EVENITY Subcutaneous Injection 105 mg Syringes

Post-marketing Database Study

The Incidence and Risk Factors for Hypocalcaemia Among Osteoporosis Patients Receiving Romosozumab or Other Antiresorptive Therapy in Japan -- A Retrospective Cohort Study Within the Medical Information Database Network (MID-NET)

Protocol

Amgen K.K.

Protocol No.: 20190207

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Summary Table of Study Protocol

Title	The Incidence and Risk factors for Hypocalcaemia Among Osteoporosis Patients Receiving Romosozumab or Other Antiresorptive Therapy in Japan -- A Retrospective Cohort Study Within the Medical Information Database Network (MID-NET)
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Country(ies) of Study	Japan
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Marketing Authorization Holder

Marketing authorization holder	Amgen K.K.
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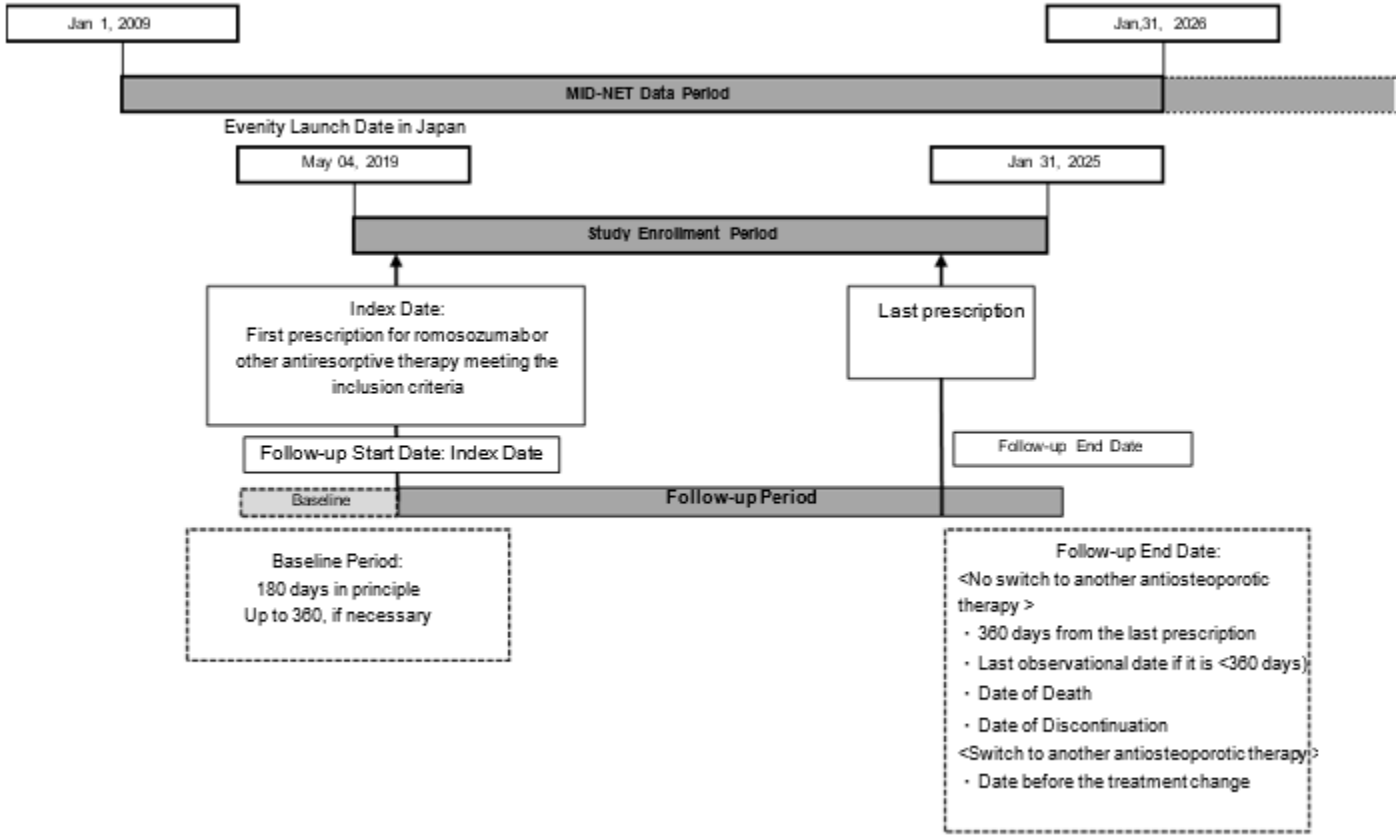
Study Design Schema



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2. List of Abbreviations

Abbreviation	Full Form
DPC	Diagnosis Procedure Combination
eGFR	estimated glomerular filtration rate
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th revision
iPTH	intact parathyroid hormone
MDV	Medical Data Vision Co., Ltd.
MID-NET®	Medical Information Database Network
PMDA	Pharmaceuticals and Medical Devices Agency
RMP	Risk Management Plan
RR	Risk Ratio
SERM	Selective Estrogen Receptor Mmodulator

3. Responsible Parties

3.1 Sponsor / Organizational Structure to Conduct the Study

Amgen K.K.

Address: Midtown Tower, 9-7-1 Akasaka, Minato-ku, Tokyo, Japan

The organizational structure to conduct the study is separately specified within Amgen K.K.

3.2 Name and Address of the Party Who Has Contracted Work and Their Scope in This Study

Name: EPS Corporation

Address: 2-23 Shimomiyabicho, Shinjuku, Tokyo

Scope of contracted work:

Support service to prepare the study protocol

4. Abstract

- Study Title:
  The incidence and risk factors for hypocalcaemia among osteoporosis patients receiving romosozumab or other antiresorptive therapy in Japan -- A retrospective cohort study within the Medical Information Database Network (MID-NET)
- Background and Rationale:
  This study is a post-marketing database study to be conducted after approval of EVENITY Subcutaneous Injection 105 mg Syringes [generic name: romosozumab] (hereinafter romosozumab) under the agreement with the Pharmaceuticals and Medical Devices Agency (PMDA) in accordance with the Pharmaceuticals and Medical Devices Act [1)] and the “Ministerial Ordinance on Good Post-marketing Study Practice for Drugs” [2,3)] in Japan.
  Sclerostin inhibition by romosozumab rapidly increases bone mass at the initiation of

treatment, inducing a greater demand for substrates involved in bone formation such as calcium, which may result in a decrease in serum calcium. Although a certain amount of information on the incidence of hypocalcaemia with romosozumab use was obtained in the clinical trials, additional information of real-world clinical practice should provide further knowledge on the incidence of hypocalcaemia with romosozumab use and factors that may influence its incidence including renal impairment. The missing information is regarded as 'Important missing information' in Risk Management Plan (RMP) for romosozumab with agreement with the PMDA. The conduct of this post-marketing database study using the MID-NET database, expected to be available for acquisition of necessary information of the real-world clinical practice, was agreed with the PMDA to examine factors that may influence the incidence of hypocalcaemia with romosozumab use.

- Research Question and Objectives:

Objectives	Endpoints
Primary	
• To evaluate the risk of hypocalcaemia in patients receiving romosozumab relative to patients receiving other antiresorptive treatments, broken down by the presence of potential risk factors for hypocalcaemia including renal impairment and others at the follow-up initiation	Primary Endpoint • Incidence of ≥ Grade 1 hypocalcaemia (< 8.5 mg/dL) Secondary Endpoints • Incidence of ≥ Grade 2 hypocalcaemia (< 8.0 mg/dL) • Incidence of ≥ Grade 3 hypocalcaemia (< 6.5 mg/dL)
Secondary	
• To summarize the incidence of hypocalcaemia among patients receiving romosozumab and other antiresorptive treatments	• Same as above
Exploratory	
• None	• None

Statistical Inference
This study is a descriptive study, and no formal hypotheses will be tested.

- Study Design

  Since this study includes collecting information such as the incidence, seriousness, and onset time of hypocalcaemia; the cohort design, which follows target populations (i.e., cohorts) over time to measure the incidence of events, is considered appropriate.

  The target populations will include osteoporosis patients treated with romosozumab or active comparators, namely antiresorptive therapies known to increase the risk of hypocalcaemia (denosumab, bisphosphonates, and selective estrogen receptor modulators [SERMs]).

It is expected that there are patients treated with treatment period with any of the above control drugs prior to the initiation of romosozumab. In addition, while patients at high risk for fractures (related to frailty or other relevant conditions) is the clinical indication for romosozumab, the other therapies may be used for a wider population including patients at low risk for fractures. Although there is no definite information on the association between fracture risk and risk for hypocalcaemia, it was considered important to minimize differences in background conditions and in assessment of endpoints between both cohorts as much as possible to minimize potential confounders and ascertainment bias.

