Summary Table of Study Protocol

Title	Clinical Characteristics, Including History of MI and Stroke, Among US Post-menopausal Women Initiating Treatment With Romosozumab and Other Anti-osteoporosis Therapies
Protocol version identifier	Amendment 1.0
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Research Question and Objectives	Among post-menopausal women initiating treatment with romosozumab or other anti-osteoporosis medications: 1. Describe the proportion of women who experienced a myocardial infarction or stroke in the year preceding administration of romosozumab or other anti-osteoporosis medications. 2. Describe demographic and clinical characteristics, including history of cardiovascular disease, cardiovascular disease 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 above, between women initiating romosozumab treatment and women initiating other anti-osteoporosis medications
Country(ies) of Study	United States

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Marketing Authorization Holder

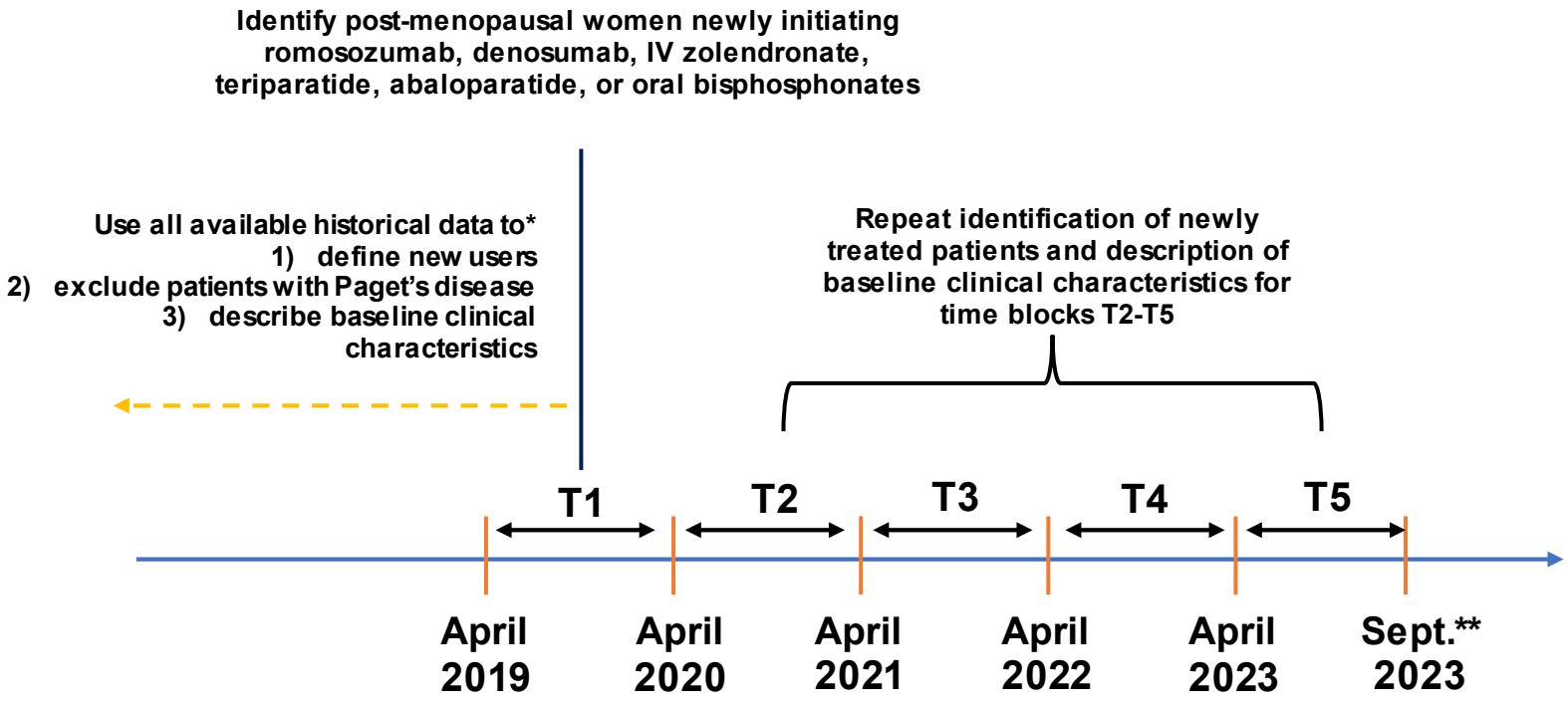
Marketing authorization holder(s)	Amgen
MAH Contact	PPD US Regulatory, Senior Manager PPD PPD (Office) PPD

Investigator's Agreement

I have read the attached protocol entitled "Clinical Characteristics, including History of MI and Stroke, among US Post-Menopausal Women Initiating Treatment with Romosozumab and Other Anti-Osteoporosis Therapies", dated *21 April 2020*, and agree to abide by all provisions set forth therein.

Signature	
Name of Investigator	Date (DD Month YYYY)
PPD	21 April 2020

Study Design Schema



* With 15 months minimum

** T5 is shorter as the final study report will be due in September 2024; analyses will be completed in April 2024 and there is an estimated data-lag of at least 6-7 months for key data elements, including romosozumab exposure, in the primary Medicare claims data source

1. Table of Contents

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2. List of Abbreviations

EHR – Electronic Health Record

FDA – United States Food and Drug Administration

MACE – Major Adverse Cardiac Event

MI – Myocardial Infarction

PMO – Post-menopausal Osteoporosis

USPI – United States Prescribing Information

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4. Abstract

- Study Title: Clinical Characteristics, including History of MI and Stroke, among US Post-Menopausal Women Initiating Treatment with Romosozumab and Other Anti-Osteoporosis Therapies
- Study Background and Rationale

Romosozumab is approved in the US for the treatment of osteoporosis in postmenopausal women at high risk for fracture. The USPI includes a boxed warning for the potential risk of myocardial infarction (MI), stroke, and cardiovascular death. Specifically, per the USPI, romosozumab should not be initiated in patients who have had a MI or stroke within the preceding year. Along with implementing these precautions in labeling, the US FDA required a study for pharmacovigilance following marketing authorization. Specifically, FDA asked to evaluate the history of MI and stroke in the year prior to initiation of romosozumab compared to the year prior to initiation of other osteoporosis agents. In addition, using an appropriate look back period, compare other

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 cardiovascular diseases), pertinent medication use (eg, other osteoporosis medications, glucocorticoids), healthcare utilization, and prescribing provider specialty among initiators of romosozumab compared to initiators of other anti-osteoporosis therapies

- Research Question and Objective(s)

Objectives	Endpoints
Primary	
Among post-menopausal women initiating treatment with romosozumab or other anti-osteoporosis medications, identified in fee-for-service (FFS) Medicare and Optum Clinformatics® Data Mart (CDM) claims data systems: • Describe the proportion of women who experienced a myocardial infarction or stroke in the year preceding administration of romosozumab or other anti-osteoporosis medications. • Describe demographic and clinical characteristics, including history of cardiovascular disease, cardiovascular disease 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 • Describe differences in demographic and clinical characteristics mentioned above, between women initiating romosozumab treatment and women initiating other anti-osteoporosis medications	• This study aims to describe patient baseline clinical characteristics only. There are no planned endpoints.
Secondary	
• Repeat primary objective analyses in secondary, claims-EHR linked datasets: 1) Medicare claims linked to PCORnet Clinical Data Research Network (CDRN) data or Optum EHR, and 2) Optum claims - Optum EHR linked dataset.	• This study aims to describe patient baseline clinical characteristics only. There are no planned endpoints.

  - Hypothesis(es)/Estimation
    The objectives of the current study are descriptive only, for patient baseline clinical characteristics before initiation of osteoporosis treatments. No hypothesis testing will be conducted.

- Study Design/Type
  This study is a retrospective, repeated analysis design within five 1-year blocks of calendar time following marketing approval of romosozumab:
  April 2019 – March 2020 (T1), April 2020 - March 2021 (T2), April 2021 - March 2022 (T3), April 2022 - March 2023 (T4), April 2023 -September 2023 (T5 is shorter as the final study report will be due in September 2024; analyses will be completed in April 2024, and there is an estimated data-lag of at least 6-7 months for key data elements, including romosozumab exposure, in the primary Medicare claims data source).

- Study Population or Data Resource
  Women older than 55 years who are new users of romosozumab, denosumab, zolendronic acid, teriparatide, abaloparatide or oral bisphosphonates will be identified repeatedly in five time-blocks (T1-T5) using fee-for-service Medicare and Optum CDM claims data.

- Summary of Patient Eligibility Criteria

Inclusion criteria:

1. New users of romosozumab, denosumab, zoledronic acid, parathyroid hormone analogs (teriparatide, abaloparatide) or oral BPs (alendronate, risedronate, ibandronate):
   1.1. New use will be defined as no prior use of that specific therapy or class of therapy (ie, oral BPs, PTH analogs) using all available historical claims data.
   1.2 New users of denosumab, zoledronic acid, PTH analogs (teriparatide, abaloparatide) or oral BPs will be required to have no previous exposure to romosozumab.
2. Patients must be women at least 55 years of age or older on the index date (ie, the date of newly initiating osteoporosis drugs)
3. A minimum of 15 months of continuous enrollment in health plan (ie, Medicare fee-for-service, Optum CDM) database preceding the index date

Exclusion criteria:

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 a prior history of non-metastatic cancer will be included if the claim for the index prescription medication is not associated with a cancer diagnosis)

- Follow-up

  Patient baseline characteristics will be described at or prior to index date; there will be no follow-up planned after the index date.

- Variables
  - *Outcome Variable(s)*
    Not applicable
  - *Exposure Variable(s)*

  There will be five osteoporosis treatment exposure groups, based on the medication prescribed on the index date:

  - subcutaneous romosozumab
  - subcutaneous denosumab
  - parathyroid hormone (PTH) analog (subcutaneous teriparatide or abaloparatide)
  - intra-venous (IV) zolendronate
  - Oral bisphosphonates (alendronate, risedronate, ibandronate)

  - *Other Covariate(s)*
    Patients' demographic and clinical characteristics, including history of cardiovascular disease, cardiovascular disease risk factors, osteoporotic fracture, risk factors for osteoporosis and osteoporosis-related fracture, other comorbidities, concomitant medication use, healthcare utilization, and prescribing provider's specialty will be described using all available historical data preceding initiation of romosozumab or other anti-osteoporosis medications.

