Summary Table of Study Protocol

Title	Post-marketing Study Evaluating the Risk of Serious Cardiovascular Events Among Osteoporotic Patients Receiving Romosozumab in Japan Using the Medical Information Database Network (MID-NET)
Protocol version identifier	Study Number 20190206; Version 1.0
Date of last version of the protocol	04 April 2024
EU Post Authorization Study (PAS) Register No	To be determined
Active Substance	Romosozumab
Medicinal Product	Evenity®
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	Primary objective To evaluate the risk of serious cardiovascular events during the initial 12 months of romosozumab therapy relative to other specific osteoporosis therapies Secondary objective To evaluate the risk of serious cardiovascular events during the initial 12 months of romosozumab therapy relative to other specific osteoporosis therapies by the level of renal insufficiency
Country(ies) of Study	Japan
Author	PPD

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen K.K.
MAH Contact	PPD Amgen K.K. Midtown Tower, 9-7-1 Akasaka, Minato-ku, Tokyo, 107-6239, Japan

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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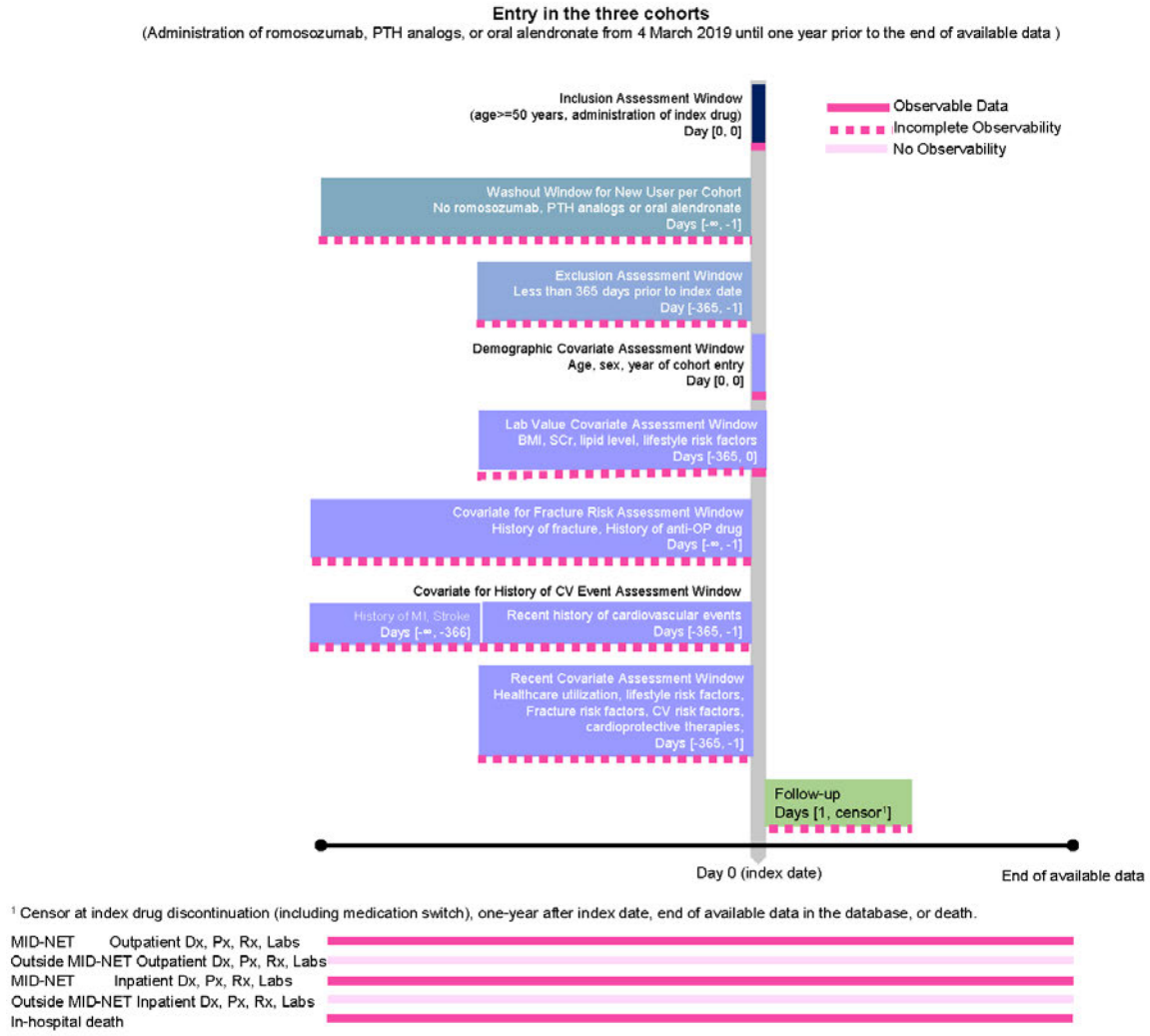
Study Design Schema



Abbreviations used in the figure: CV, cardiovascular; PTH, parathyroid hormone receptor.

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2. List of Abbreviations

Abbreviation or Special Term	Explanation
CCI	CCI
CCI	CCI
BMD	Bone mineral density
BRIDGE	Study to Compare the Safety and Efficacy of Romosozumab versus Placebo in Men with Osteoporosis
CI	Confidence intervals
CKD	Chronic kidney disease
CCI	CCI
EMR	Electronic medical records
FRAME	Fracture Study in Postmenopausal Women with Osteoporosis
GPSP	Good post-marketing study practice
ICMJE	International Committee of Medical Journal Editors
IPTW	Inverse probability of treatment weights
IQR	Interquartile range
J-RMP	Japanese Risk Management Plan
MDV	Medical Data Vision
MHLW	Ministry of Health, Labor, and Welfare
MID-NET	Medical Information Database Network
NDB	National database
PMDA	Pharmaceuticals and Medical Devices Agency
PPV	Positive predictive value
PTH	Parathyroid hormone receptor
SAP	Statistical analysis plan
SD	Standard deviation
SERM	Selective estrogen receptor modulators
SMD	Standardized mean differences
SMRW	Standardization mortality rate weighting

3. Responsible Parties

3.1 Sponsor

Role	Name
Marketing authorization holder(s)	Amgen K.K. Midtown Tower, 9-7-1 Akasaka, Minato-ku, Tokyo, 107-6239, Japan

3.2 Contract Research Organization

Contract Research Organization	Scope of Work
IQVIA Services Japan G.K. 4-10-18 Takanawa, Keikyu Dai-Ichi Building Minato-ku, Tokyo 108-0074 Japan IQVIA Solutions Japan G.K. (subcontract) 4-10-18 Takanawa, Keikyu Dai-Ichi Building Minato-ku, Tokyo 108-0074 Japan	Support protocol development Statistical analysis Medical writing Others (Project Management, self-inspection)

IQVIA Services Japan G.K. and IQVIA Solutions Japan G.K. support protocol development at the direction of Amgen K.K. However, the contract is not based on the good post-marketing study practice (GPSP) ordinance. On the other hand, the contract for statistical analysis and medical writing is based on the GPSP ordinance.