Given that the risk of hypocalcemia is typically greatest soon after initiating therapy for osteoporosis, the new-user design [14,15], including patients from the time of treatment initiation, is appropriate to avoid a variation in evaluation time points following new therapy commencement between cohorts. Propensity score matching with pre-treatment covariates obtained from the cohorts with the same methods will be used to adjust confounding. The new-user design will also reduce the potential for immortal time bias when combined with the active comparator design. It is expected that many patients with initiating romosozumab will have prior use of other osteoporosis therapies. Romosozumab patients with prior use of other osteoporosis therapies will be allowed in this study as long as 30 days have passed since discontinuation of prior therapy to provide a clinically relevant washout period associated with immediate risk of hypocalcemia from prior therapy. Therefore, prescription of romosozumab will be regarded as new initiation of romosozumab if this prescription was done following interruption of treatment with romosozumab or an active comparator for >30 days after the end date of prior treatment (i.e., romosozumab was prescribed after the end date of Grace Period for prior treatment). Similarly, prescription of an active comparator was regarded as new initiation of the comparator if this prescription was done following interruption of treatment with romosozumab or a comparator for >30 days after the end date of prior treatment (i.e., the new active comparator was prescribed after the end date of Grace Period for prior treatment).

Propensity score matching will be used to control for potential confounding differences between cohorts. The 3 steps of propensity score matching include: 1) set a time period as time block, considering the expected candidate sample size based on the results of feasibility analysis, which will be performed to specify the length of the time block and divide the entire follow-up period by the time block, 2) calculate propensity score for patients candidate for matching using appropriate covariates in each time block. Covariates used for propensity score modeling are defined based on the results of feasibility analysis, 3) perform matching of patients using propensity scores. If a patient has been treated with a comparator during a period before the initiation of romosozumab treatment, the period will be used for determination of a new user of the comparator in the control group. Important risk factors not included in the covariates used to calculate propensity scores are adjusted after review.

- Data source

  Post-marketing database study will be conducted using the MID-NET because it allows for capturing of information on the target population and drugs studied and using laboratory values required to capture hypocalcaemia as the outcome without limitation.

The period of data to be used in this study will be from January 1, 2009, when collection into the MID-NET started, until January 31, 2026.

- Selection Criteria for Study Population

    1. (1) <Conditions for extraction with script>

    Patients with diagnosed osteoporosis (M80-M82) who have documented treatment with one of the following drugs during the period from March 4, 2019 to January 31, 2025:

    Target: Romosozumab

    Active comparators: Antiresorptive therapies

        2. i Denosumab
        3. ii Bisphosphonates
        4. iii SERMs

    5. (2) Medical records at least 2 time points with an interval of ≥90 days (based on grace and gap periods) are available
    6. (3) Prescription of romosozumab or a comparator drug after the diagnosis of osteoporosis in the same month of or one month prior to the diagnosis
    7. (4) Medical records at least 6 months (180 days) before the start of follow-up (baseline period completion) is available

- Exclusion Criteria

    None

Follow-up Period

The follow-up period is defined as the time from the start date to the end date of follow-up. As for the start date, follow-up of the EVENITY group will be started on the date of being eligible for the inclusion criteria, namely the date of new initiation of romosozumab that meets the inclusion criteria. On the other hand, all the dates of initiation of comparator treatment that meet the wash-out period criteria within the same time block as the EVENITY group will be specified as candidate start dates before development of the propensity score model for the control group. In case of success in the propensity score matching, the relevant date will be defined as the start date. The end date of follow-up will be the last medical record date, death date, event occurrence date (when focused on the initial event), the day when one year has passed from the start date, romosozumab initiation date in the control group, comparator exposure end date in the control group, comparator initiation date in the EVENITY group, or romosozumab exposure end date in the EVENITY group, whichever occurs first.

The definition of continued drug exposure is based on the grace period and the gap period. The grace period is defined as a period of the duration of prescription drug use plus 30 days. The gap period is defined as a period between the date of the prescription date + the duration of prescription drug use and the next prescription date. If the gap period is longer than 30 days, this will be considered as discontinuation of drug exposure. In this case, the date on which the grace period

has elapsed since the last prescription date is defined as the end date of drug exposure.

- Definition of Variables

  Primary Endpoint

  Incidence of ≥ Grade 1 hypocalcaemia
  The event is defined as hypocalcaemia with the following calcium level of ≥ Grade 1 specified in the Criteria for Seriousness Classification of Adverse Drug Reactions (SD Notification No. 80)[4] that newly occurs during the follow-up period.
  Corrected serum calcium level, < 8.5 mg/dL (SD Notification No. 80)

  Secondary Endpoints

  – Incidence of ≥ Grade 2 hypocalcaemia
  The event is defined as hypocalcaemia with the following calcium level of Grade 2 specified in the Criteria for Seriousness Classification of Adverse Drug Reactions (SD Notification No. 80)[4] that newly occurs during the follow-up period.
  Corrected serum calcium level, < 8.0 mg/dL (SD Notification No. 80)
  Incidence of ≥ Grade 3 hypocalcaemia
  The event is defined as hypocalcaemia with the following calcium level of Grade 3 specified in the Criteria for Seriousness Classification of Adverse Drug Reactions (SD Notification No. 80)[4] that newly occurs during the follow-up period.
  Corrected serum calcium level, < 6.5 mg/dL (SD Notification No. 80)

Baseline Characteristics

- Sex, age, BMI, and Time block of index date
- Comorbidities・Past medical history
  - Renal impairment, hepatic function disorder, hypertension, diabetes mellitus, hyperthyroidism, rheumatoid arthritis
  - Previous illness reflecting the progression of the primary condition (osteoporosis)
    - ✓ History of fractures resulting from osteoporosis
      - ■ Femoral head fracture, spinal compression fracture, and other fractures of interest possibly related to osteoporosis
  - Other pre-existing conditions
    - ✓ Hypocalcaemia during 30 days before the index date
- History of medication for osteoporosis
  Bisphosphonates, estrogen preparations, active vitamin D preparations, SERMs, calcitonin, parathyroid hormone preparations, denosumab, vitamin K preparations, calcium preparations*
- Concomitant medications at the index date
  Active vitamin D preparations, calcium preparations*
- Clinical laboratory test values at baseline
  Corrected serum calcium, estimated glomerular filtration rate (eGFR), serum total bilirubin, serum alkaline phosphatase[5], 25-hydroxyvitamin D, serum intact parathyroid hormone (iPTH)

* Oral administration only

Sample Size for the Study

The study sample size is expected based on information from the open data of MIDNET. The number of patients using romosozumab in MID-NET was 693 patients in 2021 and 903 patients in 2022 (PMDA 2023). Assuming 700 romosozumab users per year is accumulated through 6 years, the expected number of romosozumab users would be 4,200 by the end of the study. According to the basic information for MID-NET users, as of 2022, a total of 30,069 patients receiving the active comparators, including 22,677 patients receiving bisphosphonates, 1,300 patients receiving SERMs, and 6,092 patients receiving denosumab, were identified as the candidates for the control group in this study.

In this study, the risk of the incidence of hypocalcaemia during receiving romosozumab caused by potential risk factors will be evaluated by comparing with other antiresorptive drugs. Table 5. in section 8.5 Study Size shows the risk ratios (RRs, defined as the incidence rate of hypocalcaemia in the EVENITY group divided by the incidence rate of hypocalcaemia in the control group) with a lower limit of the 95% CI of 1 by the incidence rate of hypocalcemia in the control group and by sample size of the subgroup of interest. Considering the previous clinical studies, past clinical studies comparing romosozumab with other drugs, and the post-marketing status of romosozumab, the lower limit of the 95% CI may exceed 1 for a RR for romosozumab relative to an active comparator of ≤3.0 if the target subgroup consists of ≥1,500 patients with an incidence rate of hypocalcaemia of ≥0.5% in the control group of the subgroup.

For patients with renal impairment, who are a subgroup to be investigated in this study, the pooled analysis of studies 20070337, 20060326, and 20101291 (an analysis in the 12-month Placebo-controlled Postmenopausal Osteoporosis (PMO) Safety Analysis Set) included 12.4% of patients (917/7,383) who had a baseline eGFR of ≥ 90 mL/min/1.73m^2, 68.7% of patients (5,073/7,383) who had mild renal impairment (60 to < 90 mL/min/1.73m^2), 18.6% of patients (1,375/7,383) who had moderate renal impairment (30 to < 60 mL/min/1.73m^2), and 0.24% of patients (18/7,383) who had severe renal impairment (< 30 mL/min/1.73m^2). Based on the data, if patients with either mild, moderate, or severe renal impairment are determined as patients with renal impairment, the numbers of such patients were expected to be approximately 3,700 in the EVENITY group and approximately 26,300 in the control group.

For the event rates on denosumab, the incidence rate of hypocalcaemia was 0.8% in the data of a phase III study of denosumab in patients with primary osteoporosis conducted in Japan, and the incidence rate of hypocalcaemia after the launch for denosumab was 1.5% according to the data of Medical Data Vision Co., Ltd. (MDV). Since the incidence rate of hypocalcaemia caused by romosozumab in clinical data from the 12-month PMO Safety Analysis Set was less than 0.4%, it was presumed that the incidence after the launch of romosozumab would not exceed that of denosumab shown in the MDV data.

Based on the above, it was considered that the risk of the incidence of hypocalcaemia in the EVENITY group and the control group could be evaluated, and that the same evaluation was feasible in the subgroup of patients with renal impairment, the focus of this study.

