284 gastrojejunal ulcer/chronic or unspecified with hemorrhage, K285 gastrojejunal ulcer/chronic or unspecified with perforation, K290 acute hemorrhagic gastritis, K920 hematemesis, K921 melena, K922

gastrointestinal hemorrhage, unspecified)

2) There are records of hospitalization ("hospitalization or DPC" in "claim type") in the same month as the diagnosis of intracranial hemorrhage, such as cerebral hemorrhage and subarachnoid hemorrhage or gastrointestinal hemorrhage in 1) above.

Rationale:

When serious intracranial hemorrhage occurs, patients are expected to be hospitalized in principle, given an injury/disease name related to the intracranial hemorrhage, undergo tests (CT, MRI, or MRA), and receive a prescription or treatment specific to the intracranial hemorrhage.

Definition 1 is a broad definition consisting of a combination of injury/disease names and the conduct of tests (expected to have the highest sensitivity). The date of onset of outcome is defined as the date of the earliest test among CT, MRI, and MRA within the same hospitalization (same "claim ID") owing to intracranial hemorrhage, such as cerebral and subarachnoid hemorrhages.

Definition 2 is a narrow definition consisting of a combination of injury/disease names and the conduct of tests and procedures or prescriptions (expected to have the highest positive predictability and specificity). The date of onset of outcome is defined as the date of the earliest test among CT, MRI, and MRA within the same hospitalization (same "claim ID") owing to intracranial hemorrhage, such as cerebral and subarachnoid hemorrhages.

For Definition 3, serious hemorrhage requiring hospitalization (intracranial or gastrointestinal hemorrhage) is defined by injury/disease name from the viewpoint of multilaterally evaluating "hemorrhage," an important potential risk of Trintellix. The date of onset of outcome is defined as the 15th day of the month of hospitalization for intracranial or gastrointestinal hemorrhage. This definition will be used for secondary analyses only.

In this study, no outcome validation was conducted. However, based on the results of a previous study[5)], it is assumed that Definition 1 is more sensitive, but has lower positive predictability and specificity than Definition 2. However, Definition 2 has higher positive predictability and specificity, and it is assumed that adding drug conditions to the treatment conditions in the preceding study using "OR" conditions will further increase the sensitivity compared to that of the preceding study (0.889 [0.673–0.889]).

If it is unlikely that the sensitivity of outcomes substantially differ between the two groups, the use of an outcome definition with a higher positive predictability is a prerequisite for obtaining correct results.[8)] In addition, if the outcome definition is strictly set to achieve high positive predictability, false-negative results may increase, resulting in a decrease in sensitivity.[8)] However, because not only treatment, but also prescription conditions are added in Definition 2, such concerns are considered to be minor, and Definition 2 will be used for the primary analysis. Sensitivity analyses will be performed in the following cases: Definition 1 is used; for Definition 2, the definition of "within the same hospitalization" is defined as "the same claim ID or the hospitalization claim ID in the following month after the start of hospitalization," the drug is limited to injection only, and the suspect flag is not taken into consideration.

13.7. Covariates and Matters Used for Them

The following covariates will be used to adjust the patient characteristics of the exposure and control groups (COV1 and COV2 will be used for multivariate analysis, and COV1 to COV3 will be used for propensity score analysis).

COV1:

- Age (continuous variable)
- Sex (male, female)

COV2:

- Antithrombotic drug administration† (Yes, No)
- NSAID administration† (Yes, No)
- Hypertension (Yes, No)

COV3:

- Administration of atypical antipsychotics† (Yes, No)
- Administration of phenothiazine antipsychotics† (Yes, No)
- Administration of tricyclic antidepressants† (Yes, No)
- Diabetes mellitus (Yes, No)
- Ischemic heart disease (Yes, No)
- Ischemic cerebral infarction (Yes, No)
- Cerebral amyloid angiopathy (Yes, No)
- Cerebral aneurysm (Yes, No)
- Brain tumor (Yes, No)
- Epilepsy (Yes, No)
- Liver disease (Yes, No)
- Renal failure (Yes, No)
- Alcohol dependence (Yes, No)
- Epistaxis (Yes, No)
- Dyslipidemia (Yes, No)
- Obesity (Yes, No)
- Metabolic syndrome (Yes, No)
- Sleep apnea syndrome (Yes, No)
- Peripheral arterial disease (Yes, No)
- Drinking history (Yes, No)*
- Smoking history (Yes, No)*

† Drug administration during Days -30 to -1

* For missing values, a category of "Unknown" is created.

Rationale:

The covariates selected included age and sex, as well as comorbidities and drug administration, which are considered risk factors for intracranial hemorrhage in the preceding studies[6) 9)], the electronic package insert of Trintellix, or other data.