4. Abstract

- Study Title

Post-marketing Study Evaluating the Risk of Serious Cardiovascular Events Among Osteoporotic Patients Receiving Romosozumab in Japan Using the Medical Information Database Network (MID-NET).

- Study Background and Rationale

In January 2019, romosozumab was approved in Japan for the treatment of osteoporosis in patients at high risk of fracture. As part of the Japanese Risk Management Plan for romosozumab, Amgen committed to conduct a post-marketing study to evaluate the risk of cardiovascular events in real-world users of romosozumab and those with renal dysfunction. The overall approach of the proposed study, including study design, the data source, endpoints, comparator group, and overall analytic approach was previously agreed upon with the agency during the consultation meeting held on January 17, 2024.

- Study Feasibility and Futility Considerations

Sample size in MID-NET has been informed by publicly available data. The confidence interval around the effect estimate is expected to have low precision due to low event rate. We followed the draft ICH M14 guidance “General Principles on Planning and Designing Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of a Medicine” to interpret the study results. Questions around the measured and unmeasured confounders, potential channeling bias, definition of baseline period, and level of renal insufficiency are addressed by National database (NDB) open data and Amgen in-house using the database provided by Medical Data Vision (MDV).

- Research Question and Objectives

The phase 3 randomized controlled trial (ARCH) showed more cardiovascular death, nonfatal MI, and nonfatal CCI in patients treated with romosozumab than in those treated with alendronate. However, this trial did not include any Japanese women. Therefore, the objective of this study is to assess the cardiovascular safety of romosozumab in Japanese patients.

Objectives	Endpoints
Primary	
• To evaluate the risk of serious cardiovascular events during the initial 12 months of romosozumab therapy relative to other specific osteoporosis therapies	• Composite endpoint of hospitalized acute myocardial infarction, cerebral hemorrhage and cerebral infarction
Secondary	
• To evaluate the risk of serious cardiovascular events during the initial 12 months of romosozumab therapy relative to other specific osteoporosis therapies by the level of renal insufficiency	• Composite endpoint of hospitalized acute myocardial infarction, cerebral hemorrhage and cerebral infarction

- CCI [redacted]
  - CCI [redacted]
  - CCI [redacted]
  - CCI [redacted]
  - CCI [redacted]
- Estimation
  - This study will estimate the hazard ratio (95% confidence interval) of hospitalized cardiovascular events for romosozumab relative to other specific osteoporosis therapies. Interpretation of the estimate will be informed by available sample size, completeness of capture for the endpoints, and the assessment of measured and unmeasured confounding.
- Study Design

  A retrospective cohort study of a new user with active comparator design
- Data Resource

  MID-NET database is a hospital-based setting of 23 hospitals from ten healthcare organizations that participate in the CCI [redacted] system. The patient-level data includes clinical, administrative and laboratory information. Previous studies showed the high validity of the diagnoses and procedure records in the CCI database, which are used to enhance healthcare service management for health policy planning. In 2022, nearly 1.5 million patients had a record in this network.

- Patient Eligibility Criteria

  Inclusion criteria

  - Three cohorts of patients defined by new initiation of romosozumab, Parathyroid hormone receptor (PTH) analogs (teriparatide, abaloparatide) or oral alendronate from 4 March 2019 onwards to one year prior to the end of available data.
  - Patients at least 50 years of age at the date of new treatment initiation.

  Exclusion criteria

  - Patient without an adequate period of records in the data source for assessment of baseline cardiovascular risk.

- Follow-up

  Patients will be followed from the initiation of romosozumab, PTH analogs or oral alendronate (index date) through the first occurrence of any of following: endpoint, discontinuation of the study medication (including medication switch), one year after index date, end of available data in the database, or death.

- Variables

  - Outcome Variables

    Two types of outcomes will be defined using algorithms that have been previously validated in Japan administrative claims databases.

CCI

- Exposure Variables

  Three cohorts will be created mutually and defined based on the prescriptions received for:

  - Romosozumab
  - PTH analogs: teriparatide, abaloparatide
  - Oral alendronate

- Covariates

  - Patient and healthcare characteristic
  - Fracture risk factors
  - Cardiovascular risk factors
  - Use of cardioprotective therapies
  - Historical use of anti-osteoporosis drugs
  - Level of renal insufficiency

- Study Sample Size

Using the MID-NET 2021 open data, we estimated the number of patients who received romosozumab, teriparatide, or oral alendronate over 5.5 years. The expected sample size for this study is: 3,850 patients for romosozumab,
8,500 patients for teriparatide, and 60,000 patients for oral alendronate.

- Data Analysis
  - Summary Statistics:

    Patient demographic and clinical characteristics will be summarized by cohort of exposure. Discrete variables will be summarized using frequencies and proportions, and continuous variables will be summarized using means and standard deviation (SD) or median and interquartile large (IQR). Incidence rate (number of events divided by person-time of follow-up) of the various outcomes in each exposure cohort will be estimated along with 95% confidence intervals (CI) as a measure of precision.

- Approach to primary objective:

  Propensity scores will be calculated for each patient using multiple logistic regression modelling based on baseline demographic characteristics and clinical characteristics. Inverse probability of treatment weights (IPTW) will be created using propensity scores to minimize the measured confounding in the comparison of patients initiating romosozumab relative to patients initiating other specific osteoporosis therapies. Standardized mean differences (SMD) will be used to assess the differences in baseline patient characteristics between the treatment groups. Negative control outcome analyses will be used to detect presence of unmeasured confounding. COX proportional hazards model in the weighted sample will be used to estimate hazard ratio.

- Approach to secondary objective:
  The same approach will be performed by the level of renal insufficiency:

  1) no chronic renal disease (or eGFR >= 90 mL/min/1.73 m^2), 2) stage I or II Chronic Kidney Disease (CKD) (or eGFR 60-89 mL/min/1.73 m^2), 3) stage III CKD (or eGFR 30-59 mL/min/1.73 m^2), or 4) stage IV or V (or eGFR < 30 mL/min/1.73 m^2).