- Data Analysis

  In order to monitor the progress of the study, the accumulation status of the patients who were or to be enrolled in this study in the MID-NET will be checked at 3 and 5 years after approval to report in the periodic safety update reports. To conduct a final review of safety information, the following main analyses will be conducted at 7 years after approval to prepare the report.

  - Primary Analysis

    To investigate the factors influencing the incidence of hypocalcaemia, a point estimate with 95% CI for the incidence rate (defined in Section 8.7.2.3 Handling of Processing Variables) and occurrence (defined in Section 8.7.2.3 Handling of Processing Variables) of hypocalcaemia in the subgroup of interest will be provided for each group. Risk ratio (treatment over control) as well as 95% CI based on a logistic regression model will be provided.
    In addition, with regard to the incidence of hypocalcaemia, the interaction between the factors of interest (covariates specified in Section 8.3.3 Covariate Assessment) and the administration of romosozumab will be examined using a logistic regression model for the incidence rate to provide a p-value. Furthermore, the occurrence will be analyzed in the same way using a Poisson regression model to present a p-value. The presence or absence of renal impairment will be a factor to be mandatorily matched at the time of propensity score matching in the subgroup analysis. This analysis should be performed after the balance between groups is maintained.

  - Other Analyses

    To investigate the onset time of hypocalcaemia, a hypocalcaemia onset curve will be estimated by using the Kaplan-Meier method for each group. A subgroup analysis will be performed for each factor of interest. The cumulative 1-year occurrence of hypocalcaemia and its 95% CI will be calculated based on the estimated hypocalcaemia incidence curves.

  - Sensitivity Analysis

    The main analyses will be done after changing the definition as described below.

    - Change the baseline period from 180 days to 1 year
    - Change the definition of the grace period from that one for as-treated analysis to unlimited (ie, ITT analysis)

5. Amendments and Updates

Version	Date	Applicable Section(s)	Description of Change(s)	Reason(s)
1.00	Sep 25, 2019	Original protocol	-	-
2.00	Jul 15, 2021	Amend 1	Study design changed	To reflect PMDA's feedback
3.00	Nov 01, 2023	Amend 2	The primary objective was clarified, the number of patients to be studied was updated, and definitions were clarified.	To reflect comments from the preliminary PMDA meeting, inquiries, and consultation records concerning epidemiologic survey protocol as well as internal review

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Osteoporosis is characterized by low bone mass and reduced bone strength, leading to increased risk of fracture.[6)] Osteoporosis and osteoporotic fractures have become a critical problem mainly in postmenopausal women, while they have also become an important clinical and public health problem in men. As the population ages, it is expected that fractures primarily caused by osteoporosis and their associated healthcare costs will greatly increase in the future. The number of patients with osteoporosis is increasing as the Japan's population ages; the number of patients with osteoporosis in Japan is estimated to be approximately 12.8 million (3 million males and 9.8 million females).[8,9)] Fractures associated with osteoporosis pose a major obstacle to patients as well as a significant economic burden to society.[7,10)] Treatment to be effective to improve bone mass and bone density without delay and reduce a risk of fracture is therefore particularly important for patients at risk for fracture. However, this need remains unmet.

Sclerostin, a glycoprotein produced inside the bone by osteocytes, works as a negative regulator of Wnt signaling. Inhibition of Wnt signaling by sclerostin in osteoblast lineage cells suppresses osteogenesis by osteoblasts and stimulates bone resorption by osteoclasts.[11-13)]

Romosozumab is a humanized anti-sclerostin monoclonal antibody that binds to sclerostin to inhibit its function. Romosozumab rapidly increases bone mass of both cancellous and cortical bones by promoting bone formation and inhibiting bone resorption. This is considered to improve bone structure and strength, leading to a decrease in the risk of fracture.

6.2 Rationale

Pharmacovigilance based on the RMP is continuously required to confirm the safety of romosozumab in the actual use experience after the launch. This study is post-marketing database study planned after approval of romosozumab under the agreement with PMDA based on the Pharmaceuticals and Medical Devices Act[1)] and the "Ministerial Ordinance on Good Post-marketing Study Practice for drugs"[2,3)] in Japan. Sclerostin

inhibition by romosozumab may rapidly increase bone mass at the initiation of treatment, which induces a greater demand for substrates involving in bone formation such as calcium, resulting in a decrease in serum calcium. Hypocalcaemia is identified as an important risk in the RMP because of the following facts: Grades 1 and 2 albumin-corrected serum calcium levels were observed in patients who received romosozumab (0.4% [14/3695 patients] in the romosozumab group and 0.1% [5/3689 patients] in the placebo group), hypocalcaemia occurred in patients with severe renal impairment or end-stage renal failure, and serious outcomes may occur when the disease worsened according to the data of clinical studies conducted in and outside Japan.

In contrast, hypocalcaemia did not occur in any patients in the Japanese population (0/308 patients) in the data of clinical studies conducted in and outside Japan. None of those patients who received romosozumab had an albumin-corrected serum calcium level of grade 3 or above.

Although a certain amount of information on the incidence of hypocalcaemia that may be caused by romosozumab has been obtained in clinical trials, the incidence of hypocalcaemia that may be caused by romosozumab, factors that may influence its incidence, and the association with renal impairment in the real-world practice after the launch have been unclear. The missing information is regarded as 'Important missing information' for Evenity in RMP with agreement with PMDA.

Based on these, this post-marketing database study will be conducted using the MID-NET database, expected to be available for acquisition of necessary information in the real-world clinical practice, to examine the factors that may influence the incidence of hypocalcaemia with romosozumab use.

6.3 Feasibility and Futility Considerations

In the MID-NET, the number of patients starting prescription of romosozumab during the inclusion period was projected to be approximately 4,200 patients. According to the basic information for MID-NET users, as of 2022, a total of 30,069 patients receiving the active comparators, including 22,677 patients receiving bisphosphonates, 1,300 patients receiving SERMs, and 6,092 patients receiving denosumab, were identified. The number of patients with renal impairment were expected to be approximately 3,700 in the EVENITY group and approximately 26,300 in the control group.

According to the consideration for sample size, the lower limit of the 95% CI may exceed 1 for RR of $\leq$3.0 for romosozumab relative to active comparators, if the incidence of hypocalcaemia is $\geq$0.5% in the control group of the target subgroup with $\geq$1,500 patients per arm.

Based on the above, it was considered that adequate estimation accuracy could be assured to achieve the purpose of this study.

6.4 Statistical Inference (Estimation or Hypothesis[es])

This study is a descriptive study, and no formal hypotheses will be tested. To evaluate the risk of hypocalcaemia in patients receiving romosozumab relative to patients receiving other antiresorptive treatments, broken down by the presence of potential risk factors for hypocalcaemia including renal impairment and others at follow-up initiation, the two-sided 95% confidence intervals will be presented, unless otherwise specified, and exploratory statistical tests may be performed with two-sided significance level of 5% as below.

- ✓ Point estimates of the incidence rate and occurrence of hypocalcaemia in the EVENITY group and the control group as well as the corresponding 95% CIs,
- ✓ Risk ratios (treatment over control) as well as the corresponding 95% CIs,
- ✓ P-values of statistical tests using regression model

7. Research Question and Objectives

– Safety Considerations

This study is planned to investigate the following safety considerations based on the RMP agreed with the PMDA.

- Important identified risk: hypocalcaemia
- Important insufficient information: safety in patients with renal impairment

7.1 Primary

To evaluate the risk of hypocalcaemia in patients receiving romosozumab relative to patients receiving other antiresorptive treatments, broken down by the presence of potential risk factors for hypocalcaemia including renal impairment and others at follow-up initiation

7.2 Secondary

- To summarize the incidence of hypocalcaemia among patients receiving romosozumab and other antiresorptive treatments

8. Research Methods

8.1 Study Design

Since this study aims to collect information such as the incidence, seriousness, and onset time of hypocalcaemia, a cohort design that follows target populations (cohorts) over time to measure the incidence of events was considered appropriate.

The target populations will include osteoporosis patients treated with romosozumab or active comparators, namely antiresorptive therapies known to increase the risk of hypocalcaemia. Drugs to be studied are presented below. The comparators were selected mainly because they are known to have a risk of being expected to cause hypocalcaemia to the same extent as that observed in patients treated with romosozumab in a Japanese routine clinical setting.

EVENITY group: romosozumab

Control group: either of the antiresorptive drugs described below:

(1) Denosumab

(2) Bisphosphonates (alendronate sodium hydrate, zoledronic acid hydrate, minodronic acid hydrate, sodium risedronate hydrate, ibandronate sodium hydrate)

(3) SERM (raloxifene hydrochloride)

It is expected that there are patients treated with treatment period with any of the above control drugs prior to the initiation of romosozumab. In addition, while patients at high risk for fractures (related to frailty or other relevant conditions) is the target population for romosozumab, control drugs can be used for a wider target population and can also be used for patients at low risk for fractures. Although there is no definite information on the association between fracture risk and risk for hypocalcaemia, minimizing differences in background conditions and in assessment of endpoints between cohorts as much as possible to minimize potential confounders and diagnostic biases.