    Demographic variables (eg, age, race) and prescribing provider's specialty will be assessed on the index date. History of myocardial infarction and stroke will be described using data in the 1-year period before the index date. For other binary or categorical variables (eg, history of disease or medication use), all available historical data will be used. For history of healthcare utilization and all other medical history in continuous format (eg, number of outpatient visits, number of fractures), a fixed 15 months look back window will be adopted. For biometric data, the most recent measurement before index date will be used for analysis (see section 8.3.3. for details).

- Study Sample Size

  The number of patients is dependent on the extent of romosozumab use in clinical practice. For the sample size estimation for this descriptive study, we have applied an assumption that romosozumab users in routine clinical practice will represent a subpopulation of PMO patients who are at higher risk of fracture compared to women with PMO who use anti-resorptive therapies, including anti-resorptive therapies with

indications for patients at high risk of fracture, eg, denosumab. Consequently, we have assumed that the size of the romosozumab patient population will be approximately 15% of the size of the denosumab PMO population observed in the ongoing post-marketing FDA commitment study for denosumab (study 20090522). Based on the same Medicare data source that are used in Study 20090522, which includes 204,706 denosumab new users after 5 years of market authorization, we expect about 30,706 romosozumab patients after 5 years of market authorization in Medicare data source.

In the Optum CDM database, 32,414 denosumab-exposed PMO patients were identified after 5 years of market authorization (data on file); by applying the same logic to this database we expect about 4,800 romosozumab patients after 5 years of market authorization in the Optum CDM data source. In the most recent 5 years of data within the linked Optum claims-Optum EHR dataset, 5,842 denosumab-exposed PMO patients were identified; hence, by applying the same logic we would expect approximately 876 romosozumab patients after 5 years of market authorization within this linked dataset (see section 8.5 for details of study size).

- Data Analysis
  All study objectives in primary analysis will be assessed in primary data sources (Medicare and Optum claims data). Categorical variables will be presented in tabular form as number and percentage; continuous variables will be presented as number, mean with standard deviation, and median with interquartile range.

  Differences in clinical characteristics will be described in four pairwise exposure groups: 1) romosozumab vs. denosumab; 2) romosozumab vs. PTH analog (teriparatide or abaloparatide); 3) romosozumab vs. zolendronate; 4) romosozumab vs. oral BPs. Standardized mean difference (SMD) will be used to characterize differences between exposure groups. SMDs are intuitive indices which measure the effect size between two groups. Compared to a t-test or Wilcoxon rank-sum test, they are independent of sample size, and therefore more appropriate to be adopted in real-world analyses of large datasets. A standardized difference of 0.1 (10 percent) between treatment groups denotes meaningful imbalance in the baseline covariate (Normand, Landrum et al. 2001).

  In addition to SMD, a propensity score (PS) will be calculated for each patient in the study cohort using multivariate logistic regression analysis, conditional on all

baseline covariates in section 8.3.3. Four pairwise 1:1 PS-matching will be conducted in the primary dataset: 1) romosozumab vs. denosumab; 2) romosozumab vs. PTH analog; 3) romosozumab vs. zolendronate; 4) romosozumab vs. oral BPs. Pre- and post-matching balance of potential confounders between exposure groups will be described and visualized by calculating SMD, with meaningful imbalance set at >0.1.

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Osteoporosis is a well-recognized public health issue with increasing urgency due to the aging of the population (Khosla and Shane 2016). Fracture is the single most important sequelae of osteoporosis. In the United States, osteoporosis-related fractures occur in approximately 1 in 2 Caucasian women who reach 50 years of age (Cosman, de Beur et al. 2014). Patients suffering from an osteoporosis-related fracture have an increased risk for future fracture and with it, frailty. Among the most important determinants of risk for repeat fracture is the recency of the first fracture. It has been shown that the risk of a second fracture is greatest (> 5-fold) within the 1 to 2 years following an initial fracture and remains greater than the risk pre-fracture for more than 20 years (van Geel, van Helden et al. 2009, Johansson, Siggeirsdottir et al. 2017).

In a study of over 377,000 postmenopausal women enrolled in US Medicare who sustained one or more clinical fractures, an initial fracture at any one of several major skeletal sites was associated with an absolute risk of second fracture at any skeletal site that increased over time: 8% to 12% within 1 year and 15% to 20% within 2 years following the initial fracture (Balasubramanian, Zhang et al. 2019). Thus, the immediate 1 to 2 years post-fracture is the time period during which postmenopausal women most need a rapid, effective pharmacologic intervention to increase bone mass and bone strength to reduce their risk of subsequent fracture and its sequelae.

A number of pharmacotherapies are available in the United States for treatment of post-menopausal osteoporosis (PMO), including denosumab, intra-venous (IV) zolendronate, oral bisphosphonates (alendronate, risedronate, ibandronate), raloxifene, and calcitonin. Of these, denosumab is indicated for treatment of women with PMO at high risk for fracture. In addition, two anabolic agents, parathyroid hormone (PTH) analogs teriparatide and abaloparatide, both indicated for treatment of women with PMO

at high risk of fracture, are also available. Nonetheless, anti-resorptive agents are used in the majority of patients with PMO, including those at high risk of fracture. In April 2019, the US FDA approved romosozumab for treatment of women with PMO at high risk of fracture.

Romosozumab is a high-affinity humanized IgG2 monoclonal antibody that binds sclerostin, an extracellular inhibitor of canonical Wnt signaling. Romosozumab neutralizes sclerostin's inhibitory function resulting in activation of canonical Wnt signaling, which promotes the dual action of increased bone formation and decreased bone resorption. This results in improvements in bone mass, structure, and strength.

The primary evidence for the efficacy and safety of romosozumab for the treatment of osteoporosis in postmenopausal women comes from two pivotal double-blind, multinational, phase 3 studies, Study 20070337 and Study 20110142. In Study 20070337, subjects were randomized to receive either romosozumab or placebo during a 12-month double-blind placebo-controlled period, following which all study subjects received denosumab for 12 months (Cosman, Crittenden et al. 2016). In Study 20110142, which was an event-driven trial, subjects were randomized to receive either romosozumab or alendronate during a 12-month double-blind period, following which all study subjects received alendronate until the end of the study (Saag, Petersen et al. 2017). Romosozumab rapidly increases BMD at the lumbar spine and hip, observed as early as 6 months (Cosman, Crittenden et al. 2016); these gains were superior to alendronate through 12 months of therapy and continued to accrue when patients were transitioned to antiresorptive therapy (Saag, Petersen et al. 2017). Romosozumab rapidly reduced fractures within 12 months (Cosman, Crittenden et al. 2016). Over a period of 24 months, anti-fracture efficacy continued after transition to antiresorptive therapy (Cosman, Crittenden et al. 2016, Saag, Petersen et al. 2017).

During the development program, an imbalance in positively-adjudicated cardiovascular serious adverse events (SAE) was observed between the romosozumab versus alendronate treatment arms in the first year in Study 20110142. This imbalance was observed specifically for myocardial infarction (MI) and stroke, with a higher incidence in the romosozumab group compared with the alendronate group. During year 1, when subjects were randomized to receive either romosozumab or alendronate, the subject incidence of positively adjudicated serious MI was 0.8% in the romosozumab group and 0.2% in the alendronate group, and the subject incidence of positively adjudicated

serious stroke was 0.6% in the romosozumab group and 0.3% in the alendronate group (Saag, Petersen et al. 2017). However, these findings were not observed in the placebo-controlled Study 20070337, where the incidence of positively-adjudicated cardiovascular SAEs, including MI and stroke, was balanced between the romosozumab and placebo groups (Cosman, Crittenden et al. 2016). The hazard ratio (HR) for time to first major adverse cardiac event (MACE), defined as CV death, non-fatal MI, or non-fatal stroke, at 12 months in Study 20110142 was 1.87 (95% CI: 1.11, 3.14) and 1.03 (0.62, 1.72) in Study 20070337. To evaluate the totality of evidence for cardiovascular events in the PMO population, a meta-analysis of the 2 pivotal fracture studies (Studies 20070337 and 20110142) was performed with appropriate statistical methodology. The HR for time to first MACE was 1.39 (95% CI: 0.97, 2.00) for the 12-month double-blind treatment period and 1.13 (95% CI: 0.93, 1.38) for the overall study period (median of 36 months).

6.2 Rationale

Romosozumab was approved in the US on April 9,2019, for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. The US FDA prescribing information (USPI) limits the duration of use with romosozumab to twelve monthly doses, following which use of anti-resorptive agents should be considered if osteoporosis therapy remains warranted. The USPI includes a boxed warning for the potential risk of myocardial infarction (MI), stroke, and cardiovascular death. Specifically, per the USPI, romosozumab should not be initiated in patients who have had a MI or stroke within the preceding year. Physicians and patients are advised to consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. If a patient experiences a MI or stroke during therapy, romosozumab should be discontinued. Major Adverse Cardiac Events (MACE) are also addressed in the Warnings and Precautions and Adverse Reactions sections of the USPI.

Along with implementing these precautions in labeling, the US FDA required the following study for pharmacovigilance following marketing authorization:

Study 1) Conduct a study using a sequential analysis design (eg, repeated analyses within five 1-year blocks of calendar time following marketing approval of romosozumab) to assess the impact of the boxed warning on prescribing of romosozumab to patients diagnosed with myocardial infarction (MI) or stroke within one year prior to treatment

initiation and assess for channeling bias. Evaluate the history of MI and stroke in the year prior to initiation of romosozumab compared to the year prior to initiation of other osteoporosis agents. In addition, using an appropriate lookback period, compare other 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 cardiovascular diseases), pertinent medication use (eg, other osteoporosis medications, glucocorticoids), healthcare utilization, and prescribing provider specialty among initiators of romosozumab compared to initiators of other anti-osteoporosis therapies.

Study 2) Conduct a comparative safety study or trial adequately designed and powered to rule out an unacceptable increase in risk of MI, stroke, and cardiovascular death among users of romosozumab compared to users of an appropriate comparator(s). The need, feasibility, design and milestones for this study or trial will be contingent upon the findings from study 1.

This protocol describes Amgen's proposal for Study 1.

6.3 Statistical Inference (Estimation or Hypothesis[es])

The objectives of the current study are descriptive only, for patient baseline clinical characteristics before initiation of osteoporosis treatments. No hypothesis testing will be conducted.