- Bias analysis:

  To inform the reliability and robustness of interpreting the results, we plan to perform a series of bias analyses that may include:

  - Evaluate completeness of follow-up capture of outcomes in MID-NET (an open healthcare system) relative to a closed healthcare system (for example, DeSC, NDB) within therapy cohort
  - Quantitative bias analysis to characterize the magnitude of uncertainty arising from systematic errors

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1.0	27 June 2024	NA	NA	The initial version.

6. Rationale and Background

6.1 Summary of the Medicinal Product of Interest

Table 1. Summary of the Medicinal Product of Interest

Date of Approval	08 January 2019
Date of Market Launch	04 March 2019
Therapeutic Classification	CCI [redacted]
Re-examination Period	8 years
Approval Number	CCI [redacted]
Brand Name	Evenity® Subcutaneous Injection 105 mg Syringes
Active Substance	Romosozumab
Dose and Formulary	Injection: Containing 105 mg of romosozumab in a prefilled syringe (1.17 mL).
Administration Route and Dosage	Adult: 210 mg of romosozumab once monthly for 12 months.
Indication	Osteoporosis in patients at high risk of fracture.
Conditions for Approval	The risk management plan should be developed and implemented as appropriate.

6.2 Safety Specification

This study investigates 1) serious cardiovascular events listed as an important potential risk and 2) safety in the patients with renal dysfunction as important missing information. This study is a part of additional pharmacovigilance activities described in the Japanese Risk Management Plan (J-RMP) for romosozumab (Evenity®).

6.3 Diseases and Therapeutic Area

Osteoporosis is a disease characterized by low bone mineral density (BMD), deterioration of bone tissue, and disrupted bone microarchitecture resulting in compromised bone strength and risk of fractures (Amgen, 2019a; LeBoff et al, 2022). Osteoporosis can be prevented and treated with lifestyle modification, medication and supplements (The Committee for Developing Guidelines for Prevention and Treatment of Osteoporosis, 2015). Pharmacologic therapeutics for anti-osteoporosis focus on reducing bone loss (using antiresorptive agents) and increasing bone formation (using anabolic agents). These approaches aim to improve bone density and strength. Antiresorptive agents, such as bisphosphonate, RANKL antibody (denosumab), estrogen replacement therapy, or selective estrogen receptor modulators (SERMs),

along with anabolic agents like PTH analogs, have demonstrated efficacy in clinical trials for reducing fracture. Additionally, supplement treatment like calcium, activated vitamin D3, and vitamin K derivatives can be beneficial. Furthermore, calcitonin salmon is used to alleviate osteoporosis-related pain (LeBoff et al, 2022; Sözen et al, 2017).

In January 2019, romosozumab was approved in Japan for the treatment of osteoporosis in patients at high risk of fracture. Romosozumab is a monoclonal antibody that binds and inhibits sclerostin, a natural inhibitor of the Wnt signaling pathway, therefore increasing bone formation and decreasing bone resorption.(Cosman et al, 2016; Lim, 2022). Two phase III, international, randomized, double-blind, placebo-controlled trials of romosozumab were evaluated for the approval in Japan: The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) (Cosman et al, 2016) and a study to compare the safety and efficacy of romosozumab versus placebo in men with osteoporosis (BRIDGE) (Lewiecki et al, 2018). Results from the FRAME trial showed risk reductions for new vertebral fractures and clinical fractures at 12 and 24 months as well as the increases in BMD at the lumbar spine, total hip, and femoral neck among patients treated with romosozumab compared to placebo (Cosman et al, 2016). Results from the BRIDGE trial demonstrated increased BMD in the romosozumab group, compared to placebo group (Lewiecki et al, 2018).

Romosozumab may potentially cause or worsen vascular calcification, but pre-clinical data indicate no impact on cardiovascular events (Amgen, 2019b). However, in an international, randomized trial of postmenopausal women with osteoporosis at high risk of fracture, romosozumab was associated with more serious cardiovascular events (2.5% versus 1.9%) than alendronate in the first 12 months (Saag et al, 2017). This trial did not include Japanese patients, unlike the FRAME study, which showed no difference (1.3% versus 1.3%) between the two treatments (Amgen, 2019b; Cosman et al, 2016). In September 2019, the Japanese package insert for romosozumab was updated in response to adverse drug reports following its launch. The revision included safety precautions related to cardiovascular events, as advised by Ministry of Health, Labor, and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) (PMDA, 2019).

6.4 Rationale

As part of the Japanese Risk Management Plan for romosozumab, Amgen committed to conduct a post-marketing study to evaluate the risk of cardiovascular events in real-world users of romosozumab and those with renal dysfunction. As renal dysfunction is

associated with higher risk of cardiovascular events (Jankowski et al, 2021) and vascular calcification, especially in people on dialysis (Amgen, 2019b), this study will examine the risk of the cardiovascular events by the level of renal insufficiency. The overall approach of the proposed study, including study design, the data source, endpoints, comparator group, and overall analytic approach was previously agreed upon with the agency during the consultation meeting held on January 17, 2024.

6.5 Feasibility and Futility Considerations

We used publicly available data to determine the sample size in MID-NET. The effect estimate's confidence interval may have low precision because of the low event rate. We used the NDB open data to describe the challenge of measured and unmeasured confounders in this study, and followed the draft ICH M14 guidance "General Principles on Planning and Designing Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of a Medicine" to perform bias analysis for study results interpretation. Given that MID-NET operates within a hospital-based setting and is currently inaccessible, we conducted feasibility assessments using Medical Data Vision (MDV) data to inform the choice of baseline period and the renal impairment level for protocol development. Amgen CfOR Data Analytics Center performed the internal analysis of MDV. The results suggest that sample size may not significantly increase even with a 3-month baseline period. In line with PMDA's recommendation, a 12-month period is set as the baseline for this study. In addition, the diagnosis of CKD stages did not have enough sensitivity to describe the level of renal impairment in the MDV data. Instead, using serum creatinine and estimated glomerular filtration rate (eGFR) can provide a more accurate and granular classification of renal insufficiency among osteoporosis patients. The MID-NET summary report I stated that more than 90% of patients who were given romosozumab (1908 out of 1989), alendronate (18,570 out of 19,118) or PTH analogs (2,978 out of 3,156) had their serum creatinine tested during 2021-2023 (PMDA, 2024a).

6.6 Statistical Inference (Estimation)

This study will estimate the hazard ratio with 95% confidence interval of cardiovascular events for romosozumab relative to other specific osteoporosis therapies. Interpretation of the estimate will be informed by available sample size, completeness of capture for the endpoints, and the assessment of measured and unmeasured confounding.