In this study, the new-user design[14,15)] is chosen in view of channeling bias and immortal time bias. Specifically, the following three procedures are performed for matching: 1) set a time period as time block, considering the expected candidate sample size based on the results of feasibility analysis and divide the entire follow-up period by the time block, 2) calculate propensity scores for candidate patients for matching using the selected covariate values in each time block. Covariates used for propensity score modeling are defined based on the results of feasibility analysis, 3) perform matching of patients using propensity scores. If a patient has been treated with a comparator during a period before the initiation of romosozumab treatment, the period will be used for judgment of a new user of the comparator in the control group. Important risk factors not included in the covariates used to calculate propensity scores are adjusted after review.

8.2 Setting and Study Population

8.2.1 Study Period

8.2.1.1 Data Period

The data period used in this study is between January 1, 2009 in which the data started to be accumulated in the MID-NET and January 31, 2026.

8.2.1.2 Observation Period

The observation period is between March 4, 2019 on which romosozumab was launched and January 31, 2026.

8.2.1.3 Enrollment Period

The enrollment period for the study population is between March 4, 2019 on which romosozumab was launched and January 31, 2025.

8.2.2 Selection Criteria for Study Population

Inclusion and exclusion criteria will be defined in 8.2.3.

8.2.3 Patient Eligibility

8.2.3.1 Inclusion Criteria

(1) <Conditions for extraction with script>

Patients with diagnosed osteoporosis (M80-M82) who have documented treatment with either romosozumab or an active comparator (see Section 8.1 Study Design) during the period from March 4, 2019 to January 31, 2025.

(2) Medical records at least 2 time points with during a period of ≥ 90 days (based on the grace and gap periods) in the database

Rationale: To enroll patients who may be periodically treated with romosozumab or an active comparator to be studied for osteoporosis, and ensure that they routinely visit the hospital observing the dosing interval of the drugs to be studied.

(3) Prescription of romosozumab or a comparator drug after the diagnosis of osteoporosis in the same month of or 1 month prior to the diagnosis

Rationale: To ensure that patients are treated with a study drug for osteoporosis.

(4) Medical records available at least 6 months (180 days) before the start of follow-up (baseline period completion)

Rationale: To ensure 180 days for the baseline period.

8.2.3.2 Exclusion Criteria

No exclusion criteria are defined because at this moment, there is no patient population anticipated to make interpretation substantially difficult in the assessment of the risk of outcome occurrence in the study.

8.2.4 Matching

The study period will be divided into several time blocks to adjust baseline characteristics between groups. For each time block, the propensity score will be calculated using a logistic regression model with the prescription of romosozumab as the dependent variable and the covariate defined prior to the start of follow-up as the explanatory variable (as described in "8.3.3 Covariate Assessment"), in order to perform time block specific propensity score matching. Details are provided in "8.3.1.7 Propensity Score Matching."

8.2.5 Baseline Period

The baseline period is 180 days, in principle. However, the history of fractures can be tracked back up to 360 days if available. The definition of each covariate is provided in "8.3.3 Covariate Assessment." The period may be revised and finalized based on the results of the feasibility analysis. The details of feasibility analysis are described in the separately prepared Feasibility Analysis Plan.

8.2.6 Study Follow-up

The period is to follow each patient's events during the observation period, which is from the start date of follow-up to the end date of follow-up. (The definitions of the start date and end date of follow-up are described in "8.3.1.4 Definition of Start Date of Follow-up Period" and "8.3.1.6 Definition of End Date of Follow-up Period", respectively.)

8.3 Variables

8.3.1 Exposure Assessment

8.3.1.1 Exposure to Romosozumab

A new prescription of romosozumab is regarded as exposure to romosozumab, and patients who meet the following criteria are assigned to the EVENITY group.

- EVENITY group

Patients have to have been newly prescribed EVENITY Subcutaneous Injection 105 mg Syringes (romosozumab). The presence of new prescription will be determined if there is

no prescribed period of romosozumab or any comparator within 30 days before prescription of romosozumab. The prescription period starts on the prescription date and is defined as follows (see Table 1 and Table 2.).

Table 1. Definition of Prescription Period for Romosozumab

Group	Drug name	Duration of Prescription Drug Use (prescription period)
EVENITY group	Romosozumab	Odd number of syringes prescribed: (Number of prescribed syringes + 1) / 2 * 30 Even number of syringes prescribed: Number of syringes prescribed / 2 * 30

Table 2. Definition of Prescription Period for the Comparators

Group	Drug name	Duration (Days) of Prescription Drug Use (prescription period)
Control group	Denosumab	180
	Bisphosphonates	Duration of prescription drug use based on the actual dosing interval
	SERMs	Duration of prescription drug use on the record made at the time of prescribing

8.3.1.2 Exposure to Control Drugs

The new prescription of the following antiresorptive drugs is defined as exposure to control drugs, and the patients who fall under the following criterion are assigned to the control group.

- Control group

  Among patients who have not been prescribed romosozumab, those who have newly received any of the following antiresorptive drugs:

  (1) Denosumab

  (2) Bisphosphonates

  (3) SERM

The presence of new prescription of each drug will be determined independently if there is no prescribed period of romosozumab or any comparator within 30 days before prescription of romosozumab. The prescription period starts on the prescription date and is defined as Table 1 and Table 2.

8.3.1.3 Definition of Cohorts

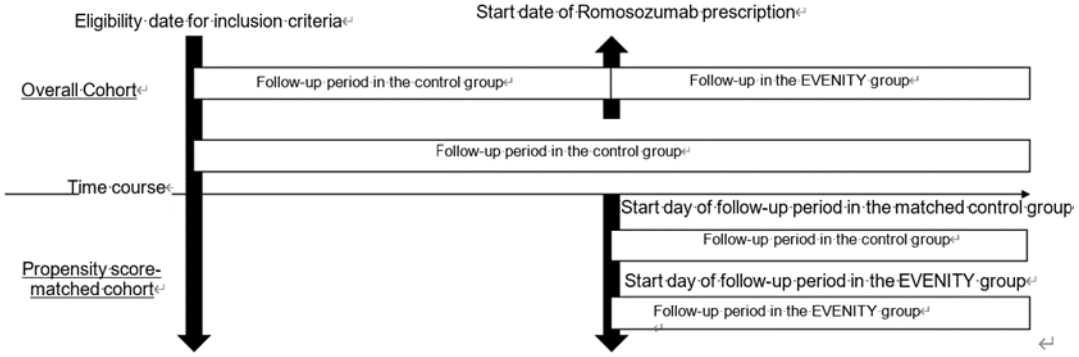
In this study, the risk of the incidence of events in the study population will be assessed using the propensity-score-matched cohort.

8.3.1.3.1 Propensity-Score-Matched Cohort

All the start dates of follow-up, which meet the criteria for wash-out period specified in Section 8.3.1.5 Definition of Continued Drug Exposure within the same time block as that including the start date of follow-up for the EVENITY group will be specified as the

start dates for the control group. The cohort will be obtained by matching based on the propensity scores in the corresponding time block (See Figure 1).

Figure 1. Definition of Follow-up Periods of the EVENITY Group and the Control Group in the Propensity-Score-Matched Cohort



8.3.1.4 Definition of Start Date of Follow-up Period

In the Propensity-score-matched Cohort, follow-up of the EVENITY group will be started on the date of being eligible for the inclusion criteria, namely the date of new initiation of romosozumab, which meets the inclusion criteria. On the other hand, all the dates of initiation of comparator treatment, which meet the wash-out period criteria within the same time block as the EVENITY group will be specified as candidate start dates before development of the propensity score model for the control group. The relevant date will be defined as the start date if success is achieved in the propensity score matching. The details of propensity score matching shall be described in "8.3.1.7 Propensity Score Matching." Therefore, the follow-up period of patients treated with romosozumab after the control follow-up will be divided into the control follow-up period and romosozumab follow-up period, which are defined separately.

8.3.1.5 Definition of Continued Drug Exposure

Continued drug exposure is defined as the period from the start date of follow-up period to the end date of drug exposure. The end date of drug exposure is defined as the end of the grace period added to the duration of prescription drug use. If the gap period between the prescription date and the next prescription date exceeds 30 days, this will be treated as the end of drug exposure, with no consideration given to the next prescription date. In this case, the date on which the grace period has elapsed since the last prescription date is defined as the end date of drug exposure.

It is expected that many patients with initiating romosozumab will have prior use of the other osteoporosis therapies. Romosozumab patients with prior use of other osteoporosis therapies will be allowed in this study as long as 30 days have passed since discontinuation of prior therapy to provide a clinically relevant washout period associated with immediate risk of hypocalcemia from prior therapy. Therefore, prescription of romosozumab was regarded as new initiation of romosozumab if this prescription was done following interruption of treatment with romosozumab or an active comparator for >30 days after the end date of prior treatment (i.e., romosozumab was prescribed after the end date of Grace Period for prior treatment). Similarly, prescription of an active comparator was regarded as new initiation of the comparator if this prescription was done following interruption of treatment with romosozumab or a

comparator for >30 days after the end date of prior treatment (i.e., the new active comparator was prescribed after the end date of Grace Period for prior treatment).