7. Research Question and Objectives

7.1 Primary

This study is designed to fulfil US FDA post-marketing requirements, specifically:

Among post-menopausal women initiating treatment with romosozumab or other anti-osteoporosis medications:

1. Describe the proportion of women who experienced a myocardial infarction or stroke in the year preceding initiation of romosozumab or other anti-osteoporosis medications
2. Describe demographic and clinical characteristics, including history of cardiovascular disease, cardiovascular risk factors, osteoporotic fracture, risk factors for osteoporosis and osteoporotic fracture, other comorbidities, concomitant medication use, and healthcare utilization using allavailable 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 compared to women initiating other anti-osteoporosis medications

All primary objectives will be conducted separately in the primary datasets specified in section 8.4.1: 1) Fee-for-service Medicare administrative claims dataset and 2) Optum Clinformatics® Data Mart [CDM]) claims dataset.

7.2 Secondary

Repeat primary objective analyses in secondary datasets specified in section 8.4.2: 1) Medicare claims linked to PCORnet Clinical Data Research Network (CDRN) data, and 2) Optum claims – Optum EHR linked dataset.

Linkage of claims datasets to clinical datasets will enable collection of more expansive information on risk factors for cardiovascular disease and osteoporotic fracture that are not available in the claims data (eg, body mass index, blood pressure, lipid levels and renal function).

8. Research Methods

8.1 Study Design

This study is a retrospective, repeated analysis design within five 1-year blocks of calendar time following marketing approval of romosozumab: April 2019 - March 2020 (T1), April 2020 - March 2021 (T2), April 2021 - March 2022 (T3), April 2022 – March 2023 (T4), April 2023 - September 2023 (T5). Baseline clinical characteristics, including history of MI and stroke, will be described in PMO women initiating romosozumab, denosumab, zolendronic acid, teriparatide, abaloparatide or oral bisphosphonates in each time block. Differences in baseline clinical characteristics will be described in four pairwise groups: 1) romosozumab vs. denosumab, 2) romosozumab vs. zolendronate, 3) romosozumab vs. PTH analogs (teriparatide or abaloparatide), and 4) romosozumab vs. oral BPs.

8.2 Setting and Study Population

Women older than 55 years-old who are new users of romosozumab, denosumab, zolendronic acid, teriparatide, abaloparatide or oral bisphosphonates will be identified repeatedly in five time-blocks (T1-T5) in the primary datasets (FFS Medicare and Optum CDM claims data). For all anti-osteoporosis exposures, multiple index dates will be allowed. For example, if patients meet the new user criteria for both zolendronate and denosumab (ie, switched from zolendronate to denosumab in a time-block), they will have two index dates, one for each drug, and contribute to both the zolendronate and the denosumab groups. New users of denosumab, zoledronic acid, PTH analogs (teriparatide, abaloparatide) or oral BPs will be required to have no previous exposure to romosozumab. Patients using other osteoporosis therapies (ie, denosumab,

zoledronate, PTH analogs, oral BPs) following previous exposure to romosozumab will be unlikely to represent general users of these therapies as their clinical histories will presumably be influenced by the boxed warning in romosozumab's USPI (ie, romosozumab should not be initiated among patients who had MI or stroke within previous 1-year).

This approach will permit inclusion of all patients exposed to romosozumab while maximizing the sample and representativeness of other anti-osteoporosis treatment groups.

In addition to receiving osteoporosis treatments, patients must be women at least 55 years of age on their index date and have had at least 15 months of continuous enrollment in health insurance database (ie, FFS Medicare or Optum CDM) preceding their index date. To ensure that the study population is comprised of women with PMO only, patients with Paget's disease of bone or those with cancer diagnosis associated with osteoporosis treatments will be excluded (see 8.2.2 for details).

8.2.1 Study Period

There will be five 1-year blocks of calendar time following marketing approval of romosozumab: April 2019 - March 2020 (T1), April 2020 - March 2021 (T2), April 2021 - March 2022 (T3), April 2022 - March 2023 (T4), April 2023 - September 2023 (T5 is shorter as the final study report will be due in September 2024; analyses will be completed in April 2024, and there is an estimated data-lag of at least 6-7 months for key data elements, including romosozumab exposure, in the primary Medicare claims data source).

8.2.2 Subject/Patient/Healthcare Professional Eligibility

8.2.2.1 Inclusion Criteria

Eligible patients will be identified during each of five 1-year blocks of calendar time: April 2019 - March 2020 (T1), April 2020 - March 2021 (T2), April 2021 - March 2022 (T3), April 2022 - March 2023 (T4), April 2023 - September 2023 (T5):

1. New users of romosozumab, denosumab, zoledronic acid, PTH analogs (teriparatide, abaloparatide) or oral BPs:
    - 1.1 New use will be defined as no prior use of that specific therapy or class of therapy (eg, oral BPs, PTH analogs) using all available historical claims data.
    - 1.2 New users of denosumab, zoledronic acid, PTH analogs (teriparatide, abaloparatide) or oral BPs will be required to have no previous exposure to romosozumab.

2. Patients must be women at least 55 years of age or older on the index date
3. A minimum of 15 months of continuous enrollment in health plan (ie, FFS Medicare, Optum CDM) database preceding the index date

8.2.2.2 Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

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 pre-index claims with physician diagnosis for metastatic cancer (ie, ICD9 198 or ICD10 equivalent; patients with a prior history of non-metastatic cancer will be included if the claim for the index prescription medication is not associated with a cancer diagnosis)

8.2.3 Matching

Four pairwise 1:1 propensity score (PS)-matching will be conducted in the primary dataset: 1) romosozumab vs. denosumab; 2) romosozumab vs. PTH analog; 3) romosozumab vs. zolendronate; 4) romosozumab vs. oral BPs.

8.2.4 Baseline Period

This study will use all available historical data before the index date, with 15 months minimum, for applying selection criteria and assessment of all clinical characteristics defined in section 8.3.3.

8.2.5 Study Follow-up

Patient characteristics will be described at or prior to the index date; there will be no follow-up after the index date.

8.3 Variables

8.3.1 Exposure Assessment

There will be five osteoporosis treatment exposure groups, based on the medication prescribed on the index date:

- subcutaneous romosozumab
- subcutaneous denosumab
- PTH analogs (subcutaneous teriparatide or abaloparatide)
- IV zolendronate
- Oral BPs (alendronate, risedronate, ibandronate)

Ascertainment of romosozumab will be based on anticipated procedure codes for romosozumab administration and national drug codes (NDC) for treatment. A drug specific procedure code for romosozumab, J3111, was issued on October 1, 2019;

romosozumab use prior to this time will be identified using algorithms based on the occurrence of non-specific HCPCS codes (eg, J3490, J3590) in combination with the presence of osteoporosis diagnosis code, dosing (ie, units dispensed, and frequency), and possibly also drug cost. We do not anticipate any other non-specific HCPCS procedure codes being used for the treatment of osteoporosis during 2019 that might yield misclassification of romosozumab. A similar approach has previously been used for identification of other newly approved medications, including denosumab, in Medicare claims data (Curtis, Xie et al. 2013). Ascertainment of other osteoporosis treatments, including oral and injectable bisphosphonates, denosumab, teriparatide, and abaloparatide, will be based on drug-specific NDC and procedure codes (see Appendix A for the full list of codes).

8.3.2 Outcome Assessment

Not applicable

8.3.3 Covariate Assessment

The table below provides a listing of patient characteristics that will be ascertained using the primary (claims) and secondary (claims-EHR linked) datasets. The table illustrates data availability and variable formats (numerical or categorical/binary) in the datasets. The claims databases will be used as the primary data source; these data will be linked and supplemented using information available in EHR that are absent in claims data.

Demographic variables (eg, age, race) and prescribing physician's specialty will be assessed on the index date. History of myocardial infarction and stroke will be described using data in 1-year period before the index date. For other binary or categorical variables (eg, history of disease or medication use), all available historical data will be used as this approach has been shown to have better sensitivity and less misclassification (Brunelli, Gagne et al. 2013) than using a fixed historical period. For history of healthcare utilization and all other medical history in continuous format (eg, number of fractures), a fixed 15-months look back window will be adopted. For biometric data, the most recent measurement before the index date will be used for analysis.

For non-biometric study variables (eg, comorbidities and medications), we will use ICD-9/10 codes, Healthcare Common Procedure Coding System (HCPCS) and National Drug Code (NDC) codes. For biometric data in PCORnet, height, weight, BMI and blood pressure can be retrieved from vital_table; lab test results such as blood glucose, HDL-C and LDL-C can be retrieved by LONIC codes in Lab_result table (see the full PCORnet data dictionary here: https://pcornet.org/wp-content/uploads/2019/09/PCORnet-Common-Data-Model-v51-2019_09_12.pdf). Similarly, in Optum EHR, labs are mapped according to therapeutic category, lab names are standardized, and results are recorded

in the LABS data file. Lifestyle and biometric data are captured in the OBSERVATIONS data file.

The full list of operational definitions are provided in section 6 of statistical analysis plan (SAP).