7. Research Question and Objectives

The phase 3 randomized controlled trial (ARCH) showed more cardiovascular death, nonfatal MI, and nonfatal CCI in patients treated with romosozumab than in those treated with alendronate. However, this trial did not include any Japanese women. Therefore, the objective of this study is to assess the cardiovascular safety of romosozumab in Japanese patients when compared to other anti-osteoporosis medications.

7.1 Primary

The objective of this study as follows:

To evaluate the risk of serious cardiovascular events during the initial 12 months of romosozumab therapy relative to other specific osteoporosis therapies.

romosozumab vs. PTH analogs
romosozumab vs. oral alendronate

7.2 Secondary

To evaluate the risk of serious cardiovascular events during the initial 12 months of romosozumab therapy relative to other specific osteoporosis therapies by the level of renal insufficiency

romosozumab vs. PTH analogs
romosozumab vs. oral alendronate

8. Research Methods

8.1 Study Design

This is a retrospective cohort study employing a new user with active comparator design, using secondary data and conducting analyses in MID-NET database.

8.2 Setting and Study Population

8.2.1 Study Period

Patients will be identified for inclusion into the study population between 04 March 2019 (initial date of use for specific coding for romosozumab, PTH analogs (teriparatide, abaloparatide) or oral alendronate) through and the date of data extraction. Data availability will extend to 365 days prior to index date to accommodate the identification of eligible patients. Patients will be eligible to enter the cohort up to one year prior to the end of available data, ensuring a potential minimum follow-up period of one year.

8.2.2 Subject Eligibility

8.2.2.1 Inclusion Criteria

Three cohorts of patients defined by new initiation of romosozumab, PTH analogs (teriparatide, abaloparatide) or oral alendronate from 4 March 2019 onwards to one year prior to the end of available data.

Patients at least 50 years of age at date of new treatment initiation.

8.2.2.2 Exclusion Criteria

Patients without at least 365 days before new treatment initiation.

8.2.3 Matching

Not applicable

8.2.4 Baseline Period

The baseline period will be identified as 365 days before the index date (exclusion the index date). For three cohorts of patients with study medication (romosozumab, PTH analogs (teriparatide, abaloparatide) or oral alendronate), we will use all historical data prior to index date (exclusive) to identify new use of the index drug.

8.2.5 Study Follow-up

Patients will be followed from the initiation of romosozumab, PTH analogs or oral alendronate (index date) through the first occurrence of any of following: endpoint, discontinuation of the study medication (including medication switch), one year after index date, end of available data in the database, or death.

8.3 Variables

8.3.1 Exposure Assessment

1. Romosozumab: the dosing interval for romosozumab 210mg (Evenity®) is once every 30 days. Patients will be considered continuously exposed to Evenity until a gap beyond the dosing interval is observed. The censoring date for treatment discontinuation will be the last administration date plus an appropriate window defined in statistical analysis plan (SAP).

2. PTH analogs: the dosing intervals for teriparatide vary by dosage form. Patients will be considered continuously exposed to teriparatide until a gap beyond the dosing interval is observed. In addition, abaloparatide is once daily from a self-injector. Patients will be considered continuously exposed to abaloparatide until a gap beyond the dosing interval is observed. The censoring date for treatment

discontinuation will be the last administration date plus an appropriate window defined in SAP.

3. Oral alendronate: The dosing intervals for alendronate vary by prescription. Days' supply associated with the prescription will be used to determine the dosing interval. Patients will be considered continuously exposed from the date of first prescription until a gap beyond the completion of the last day's supply and next prescription is observed. The censoring date for treatment discontinuation of oral bisphosphonates will be the last dispensing date plus an appropriate window defined in SAP.

8.3.2 Outcome Assessment

Outcome of primary objective and secondary objective:

Cardiovascular end points will be defined using algorithms that have been previously validated in Japan administrative claims databases and recommended by agency (Ando et al, 2018; Nakai et al, 2021; PMDA, 2023a; PMDA, 2023b; PMDA, 2023c).

Endpoint will be the first admission date for each outcome, and the event will be identified with a diagnosis related to primary, admission-causing or most-resourcing categories.

We will use the admission date as the event date to capture the earliest sign of the event. We recognize that the admission date may not represent the actual onset of event if it occurs during hospitalization. However, we expect that this effect is likely small in general, since the average hospital stay related to cardiovascular events was reported to be approximately 15 days (JCS, 2023). Moreover, the subgroup of the patients using index medication (ie, romosozumab, teriparatide, or oral alendronate) during hospitalization is less than 10%) (MHLW, 2023a). Therefore, the use of admission date as the date of event occurrence is appropriate for this study.

- CCI [redacted]

Table 2. Algorithms of outcome definitions

Outcome	Definition
CCI	

CCI

8.3.3 Covariate Assessment

Covariates that might influence osteoporosis treatment choice (ie, measures of prognosis) and are risk factors for various adverse events that could be assessed in safety evaluation are included to control for confounding. Sex, age and year of index date will be included as a covariate. All available historical data will be used to assess

history of fracture, history of pharmacologic therapy for osteoporosis, history for cardiovascular risk factor, history of cardioprotective therapies and or osteoporosis-related medication. Each covariate will be identified using a case ascertainment algorithm that incorporates individual or combinations of inpatient and outpatient ICD-10 diagnosis codes, drug codes, procedure codes, laboratory test codes, and date information from the MID-NET system. Covariates with a prevalence of 0.5% or less in the feasibility assessment within MID-NET will not be included in this study.

Table 3. List of covariates

Characteristic	MID-NET	Note/ Covariate assessment period
Age, mean (SD)	Yes	On index date
Race/ethnicity	No	Most of all is Japanese
Sex (Male, female)	Yes	On index date
Year of cohort entry	Yes	On index date
Lifestyle risk factors		The closest measurement taken within one year before the index date, including the index date itself.
Smoking index	Yes	This information might be only recorded when patients are admitted to the hospital.
Information of lab value		The closest measurement taken within one year before the index date, including the index date itself.
Height, cm, mean (SD)	Yes	
Weight, kg, mean (SD)	Yes	
Body mass index, mean (SD)	Yes	Calculated with height and weight, kg/m^2
Serum creatinine, mg/dL, mean (SD)	Yes	
eGFR, mL/min/1.73 m^2	Yes	% among three cohorts to be confirmed
Level of renal insufficiency[a]		Calculated with serum creatine level. Classified into four groups. >= 90 (Normal); 60 -< 90 (Mild); 30 -< 60 (Moderate); < 30 (Severe)
Fasting plasma glucose, mg/dL, Mean (SD)	Yes	
HbA1c, %, Mean (SD)	Yes	
HDL-C, mg/dL, Mean (SD)	Yes	
LDL-C, mg/dL, Mean (SD)	Yes	
Triglyceride level, mg/dL, Mean (SD)	Yes	
History of healthcare utilization		Within one year prior to index
Number of inpatient hospitalizations	Yes	
Number of outpatient visits	Yes	
Number of cardiovascular-related hospital days	Yes	
Number of serum creatinine tests	Yes	% among three cohorts to be confirmed
Number of lipid-related lab tests	Yes	% among three cohorts to be confirmed
History of fracture	Yes	All available history unless otherwise specified
Any fracture	Yes	
Vertebral fractures	Yes	
Hip fracture	Yes	