8.3.1.5.1 Grace period

In this study, an as-treated analysis (analysis based on actual duration of drug exposure) is planned for main analyses excluding other sensitivity analyses specified in Section 8.7.3.3.4 Other Sensitivity Analyses, and a grace period is defined as a period of the duration of prescription drug use plus 30 days added to that period. The grace period of each drug is as follows:

Table 3. Definition of Grace Period for Individual Drugs

Group	Drug Name	Grace Period (Days): Duration of Prescription Drug Use (prescription period) + 30
EVENITY group	Romosozumab	Odd number of syringes prescribed: (Number of prescribed syringes + 1) / 2 * 30 + 30 Even number of syringes prescribed: Number of prescribed syringes / 2 * 30 + 30
Control group	Denosumab	180 + 30
	Bisphosphonates	Duration of prescription drug use based on the actual dosing interval + 30
	SERM	Duration of prescription drug use on the record made at the time of prescribing + 30

8.3.1.5.2 Gap Period

The gap period is defined as a period from the date of prescription plus the number of days of prescription to the next prescription date. If the gap period exceeds 30 days, this will be considered as discontinuation of drug exposure. In this case, the date on which the grace period has elapsed since the last prescription date is defined as the end date of drug exposure.

8.3.1.6 Definition of End Date of Follow-up Period

The date on which any of the following events occurs first will be the end date.

(1) Date of the last medical record in the database

(2) Date of death

(3) Date of event onset (when focusing on only the first event)

(4) Date on which one year has passed since the start date of follow-up period (when the duration of follow-up period is limited)

(5) Date on which treatment of romosozumab is started in the control group

(6) End date of comparator drug exposure in the control group (not to be considered in an ITT analysis)

(7) Date on which treatment of control drugs is started in the EVENITY group

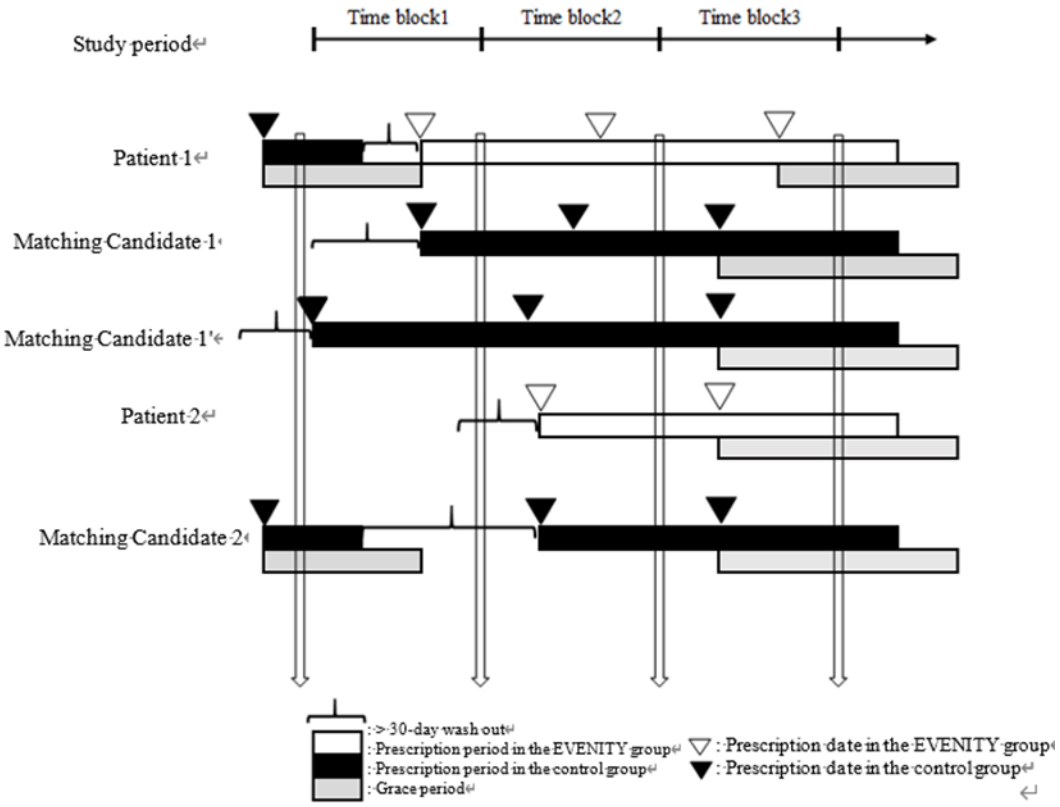
(8) End date of romosozumab exposure in the EVENITY group (not to be considered in an ITT analysis)

8.3.1.7 Propensity Score Matching

The study period will be divided into several time blocks for adjustment for baseline characteristics between groups. For each time block, the propensity score will be calculated using a logistic regression model with the prescription of romosozumab as the dependent variable and the covariate defined prior to the start of follow-up as the explanatory variable (as described in "8.3.3 Covariate Assessment"), in order to perform time block-specific propensity score matching. The duration of a time block is set as 6 months at this time, but the most appropriate duration will be selected based on the results of the feasibility analysis, which will be performed to see the sample size, baseline characteristics before and after matching, and other relevant items in each time block, prior to the primary analysis.

All the dates of new prescription initiation of antiresorptive drugs (denosumab, bisphosphonates, or SERM) for candidate control patients in each time block will be candidate dates for the start date of the follow-up period in the control group to be matched with the start date of the follow-up period in the EVENITY group. If a single patient has more than 1 candidate date for the start date of the follow-up period in the control group within 1 time block, the first date of new prescription initiation in that time block will be used. The start date of the follow-up period in the control group matched with the start date of the follow-up period in the EVENITY group will be the formal start date of the follow-up period in the Propensity-score-matched Cohort. Similar to the EVENITY group, covariates will be calculated based on the information about the candidate start dates of the follow-up period. In order to avoid immortal time bias, if there is a follow-up period as the control group before the follow-up period as the EVENITY group even in patients who will be assigned to the EVENITY group in the future, the period will be treated as a candidate for matching with the EVENITY group.

Figure 2. Summary of Candidate Start Dates and Follow-up Periods Using Time Blocks



If covariates are unbalanced after matching, covariates to be included in the propensity score model as well as the propensity score model will be reviewed as follows. The details shall be described in statistical analysis plan.

- Change covariates to be included in the model
- Change categories for covariates
- Trim extreme values in the distribution of propensity scores

8.3.2 Outcome Assessment

The corrected serum calcium level specified in the Criteria for Seriousness Classification of Adverse Drug Reactions (SD Notification No. 80)[4)] was used for the definition of hypocalcaemia. The calculation method for corrected serum calcium levels is described in "8.7.2.3 Handling of Processing Variables

8.3.2.1 Primary Endpoint

8.3.2.1.1 Incidence of ≥ Grade 1 Hypocalcaemia (< 8.5 mg/dL)

The event is defined as hypocalcaemia with the following calcium level of ≥ Grade 1 specified in the Criteria for Seriousness Classification of Adverse Drug Reactions (SD Notification No. 80)[4)] that newly occurs during the follow-up period.

Corrected serum calcium level of < 8.5 mg/dL (SD Notification No. 80)

The date of event onset will be the date on which the laboratory value meeting the criteria is measured for the first time during the follow-up period.

8.3.2.2 Secondary Endpoints

8.3.2.2.1 Incidence of ≥ Grade 2 Hypocalcaemia (< 8.0 mg/dL)

The event is defined as hypocalcaemia with the following calcium level of Grade 2 specified in the Criteria for Seriousness Classification of Adverse Drug Reactions (SD Notification No. 80)[4)] that newly occurs during the follow-up period.

Corrected serum calcium level, < 8.0 mg/dL (SD Notification No. 80)

The date of event onset will be the date on which the laboratory value meeting the criteria is measured for the first time during the follow-up period.

8.3.2.2.2 Incidence of ≥ Grade 3 Hypocalcaemia (< 6.5 mg/dL)

The event is defined as hypocalcaemia with the following calcium level of Grade 3 specified in the Criteria for Seriousness Classification of Adverse Drug Reactions (SD Notification No. 80)[4)] that newly occurs during the follow-up period.

Corrected serum calcium level, < 6.5 mg/dL (SD Notification No. 80)

The date of event onset will be the date on which the laboratory value meeting the criteria is measured for the first time during the follow-up period.

8.3.3 Covariate Assessment

Covariates are listed in the table below. The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Codes and YJ Codes used for the definitions are provided in the statistical analysis plan.

If data on important covariates are missing in many cases, the effect of these missing data on the analysis results will be evaluated at the time of preparation of statistical analysis plan or analysis to judge the appropriateness of including the relevant variable as a covariate.

