1. ABSTRACT

- **Title**

  Clinical Characteristics, Including History of Myocardial Infarction and Stroke, Among United States Post-Menopausal Women Initiating Treatment With Romosozumab and Other Anti-osteoporosis Therapies

  Abstract Date: 13 February 2025

  Name and Affliliation of Main Author: [redacted] (Center for Observational Research, Amgen Inc.)

- **Keywords**

  romosozumab, osteoporosis, postmenopausal osteoporosis (PMO), myocardial infarction (MI), stroke

- **Rationale and Background**

  Romosozumab was approved in the United States (US) in April 2019 for the treatment of osteoporosis in postmenopausal women at high-risk for fracture. The US Prescribing Information (USPI) includes a boxed warning for the potential risk of MI, stroke, and cardiovascular (CV) death. Specifically, per the USPI, romosozumab should not be initiated in patients who have had MI or stroke within the preceding year. Along with implementing these precautions in labeling, the US Food and Drug Administration (FDA) required a study for pharmacovigilance after marketing authorization. Specifically, FDA asked Amgen to evaluate the feasibility of a postmarketing study assessing the CV safety of romosozumab. In this study, history of MI and stroke in the year before initiation of romosozumab compared with the year before initiation of other anti-osteoporosis agents was evaluated. In addition, relevant patient characteristics measured at baseline including patient demographics, history of fractures or falls, fracture risk scores, pertinent comorbidities (eg, other history of MI, stroke, other CV diseases), pertinent medication use (eg, other anti-osteoporosis medications, glucocorticoids), healthcare utilization, and prescribing physician's specialty among initiators of romosozumab were compared with initiators of other anti-osteoporosis therapies.

- **Research Question and Objectives**

  Primary Objectives

  This study was designed to fulfill a US FDA postmarketing requirement. Among postmenopausal women initiating treatment with romosozumab or other anti-osteoporosis medications:

  1. Describe the proportion of women who had experienced a MI or stroke in the year preceding initiation of romosozumab or other anti-osteoporosis medications.
  2. Describe the demographic and clinical characteristics, including history of CV disease, CV risk factors, osteoporotic fracture, risk factors for osteoporosis and osteoporotic fracture, other comorbidities, concomitant medication use, and healthcare utilization using all available historical data preceding initiation of romosozumab or other anti-osteoporosis medications.
  3. Describe differences in demographic and clinical characteristics mentioned in (1) and (2) above between women initiating romosozumab treatment and women initiating other anti-osteoporosis medications.

  All primary objective analyses were conducted separately in the primary datasets:

1. Optum Clinformatics® Data Mart (CDM) claims dataset
2. Fee-for-service (FFS) Medicare administrative claims dataset

Secondary Objectives

The primary objective analyses were conducted separately in secondary datasets of:
1) Medicare claims linked to National Patient-centered Clinical Research Network (PCORnet) Clinical Data Research Network (CDRN) data, and
2) Optum claims – Optum Electronic Health Record (EHR) linked dataset (MarketClarity).

- **Study Design**

This study was a retrospective, and repeated analysis design within five 1-year blocks of calendar time after marketing approval of romosozumab: April 2019 – March 2020 (T1), April 2020 – March 2021 (T2), April 2021 – March 2022 (T3), April 2022 – March 2023 (T4), and April 2023 – September 2023 (T5). Women 55 years and older who were new users of romosozumab, denosumab, zoledronate, teriparatide, abaloparatide or oral bisphosphonates (BPs) were identified repeatedly in 5 time-blocks (T1-T5) in the primary datasets (FFS Medicare and Optum CDM Claims data). Baseline clinical characteristics, including history of MI and stroke, were described in women with PMO initiating romosozumab, denosumab, zoledronate, parathyroid hormone (PTH) analogs (teriparatide, abaloparatide), or oral BPs. Differences in baseline clinical characteristics were described in 4 pairwise groups:

1. romosozumab vs denosumab
2. romosozumab vs zoledronate
3. romosozumab vs PTH analogs (teriparatide or abaloparatide)
4. romosozumab vs oral BPs (alendronate, risedronate, ibandronate)