Characteristic	MID-NET	Note/ Covariate assessment period
History of fracture hospitalizations	Yes	
Osteoporosis diagnosis	Yes	
History of use of anti-osteoporosis drugs		All available history unless otherwise specified
Oral bisphosphonates	Yes	
IV bisphosphonates	Yes	
Anti-RANKL antibody (Denosumab)	Yes	
PTH analogs (Teriparatide or abaloparatide)	Yes	
Selective estrogen receptor modulators (Raloxifene, bazedoxifene)	Yes	
Estrogen replacement therapy	Yes	
Historical use of the medication that increased fracture or osteoporosis risk	**Yes**	Fracture/OP risk factors, Within one year prior to index
Anticonvulsant		
Antidepressant	Yes	
Antiparkinsonian	Yes	
Antipsychotic	Yes	
Benzodiazepine	Yes	
NSAIDs and COX-2 inhibitor	Yes	
Corticosteroids (oral or injectable)	Yes	
Opioids	Yes	
Proton-pump inhibitor	Yes	
History of other comorbidities that increased fracture or osteoporosis risk		Fracture/OP risk factors. Within one year prior to index
Rheumatoid arthritis	Yes	
Systemic Lupus Erythematosus	Yes	
Chronic obstructive pulmonary disease	Yes	
Asthma	Yes	
Pneumonia	Yes	
Parkinsonism	Yes	
Dementia	Yes	
Depression	Yes	
Schizophrenia	Yes	
Sepsis or septicemia	Yes	
Sleep apnea	Yes	
Vitamin D deficiency	Yes	
History of cardiovascular events		All available history unless otherwise specified
Myocardial infarction within 1 year prior to index	Yes	Within one year prior to index
Myocardial infarction ≥ 1 year prior to index	Yes	>= 1 year prior to index
CCI within 1 year prior to index	Yes	Within one year prior to index
CCI ≥ 1 year prior to index	Yes	>= 1 year prior to index
History of CV risk factors		Within one year prior to index
Atherothrombosis	Yes	
Heart failure	Yes	
Peripheral artery disease	Yes	

Characteristic	MID-NET	Note/ Covariate assessment period
Cerebrovascular disease	Yes	
Coronary artery disease	Yes	
Angina (including stable and unstable)	Yes	
Atrial fibrillation	Yes	
Conduction disorder	Yes	
Hypertension	Yes	
Hyperlipidemia	Yes	
Hypercholesterolemia	Yes	
Obesity	Yes	
Peripheral vascular disease	Yes	
Transient ischemic attack	Yes	
Type 2 diabetes mellitus	Yes	
CKD	Yes	
Chronic kidney disease (stage III, IV and V) without dialysis	Yes	
Chronic kidney disease (stage III, IV and V) with dialysis	Yes	
End stage renal disease	Yes	
History of cardioprotective therapies		Within one year prior to index
Diuretic		Antihypertensive
Beta-blocker		Antihypertensive
Calcium Channel blockers		Antihypertensive
Angiotensin Converting Emzyme (ACEI)/ Angiotensin Receptor Blockers (ARBs)	Yes	Antihypertensive
Insulin	Yes	Anti-diabetes
Metformin	Yes	Anti-diabetes
GLP-1 receptor agonists	Yes	Anti-diabetes
Thiazolidinediones	Yes	Anti-diabetes
Sulfonylureas	Yes	Anti-diabetes
SGLT- 2 inhibitors	Yes	Anti-diabetes
DPP- 4 inhibitors	Yes	Anti-diabetes
Statins (any kind)	Yes	lipid lower agents
Ezetimide	Yes	lipid lower agents
Statins + ezetimide combinations	Yes	lipid lower agents
PCSK9i	Yes	lipid lower agents
Other lipid lowering drugs (fibrates, gemifibrozil, Niacin, Cholestyramine)	Yes	lipid lower agents
Aspirin	Yes	Antiplatelets/ antithrombotic
Clopidogrel and other antiplatelet	Yes	Antiplatelets/ antithrombotic
Anticoagulants	Yes	Antiplatelets/ antithrombotic
Digoxin	Yes	Antiarrhythmic
Amiodarone and other antiarrhythmic	Yes	Antiarrhythmic
Antianginal nitrate	Yes	Antianginal agents
Antianginal ranolazine	Yes	Antianginal agents

a. To calculate eGFR please use below formula: For females: eGFR = 194 x $SCr^{-1.094}$ x $Age^{-0.287}$ x 0.739; For males: eGFR = 194 x $SCr^{-1.094}$ x $Age^{-0.287}$

8.3.4 Validity and Reliability

In the Japanese healthcare system, outcome definitions of CCI [redacted] have been validated in the hospital-based setting from different data sources. Previous studies have reported that the positive predictive value (PPV) for CCI [redacted] ranged from 78.3% to 93.4% (Ando et al, 2018, Nakai et al, 2021). Moreover, the outcome definitions of CCI [redacted] will follow the PMDA's outcome validation reports, which showed that the PPV for CCI [redacted] was reported to be 94.22% (95% CI: 89.63-97.19) and the PPV for CCI [redacted] was 84.26% (95% CI: 78.96-88.67) (PMDA, 2023b; PMDA, 2023c). Due to the limited resources, a chart review of all the patients in the hospital or a sufficiently large random sample of the hospitalized patients was not possible, so a full set of validity measures such as specificity and NPV are not generally available.

8.4 Data Sources

This study is based on the secondary data use of the MID-NET developed by the PMDA. MID-NET is a health information database composed of electronic medical records (EMRs), claims data, and CCI [redacted] data from 23 hospitals across ten healthcare organizations. As of December 2022, the database contains data from approximately 6.05 million patients (Yamaguchi et al, 2019), and nearly 1.5 million patients had a record in this network in 2022. The stored data is periodically updated, with updates occurring every week or every 1-3 months depending on the type of data. The available data for analysis includes information on patients' diagnoses, laboratory test results, dosage, and duration of medication administration, as well as details of medical procedures such as surgery dates and types of clinical examinations.