Table 4. List of Covariates Used in This Study

Covariate Name		Determination Category	Determination Period	Remarks	Data type
Sex		Male/Female	At the start of follow-up period		SS-MIX2
Age		Continuous quantity	At the start of follow-up period		SS-MIX2
Age (Category 1)		< 15 years/15 to < 65 years/≥ 65 years	At the start of follow-up period		SS-MIX2
Age (Category 2)		< 65 years/≥ 75 years	At the start of follow-up period		SS-MIX2
BMI		Continuous quantity	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		DPC (calculated based on height and weight)
BMI (Category)		< 18.5/18.5 to < 25/≥ 25	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		DPC
Time block at the start of follow-up period		1st (201903 to 20yymm)/ 2nd (20yymm to 20yymm)/ 3rd (20yymm to 20yymm)/ 4th (20yymm to 20yymm)/	At the start of follow-up period	The width of the time block will be determined based on the results of feasibility analysis	SS-MIX2
Previous illnesses during the baseline period					
	Hypocalcaemia	No/Yes	30 days prior to the start of follow-up period		SS-MIX2 Health insurance claim
	Renal impairment	No/Yes	Baseline period		SS-MIX2 Health insurance claim

Table 4. List of Covariates Used in This Study

Covariate Name		Determination Category	Determination Period	Remarks	Data type
	Hepatic function disorder	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Hypertension	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Diabetes mellitus	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Hyperthyroidism	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Rheumatoid arthritis	No/Yes	Baseline period		SS-MIX2 Health insurance claim
Previous illnesses reflecting the progression of the primary condition (osteoporosis)					
	History of femoral head fracture	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	History of spinal compression fracture	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	History of other fractures of interest possibly related to osteoporosis	No/Yes	Baseline period		SS-MIX2 Health insurance claim
With or without history of medical therapy for osteoporosis					
	Bisphosphonates	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Estrogen preparations	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Active vitamin D preparations	No/Yes	Baseline period		SS-MIX2 Health insurance claim

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Table 4. List of Covariates Used in This Study

Covariate Name		Determination Category	Determination Period	Remarks	Data type
	SERMs	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Calcitonin	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Parathyroid hormone preparations	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Denosumab	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Vitamin K preparation	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Calcium preparation (oral)	No/Yes	Baseline period		SS-MIX2 Health insurance claim
Concomitant medications at the start of follow-up period					
	Active vitamin D preparations	No/Yes	Baseline period		SS-MIX2 Health insurance claim
	Calcium preparation (oral)	No/Yes	Baseline period		SS-MIX2 Health insurance claim
Corrected serum calcium level		Continuous quantity	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		SS-MIX2
eGFR		Continuous quantity	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		SS-MIX2
eGFR (Category 1)		≥ 90 / 60 to < 90 / 30 to < 60 / < 30 / Unmeasured (mL/min/1.73m^2)	At the start of follow-up period or measurement at the closest time point to the start of follow-up period	Use for exact matching	SS-MIX2

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Table 4. List of Covariates Used in This Study

Covariate Name		Determination Category	Determination Period	Remarks	Data type
eGFR (Category 2)		≥ 90 / 60 to < 90 / 30 to<60 / < 30 to< 15/ < 15 / Unmeasured (mL/min/1.73m ^2)	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		SS-MIX2
Serum total bilirubin		Continuous quantity	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		SS-MIX2
Serum alkaline phosphatase[5)]		Continuous quantity	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		SS-MIX2
25-hydroxyvitamin D		Continuous quantity	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		SS-MIX2
Serum iPTH		Continuous quantity	At the start of follow-up period or measurement at the closest time point to the start of follow-up period		SS-MIX2

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8.3.4 Validity and Reliability

8.3.4.1 Validation of Drug Exposure

Since MID-NET to be used as the database cannot obtain information on the actual exposure status, available prescription information is used as the information on the exposure instead. In general, prescription information may overestimate the information on drug exposure. However, the information was considered acceptable to assess the exposure because patients do not self-inject romosozumab at the start of this study. Among the control drugs, those that can be self-injected and those that are taken daily may differ from the actual exposure status although the discrepancy was considered difficult to be checked through a validation study because the information on patient compliance has not been collected. Therefore, the discrepancy between the prescription status of antiresorptive drugs and the actual drug exposure status is limitation in this study.

8.3.4.2 Validation of Outcome

The outcome of hypocalcaemia, which is the primary endpoint of this study, is defined using only laboratory values based on clinical practice guidelines. Validation studies are not required because a definition using laboratory values is an objective measure.

No validation studies for the definition of the outcome in this study will therefore be performed.

8.4 Data Sources

The data used in this study will be extracted from the MID-NET system. MID-NET is constructed and operated by PMDA for the purpose of evaluating the safety of drugs and other medical treatments mainly based on the regulatory requirements using electronic medical care information in the database. MID-NET contains the standardized and coded data of electronic medical records, medical insurance claims data, and DPC data including laboratory values obtained in 2009 or later from more than 5 million patients. The data are provided by 23 hospitals from 10 healthcare organizations (as of December 2021), mainly university hospitals. [16)]

This post-marketing database study will be conducted using the MID-NET because the database can provide necessary data to evaluate safety in patients with hypocalcaemia and renal impairment.

8.5 Study Size

The study sample size is expected based on information from the open data of MIDNET. The number of patients using romosozumab in MID-NET was 693 patients in 2021 and 903 patients in 2022 (PMDA 2023). Assuming 700 romosozumab users per year is accumulated through 6 years, the expected number of romosozumab users would be 4,200 by the end of the study. According to the basic information for MID-NET users, as of 2022, a total of 30,069 patients receiving the active comparators, including 22,677 patients receiving bisphosphonates, 1,300 patients receiving SERMs, and 6,092 patients receiving denosumab, were identified as the candidates for the control group in this study.

In this study, the risk of the incidence of hypocalcaemia during receiving romosozumab caused by potential risk factors will be evaluated by comparing with other antiresorptive drugs. **Table 5** shows the risk ratio (RR, defined as the incidence rate of hypocalcaemia in the EVENITY group divided the by the incidence rate of hypocalcaemia in the control group) with a lower limit of the 95% CI of 1 by the incidence rate of hypocalcemia in the control group and by sample size of the subgroup of interest. Considering the previous clinical studies, past clinical studies comparing romosozumab with other drugs, and the post-marketing status of romosozumab, the lower limit of the 95% CI may exceed 1 for RR of $\leq$3.0 for romosozumab relative to active comparators, if the incidence of hypocalcaemia is $\geq$0.5% in the control group of the target subgroup with $\geq$1,500 patients per arm.

Table 5. Risk Ratio With Lower Limit of 95% Confidence Interval Is Equal to 1 by Anticipated Sample Size per arm and Incidence Rate of Hypocalcaemia in Control Group.

Incidence Rate of Hypocalcaemia in Control Group	0.4%	0.5%	1.0%	2.0%	3.0%
1,500 patients/arm	2.56	2.34	1.86	1.57	1.45
2,000 patients/arm	2.29	2.12	1.73	1.49	1.39
2,500 patients/arm	2.12	1.97	1.64	1.43	1.34
3,000 patients/arm	2.00	1.87	1.58	1.39	1.31
4200 patients/arm	1.81	1.71	1.48	1.32	1.26

For patients with renal impairment, which is a subgroup to be investigated in this study, among the patients of the safety analysis set in the 12-month Placebo-controlled Postmenopausal Osteoporosis (PMO) Safety Analysis Set (in the pooled analysis of studies 20070337, 20060326, and 20101291), 12.4% of patients (917/7,383) had baseline eGFR of $\geq$ 90 mL/min/1.73m^2, 68.7% of patients (5,073/7,383) had mild renal impairment (60 to $<$ 90 mL/min/1.73m^2), 18.6% of patients (1,375/7,383) had moderate renal impairment (30 to $<$ 60 mL/min/1.73m^2), and 0.24% of patients (18/7,383) had severe renal impairment ($<$ 30 mL/min/1.73m^2). Based on the data, if patients with either mild, moderate, or severe renal impairment are determined as patients with renal impairment, the numbers of such patients were expected to be approximately 3,700 the EVENITY group and approximately 26,300 in the control group

For the event rates, the incidence rate of hypocalcaemia was 0.8% in the data of a phase III study of denosumab in patients with primary osteoporosis conducted in Japan, and the incidence rate of hypocalcaemia after the launch for denosumab was 1.5% according to the data provided by MDV. Since the incidence of hypocalcaemia caused by romosozumab in the clinical study data (Studies 20070337, 20060326, and 20101291) was less than 0.4%, it was presumed that the incidence after the launch of romosozumab would not exceed that of denosumab shown in the MDV data. As reference, the incidence of hypocalcaemia in patients using romosozumab or denosumab during a clinical study or after the launch are shown in Table 6.

Table 6. Incidences of Hypocalcaemia in Patients Using Romosozumab or Denosumab

	Romosozumab	Denosumab
Clinical study	0.4%*	0.8%***
After the launch	This study	1.5%**

* Corrected serum calcium level of < 8.3 mg/dL

** Corrected serum calcium level of < 8.5 mg/dL (MDV data)

*** A phase 3 study in patients with primary osteoporosis conducted in Japan

Based on the above, it was concluded that the risk of the incidence of hypocalcaemia in the EVENITY group and the control group could be evaluated, and that the same evaluation was feasible in both groups in the subgroup analysis of patients with renal impairment, which is a subgroup of interest in this study.

8.6 Data Management

8.6.1 Obtaining Data Files

Since the MID-NET data cannot be transferred outside the MID-NET on-site center, MID-NET users will process and analyze all data at the MID-NET on-site center.