- **Setting**

This final report covers full T1 (April 2019 – March 2020), T2 (April 2020 – March 2021), T3 (April 2021 – March 2022), T4 (April 2022 – March 2023) and T5 (April 2023 – September 2023) time periods in the primary data source of Optum CDM and Medicare Parts A, and B datasets, and secondary data source of Optum EHR and Medicare Parts A and B PCORnet datasets. Data from Medicare Part D (eg, oral BPs and PTH analogs) had a longer administrative data lag than Medicare Parts A and B (romosozumab, denosumab, zoledronate). Thus, the results covering the full T1 (April 2019 – March 2020), T2 (April 2020 – March 2021), T3 (April 2021 – March 2022), and partial T4 (April 2022 – September 2022) time periods are provided in this report as planned.

- **Subjects and Study Size, Including Dropouts**

Patients were included if they were:

Women at least 55 years of age or older on the index date (ie, the date of newly initiating an osteoporosis drug) with a minimum of 15 months of continuous enrollment in a health plan (ie, FFS Medicare, Optum CDM) database preceding the index date were included.

Patients were also required to be new users of romosozumab, denosumab, zoledronate, PTH analogs (teriparatide, abaloparatide), or oral BPs (alendronate, risedronate, ibandronate):

1. New user was defined as no prior use of that specific therapy or class of therapy (ie, oral BPs, PTH analogs [teriparatide, abaloparatide]) using all available historical claims data.
2. New users of denosumab, zoledronate, PTH analogs (teriparatide, abaloparatide), or oral BPs were required to have no previous exposure to romosozumab using all available history.
3. In each of the 4 planned romosozumab-comparator pairs, new romosozumab users were required to have no exposure to the specific comparator drug in the pairwise comparison within 15 months before romosozumab initiation. That is, for example, in romosozumab-denosumab pair, romosozumab users exposed to denosumab within 15 months before romosozumab initiation were excluded.

Patients were excluded if they had:

1. History of Paget's disease of bone before the index date.
2. Presence of a cancer diagnosis on the same claim as the index anti-osteoporosis medication or any pre-index claims with physician diagnoses of metastatic cancer. Patients with history of nonmetastatic cancer were included if the claim for the index prescription medication was not associated with a cancer diagnosis.

Study Sample Size

The number of patients was dependent on the extent of romosozumab, and other anti-osteoporosis medications used in routine clinical practice.

- **Data Sources and Methods**

In this study- 1) FFS Medicare administrative claims data and 2) Optum CDM Claims data as primary datasets and 1) Medicare claims linked to PCORnet CDRN data, and 2) Optum claims – Optum EHR linked dataset as secondary datasets were used to analyze the study objectives.

During April 2019 to September 2019, the early period of romosozumab availability in the US, there were no specific Healthcare Common Procedure Coding System (HCPCS) codes that could be used to identify romosozumab. The algorithm used to identify records of nonspecific HCPCS codes (J3490, J3590) suggestive of identifying patients taking romosozumab also required all of the following criteria for claims containing these nonspecific HCPCS codes: (1) osteoporosis diagnosis codes (M80.*, M81.*), (2) drug pricing amounts equal to $1879, $1934, $967, and $939, or units equal to 210 mg for the nonspecific HCPCS code, (3) dosing intervals between 28 to 35 days, and (4) removing claims that also had specific HCPCS codes indicating other anti-osteoporosis drugs (eg, zoledronate, denosumab) or surgery-related medications (conscious sedation, parenteral opioids). This algorithm has been validated with positive predictive value $>$ 99% compared with the gold standard of electronic medical record review in a large community practice-based research network of providers who prescribe romosozumab.

Patient's demographic and clinical characteristics, including history of CV disease, CV disease risk factors, osteoporotic fracture, risk factors for osteoporosis and osteoporosis-related fracture, other comorbidities, concomitant medication use, healthcare utilization, and prescribing physician's specialty were described using all available historical data preceding initiation of romosozumab or other anti-osteoporosis therapies.