Characteristic	Available in primary data sources (claims)	Available in Secondary data sources (claims-EHR linked data)	Numerical (N) or categorical/binary (C)	Covariate assessment period
Demographic characteristics				On the Index date
Age	X	X	N	
Race/ethnicity	X	X	C	
Geographical Region (eg, Midwest, Northeast, South, West)	X	X	C	
Prescribing physician's characteristics				On the Index date
Prescribing physician's specialty	X	X	C	
History of healthcare utilizations				a fixed 15 months before the index date
Number of inpatient hospitalizations	X	X	N	
Number of outpatient visits	X	X	N	
Number of emergency room visits	X	X	N	
Number of endocrinology visits	X	X	N	
Number of rheumatology visits	X	X	N	
Flu vaccination	X	X	C	
Pneumonia vaccination	X	X	C	
Number of cardiology visits	X	X	N	
Number of cardiovascular-related hospital days	X	X	N	
Number of lipid-related lab tests	X	X	N	
Number of electrocardiograms	X	X	N	
History of cardiovascular events				All available historical data except for those specified
Myocardial infarction (recent)	X	X	C	1-year before the index date

Characteristic	Available in primary data sources (claims)	Available in Secondary data sources (claims-EHR linked data)	Numerical (N) or categorical/binary (C)	Covariate assessment period
Myocardial infarction (past)	X	X	C	
Angina	X	X	C	
Stroke (recent)	X	X	C	1-year before the index date
Stroke (past)	X	X	C	
Transient ischemic attack	X	X	C	
Coronary revascularization procedures	X	X	C	
Coronary artery bypass graft procedure	X	X	C	
Non-coronary revascularization procedures	X	X	C	
Heart failure	X	X	C	
Peripheral artery disease	X	X	C	
History of comorbidities				All available historical data except for those specified
Combined comorbidity score	X	X	C	
FRAX score - BMI	No	Limited	N	
FRAX score – BMD	No	Limited	N	
Osteoporosis diagnosis	X	X	C	
Hip fracture	X	X	C	
Vertebral fracture	X	X	C	
Other fractures	X	X	C	
History of fall	X	X	C	
Number of fracture hospitalizations	X	X	N	a fixed 15 months before the index date
Rheumatoid arthritis	X	X	C	
Systemic Lupus Erythematosus	X	X	C	
Chronic obstructive pulmonary disease	X	X	C	
Asthma	X	X	C	
Type II Diabetes mellitus	X	X	C	
Non-dialysis chronic kidney disease (stage III, IV and V)	X	X	C	

Characteristic	Available in primary data sources (claims)	Available in Secondary data sources (claims-EHR linked data)	Numerical (N) or categorical/binary (C)	Covariate assessment period
Chronic kidney disease on dialysis	X	X	C	
Hypertension	X	X	C	
Hyperlipidemia	X	X	C	
Arrhythmia (eg, atrial fibrillation, dysrhythmia)	X	X	C	
Parkinsonism	X	X	C	
Dementia	X	X	C	
Depression	X	X	C	
History of osteoporosis and CV-related medication use				All available historical data
Oral bisphosphonates	X	X	C	
IV bisphosphonates	X	X	C	
Denosumab	X	X	C	
Teriparatide or abaloparatide	X	X	C	
Raloxifene	X	X	C	
Oral steroids	X	X	C	
Anticoagulants	X	X	C	
Antidepressants	X	X	C	
Angiotensin Converting Enzyme inhibitors (ACEi) /Angiotensin Receptor Blockers (ARBs)	X	X	C	
Diuretics	X	X	C	
Calcium channel blockers	X	X	C	
Antiplatelets/antithrombotics	X	X	C	
Statins	X	X	C	
Ezetimide	X	X	C	
Statins + ezetimide combination	X	X	C	
PCSK9i	X	X	C	
Other lipid lowering drugs (fibrates, gemfibrozil, Niacin, Cholestyramine)	X	X	C	
NSAIDs and COXIBs	X	X	C	
Opioids	X	X	C	
Insulin	X	X	C	
Other diabetes medications	X	X	C	
Antiparkinson disease medications	X	X	C	

Characteristic	Available in primary data sources (claims)	Available in Secondary data sources (claims-EHR linked data)	Numerical (N) or categorical/binary (C)	Covariate assessment period
Antidementia medications (eg, cholinesterase inhibitors)	X	X	C	
Hypnotics (eg, Benzodiazepines)	X	X	C	
Hormone replacement therapy	X	X	C	
Lifestyle risk factors				All available historical data
Smoking	Very limited	X	C	
Alcohol	Very limited	Only available in Optum EHR	C	
Biometric data				Most recent value recorded before the index date
Height	No	X	N	
Weight	No	X	N	
Body mass index (calculated based on height and weight information)	No	X	N	
Bone mineral density	No	X (limited)	N	
Blood pressure	No	X	N	
Blood glucose	No (limited)	X	N	
HbA1C	No (limited)	X	N	
HDL	No (limited)	X	N	
LDL	No (limited)	X	N	

8.3.4 Validity and Reliability

The current study will describe history of baseline clinical characteristics only, no clinical outcomes will be included. Please see section 8.3.1 and section 8.7.2.2 for details on methods to capture exposure and baseline characteristics.

8.4 Data Sources

Several large datasets will be used in this study. These datasets share the following key characteristics, making them fit-for-purpose:

- Large and representative patient populations with PMO, allowing for adequate sample sizes to capture history of relatively rare clinical events such as MI, stroke, fracture

- Ability to accurately capture diagnosis, procedure, and medication codes to identify patients with PMO and clinical histories such as occurrence of key clinical events, comorbidities, risk factors, and medication use

8.4.1 Primary Datasets

This study will use 1) Fee-for-service Medicare administrative claims data and 2) Optum Clinformatics® Data Mart [CDM]) claims data as primary datasets to analyze study objectives.

Medicare administrative claims database

Medicare is a national health plan that covers older and disabled populations in the U.S. Currently, it provides coverage for a variety of health services, for more than 90% of the US elderly population (≥65 years of age).. As such, it represents a large proportion of the female population that is at risk of post-menopausal osteoporosis, as well as a substantial majority of women who may be eligible to receive romosozumab in the United States. The following Medicare claims files will be used in the proposed study:

- Medicare Part A claims files, which include services provided in the hospital (inpatient), the hospital outpatient department (outpatient), skilled nursing facility (SNF), hospice, or by home health agencies (HHA).
- Medicare Part B claims files, which include physician/supplier services, as well as services from clinical laboratories, ambulance, stand-alone ambulatory surgical centers, injectable medications and durable medical equipment.
- Medicare Part D claims files, which include prescription drugs. Prescription drug coverage through Part D has been available to Medicare beneficiaries since 2006, and the majority of eligible beneficiaries are now enrolled in Part D plans (72% of all eligible beneficiaries as of 2015) (Hoadley 2015).

Medicare beneficiaries with Medicare Part A and B coverage are referred to as having Fee for Service coverage. They may obtain coverage from Medicare Advantage plans as an adjunct or alternative to Fee for Service coverage. In this study, data for female Medicare beneficiaries age ≥ 65 years with fee for service without Medicare Advantage and with prescriptive coverage will be included. Historically, approximately 70% of all Medicare beneficiaries have fee-for-service Medicare, and the remainder have Medicare Advantage.

Data from US Medicare have frequently been used to characterize drug safety in bone health and other therapeutic areas (Xue, Ma et al. 2013). US Medicare represents the largest data system in the proposed study.

Optum administrative claims database

Optum Clinformatics® Data Mart (CDM) is a medical claims database which represents the medical experience of insured employees and their dependents from both affiliated commercial and Medicare Advantage plans. Patients must have both medical and pharmacy coverage to be included in the database. There were approximately fifty-eight million unique patients in the database through March, 2018. The underlying insured population from which the data are drawn spans across all 50 US states (46% - South, 9% - Northeast, 22% - West, 23% - Midwest), and is racially/ethnically diverse (56% - White, 9% - African American, 11% - Hispanic, 4% - Asian, 14% - Other/Unknown). Fifty-one percent of plan participants are female; 22% are 17 years of age or younger, 14% are older than 65+, and the remaining 64% are 18 - 64 years of age. The CDM is a de-identified, Health Insurance Portability and Accountability (HIPAA) compliant, closed system of claims, which undergoes audits and quality control procedures by the insurer at regular intervals.

The CDM contains fully adjudicated eligibility, pharmacy, procedure, and medical claims data for patients enrolled in a large US health plan (UnitedHealth Group). The health plan provides coverage for physician, hospital, and prescription drug services, and captures medical claims or encounter data from all available health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of provided services. The coding of medical claims conforms to insurance industry standards, including the use of designated claims forms (eg, physicians use the Health Care Financing Agency [HCFA]-1500 format and hospitals use the UB-92 format). Each facility inpatient admission record contains information on diagnoses (recorded using the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] and ICD-10-CM diagnosis codes), procedures (recorded with ICD-9-CM and ICD-10-CM procedure codes, Current Procedural Terminology [CPT] codes, or HCFA Healthcare Common Procedure Coding System [HCPCS] codes), and Present on Admission (POA) codes. Data are linked at the patient level by a unique identifier that is consistent across services, health plans, and time, and, so, patients can be tracked over multiple years even if they switch health plans. For approximately 20% of patients who have tests performed at laboratories that contract with United Healthcare, laboratory test results can be linked to medical and pharmacy claims data within the CDM. Undiagnosed conditions, and lifestyle and biometric factors (eg, smoking status) are not well captured in claims data.

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The following pharmacy claims data allow for longitudinal tracking of medication refill patterns and changes in medications used:

- National Drug Code (NDC)
- Medication Brand Name
- Generic Classification
- Medication Strength
- Quantity Prescribed
- Days of Supply
- Fill Date
- De-identified Patient and Prescriber Codes

8.4.2 Secondary Datasets

Additional linkage of the primary datasets to electronic health records (EHR) will be conducted to acquire additional clinical characteristic variables that are not available in the Medicare/Optum claims databases (eg, HDL/LDL, cholesterol, blood gluclose/HbA1C, etc). The clinical/EHR datasets include:

1. PCORnet Clinical Data Research Network (CDRN)

   Three clinical data research networks (CDRNs), including Mid-South, OneFlorida, and Path, within the National Patient-Centered Clinical Research Network (PCORnet), are included in this study (Fleurence, Curtis et al. 2014). They were selected based on multiple factors including (1) the large-scale availability of electronic health record (EHR) data (> 50M unique patients in these three networks) that is linkable to national claims data, (2) the regional representation and geographic diversity that they provide, and (3) a site feasibility study conducted by PCORnet.

   The OneFlorida Data Trust is a repository of statewide health-care data that is regularly updated with the inclusion of new partners and data refreshes from existing partners. The Data Trust contains claims and encounter data for Floridians enrolled in Medicaid and robust patient-level electronic health record data from public and private health care systems, including diagnoses, procedures, medications, patient demographics, unique patient codes for re-identification by consortium partners and other data elements in the PCORnet Common Data Model (CDM). In total, the Data Trust contains data for more than 15.8 million Floridians (https://onefloridaconsortium.org/data/).

The Mid-South Clinical Data Research Network (CDRN) encompasses three large health systems: (1) Vanderbilt Health System (VU) with electronic medical records for over 2 million patients, (2) the Vanderbilt Healthcare Affiliated Network (VHAN) which currently includes over 40 hospitals, hundreds of ambulatory practices, and over 3 million patients in the Mid-South, and (3) Greenway Medical Technologies, with access to 24 million patients nationally.