8.6.2 Linking Data Files

No linkage to other data sources other than MID-NET are planned in this study. Links among individual files storing the information on electronic medical records, medical insurance claims data, and DPC data contained in MID-NET are made using patient identification codes uniquely given by the MID-NET system.

8.6.3 Review and Verification of Data Quality

The reliability of the MID-NET system and data have been guaranteed by the PMDA from five perspectives below.

i. Data Reliability (whether the data are accurately stored)

The data from the hospital information system (electronic medical records, medical insurance claims data, and DPC data) are deidentified and standardized and then transferred to the integrated data source installed at each cooperating medical institution.

MID-NET, with the cooperation from the cooperating medical institutions, checks whether the data is accurately stored by extracting data from both the hospital information system and the integrated data source and comparing the number and contents of the data. The linking capability among information types of integrated data source has also been confirmed.

ii. Reliability of Standardization (whether standard codes and other relevant information are accurately provided)

In the integrated data source set up at each cooperating medical institution, various standard codes and other relevant information are provided to the transferred data while referring to the mapping table and the master.

MID-NET creates a program that reproduces the standardization process (mapping) to check whether the standard codes and other relevant information are accurately given in the integrated data source, by comparing the content of the mapping performed in the integrated data source with the content of the mapping performed in this program.

iii. Reliability of Extract Function (whether data is accurately extracted)

MID-NET checks for the consistency between results extracted by the extract system based on the integrated data source and those processed by the SAS program (i. Verification of Extract Function). The system also checks for the

consistency between the results processed by the primary statistical processing system based on the extracted results and the results processed by the SAS program (ii. Verification of Statistical Process Function). These comparisons ensure that the data is extracted accurately from the integrated data sources.

iv. Reliability of Transmit Function (whether data is accurately transmitted)

Data extracted from integrated data sources installed at cooperating medical institutions are transmitted to the Multi-site Integrated Data Processing Center in the form of encrypted ZIP files through dedicated lines.

MID-NET ensures that the data is being accurately transmitted by comparing ZIP files before and after transmission to check whether there are no changes.

v. Reliability of SAS Transformation (whether SAS transformation is accurately performed)

ZIP files transmitted to the Multi-site Integrated Data Processing Center from cooperating medical institutions are decoded and transformed into SAS data sets.

MID-NET checks whether CSV files contained in ZIP files are accurately transformed into SAS data sets using SAS data transformation program.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Check of Accumulation Status

The accumulation status of the patients who were or to be enrolled in this study in MID-NET will be checked at 3 and 5 years after approval to report in the periodic safety reports.

8.7.1.2 Interim Analysis

Not scheduled.

8.7.1.3 Main Analysis

In order to conduct a final review of safety information, the analyses described in “8.7.1 Planned Analyses” will be conducted at 7 years after approval to prepare the report.

8.7.2 Planned Methods of Analysis

8.7.2.1 General Methods

8.7.2.1.1 Descriptive Statistics

Continuous variables are summarized by number of patients with observation, number of patients with missing, mean, standard deviation, median, lower and upper quartiles, minimum, and maximum. Classification variables are summarized as the number and percentage of patients for each category item.

8.7.2.1.2 Level of significance

The significance level of a test is set as 5%, two-tailed, unless otherwise specified. A two-sided 95% CI will be constructed, unless otherwise specified.

8.7.2.2 Handling of Missing Values, Incomplete Data and Losses to Follow-up

The incidence of missing values will be checked with the number of patients with missing descriptive statistics. No imputation of missing values will be performed. If no medical records exist after the start date of the follow-up period, the patient will be treated as loss to follow-up to be removed from the analysis.

8.7.2.3 Handling of Processing Variables

– BMI

BMI (kg/m^2) = weight (kg)/height $(m)^2$

– Corrected serum calcium level

The serum calcium level will be corrected based on the serum albumin level measured at the same time or 2 weeks before or after the serum calcium level was measured, using the formula below. However, if more than one serum albumin measurement exists within the period of 2 weeks before or after the measurement, the measurement on the date closest to the measurement date of serum calcium should be used to calculate the corrected serum calcium value. If more than one nearest measurement date exists, the value measured on the earliest date will be used to calculate the corrected serum calcium. For both serum calcium and albumin, if more than one measurement exists on the same date, the value measured at the earliest time will be used for the calculation.

1) When a serum albumin level is < 4.0 g/dL:

Corrected serum calcium level (mg/dL)

= actual measured serum calcium level (mg/dL) + 4 - serum albumin level (g/dL).

2) When a serum albumin level is ≥ 4.0 g/dL:

Corrected serum calcium level (mg/dL) = actual measured serum albumin level (g/dL)

3) When serum albumin is not measured:

Corrected serum calcium level will not be calculated

– eGFR (mL/min/1.73 m2)

Male: eGFR ($mL/min/1.73\ m^2$) = $194 \times Cr^{-1.094} \times age^{-0.287}$

Female: eGFR ($mL/min/1.73\ m^2$) = $194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$

– Incidence rate

Incidence rate = number of patients with event / number of patients treated (EVENITY or control group)

– Occurrence

Occurrence = number of events / follow-up period (person-years)

– Risk ratio

Risk ratio = Incidence rate (EVENITY group) / Incidence rate (control group)

8.7.2.4 Descriptive Analysis

8.7.2.4.1 Patient Composition

The following numbers of patients will be provided in the flow chart.

- Number of patients enrolled
- Number of patients excluded
- ✓ Number of patients by reason for exclusion
- Number of patients in the propensity-score-matched Cohort
- ✓ Number of patients in the control group
- ✓ Number of patients in the EVENITY group

8.7.2.4.2 Baseline Characteristics

For the covariates described in "8.3.3 Covariate Assessment," descriptive statistics values will be calculated for each group. The same analysis will be separately performed for patients with or without corrected serum calcium measurement during the observation period.

8.7.2.4.3 Frequency of Serum Calcium Measurement During the Observation Period

The frequency of corrected serum calcium measurements will be checked for each group.

- ✓ According to the MDV data, the mean numbers of serum calcium and albumin measurements during the first year after the first prescription in patients who were prescribed denosumab were 4.39 and 5.16, respectively, when the denominator was the number of patients with at least one measurement. Since the patients with at least one measurement was 10% of the total, the mean numbers of measurements may decrease to 0.439 and 0.516, respectively, if the patients with no measurements are included in the denominator.

For the following items, descriptive statistics values will be calculated for each group.

- The observed corrected serum calcium during the observation period will be described using the number of patients with observation, number of patients with missing, mean, standard deviation, median, lower and upper quartiles, minimum, and maximum.
- The frequency of measurements of corrected serum calcium during the observation period will be described using the number of patients and a percentage of the number to target patients, by the number of measurements.

8.7.3 Analysis of the Primary, Secondary, and Exploratory Endpoints

Details of analyses are described in the following sub-sections.

8.7.3.1 Analysis of Primary Endpoint

8.7.3.1.1 ≥ Grade 1 hypocalcaemia

- Primary Analysis

To investigate the factors influencing the incidence of ≥ Grade 1 hypocalcaemia, a point estimate with 95% CI for the incidence rate and occurrence of ≥ Grade 1 hypocalcaemia

in the subgroup of interest will be provided for each group. Risk ratio (treatment over control) as well as 95% CI based on the logistic regression model will be provided.

In addition, with regard to the incidence of ≥ Grade 1 hypocalcaemia, the interaction between the factors of interest (i.e., covariates described in “8.3.3 Covariates with Descriptions”) and the administration of romosozumab will be examined using a logistic regression model for the incidence rate to provide a p-value. Furthermore, the occurrence of event will be analyzed in the same way using a Poisson regression model to provide a p-value. The presence or absence of renal impairment will be a factor to be mandatorily matched at the time of propensity score matching in the subgroup analysis. This analysis should be performed after the balance between groups is maintained.

The subgroup of interest is described in Appendix 2.

– Other Analyses

To investigate the onset time of ≥ Grade 1 hypocalcaemia, the ≥ Grade 1 hypocalcaemia onset curve will be estimated by using the Kaplan-Meier method for each group. A subgroup analysis will be performed for each factor of interest. The cumulative 1-year occurrence of hypocalcaemia and its 95% CI will be calculated based on the estimated hypocalcaemia incidence curves.

The subgroup of interest is described in Appendix 2.

8.7.3.2 Analysis of Secondary Endpoint

8.7.3.2.1 ≥ Grade 2 Hypocalcaemia

Similarly, ≥ Grade 2 hypocalcaemia will be analyzed as described in "8.7.3.1.1 ≥ Grade 1 hypocalcaemia".

8.7.3.2.2 ≥ Grade 3 Hypocalcaemia

Similarly, ≥ Grade 3 hypocalcaemia will be analyzed as described in "8.7.3.1.1 (Grade 1 hypocalcaemia".

8.7.3.3 Sensitivity Analysis

8.7.3.3.1 Subgroup Analysis

Not applicable

8.7.3.3.2 Stratified Analysis

Not applicable

8.7.3.3.3 Sensitivity Analysis for Residual Confounding and Bias

To investigate the underestimation of the incidence rate and occurrence of hypocalcaemia caused by the low frequency of serum calcium and serum albumin measurements, the following analyses will be performed for each group.