8.5 Study Size

The study sample size is expected based on information from the open data of MID-NET. There were 693 romosozumab users, 1,551 PTH analogs users in MID-NET in 2021 (PMDA, 2024b). Assuming 700 romosozumab users per year is accumulated through 5.5 years, the expected number of romosozumab users would be 3,850 by the end of the study. The number of users who would use PTH analogs and oral alendronate are expected to be 8,500 and 60,000, respectively.

Table 4 provides the 95% CI estimates for HR when 1.0 in HR, 3,850 patients in romosozumab, 8,500 patients in PTH analogs and 60,000 patients in oral alendronate, 0.6 or 0.8 years of follow-up period and 0.004 or 0.01 in incidence rates of

cardiovascular outcomes. The incidence rate of cardiovascular outcomes was based on previous literature (Ishikawa et al, 2008).

Table 4. 95% CI estimate for Hazard Ratio 1.0

CV outcome (IR per one person-year)	Follow-up Time	Estimated 95% CI	
		8,500 patients in PTH analogs	60,000 patients in oral alendronate
0.004	0.6	(0.45, 2.18)	(0.50, 1.91)
	0.8	(0.50, 1.94)	(0.54, 1.75)
0.01	0.6	(0.61, 1.63)	(0.65, 1.52)
	0.8	(0.66, 1.54)	(0.70, 1.45)

Abbreviations used in the table: CI, confidence interval; CV, cardiovascular; IR, incidence rate; PTH, parathyroid hormone receptor.

8.6 Data Management

Amgen will take responsibility for application for the study permits, obtaining necessary approvals, and access to the study data. The data will be stored and analyzed in accordance with the MID-NET Utilization Guidelines (PMDA, 2024c).

8.6.1 Obtaining Data Files

Trained and registered MID-NET users can centrally extract MID-NET data using the extraction script from the on-site center. They can access the analysis dataset and the statistical information generated from it within the MID-NET data center, either from the on-site center or from a remote MID-NET environment. The remote connection requires IT security management.

The planned criteria of the patients to be extracted from MID-NET is listed as follows:

- Patients who used any of the study medications (romosozumab, PTH analogs, or oral alendronate) after 4 March 2019.

8.6.2 Linking Data Files

All patient-level data contained in the MID-NET database will be extracted by the criteria in Section 8.6.1 and linked by the unique identifier provided in the data system.

8.6.3 Review and Verification of Data Quality

The general principles and procedures for reviewing and verifying data quality will be described in detail in the SAP. All data checks to be performed on completeness, plausibility and consistency of collected data will be described in detail with identification of data discrepancies. The reliability of the data in MID-NET is ensured by PMDA from

the following points: data reliability, reliability of data standardization, reliability of data extraction, reliability of data transmission to the data center and reliability of conversion to SAS data (Nakashima et al, 2018).

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Feasibility Analyses

A detailed feasibility step will be applied in order to define and operationalize the key design elements in the MID-NET database. Considering the data relevance and reliability, we will assess the availability of laboratory information (eg, serum creatine or eGFR), date of administration, day supply of the prescriptions, and relevant diagnosis to test the validity of coding algorithms.

8.7.1.2 Primary Analysis

To describe the study population, we will compute summary statistics for patient demographics and clinical characteristics as of the index date, stratified by the index treatment. Discrete variables will be summarized using frequencies and proportions, and continuous variables will be summarized using means and standard deviation (SD) or medians and interquartile range (IQR), as appropriate. For this study, propensity scores will be estimated and used to create IPTW for each patient in each pairwise treatment comparison. We will then assess the comparability of the weighted cohorts in each comparison, estimate the hazard ratio for each comparison and perform additional analyses to support the result interpretation.

8.7.1.3 Secondary Analysis

For secondary objective, we will use the same method that we used in primary analysis and restrict to a subset that have available information on renal insufficiency. Since romosozumab and oral alendronate have a warning for use in patients with creatinine clearance less than 30 mL/min/1.73 m^2, patients treated with these therapies may exhibit a lower prevalence of renal insufficiency compared to those treated with PTH analogs. To ensure the comparability between treatment groups, we will limit the analyses to patients with similar levels of renal function to mitigate potential bias. The subgroup analyses will be performed based on the following criteria: 1) no chronic renal disease (or eGFR >= 90 mL/min/1.73 m^2), 2) stage 1 or II CKD (or eGFR 60-89 mL/min/1.73 m^2), 3) stage III CKD (or eGFR 30-59 mL/min/1.73 m^2), or 4) stage IV or V (or eGFR < 30 mL/min/1.73 m^2).

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

Given that MID-NET database is not accessible for now, descriptive analysis will be conducted prior to propensity score weighting portion of this study. To describe the incidence rate for outcomes, by romosozumab therapy, by PTH analogs, and by oral alendronate, the number of patients with events will be divided by person-time of follow-up. Incidence rate as well as hazard ratio will be accompanied by the corresponding 95% confidence intervals (CI) as a measure of precision.

We assume that measured and unmeasured confounding exist, and plan to perform a set of analyses to assess the comparability between treatment groups. Standardized mean differences (SMD) will be used to assess how different the baseline characteristics are between the treatment groups before and after propensity score weights are applied. We will consider the measured confounders with SMD values less than 0.1 as having negligible differences (Austin, 2009). In addition, negative control outcome analyses will be performed to rule out any potential unmeasured confounders (McGrath et al., 2020). For each negative control outcomes, risk difference and risk ratio in negative control outcomes will be calculated. The comparability of treatment groups will be explored by examining overall trends in effect estimates and the precision of CI across all negative control outcomes within an exposure contrast. We will assume there is significant uncontrolled confounding if the measure of association is not likely to be null.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

There will be no imputation of missing data in this study. A proportion of patients has laboratory information in the data source. Given that MID-NET is hospital-based data network and does not include information from other resources, this study will use extra data sources to describe how complete the capture for the endpoints is in a closed healthcare system within therapy cohorts. This way, we might be able to assess the possible size and effect of incomplete capture/ misclassification of endpoints between treatment groups on planned main analysis.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

To summarize the study population selection from the MID-NET database based on the study eligibility criteria, an attrition table will be provided. It will show the counts and percentages of excluded and remaining patients for each inclusion/exclusion criterion at every step of patient selection.

8.7.2.3.2 Description of Patient Characteristics

Patient demographic and clinical characteristics during the baseline period will be summarized and by treatment groups.

8.7.2.4 Analysis of the Primary, Secondary, and CCI

Primary endpoint is consistent with primary objective.

- Composite endpoint of hospitalized AMI, cerebral hemorrhage and cerebral infarction

Secondary endpoint is consistent with secondary objective.