PaTH is a Clinical Research Network comprised of Geisinger Health System, Johns Hopkins University, Johns Hopkins Health System, Penn State College of Medicine, Penn State Milton S. Hershey Medical Center, Temple Health System, Lewis Katz School of Medicine at Temple University, the University of Pittsburgh, UPMC and UPMC Health Plan, The Ohio State University, The Ohio State University Wexner Medical Center, University of Michigan, and Michigan Medicine (https://www.pathnetwork.org/).

Data marts in PCORnet all follow the PCORnet Common Data Model (CDM) v3.1, which contains 15 data domains in relational schemas, including patient demographics, enrollment status, death status, cause of death, biometric data (eg, height, weight, and blood pressure), conditions (ie, diagnosed and self-reported health conditions and diseases), encounters, diagnoses (ie, results of diagnostic process and medical coding within healthcare delivery), procedures, prescribing (ie, provider orders for medications), dispensing (ie, outpatient pharmacy dispensing; eg, filled prescriptions), and laboratory results. A clinical phenotype was sent to the CDRNs requesting that each site estimate their total cohort based on women >65 in Medicare with an osteoporosis diagnosis and history of osteoporosis medication use (denosumab, teriparatide, alendronate, zolendronate). Availability was also provided for the clinical covariates of interest: BMI, blood pressure, blood glucose, HbA1C, LDL-C, HDL-C, and triglycerides (see Table 1 below for details).Based on these feasibility results and the confirmed linkage method between Medicare and PCORnet (see response to question #11 for details), we will include these three PCORnet CDRN sites. .

Table 1. Availability of Biometric Data in Post-menopausal Women Under Medicare Coverage in PCORnet

	PATH (N=90,043)	Mid-South (N=279,449)	OneFlorida (N=135,218)
BMI	96.73%	69.30%	76.96%
Blood pressure	97.57%	71.31%	77.60%
Blood glucose	79.76%	64.70%	65.89%
HbA1C	17.82%	26.02%	30.28%
LDL-C	52.88%	42.06%	46.34%
HDL-C	58.69%	42.54%	41.48%
Triglycerides	41.86%	41.46%	42.19%

2. Optum EHR

The Optum Electronic Health Record (EHR) data asset is a patient-level database sourced and consolidated across EMR systems which are deployed at larger, integrated delivery networks (IDNs), as well at ambulatory-only networks. There were ninety-seven million unique patients in the Optum EHR database through March,2018. The EHR study population is geographically diverse (28% - South, 13% - Northeast, 13% - West, 41% - Midwest, 7% - Unknown), with relatively long follow-up (>47% have activity in the database for three years or longer). Patients are sourced either from integrated delivery networks (IDNs) (81%) or ambulatory-only networks (19%), which collectively represent over 140,000 providers, 7,000 claims, and 760 hospitals. In addition to the extensive clinical data usually captured in claims databases, the Optum EHR database contains information on vital signs, body measurements, lifestyle observations, biomarkers, and over 350 labs.

For secondary analyses, we will use data from the integrated Optum data asset, which combines information from the Optum Clinformatics® Data Mart (containing claims data) with the Optum EHR data. Through March 2018 there were 15 million patients with linked EHR and claims data, representing 26% of the total population with claims data.

For secondary analyses using Medicare-linked data, the Medicare claims data will be linked to the PCORnet clinical datasets. Amgen continues to evaluate with Optum the possibility and proposed linkage methods for Medicare – Optum EHR data. If feasible, we may consider adding this as an amendment to study 20190205 in the future.

8.5 Study Size

The number of patients is dependent on the extent of romosozumab use in clinical practice. For the sample size estimation for this descriptive study, we have applied an assumption that romosozumab users in routine clinical practice will represent a subpopulation of PMO patients at higher risk of fracture compared to women with PMO who use anti-resorptive therapies, including anti-resorptive therapies with indications for patients at high risk of fracture, eg, denosumab. In previous studies ((Yusuf, Cummings et al. 2018); Study 20090522), approximately 10-15% of PMO women exposed to denosumab therapy had a recent history of osteoporotic fracture. Based on this observation, as well as data to indicate that the number of PMO patients treated with the anabolic agent teriparatide represent approximately 15-20% of the number of PMO patients treated with denosumab (data on file), we have assumed that the size of the romosozumab patient population will be approximately 15% of the size of the denosumab PMO population observed in the ongoing postmarketing FDA commitment study for denosumab (study 20090522). The inclusion / exclusion criteria were similar between study 20090522 and 20190205 (ie, includes PMO women ≥ 55 years and excludes patients with Paget's disease and cancer at baseline), however numbers in study 20090522 did not apply a new users definition. After applying the new users definition based on the same Medicare data source that are used in Study 20090522, which includes 204,706 denosumab PMO patients after 5 years of market authorization, we expect about 30,706 romosozumab patients after 5 years of market authorization in Medicare data source.

In the Optum CDM database, 32,414 denosumab-exposed PMO patients were identified after 5 years of market authorization (data on file); by applying the same logic to this database we expect about 4,800 romosozumab patients after 5 years of market authorization in Optum CDM data source. In the most recent 5 years of data within the linked Optum claims-Optum EHR dataset, 5,842 denosumab-exposed PMO patients were identified; hence, by applying the same logic we would expect approximately 876 romosozumab patients after 5 years of market authorization within this linked dataset. Similar logics were applied in Medicare-PCORnet dataset and numbers are provide below.

Table 2. Sample Size Estimation for Study Drugs in Study 20190205 in the Primary and Secondary Datasets

	Primary dataset		Secondary dataset	
	Medicare	Optum	Medicare-PCORnet linked	Optum claims - EHR linked
Romosozumab	30,706	4,862	3,887	876
Denosumab	204,706	32,414	25,911	5,842
PTH analogs	44,927	11,036	7,168	1,604
Zolendronate	114,099	22,648	18,257	5,187
Oral BPs[a]	557,099	134,451	88,886	74,307

[a] Alendronate, risedronate and ibandronate

8.6 Data Management

The data source, including data from electronic medical records and administrative claims, is created for the delivery of health care. To enable use of the data source for research, analytical files must be built that define the study cohort and algorithms are used to identify exposures, covariates, and outcomes. Best practices will be used for the reporting of the detailed information behind these operational and design decisions to allow other researchers to reproduce the study conduct.

For the Optum CDM database, the verification of data quality follows Optum's standard operating procedures (SOPs), which are consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org). In particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

The validation for the creation of analytic files typically involves a combination of a review of SAS program log and output files, independent coding, a review of program processes and documentation to ensure departmental SOPs are followed, and reconciliation of programming code with specifications. Individual programs are documented and revised as needed until sign-off by a validator using a validation/programming log.

8.6.1 Obtaining Data Files

The Medicare data will be licensed to and analyzed by members of the research team at UAB who will access the data through the Center for Medicare and Medicaid Services (CMS) Virtual Data Research Center (VRDC). The VRDC is a relatively new data enclave that provides more timely access than other means of obtaining CMS data. Data

will be updated as often as quarterly, with a slightly less than 6 months lag in the data availability for the medical claims data (parts A and B). Although it may change over the project period, the data lag for part D (pharmacy) data historically has been 15-18 months. Summary data in aggregate can be downloaded from the VRDC as aggregated data, with CMS restrictions against showing any cell size with counts < 11.

The PCORnet data are initially queried through the PCORnet coordinating center, led by the Duke Clinical Research Institute. The participating PCORnet Clinical Data Research Networks (CDRNs) each will search for patients using similar methods to the claims data searches described above and will securely upload the needed information in the PCORnet data model format to the CMS VRDC for linkage and analysis by the study team. It will already have been normalized to the PCORnet Common Data Model, greatly facilitating analysis. PCORnet data are expected to be available with a slightly less than 6 months data lag at all CDRNs, and will be refreshed quarterly.

The Optum claims and Optum claims-EHR linked datasets will be analyzed by members of the research team at Amgen. Optum CDM claims data are received via download using Amazon WorkSpace (AWS) S3 buckets. Data may be encrypted with a password sent separately. A manifest detailing contents (list of tables, fields, and number of rows) is also included in the transfer to enable Amgen to verify that the transfer completed successfully.

8.6.2 Linking Data Files

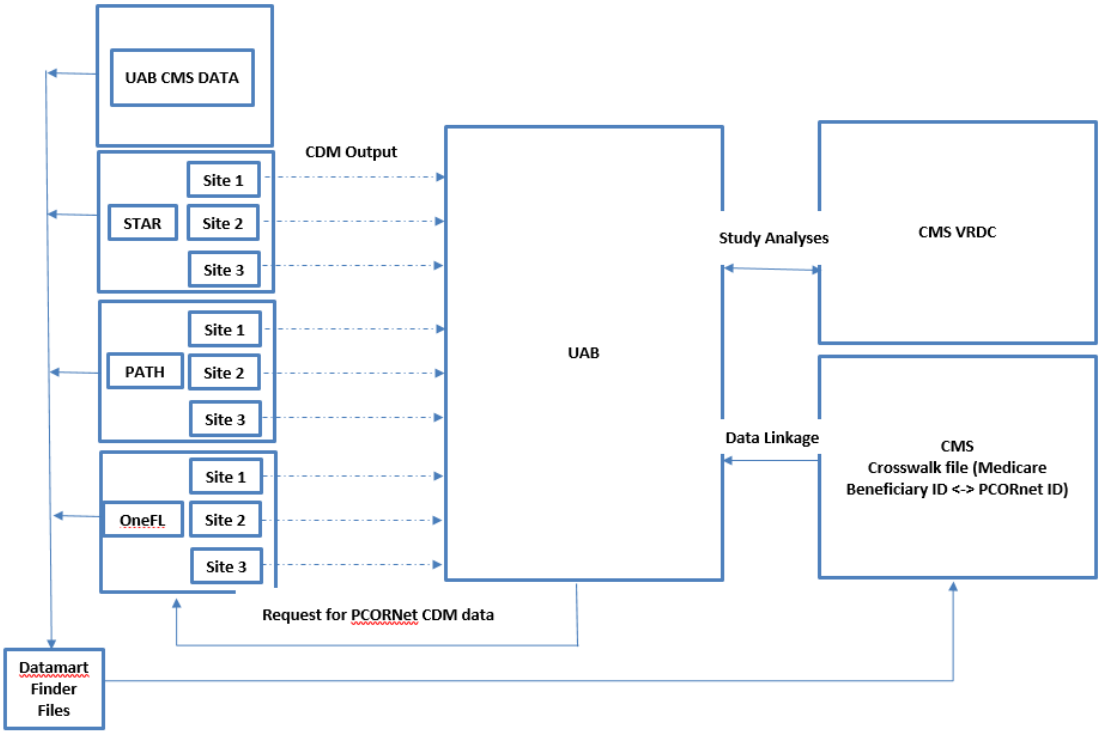
Medicare claims – PCORnet

The current study will link Medicare claims with PCORnet through the following methods and steps:

1. The CMS Chronic Condition Data Warehouse (CCW) has the ability to extract data from Medicare research identifiable files at the individual beneficiary level using finder files. See the CMS CCW Finder File Encryption Policy guidance document, page 2, https://www2.ccwdata.org/web/guest/request-data for information on the different finder file types.
2. The participating PCORnet Clinical Data Research Networks (CDRNs) sites will identify patients and prepare finder files using social security numbers (SSN) or Medicare Health Insurance Claim (HIC) identifiers for linkage of all patients meeting inclusion criteria.
3. A single finder file at each PCORnet data mart will be paired with the corresponding PCORnet patient ID and will be submitted by each data mart directly to the Centers for Medicare and Medicaid Services (CMS) for matching claims data.