– The incidence rate and occurrence of hypocalcaemia will be calculated when the number of patients with at least one measurement of serum calcium during the observation period is set as the population.

✓ A true estimate of the incidence rate and occurrence of hypocalcaemia is considered to exist between the values from the primary endpoint and from this sensitivity analysis. The true estimate can be inferred not to exceed the incidence rate and occurrence from this sensitivity analysis. If the hypothesis that the frequency of measurement is higher in patients prone to hypocalcaemia can be clinically provided,

the discussion about the true estimate to be lower than the estimate from this sensitivity analysis will be feasible. It is planned to discuss whether it is clinically acceptable based on the estimate from this sensitivity analysis.

8.7.3.3.4 Other Sensitivity Analyses

- With regard to "8.7.3.1 Analysis of Primary Endpoint", the results when the baseline period is changed to 1 year will be provided.
- With regard to "8.7.3.1 Analysis of Primary Endpoint" the results when the grace period is changed to unlimited (for an ITT analysis) from the one for an as-treated analysis as the main analysis will be provided.

8.8 Quality Control

MID-NET used as a database is a database operated by PMDA. MID-NET contains the standardized and coded data of electronic medical records, medical insurance claims data, and DPC data including laboratory values obtained in 2009 or later, which are provided by 23 hospitals from 10 healthcare organizations, mainly university hospitals. This is a database system whose reliability is assured by PMDA.

Data handling, records retention, and preparation and storage of analysis programs will be performed in accordance with the written procedure of this study.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of the Study Design

8.9.1.1 Misassessment and Misclassification

8.9.1.1.1 Misassessment of Drug Exposure

Since MID-NET to be used as the database cannot obtain information on the drug exposure, available prescription information is used as the information on the exposure instead. In general, prescription information may overestimate the information on drug exposure. However, the information is considered acceptable to assess the exposure because patients do not self-inject romosozumab. In contrast, among the control drugs, those that can be self-injected and those that are taken daily may differ from the actual exposure status although the discrepancy was considered difficult to be checked through a validation study because the information on patient compliance has not been collected. Therefore, the discrepancy between the prescription status of antiresorptive drugs and the actual drug exposure status is a limitation in this study. In this case, the risk ratio may move toward a greater difference because the actual exposure may be smaller in the control group.

8.9.1.1.2 Misassessment of Follow-up Period

The follow-up period will be assessed based on prescription information, death information, and the observation period of this study although MID-NET used as a database do not necessarily obtain death information. There is therefore a possibility to overestimate the follow-up period. However, the influence is minimal because no prescription information will be generated after the date of death.

8.9.1.1.3 Misassessment and Misclassification of Hypocalcaemia.

Blood calcium may not have been measured in patients who do not have apparent symptoms of hypocalcaemia or who are judged to be at low risk for hypocalcaemia by physicians, leading to a possibility that patients with hypocalcaemia are enrolled as well as a possibility of underestimating the incidence of hypocalcaemia after the prescription of romosozumab.

8.9.1.2 Information Bias

In this study, the effect of the number of measurements of blood calcium on the outcome is not examined. Therefore, if some patients have more opportunities to measure blood calcium due to comorbidities or the use of concomitant medications, a possibility that the incidence may be high due to frequent measurements in such subgroup cannot be ruled out.

8.9.1.3 Selection Bias

MID-NET, which is used as a database, consists of data from patients attending the cooperative medical institutions, which are 23 hospitals from 10 healthcare organizations, mainly university hospitals. For this reason, the information on the patients attending regular hospitals and clinics is not included. From this point, if it is common to transfer patients whose conditions become stable after a certain period has passed since starting treatment to regular hospitals or clinics near their homes, there may be a higher proportion of patients with other severe comorbidities or unstable post-treatment conditions. In addition, dialysis patients with osteoporosis may attend regular hospitals or clinics near their homes. Based on the above, the extent to which obtained results can be generalized needs to be carefully discussed.

8.9.1.4 Confounding

In this study, confounders are handled using propensity score matching. However, a lack of important information such as duration of osteoporosis and bone mineral density does not enable to rule out unmeasured confounders.

8.9.2 External Validity of Study Design

The medical institutions cooperating for MID-NET used as a database consist of 23 hospitals from 10 healthcare organizations, which are relatively large-scale medical institutions such as university hospitals and regional core hospitals. Since the database tends to include relatively severe patients in the acute phase, the generalizability of the results requires careful consideration. In addition, because the information in this database cannot be linked to the information in other medical institutions, observational period is finished when patients change the institutions, but they still continue the treatment, and therefore, long-term analysis may not be available.

8.9.3 Analysis Limitations

Since the incidence of the events is expected to be low, the examination of confounders may be inadequate. In addition, the model may be unstable because the expected incidence of hypocalcaemia is low.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

A lack of important information such as duration of osteoporosis and bone mineral density does not enable to rule out unmeasured confounders. Serious events with emergency transport may also not have been captured because information from other hospitals is not connected.

8.10 Other Aspects

N/A

9. Protection of Human Subjects

9.1 Informed Consent

This study uses MID-NET database managed by PMDA. All information in MID-NET database can be analyzed with an anonymized format at the designated and restricted on-site center. Therefore, informed consent is not required.

9.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

PMDA conducts scientific and ethical reviews when Amgen's requests for using MID-NET data will be submitted.

9.3 Confidentiality

All data accumulated in MID-NET are deidentified when the data is transmitted from cooperating medical institutions, being unable to identify source patients from the data.

9.4 Subjects Decision to Withdraw

N/A

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

In this study, the analyses will be performed with secondary use of electronic medical record database such as electronic medical records and medical insurance claims data. The safety results described in "7.1 Primary " will be documented and reported as this study report. Individual safety reporting to Amgen is not mandatory. Safety information suspected to be related to pharmaceuticals will be reported to regulatory agencies in accordance with the requirements of each country.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may revise the protocol at any time under the agreement with PMDA.

12. Plan for Disseminating and Communicating Study Results

Based on the regulations in Japan and agreements with PMDA, the actual accumulation status will be checked 3 and 5 years after approval, and the results will be reported to PMDA in the periodic safety report to confirm the progress of this study.

The final report of this study is scheduled in April 2027. Based on the regulations in Japan, the final report prepared will be submitted to PMDA.

Moreover, based on the MID-NET utilization guideline[17)], the results obtained by utilizing MID-NET are to be published from the viewpoint of the public benefits for the purpose of utilizing MID-NET, in principle. Therefore, the results of this study may be published through academic conferences and medical journals.

12.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations, which states:

1. Authorship credit should be based on
    i. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data
    ii. Drafting the article or revising it critically for important intellectual content
    iii. Final approval of the version to be published
    iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

    Authors should meet conditions i through iv.
2. When a large, multicenter group has conducted the work, the group should identify individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
3. Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
4. All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
5. Each author needs to have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. Compensation

N/A

14. References

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2. Ministry of Health, Labour and Welfare ordinance No. 171, Ministerial Ordinance on Good Post-marketing Study Practice for Drugs; December 20, 2004
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4. Notification by the General Affairs Division and the Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare. 2016 of the Grant for Health, Labour and Welfare Administration Promotion Survey Project (Special Research Project for Health, Labour Sciences), “Research on Promotion of Adverse Drug Reaction Reporting Utilizing the Function of Pharmacies and Pharmaceutical Departments (Information)”; July 10, 2017
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17. Guidelines for Utilization of MID-NET Database; April 2018 (revised in April 2021)

15. Appendices

Appendix 1. ENCePP Checklist for Research Protocol

Study title: The incidence and risk factors for hypocalcaemia among osteoporosis patients receiving romosozumab or other antiresorptive therapy in Japan -- A retrospective cohort study within the Medical Information Database Network (MID-NET)				
EU PAS Register® number: To be determined Study reference number (if applicable):				
Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8.2.1
1.1.2 End of data collection[2]	☒	☐	☐	8.2.1
1.1.3 Progress report(s)	☒	☐	☐	8.7.1.1
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	6.4
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7.3
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	8.2.3
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.2.1
4.2.2 Age and sex	☐	☒	☐	
4.2.3 Country of origin	☒	☐	☐	6.2
4.2.4 Disease/indication	☒	☐	☐	8.1
4.2.5 Duration of follow-up	☒	☐	☐	8.2.6
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.3

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	8.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	8.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.3.1

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.2.4
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.2.4
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.2.4

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3

9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.2.4
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.7.3.3.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2.2
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7.3.3.4

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6.3
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	6.3, 8.5

Comments:

ESection 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.3

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	11.1

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the PPD

protocol:

Date: dd/Month/year November 1, 2023

Signature: _____

Appendix 2. Subgroup Classification

Category to Examine Safety in Patients with Renal Impairment

Item	Category
eGFR (Category 1)	≥ 90 / 60 to < 90 / 30 to < 60 / < 30 / Unmeasured (mL/min/1.73m^2)

Appendix 3. Milestones

Milestones	Planned date
Start date of observation	March 4, 2019 (release date of this drug)
End date of observation	January 31, 2026
Final analysis	January 2026
Completion of the study report	December 2026