The number of patients with outcomes in this study is expected to be approximately 50 to 100[10)], COV1 and COV2, which are relatively important potential confounding factors, are used, assuming that the explanatory variable of the multivariate analysis, primary analysis, is approximately 5 to 10. For COV2, antithrombotic drugs and NSAIDs, for which previous studies

have reported that concomitant use with SSRIs increased the risk of intracranial hemorrhage[3) 11)], and hypertension, which is the largest risk factor for cerebral hemorrhage[6)] and has the highest prevalence in the feasibility study, are selected.

For COV1, data from the index date will be obtained. For complications of COV2 and COV3, data during the look-back period will be obtained considering the treatment intervals. For drug administration in COV2 and COV3, data on days -30 to -1 from the index date will be obtained, assuming that concomitant drugs are used on or after the index date.

13.8. Validation

Scope of validation in “Development of basic principles in conducting a validation study of outcome definitions used for post-marketing database studies (July 31, 2020) (PMDA/CRS Notification No. 0731002/PMDA/CPE Notification No. 0731002) (Director of Center for Regulatory Science/Director of Center for Product Evaluation, Pharmaceuticals and Medical Devices Agency)”: It is judged that the study does not align an investigation conducted to serve as the main grounds for specific safety measures, and therefore validation is not performed in this study.

13.9. Items to be Analyzed and Methods

The dataset to be used in this study will be obtained by the following process: JMDC Inc. performs its own data cleaning and data check from the viewpoint of quality assurance; the data between November 2018 and November 2023 are extracted; and then the dataset that meets the inclusion/exclusion criteria is created.

A summary of the analysis is presented below. The details are specified in a separately prepared statistical analysis plan, and the figures and tables concerning the main results, which are described in the study report, are provided in Appendix 3.

Primary analysis

- Using Definition 2, the incidence rate of intracranial hemorrhage (per 10,000 person-years) in the Trintellix and control groups will be estimated, and the hazard ratio of Trintellix relative to the control will be calculated (crude and adjusted).

  Covariates: [COV1] age and sex, and [COV2] antithrombotic drug administration, NSAID administration, and hypertension

Secondary analysis

- The survival function will be graphically presented using the Kaplan–Meier method, and the time to onset of intracranial hemorrhage will be evaluated.
- Using Definition 2, the incidence rate of intracranial hemorrhage (per 10,000 person-years) for each SSRI* will be estimated in the control group.
  If there is a large difference in the incidence rate of outcomes between SSRIs, additional analysis with an appropriate control group will be performed to appropriately interpret the relative risks of Trintellix to SSRIs for intracranial hemorrhage.
- Using Definition 3, the incidence rate of serious hemorrhage requiring hospitalization (intracranial or gastrointestinal hemorrhage; per 10,000 person-years) in the Trintellix and control groups will be estimated, and the hazard ratio of Trintellix relative to the control will be calculated (crude and adjusted).

  Covariates: [COV1] age and sex, and [COV2] antithrombotic drug administration, NSAID administration, and hypertension
- Using Definition 3, the incidence rate of serious hemorrhage (intracranial or gastrointestinal hemorrhage; per 10,000 person-years) with each SSRI* will be estimated for the control group.
  If there is a large difference in the incidence rate of outcomes between SSRIs, additional analysis with an appropriate control group will be performed to appropriately interpret the relative risks of Trintellix to SSRIs for serious hemorrhage (intracranial or gastrointestinal hemorrhage).

  * Classified by the name of the ingredient administered on the index date.

Sensitivity analysis

- The robustness of the primary analysis will be confirmed by observing how much the results of the primary analysis is changed by each of the following changes: change of the look-back period (changed to a period of 1 year [360 days] prior to the day before the index date), change of the prescription continuation period (the gap period and the grace period are changed to 90 days), and change of the definition of outcome (changed to Definition 1; for Definition 2, “within the same hospitalization” is defined as “the same claim ID or the hospitalization claim ID in the following month after the start of hospitalization,” the drug is changed to injection only, and the suspect flag is changed to “not considered”).
- In addition to [COV1] and [COV2], to adjust approximately 20 covariates [COV3] that are suggested to possibly affect the outcome in the preceding research and Trintellix package insert, the covariates of COV1 to COV3 will be combined in one propensity score, which will be added to the models (adjustment). The adjusted hazard ratio of the Trintellix group relative to the control group will be calculated.

14. Number of Study Participants and the Rationale

A feasibility study[*1] using the DB was conducted before the main study. The results demonstrated that the number of patients with depression required drug therapy between November 2019 (launch date) and January 2022 was approximately 172,000. The number of patients in the exposure and control groups that satisfied the inclusion and exclusion criteria was approximately 11,000 and 76,000, respectively. Considering that the enrollment period in this study was up to November 2022, it is estimated that approximately 14,000 and 101,000 patients will be enrolled in the Trintellix and control groups, respectively.