Demographic variables (eg, age, race) and prescribing physician's specialty were assessed on the index date. The proportion of women who had an MI or stroke event in the year preceding index date were described using published algorithms. For MI and stroke history and other binary or categorical variables (eg, history of disease or medication use), all available historical data were used as this approach has shown to have better sensitivity and less misclassification. For history of healthcare utilization and all other medical history in continuous format (eg, number of outpatient visits, number of fractures), a fixed 15-month look back window was used. For biometric data, the most recent measurement before index date using all available history was used for analysis. Given Centers for Medicare and Medicaid Services cell suppression policy, a value of 1 to 10 from Medicare and Medicare PCORnet-linked datasets was suppressed and reported as "<11" instead. A value of "REDACTED" was also applied to avoid the possibility of revealing a suppressed value with calculation.

Propensity scores (PS) were predicted from logistic regression models estimating the odds of receiving a comparator medication (vs. romosozumab) conditional on all baseline covariates. Propensity score models were estimated for all pairwise treatment comparisons with romosozumab: 1) denosumab; 2) PTH analog (teriparatide or abaloparatide); 3) zoledronate; and 4) oral BP. A standardized mean difference (SMD) was used to characterize differences in distributions of potential confounders between treatment groups. When the absolute value of the difference (|SMD|) exceeds 0.10 (10.0%), it signals a meaningful imbalance in the distribution of potential baseline confounders. Pre- and postmatching balance of potential confounders between treatment groups were described and visualized by calculating SMD, with meaningful imbalance set at $>$ 0.1.

Four sensitivity analyses were performed for this study:

- Sensitivity 1: To account for potential differences in length of available look back period (ie, duration of historical claims data) between patients (eg, older patients may have longer historical data in Medicare than younger patients), a fixed 15-month look back window was adopted to assess all covariates specified in protocol for both primary and secondary analysis.
- Sensitivity 2: To evaluate the extent to which secondary (claims-EHR linked) datasets were representative of primary (claims-only) datasets.
- Sensitivity 3: A subgroup analysis that included only new users who were unexposed to romosozumab or a comparator drug at any time before the study drug initiation. That is, romosozumab users exposed to a comparator drug using all available patient history before romosozumab initiation were excluded from the romosozumab-comparator matched pairs.
- Sensitivity 4: To evaluate the primary and secondary objectives had patients initiating romosozumab resembled patients receiving comparator medications (ie, had the expectation of channeling been absent), standardized mortality ratio (SMR) weighting was conducted to make romosozumab patients appear more like comparator patients.

- **Results**

Primary Setting

- Before PS matching, the distributions of age, various chronic comorbidities and other concomitant medications were generally similar when comparing patients receiving romosozumab with patients receiving other anti-osteoporosis medications. Oral BPs and intravenous (IV) zoledronate users were closest to romosozumab users in terms of age.
- The proportion of patients with recent or any history of MI or stroke was similarly low (SMD $\leq$ 0.1) across all treatment groups (0.2% to 0.4%), but numerically lower among romosozumab users (0.1% to 0.2%).
- Romosozumab was most similar to IV zoledronate and oral BPs in terms of any history of MI/stroke, and to IV zoledronate with respect to CV-related comorbidities. Romosozumab users were most similar to PTH analog users in terms of fracture history. However, there were small differences observed within each paired comparison for select characteristics. Healthcare utilization was lower in the denosumab, IV zoledronate, and oral BP groups, while higher in the PTH analog group. Romosozumab users experienced more fractures and a higher proportion received prior treatment for osteoporosis as compared with denosumab, zoledronate, and oral BP users.
- After PS matching, patient characteristics were well balanced across all matched pairs.
- After adjusting for only the baseline covariates available in the claims-only databases, adequate balance in baseline metabolic and CV biomarkers (that are only available in the claims-EHR databases) across all matched pairs was observed.