See below figures for details of data flow between PCORnet Data Marts and CMS VRDC.

Figure: Study Schema of Data Flow between PCORnet Data Marts and CMS VRDC



Optum Claims – Optum EHR Linkage

Optum's Integrated Claims-Clinical dataset combines adjudicated claims data with Optum's Electronic Health Record (EHR) data. Optum's longitudinal EHR clinical repository from Optum Analytics is derived from more than 50 healthcare provider organizations in the United States, that includes more than 700 hospitals and 7000 clinics, treating more than 100 million patients receiving care in the United States. Optum's Integrated Claims-EHR dataset is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum® and customer data use agreements. The Integrated dataset, which uses both salting and cryptographic hashing, links both claims and clinical data for approximately 24 million matched individuals. Only three, high-probability matching levels are accepted: 1) Social Security Number + Date of Birth + Last Name + First Name; 2) Social Security Number + Date of Birth; and 3) Date of Birth + Last Name + First Name + State + Zip code. If multiple matches are found, those matches are excluded. Standardized cleaning is performed on both the claims and EHR data to maximize the likelihood of matching (eg,

invalid zip codes or social security numbers are discarded). The performance characteristics of the linkage is not currently available but is expected to be highly accurate since it mostly relies on SSN and there are standard QC process as described above.

8.6.3 Review and Verification of Data Quality

Medicare datasets

The quality of claims data from Medicare Part A and B, claims billed by health care providers and institutions, are generally considered good as they are audited by CMS and submission of fraudulent claims may result in serious consequences. However, the accuracy of exposure and outcomes ascertained from the claims varies by the exposure and outcomes of interest. In general, significant and acute clinical events are better captured (eg, MI, stroke, hip fracture) than chronic conditions that may or may not be treated; similarly, costly medications administered in physician offices (eg, romosozumab, denosumab) are reliably documented whereas Medicare claims do not capture the use of over-the-counter medications such as NSAIDs.

The UAB analytical team will check the quality of data by removing individuals whose demographic data are not consistently recorded (eg, inconsistent Date of Birth) and will construct a detailed flow diagram of the selection criteria for the final study population. With regards to the capture of key clinical events of interest such as MI, stroke, and fractures, the analysis will use validated algorithms with high positive predictive value (PPV). Similarly, when describing history of other clinical events and comorbidities analyses will use validated algorithms where applicable and will rely on the clinical expertise of the investigators in cases where validated algorithms are not available or applicable.

Optum CDM

The Optum CDM is a de-identified, Health Insurance Portability and Accountability (HIPAA) compliant, closed system of claims, which undergo audits and quality control procedures by the insurer at regular intervals. The coding of medical claims conforms to insurance industry standards, including the use of designated claims forms (eg, physicians use the Health Care Financing Agency [HCFA]-1500 format and hospitals use the UB-92 format).

Data received from Optum CDM are checked against the vendor-provided manifest to verify that every table, field and row they sent was received by Amgen. Amgen runs

additional data quality checks, and custom data checks comparing prior refreshes to the current data.

Optum EHR

The Optum EHR data is sourced from multiple EHR systems, including those from physician offices, small-group practices, multi-specialty practices, and large integrated delivery networks. As EHR data flow through provider networks to Optum, integrity checks are done on the different data elements. Examples of data quality checks performed include: expected values, formats, and historic and expected norms of the different data elements in the EHR data. Next, data from the various EHR systems are processed and converted to a common data structure, resulting in creation of the following analytic data tables: patient/member, encounter, visit, diagnoses, procedure, labs, prescriptions, as well as a number of tables based on natural language processing of provider notes. The steps included in the review and further verification of data quality of EHR data may include one or more of the following: validation, normalization, standardization, and mapping. For example, prescription information in EHR systems captures what the provider intends the patient to take, but the relevant NDC/HCPCS codes may not be captured. In this scenario, medication mapping from the medication name may be necessary to derive the relevant NDC/HCPCS code

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Interim Analysis/Analyses

There will be 4 interim analyses planned in year 2020, 2021, 2022 and 2023. Planned analyses for primary and secondary objectives will be repeated each year and will reflect data availability due to the administrative data lag (eg, ~ 6 months lag for Medicare part A and B, 15-18 months lag for Medicare part D, ~12 months for Optum CDM) before submitting the interim report in each year.

Results will be updated as data become available for interim reports. For example, for the first interim report, it will reflect romosozumab data for the April 2019 – September 2019 time period given the ~6 month data lag in Medicare Part B. We will report the first full year of romosozumab data (pre-specified T1, April 2019 – March 2020) in the 2nd interim report. Note also that due to the anticipated 15-18 month data lag in Medicare part D, ie, prescription drug claims data, early reports will contain information that are not reliant on these data, and reports will be updated with complete results pertaining to prescription drug claims in subsequent reports. For example, information on exposure to

injectable osteoporosis therapies including romosozumab, denosumab and IV bisphosphonate are not reliant on Medicare part D data. Similarly, history of clinical diagnoses and hospitalizations are not reliant on Medicare part D data. Hence, early interim reports will contain information on romosozumab, denosumab, IV bisphosphonate cohorts and their histories of clinical diagnoses, hospitalizations, healthcare utilization, and available supplementary information from linked EHR data. Data on oral bisphosphonate exposures, as well as history of oral concomitant medication use for all OP cohorts, will be made available in subsequent annual reports as data become available for the corresponding study year (eg, complete data on oral BPs and histories of concomitant medication use for the 2019-2020 study cohort will become available by 2022).

Table 3. Expected Data Availability in Each Interim Report and Final Report

	Interim report #1, September 2020	**Interim report #2, September 2021**	**Interim report #3, September 2022**	**Interim report #4, September 2023**	**Final report, September 2024**
Medicare-based analyses					
• Injectable osteoporosis therapies including romosozumab, denosumab, and PTH analogs • Histories of clinical diagnoses, hospitalizations, and healthcare utilization	Partial T1 (April 2019 – Sept 2019)	Partial T2 (April 2020~ Sept 2020), and full T1 (ie, April 2019-March 2020)	Partial T3 (April 2021~ Sept 2021), and full T1 and T2 (ie, April 2019 – March 2021)	Partial T4 (April 2022~ Sept 2022), and full T1-T3 (ie, April 2019 – March 2022)	Full pre-specified T1-T5 (ie, April 2019 – Sept 2023)
• Oral medications	No data available for 1st interim report	No data available for 2nd interim report	Full T1 (April 2019 – March 2020)	Full T1 and T2 (April 2019 – March 2021)	Full T1 - T3 (April 2019 – March 2022)
Optum CDM-based analyses					
• Injectable osteoporosis therapies including romosozumab, denosumab, and PTH analogs • Histories of clinical diagnoses, hospitalizations, and healthcare utilization • Oral medications	No data available for 1st interim report	Full T1 (April 2019 – March 2020)	Full T1 and T2 (April 2019 – March 2021)	Full T1 - T3 (April 2019 – March 2022)	Full T1 – T4 (April 2019 – March 2023)

8.7.1.2 Primary Analysis

Among post-menopausal women initiating treatment with romosozumab or other anti-osteoporosis medications:

1. Describe the proportion of patients who experienced a myocardial infarction or stroke in the year preceding initiation of romosozumab or other anti-osteoporosis medications
2. Describe demographic and clinical characteristics, including cardiovascular disease, cardiovascular risk factors, osteoporotic fracture, risk factors for osteoporosis and osteoporosis-related fracture, other comorbidities, concomitant medication use, and healthcare utilization using all available lookback period 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 compared to women initiating other anti-osteoporosis medications

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

All planned statistical analyses are descriptive, no hypothesis testing will be conducted.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

In primary analyses, included variables will be defined using claims data. Patients will be categorized as having a comorbidity or receiving a concomitant medication using algorithms based on the presence of claims for services with associated diagnoses or medications as relevant; otherwise, that patient will be categorized as not having the comorbidity or treated with the medication. This is imperfect as the absence of a claim does not necessarily mean the absence of the comorbidity or drug exposure, although in most circumstances absence of a claim does correlate with absence of condition. However, this study will use all available historical claims data to characterize patients' clinical history, which may maximize the sensitivity and minimize chances for misclassification of a comorbidity or concomitant medication.

In secondary analyses, data on biometric covariates that are absent within the claims databases (eg, lifestyle factors such as smoking, laboratory values such as blood pressure) will be supplemented via linkage with information available in the EHR (ie, PCORnet and Optum EHR) datasets. The percentage of missing of these biometric variables will be described. There could be two types of missingness: 1) the physician ordered the test but the result was missing in the supplemental EHR, or 2) the test was never ordered. Using specific HCPCS/CPT codes in the claims data (primary data source), we can evaluate whether or not a patient had a test ordered. Conditional on patients having tests done as indicated via the claims data, we may or may not get the test results in the supplemental EHR data.

It is possible to construct multivariable logistic regression models to evaluate the association between patient baseline characteristics available in the claims and the two types of missingness noted above. However, we consider this kind of analysis as exploratory given it is not easy to make inferences about patient characteristics based on whether the lab results are available or not. A retrospective study using secondary data is less likely to be fit-for-purpose for this topic.

Loss to follow-up is not applicable as no follow-up will be involved in the current study.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Flow charts, starting with the number of all patients with PMO initiating treatment with romosozumab and other osteoporosis therapies in each data source and ending with the number of romosozumab and other osteoporosis drugs treated patients included in study, will be used to describe the application of inclusion and exclusion criteria.