- Composite endpoint of hospitalized AMI, cerebral hemorrhage and cerebral infarction

CCI

We will use two methods to estimate the incidence of each endpoint. First, we will calculate simple incidence rates (total number of patients with at least one event in the cohort divided by the sum of person-time to the first censoring event in the cohort) multiplied by 100 for each outcome and cohort. These rates do not account for treatment selection. Second, we will estimate propensity scores for each patient in the cohort using multivariable logistic regression with baseline covariates related to patient and clinical characteristics (see Section 8.3.3). The propensity score balances the distribution of observed covariates between treatment groups. We will include covariates that are either true confounders (to reduce bias) or related to the outcome (to increase precision). We will avoid covariates that are only related to the exposure but weakly related to the outcome, as they may decrease precision without reducing bias much (Brookhart et al, 2006). We will use inverse probability of treatment weights (IPTW) to estimate the rates of each outcome by time t in the overall patient population.

Specifically, $F(T(a) < t)$ will be estimated with:

$$F(T(a) < t) = \frac{1}{n} \sum_{i=1}^{n} \frac{I(T_i < t) I(A_i = a) \Delta_i}{Pr(\Delta_i = 1 | A_i, W_i)}$$

where A_i is an indicator of the observed treatment assignment, $T(a)$ is the time of the (possibly counterfactual) outcome that would be observed if the patient were treated with $A_i=a$, and Δ_i is an indicator that the patient was uncensored.

The propensity score model, $\Pr(A_i=a|W_i)$, will be estimated using logistic regression, and will contain a rich set of baseline covariates detailed in Section 8.3.3. We will estimate the hazard ratio and 95% confidence interval bands at 12 months by using COX proportional hazards model. Patients will be censored if any of the following happen: they discontinue the study medication (or switch to a different medication), one year from the start of study medication (index date), end of available data in the database, or death, whichever is earliest.

For the secondary, the same approach will be performed by the level of renal insufficiency.

Using the negative control outcomes, we will determine whether we still observe unmeasured confounding (ie, a non-null association between treatment groups and negative control outcomes) after adjusting for measured confounders. However, it is possible that our negative control outcomes do not account for all the different and relevant domains of unmeasured confounding and, therefore, we could have some bias in our assessment of residual confounding. Negative control outcomes will be identified with the help of the Japanese KOLs, in order to include the most relevant negative control outcomes for the Japanese population. Negative control outcomes will be assessed in the 1 year following index date. The potential negative control outcomes may include:

- Hospital for trauma or injury
- Dementia (fragility bias)
- Health-seeking behavior related to healthy-user bias (To be determined)

An NCO should be independent of the exposure, share the same confounders as the outcome of interest and be measurable and common enough in the target population to allow for effect estimation. The SAP will describe the criteria for selecting an NCO that reflect the confounding processes and how the rules are made that determine how to interpret NCO effect estimates.

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

N/A

8.7.2.5.2 Stratified Analysis

N/A

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

We will apply quantitative bias analyses to assess the extent of unmeasured confounding. We will explore one or more of the following methods. The rule-out method has been described previously (Schneeweiss S, 2006), is publicly available (Division of Pharmacoepidemiology and Pharmacoeconomics [DoPE], 2020) and has been applied extensively in the literature (Weintraub WS et al, 2012). An alternative method of evaluating unmeasured confounding involves assessing the strength of the measured confounders by removing each confounder individually from the model to develop a distribution of the point estimate of the hazard ratios to display the strength of the measured confounding. Assuming the unmeasured confounders fall within this distribution, the distribution can be used to inform the potential magnitude and direction of the unmeasured confounders on the validity of the effect estimate. Ding proposed a sensitivity analysis without imposing any assumptions on the unmeasured confounders. (Ding and VanderWeele, 2016). This quantitative bias analysis assesses the impact of unmeasured confounding at a range of confounding magnitudes. Another approach, the E-value provides the minimum strength of association on the RR scale that an unmeasured confounder would need to have with both the treatment and the outcome to move the treatment-outcome association to a specified level, conditional on measured covariates (VanderWeele and Ding, 2017). Upper bounds on the bias will be estimated and E-values will be calculated for the assessment of magnitude of bias due to unmeasured confounding.

8.7.2.5.4 Other Sensitivity Analysis

If the treatment effect varies with the propensity score, different methods will yield different result. Our primary analysis employs IPTW, which aims to balance the distribution of confounding variables between treated and untreated groups while closely approximating the overall study population. Additionally, we will conduct a sensitivity analysis using standard mortality ratio weighting (SMRW) to preserve the results of one of treatment arms (Brookhart M et al., 2013; Stürmer T et al., 2014). Considering the precautionary use of romosozumab as indicated in the labeling, it is possible that some

patients may have unmeasured contraindication for romosozumab. By applying SMRW to make the romosozumab group resemble the comparator group, we can estimate the average treatment effect in the population that was not affected by the warning.

8.7.3 Analysis of Safety Endpoints

This study is designed assess the potential risk of cerebrovascular and cardiovascular outcomes among patients exposed to romosozumab for treatment of osteoporosis. All study analyses are relevant to assessment of this potential risk.

8.8 Quality Control

MID-NET is a database operated by PMDA. MID-NET has standardized and coded data on EMR, claims, CCI data from medical institutions that provide the data to the MID-NET. Reliability for the data related to this study will be consulted with PMDA if deemed to be needed.

Data handling, record keeping, preparation and storage of analysis programs shall be carried out in accordance with the procedure of this study.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

Presence of diagnosis code on a medical claim is not positive presence of disease, as the diagnosis may be incorrectly coded or included as a rule-out criterion rather than indicating actual disease. We expect this bias to be non-differential with respect to cardiovascular risk and thus for the resulting effect estimate to be biased toward the null.

8.9.1.1 Measurement Error(s)/Misclassification(s)

MID-NET is an open healthcare system that may result not capture all the relevant data on exposure, outcome and covariates for the study. Since romosozumab appears to have more complete data related to other specific therapies in the MID-NET system, we will evaluate it with an external database that is a closed healthcare system. This will help us assess if there is any differential bias between the treatment groups. Moreover, the information on social behavior such as smoking because the history of smoking is only available in inpatient claims. Since alcohol consumption and risk of fall could not be directly measured from the diagnoses, these variables were not included in this study.

8.9.1.2 Information Bias

We will be ascertaining information for all patients using the same method (extracting information from administrative claims), so we expect there will be no differential information acquisition for patients with and without outcome of interest.