Sensitivity Analyses

- In the first sensitivity analysis, the influence of the length of the available look-back period on the differences in the prevalence of baseline comorbidities between romosozumab and the comparators was minimal.
- In the second sensitivity analysis, the vast majority of baseline covariates were similar (SMD $\leq$ 0.1) when comparing the distribution of covariates between claims-only and claims-EHR databases. Patients in Optum CDM had a lower baseline prevalence of CV-related comorbidities and less medication use across all treatment groups than patients in Optum EHR-linked data.
- Patients identified in Medicare Parts A, B, and D PCORnet had more healthcare utilization and higher baseline prevalence of rheumatoid arthritis across all treatment groups compared with patients in Medicare Parts A, B, and D datasets.
- The baseline patient characteristics, including CV comorbidities, history of MI/stroke, atherosclerotic cardiovascular disease (ASCVD) risk categories, were comparable between a subgroup of patients where all available history was used to exclude those with prior exposure to the comparator medication (sensitivity analysis 3) and primary settings.
- After SMR weighting (sensitivity analysis 4), all covariates including baseline CV events including MI, and stroke were well balanced when comparing individuals

receiving romosozumab with individuals receiving denosumab and PTH analogs (SMD $\leq$ 0.1).

- After using standardized mortality ratio weighting (SMRW) to adjust for claims-only covariates, adequate balance (more so in Optum vs Medicare claims-EHR databases) of baseline metabolic and CV biomarkers when comparing romosozumab to denosumab and PTH analog users was observed.

- **Discussion and Conclusion**

  Before PS adjustment, the prevalence of recent and any history of MI and stroke were similarly low across all treatment groups, though numerically lower in romosozumab, in both the Medicare and Optum claims databases. Similar proportions of patients across all treatment comparisons were at high-risk for CV disease according to the ASCVD risk scores in both claims-EHR patient populations, further indicating similarities in overall CV risk between treatment groups. Although a lower likelihood of romosozumab use (vs. comparator osteoporosis medication) was observed among patients with recent and any history of MI and stroke in minimally adjusted models (adjusted for key baseline characteristics, including age, race/ethnicity, geographic region, prescribing physicians specialty, history of healthcare utilization, combined comorbidity score, and fracture history), any channeling of lower CV risk patients to romosozumab due to the boxed warning in the USPI was able to be addressed using different adjustment methodologies (PS matching, SMR weighting, inverse probability of treatment weighting). All baseline covariates including any differences in CV history, comorbidities, and medication use were sufficiently balanced between treatment groups in both the Optum and Medicare claims databases. These findings were consistent with the fourth interim report dated 22 September 2023. The overall results of the primary analysis were consistent with sensitivity analyses in all databases.

  The claims-EHR patient population was similar to the claims-only patient population in both the Optum and Medicare databases. The high level of concordance in the direction and magnitude of SMDs when evaluating the association between baseline covariates and the treatment groups both before and after PS matching indicated a consistent causal structure (ie, exposure-confounder associations were similar) between the claims-only and claims-EHR databases. Consistency in the causal structure (not necessarily similarity in the distribution of baseline covariates) between both databases was needed to use the information from the claims-EHR database to interpret the extent of potential unmeasured confounding of the primary claims-only effect estimate.

  The ability to balance important biometric covariates in both the Medicare Parts A, B, and D PCORnet and Optum EHR databases adjusting for only claims-based baseline covariates suggested that any confounding due to these unmeasured covariates was negligible in the claims-only databases. The smaller sample size and larger proportion of patients with missing values for the biometric variables in the Medicare PCORnet database made it difficult to balance the biometric covariates across all adjustment approaches. The inclusion of more primary care (nonspecialty) PCORnet sites would increase the number of patients who had claims and EHR information, decrease the amount of missingness for the key biometric variables of interest, and enhance evaluation of potential unmeasured confounding in a noninterventional, comparative safety study using claims databases.

  The results from the final report demonstrated that any small differences in recent MI and stroke resulting from channeling from romosozumab's black box warning were sufficiently balanced in both the Medicare and Optum claims databases. After

adjusting for only the covariates available in claims databases, adequate balance of biometric covariates in both the Medicare PCORnet and Optum EHR databases was observed indicating that potential unmeasured confounding through these biometric covariates would be negligible in a claims--only, comparative safety study. Given the results presented in this report, Amgen believes that the Medicare and Optum claims databases are fit-for-purpose to facilitate a robust assessment of the CV risk associated with romosozumab using a noninterventional study design.

- **Marketing Authorization Holder**

  Amgen Inc.

- **Names and Affiliations of Principal Investigators**

  [redacted]

  University of Alabama at Birmingham Division of Clinical Immunology and Rheumatology