8.7.2.3.2 Description of Subject/Patient Characteristics

Patient demographic and clinical characteristics during the baseline period will be summarized. (see section 8.3.3 for details).

8.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

8.7.2.4.1 Primary Analysis

All study objectives for the primary analysis will be assessed separately in each primary data source, ie, FFS Medicare and Optum CDM claims data. Categorical variables will be presented in tabular form as number and percentage; continuous variables will be presented as number, mean with standard deviation, and median with interquartile range.

Differences in clinical characteristics will be described in four pairwise exposure groups: 1) romosozumab vs. denosumab; 2) romosozumab vs. PTH analog (teriparatide or abaloparatide); 3) romosozumab vs. zolendronate; 4) romosozumab vs. oral BPs. Standardized mean difference (SMD) will be used to characterize differences between exposure groups. SMDs are intuitive indices which measure the effect size between two groups. Compared to a t-test or Wilcoxon rank-sum test, they are independent of sample size, and therefore more appropriate to be adopted in real-world analyses of large data. In brief, the absolute SMD for binary variables is the absolute difference in proportions of the variable between exposed (romosozumab in this study) and non-exposed subjects (other osteoporosis treatments) standardized to the variation in the variable (ie, the standard deviation). It has a minimum value of 0 (“perfect” balance) but no maximum value. For continuous variables, SMD is the absolute difference in the means of variables in treated and untreated subjects standardized to the variation

(Austin 2009). A standardized difference of 0.1 (10 percent) denotes meaningful imbalance in the baseline covariate (Normand, Landrum et al. 2001).

In addition to SMD, a common summary statistic in pharmacoepidemiology, a propensity score (PS) will be calculated for each patient in the study cohort using multivariate logistic regression analysis, conditional on all baseline covariates in section 8.3.3. The PS is a balancing score: conditional on the PS, the distribution of observed baseline covariates will be similar between treatment group of interest and the comparator group. Given that biometric data will only be available in a subset of the study population identified from the primary dataset, the propensity score model will be built based on all claims-based variables as described in protocol section 8.3.3.

Four pairwise 1:1 PS-matching will be conducted in the primary dataset: 1) romosozumab vs. denosumab; 2) romosozumab vs. PTH analog; 3) romosozumab vs. zolendronate; 4) romosozumab vs. oral BPs. Pre- and post-matching balance of potential confounders between exposure groups will be described and visualized by calculating SMD, with meaningful imbalance set at >0.1. Although not included in the final PS model, the balance of biometric variables will be described as SMDs in the subset of the PS matched population with biometric data available. This method and process has been described and adopted in a recent USFDA-sponsored real-world study using similar datasets (Patorno, Schneeweiss et al. 2019).

Evaluation of differences in baseline and historical clinical characteristics between patients initiating romosozumab and those initiating other OP medications, through SMD for individual variables and visual assessment of the extent of overlap between PS distributions, will permit an assessment of the potential channeling bias in prescription of romosozumab.

8.7.2.4.2 Secondary Analysis

All analyses which support the evaluation of the primary objectives will be repeated in the secondary datasets specified in 8.4.2 (claims-EHR linked datasets). This will provide additional information for variables that are unavailable in claims database (eg, LDL/HDL, cholesterol, blood glucose/HbA1C, etc.). For variables that are available in both claims and EHR (eg, diagnosis or medical procedure), records will be retrieved from claims data. For variables that are only available in EHR (eg, biometric data), descriptive analysis as specified in primary analysis will be conducted. For variables where missing values are expected, ie, biometric data from EHR, the percentage of missing will be described first. SMD will then be calculated for each variable, using only non-missing data, and presented for each pairwise exposure group.

8.7.2.5 Sensitivity Analysis

Two sensitivity analyses are planned for the current study:

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-months look back window will be adopted to assess all covariates specified in protocol section 8.3.3 for both primary and secondary analysis.
2. To evaluate the representativeness of the secondary (claims-EHR linked) dataset through following process:
    I. If there were n_i number of individuals in the claims-EHR linked subset for exposure group i [subcutaneous romosozumab, subcutaneous denosumab, parathyroid hormone analog (subcutaneous teriparatide or abaloparatide), intra-venous zolendronate, or oral bisphosphonates (alendronate, risedronate, ibandronate)]
    II. Obtain a bootstrap (sampling with replacement) sample size n_i from the claims data for each exposure group.
    III. Calculate the standardized mean difference (SMD) between the bootstrap sample and the claims-EHR linked subset for each exposure group for claims-based variables
    IV. Repeat this process at least 1000 times to obtain 1000 SMDs for each covariate and exposure group.
    V. Generate a box plot of the SMDs by each covariate.

This process should inform whether on average, there were any major differences between the linked sample and a sample that was selected randomly among those in the claims data.

Results for sensitivity analysis will be provided in the final report.

8.7.2.5.1 Subgroup Analysis

Not applicable

8.7.2.5.2 Stratified Analysis

Not applicable.

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

8.7.2.5.4 Other Sensitivity Analysis

Not applicable.

8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Safety data will not be collected or analyzed in this study.

8.8 Quality Control

Independent production and quality control programming will be performed for all analyses.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error(s)/Misclassification(s)

All included variables will be defined using claims data. Patients will be categorized as having a comorbidity or receiving a concomitant medication if a claim for services with an associated diagnosis or medication is present; otherwise, that patient will be categorized as not having the comorbidity or treated with the medication. This is imperfect as the absence of a claim does not necessarily mean the absence of the comorbidity or drug exposure, although in most circumstances absence of a claim does correlate with absence of condition. However, this study will use all available historical claims, which may minimize chances for misclassification of a comorbidity or concomitant medication. In secondary analyses, data on relevant covariates that are absent within the claims databases (eg, lifestyle factors such as smoking, laboratory values such as blood pressure) will be supplemented via linkage with information available in the PCORnet and Optum EHR.

8.9.1.2 Selection Bias

The study design of current protocol aims to include the treated postmenopausal osteoporosis population as broad as possible, and minimum exclusion criteria will be applied (patients with history of Paget's disease and aged below 55 years). In addition, the FFS Medicare and Optum CDM data bases will allow us to include US elderly and commercial-insured population, thus the impact of selection bias is expected to be small.

8.9.2 External Validity of Study Design

Medicare is a national health plan that covers older and disabled populations in the U.S. Currently, it provides coverage for more than 90% of the elderly population (≥65 years of age) in the U.S. for a variety of health services. As such, it represents a large proportion of the female population that is at risk of post-menopausal osteoporosis, as well as a substantial majority of women who may be eligible to receive romosozumab in the United States, and thus generalizability should be excellent, with minimal risk for selection bias.

Optum Clinformatics® Data Mart (CDM) is a medical claims database which represents the medical experience of insured employees and their dependents from both affiliated commercial and Medicare Advantage plans. Patients must have both medical and

pharmacy coverage to be included in the database. There were approximately fifty-eight million unique patients in the database through March,2018. The underlying insured population from which the data are drawn spans across all 50 US states (46% - South, 9% - Northeast, 22% - West, 23% - Midwest), and is racially/ethnically diverse (60% - White, 9% - African American, 13% - Hispanic, 4% - Asian, 14% - Other/Unkown). Therefore, Optum CDM also has a good representativeness of insured employees.

8.9.3 Analysis Limitations

All analyses planned in the current study are descriptive, without hypothesis testing and thus potential limitations of residual confounding using real-world data is not applicable.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

See section 8.9.1.2 for details.

9. Protection of Human Subjects

9.1 Informed Consent

Informed consent will not be required for a study containing only de-identified secondary data.

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

10.1 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from Medicare and Optum administrative data and no safety data will be collected.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

The study protocol, four interim reports and the Observational Research Study Report (ORSR) of results will be submitted to the USFDA.

12.1 Publication Policy

The study results will be submitted for publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

1. 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.

- 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.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- 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.

13. References

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14. Appendices

Appendix A. Drug Codes to Identify Osteoporosis Medications

Criterion_Name	Code_Type	Code
Romosozumab	HCPCS	J3111
Zoledronic acid	HCPCS	J3488
Zoledronic acid	HCPCS	Q4095
Ibandronate	HCPCS	J1740
Ibandronate	HCPCS	C9229
Calcitonin	HCPCS	J0630
Teriparatide	HCPCS	J3110
Denosumab	HCPCS	C9272
Denosumab	HCPCS	J0897
Denosumab	NDC	55513071001
Zoledronic acid	NDC	00078043561
Zoledronic acid	NDC	35356035101
Zoledronic acid	NDC	47335096241
Zoledronic acid	NDC	25021082682
Zoledronic acid	NDC	00143964201
Zoledronic acid	NDC	23155017031
Zoledronic acid	NDC	25021080166
Zoledronic acid	NDC	42023015101
Zoledronic acid	NDC	43598033011
Zoledronic acid	NDC	47335003540
Zoledronic acid	NDC	53150087101
Zoledronic acid	NDC	55111068507
Zoledronic acid	NDC	60505611000
Zoledronic acid	NDC	23155018631
Zoledronic acid	NDC	42023016301
Zoledronic acid	NDC	43598033111
Zoledronic acid	NDC	55111068852
Zoledronic acid	NDC	25021083082
Teriparatide	NDC	00002897101
Teriparatide	NDC	54868540600
Teriparatide	NDC	00002840001
Teriparatide	NDC	00075205053

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Criterion_Name	Code_Type	Code
alendronate	NDC	00006003121
alendronate	NDC	00006003144
alendronate	NDC	00006007721
alendronate	NDC	00006007744
alendronate	NDC	00006027044
alendronate	NDC	00006071021
alendronate	NDC	00006071044
alendronate	NDC	00006092531
alendronate	NDC	00006092558
alendronate	NDC	00006093628
alendronate	NDC	00006093631
alendronate	NDC	00006093658
alendronate	NDC	00006093672
alendronate	NDC	00006093682
alendronate	NDC	00006383334
alendronate	NDC	00093514001
alendronate	NDC	00093514056
alendronate	NDC	00093514101
alendronate	NDC	00093514156
alendronate	NDC	00093517120
alendronate	NDC	00093517129
alendronate	NDC	00093517144
alendronate	NDC	00093517219
alendronate	NDC	00093517220
alendronate	NDC	00093517229
alendronate	NDC	00093517244
alendronate	NDC	00178010102
alendronate	NDC	00378356601
alendronate	NDC	00378356701
alendronate	NDC	00378356822
alendronate	NDC	00378356893
alendronate	NDC	00378356899