8.9.1.3 Selection Bias

Given that the follow-up period of this study is relatively short, the likelihood of participants being lost to follow-up may be low. However, if we observe that the censoring varies between treatment groups, we cannot completely eliminate the risk of selection bias. Additionally, the availability of the laboratory information may be affected by patient characteristics and medical practice (Komamine et al., 2021). The potential selection bias cannot be avoided completely.

8.9.1.4 Confounding

While we include a comprehensive list of baseline covariates to estimate the propensity score and apply IPTW to account for the potential confounding caused by the initial treatment assignment. However, residual confounding may be a potential risk as always. We will use negative control outcomes and quantitative bias analysis to assess the potential for residual confounding from the unmeasured confounders.

8.9.2 External Validity of Study Design

Since MID-NET is a distributed data network system that serves as regional core hospitals with an emergency department, the population identified from this network may not be generalizable to those who visit primary care.

8.9.3 Analysis Limitations

This study aims to estimate the 1-year cardiovascular events risk with study medications. Not taking into account the death from other causes may increase the risk of cardiovascular event, but a possible overestimate of the risk of cardiovascular events could be a conservative approach. However, we assume that the traditional survival analysis and the competing risk approach may not differ much because follow-up time is shorter or the competing risk is low (Berry et al. 2010). In certain exposure contrasts that have smaller sample size, it may be difficult to fit an outcome model with all covariates. In this instance, we will reduce the number of covariates in the model, by removing those covariates with very low prevalence. All decisions on model building will be made in SAP.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

The variables in this study, including osteoporosis therapy (based on prescription claims or lack thereof), and presence of comorbidities, procedures, and concomitant medications, will be measured by searching for diagnosis, procedure, and drug codes. Thus, the data will be captured to the extent that the database is appropriately populated with these codes. We will test whether the missingness is differential and understand the

impact on result interpretation by using an external database that is a closed healthcare system.

9. Protection of Human Subjects

9.1 Informed Consent

This study uses MID-NET, which does not require informed consent from patients as the database is operated under the MID-NET Utilization Guidelines (PMDA, 2024c).

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

This post-marketing study is not subject to “Ethical Guidelines for Medical and Biological Research Involving Human Subjects” (MHLW, 2023b) because it falls within the scope of "The Ministerial Order on Standards for Post-Marketing Surveillance and Trials of Pharmaceuticals (MHLW No. 171 of 2004)” (MHLW, 2004). IRB/IEC review for the ethical guidelines is not required. However, it is necessary to apply for the use of MID-NET to the PMDA and to receive the approval after their scientific and ethical review.

9.3 Patient Confidentiality

All data in MID-NET is anonymized when transmitted by the medical institutions. Therefore, it is impossible to identify the patient from the data.

9.4 Subjects Decision to Withdraw

This study does not have mechanism to allow the patients to withdraw from the study. The medical institutions that provide their data to the MID-NET and the PMDA will secure the opportunity for the patients to refuse the use of their information through the announcement at the medical institutions and PMDA’s disclosure about the information related to the use of the MID-NET.

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

10.1 Definition of Reportable Events

10.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s).

The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

10.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other medically important serious event" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other medically important serious events" refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse involving an Amgen product,
- Use of an Amgen product while pregnant and/or breast feeding,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental or Occupational exposure,
- Any lack or loss of intended effect of the product(s).

10.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

10.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from MID-NET, a health information database composed of EMRs, claims data, and CCI data. The safety outcomes that are listed in Section 8.3.2 Outcome Assessment will be documented and analyzed in this study. These will be reported in aggregate in the final study report as incidence rates. See Section 8.3.2 Outcome Assessment for safety outcomes and definitions. Reportable events suspected to be related to any Amgen medicinal product, combination product or device should be spontaneously reported to Amgen within one business day of investigator/vendor awareness. A list of all Amgen medicinal products can be found in the following link: https://wwwext.amgen.com/amgen-worldwide

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country: https://wwwext.amgen.com/contact-us/product-inquiries

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting. Reportable events suspected to be related to any non-Amgen medicinal product should be reported to the local authority in line with the local country requirements.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol based on agreements with PMDA.

12. Plans for Disseminating and Communicating Study Results

In accordance with J-RMP, the number of romosozumab users in MID-NET will be checked 5 years after the approval to confirm the progress of the study, and the results

will be reported in the safety periodic reports. In accordance with national regulations, the final report prepared is submitted to the PMDA.

In addition, based on the MID-NET Utilization Guidelines (PMDA, 2024c), results obtained through the utilization of MID-NET are, in principle, published from the viewpoint of public interest.

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 for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) 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 1, 2, and 3 and 4.

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

All publications (eg, 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.

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14. Appendices

Appendix A. List of Stand-alone Documents

No.	Document Reference Number	Date	Title
None			

Appendix B. ENCePP Checklist for Study Protocols

Study title: Post-marketing Study Evaluating the Risk of Serious Cardiovascular Events Among Osteoporotic Patients Receiving Romosozumab in Japan Using 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)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☐	☒	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.4
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[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.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1, 8.4
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☐	☒	☐	
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, 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
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	☒	☐	☐	8.2.2
	4.2.3 Country of origin	☒	☐	☐	6
	4.2.4 Disease/indication	☒	☐	☐	8.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	8.2.5
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.1

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? (eg, 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? (eg, 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? (eg, 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? (eg, 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? (eg, 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? (eg, confounding by indication)	☒	☐	☐	8.7.1, 8.9.1.4
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	8.3.1, 8.9.1.2
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.2.5, 8.9.1.3

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, 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? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
9.1.2 Outcomes? (eg, 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?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (eg,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?	☒	☐	☐	8.7.2.3
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7.2.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
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?	☒	☐	☐	8.9.1.3
12.1.2 Information bias?	☒	☐	☐	8.9.1.2
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.91.4
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	6.5, 8.7.1.1

Comments:

Section 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 (eg, 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 protocol: PPD

Date: dd/Month/year 04 April 2024

Signature: _____

Appendix C. Milestones of This Study

Milestone	Planned Date
Completion of the study protocol (V1.0)	April 2024
Start of feasibility analysis	October 2024
Completion of the SAP	December 2025
Start of analysis	January 2026
Completion of the study report	December 2026

Approval Signatures

Document Name:	Protocol Original romosozumab 20190206
Document Description:	Evenity PMS assessing the Serious CV Events among osteoporotic patients in Japan
Document Number:	CLIN-000329621
Approval Date:	02 Aug 2024
Type of Study Protocol:	Original
Protocol Amendment No.:	

Document Approvals	
Reason for Signing: Functional Area	Name: PPD Date of Signature: 02-Aug-2024 16:16:10 GMT+0000