Renoux et al. reported the following findings: Using the Clinical Practice Research Datalink in the United Kingdom, 1.36 million or more adults who had started taking SSRIs or tricyclic antidepressants for the first time between 1 January 1995 and 30 June 2014 were followed up for a mean period of 5.8 years. The results showed that 3,036 patients were diagnosed with intracranial hemorrhage (3.8 cases per 10,000 patients per year; that is, the incidence rate per year was 0.038%), and risk of intracranial hemorrhage with SSRIs increased by 17% compared with that of tricyclic antidepressants.[3)] In addition, the incidence of cerebral hemorrhage is considered to be 2.4 times higher in Asians than that in non-Asians.[12)] Therefore, the estimated incidence rate of intracranial hemorrhage with SSRIs per year in this study was assumed to be 0.09%.
In contrast, using the sample size calculation formula (Formula 6.9), which is proposed for comparative research in the post-marketing surveillance in a technical book "Sample Sizes for Clinical, Laboratory and Epidemiology Studies,[13)]" the sample sizes required to detect a two-fold increase in the incidence rate of intracranial hemorrhage (i.e., an additional 0.09% increase in the incidence rate per year of intracranial hemorrhage) for Trintellix compared to that with SSRIs are calculated to be 13,242 patients for the exposure group (Trintellix group) and 92,694 patients for the non-exposure group (control group), assuming the allocation ratio (control group:Trintellix group) of 7:1, the two-sided significance level (α) of 0.05, and the power (1-β) of 0.8 (with the one-sided significance level of 0.05, the sample sizes are 10,644 and 74,508 patients, respectively).

Therefore, considering future data accumulation and other factors, the DB should be adequately studied.

*1: Appendix 4. Information on the Number of Patients to Be Studied That Is Available From the Medical Information Database (Part 2)

15. Limitations of the Study

- The DB includes members of health insurance societies; therefore, it does not include older adults aged 75 years or older. The number of individuals aged 65 years or older is small; however, the number of patients with depression in Japan is highest in their 40s.[14)] Therefore, the DB is considered a suitable database for the comparison of adverse events between Trintellix and SSRIs.
- Although the study has high traceability, members are lost to follow-up owing to withdrawal from health insurance societies or termination of contracts with individual health insurance societies.
- If the name of the injury or disease is entered for insurance claims or other purposes, the name may differ from the actual diagnosis.
- The analyses are performed using prescription data and do not capture the actual status of drug administration.
- Key data on the risk factors of intracranial hemorrhage (e.g., drinking and smoking histories) are available only for certain members. However, drinking and smoking histories have a lower priority as a confounding factor than age, sex, antithrombotic drug administration, NSAID administration, and hypertension, which are included in the primary analysis. Therefore, drinking and smoking histories will be included in the additional propensity score analysis only.

16. Retention of Records

Records will be stored appropriately in accordance with written procedures.

17. References

1) Treatment Guidelines by the Japanese Society of Mood Disorders. II. Depression (DSM-5)/Major Depressive Disorder 2016. Introduction revised on 24 July 2019. Mood Disorder Treatment Guideline Preparation Committee, the Japan Society of Mood Disorders
2) Tyrka A, et al., Psychotic major depression: a benefit-risk assessment of treatment options. Drug Saf 29:491-508,2006.
3) Christel R, et al., Association of Selective Serotonin Reuptake Inhibitors With the Risk for Spontaneous Intracranial Hemorrhage. JAMA Neurol. 2017;74(2):173-180
4) Sacco R, et al. An updated definition of stroke for the 21st Century. A statement for healthcare professionals from the American Heart Association / American Stroke Association. Stroke. 2013; 44: 2064-2089.
5) Kazuya F, et al., Accuracy of Japanese claims data in identifying diabetes-related complications. Pharmacoepidemiol Drug Saf. 2021;30:594–601.
6) Japan Stroke Society Guideline 2021 for the Treatment of Stroke, the Japan Stroke Society, Guideline for the Treatment of Stroke Committee
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.
8) Masao Iwagami, Report of "Task force on validation of indicators obtained from health insurance claims information mainly consisting of injury/disease names in Japan"
9) Sigrid B, et al., Risk of intracerebral hemorrhage associated with phenprocoumon exposure: a nested case–control study in a large population-based German database. pharmacoepidemiology and drug safety 2010; 19: 722–730
10) Vittinghoff, E, et al., Relaxing the Rule of Ten Events per Variable in Logistic and Cox Regression. American Journal of Epidemiology 2007; 165(6): 710–718
11) Mendel D, et al., Cyclooxygenase Selectivity of Nonsteroidal Anti-inflammatory Drugs and Risk of Stroke. Arch Intern Med. 2008;168(11):1219-1224
12) Masatsugu Hori, Learn about characteristics of Japanese from large-scale clinical studies. Heart Vol. 47 No. 2 (2015)
13) Sample Sizes for Clinical, Laboratory and Epidemiology Studies, Kyoto University Press
14) Patient Survey/2011 Patient Survey First Volume (Nationwide): http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001103073 (Accessed Sep 5, 2022)

18. **Appendices**

[redacted]