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Criterion_Name	Code_Type	Code
alendronate	NDC	00378356922
alendronate	NDC	00378356993
alendronate	NDC	00378356999
alendronate	NDC	00555071951
alendronate	NDC	00555071954
alendronate	NDC	00555072051
alendronate	NDC	00555072054
alendronate	NDC	00591003104
alendronate	NDC	00591007704
alendronate	NDC	00591317104
alendronate	NDC	00591317304
alendronate	NDC	16252059902
alendronate	NDC	16252059944
alendronate	NDC	16252060102
alendronate	NDC	16252060144
alendronate	NDC	16590049104
alendronate	NDC	16590071804
alendronate	NDC	16590071820
alendronate	NDC	16590071830
alendronate	NDC	16590099930
alendronate	NDC	16714063101
alendronate	NDC	16714063102
alendronate	NDC	16714063201
alendronate	NDC	16714063202
alendronate	NDC	16714063301
alendronate	NDC	16714063302
alendronate	NDC	21695090104
alendronate	NDC	21695090204
alendronate	NDC	23490917401
alendronate	NDC	24658016271
alendronate	NDC	24658016273
alendronate	NDC	24658016371

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Criterion_Name	Code_Type	Code
Alendronate	NDC	24658016373
alendronate	NDC	33261055401
alendronate	NDC	33261099301
alendronate	NDC	35356059404
alendronate	NDC	41616063583
alendronate	NDC	41616063588
alendronate	NDC	41616063683
alendronate	NDC	41616063688
alendronate	NDC	41616063768
alendronate	NDC	41616063868
alendronate	NDC	42254022604
alendronate	NDC	47335063768
alendronate	NDC	47335063868
alendronate	NDC	49999050104
alendronate	NDC	51079094105
alendronate	NDC	51079094205
alendronate	NDC	51224030110
alendronate	NDC	54569486600
alendronate	NDC	54569521800
alendronate	NDC	54569539900
alendronate	NDC	54569604700
alendronate	NDC	54569605000
alendronate	NDC	54569605001
alendronate	NDC	54868385700
alendronate	NDC	54868438400
alendronate	NDC	54868446200
alendronate	NDC	54868446201
alendronate	NDC	54868446300
alendronate	NDC	54868548000
alendronate	NDC	54868586000
alendronate	NDC	54868586100
alendronate	NDC	54868586101

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Criterion_Name	Code_Type	Code
alendronate	NDC	54868586200
alendronate	NDC	55045390801
alendronate	NDC	55045391501
alendronate	NDC	55048000504
alendronate	NDC	55111058801
alendronate	NDC	55111058830
alendronate	NDC	55111058901
alendronate	NDC	55111058930
alendronate	NDC	55111059048
alendronate	NDC	55111059248
alendronate	NDC	55887051620
alendronate	NDC	55887051630
alendronate	NDC	55887051660
alendronate	NDC	55887051682
alendronate	NDC	55887051690
alendronate	NDC	58016061300
alendronate	NDC	58016061304
alendronate	NDC	58016061320
alendronate	NDC	58016061330
alendronate	NDC	58016061360
alendronate	NDC	58016061390
alendronate	NDC	58016078800
alendronate	NDC	58016078830
alendronate	NDC	58016078860
alendronate	NDC	58016078890
alendronate	NDC	59746024202
alendronate	NDC	59746024402
alendronate	NDC	60429005572
alendronate	NDC	60429005574
alendronate	NDC	60429005672
alendronate	NDC	60429005674
alendronate	NDC	60429077304

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Criterion_Name	Code_Type	Code
Alendronate	NDC	60429077312
alendronate	NDC	60505259201
alendronate	NDC	60505259203
alendronate	NDC	60505259301
alendronate	NDC	60505259303
alendronate	NDC	60505259404
alendronate	NDC	60505259602
alendronate	NDC	60505259604
alendronate	NDC	60505259608
alendronate	NDC	63874008901
alendronate	NDC	65862032730
alendronate	NDC	65862032804
alendronate	NDC	65862032904
alendronate	NDC	67801032003
alendronate	NDC	67877024031
alendronate	NDC	67877024033
alendronate	NDC	67877024131
alendronate	NDC	67877024133
alendronate	NDC	68071079030
alendronate	NDC	68071079130
alendronate	NDC	68071157704
alendronate	NDC	68084032264
alendronate	NDC	68084032294
alendronate	NDC	68115075504
alendronate	NDC	68115079300
alendronate	NDC	68258301401
alendronate	NDC	68258598801
alendronate	NDC	68258598802
alendronate	NDC	68258598902
alendronate	NDC	69097022316
alendronate	NDC	69097022376
alendronate	NDC	69097022416

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Criterion_Name	Code_Type	Code
alendronate	NDC	69097022476
alendronate	NDC	69543013004
alendronate	NDC	69543013012
alendronate	NDC	69543013104
alendronate	NDC	69543013112
alendronate	NDC	69543013120
alendronate	NDC	76439013004
alendronate	NDC	76439013012
alendronate	NDC	76439013104
alendronate	NDC	76439013112
alendronate	NDC	76439013120
ibandronate	NDC	00004018523
ibandronate	NDC	00004018682
ibandronate	NDC	00004018683
ibandronate	NDC	00378521553
ibandronate	NDC	00591377011
ibandronate	NDC	00591377031
ibandronate	NDC	12280041203
ibandronate	NDC	16590040003
ibandronate	NDC	35356042303
ibandronate	NDC	42291033603
ibandronate	NDC	47781010307
ibandronate	NDC	47781010333
ibandronate	NDC	54868532200
ibandronate	NDC	54868532201
ibandronate	NDC	55111057503
ibandronate	NDC	55111057511
ibandronate	NDC	55887064103
ibandronate	NDC	60505279500
risedronate	NDC	00093309829
risedronate	NDC	00093309844
risedronate	NDC	00093309956

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Criterion_Name	Code_Type	Code
risedronate	NDC	00093550944
risedronate	NDC	00149047101
risedronate	NDC	00149047103
risedronate	NDC	00149047201
risedronate	NDC	00149047204
risedronate	NDC	00149047501
risedronate	NDC	00149047701
risedronate	NDC	00149047801
risedronate	NDC	00149047803
risedronate	NDC	00378404493
risedronate	NDC	00378415032
risedronate	NDC	00378415053
risedronate	NDC	00430047115
risedronate	NDC	00430047203
risedronate	NDC	00430047207
risedronate	NDC	00430047801
risedronate	NDC	00430047802
risedronate	NDC	00430097903
risedronate	NDC	00591204403
risedronate	NDC	00591204454
risedronate	NDC	00591207504
risedronate	NDC	00591207539
risedronate	NDC	00591210230
risedronate	NDC	00591387604
risedronate	NDC	16590072104
risedronate	NDC	23490924500
risedronate	NDC	47335092860
risedronate	NDC	47335092867
risedronate	NDC	49999044804
risedronate	NDC	54569546200
risedronate	NDC	54868438600
risedronate	NDC	54868467100

Appendix A. Drug Codes to Identify Osteoporosis Medications

Criterion_Name	Code_Type	Code
risedronate	NDC	54868551800
risedronate	NDC	54868606900
risedronate	NDC	55887068504
risedronate	NDC	60505309702
risedronate	NDC	60505309704
risedronate	NDC	60505316500
risedronate	NDC	65862051730
risedronate	NDC	65862051904
risedronate	NDC	65862051908
risedronate	NDC	66105015703
risedronate	NDC	68115068104

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Amendment - 1.0

Protocol Title: Clinical Characteristics, Including History of MI and Stroke, Among US Post-menopausal Women Initiating Treatment With Romosozumab and Other Anti-osteoporosis Therapies

Amgen Protocol Number 20190205

Amendment Date: 21 April 2020

Rationale:

The previous "conditional approved" protocol version (dated 10-10-2019) was sent to USFDA for review by 31-10-2019. The current version of study protocol has been updated based on recent Amgen responses to USFDA information request on 24th February, and has been reviewed by Evenity GDL, GRL, GSL, GSO and CfOR Senior management.

Description of Changes:

All changes were based on Amgen responses to USFDA information request letter.

Section: Abstract

Change: Sample size from 255,144 -> 204,706; 38,000 -> 30,706

Add: Four pairwise 1:1 PS-matching will be conducted in the primary dataset: 1) romosozumab vs. denosumab; 2) romosozumab vs. PTH analog; 3) romosozumab vs. zolendronate; 4) romosozumab vs. oral BPs. Pre- and post-matching balance of potential confounders between exposure groups will be described and visualized by calculating SMD, with meaningful imbalance set at >0.1.

Section: 8.2.3

Add: Four pairwise 1:1 propensity score (PS)-matching will be conducted in the primary dataset: 1) romosozumab vs. denosumab; 2) romosozumab vs. PTH analog; 3) romosozumab vs. zolendronate; 4) romosozumab vs. oral BPs

Section 8.3.3

Add: For non-biometric study variables (eg, comorbidities and medications), we will use ICD-9/10 codes, Healthcare Common Procedure Coding System (HCPCS) and National Drug Code (NDC) codes. For biometric data in PCORnet, height, weight, BMI and blood pressure can be retrieved from vital_table; lab test results such as blood glucose, HDL-C and LDL-C can be retrieved by LONIC codes in Lab_result table (see the full PCORnet data dictionary here: https://pcornet.org/wp-content/uploads/2019/09/PCORnet-Common-Data-Model-v51-2019_09_12.pdf). Similarly, in Optum EHR, labs are mapped according to therapeutic category, lab names are standardized, and results are recorded in the LABS data file. Lifestyle and biometric data are captured in the OBSERVATIONS data file.

The full list of operational definitions are provided in section 6 of statistical analysis plan (SAP).

Section 8.4.2

Add: They were selected based on multiple factors including (1) the large-scale availability of electronic health record (EHR) data (> 50M unique patients in these three networks) that is linkable to national claims data, (2) the regional representation and geographic diversity that they provide, and (3) a site feasibility study conducted by PCORne

Page 29, A clinical phenotype was sent to the CDRNs requesting that each site estimate their total cohort based on women >65 in Medicare with an osteoporosis diagnosis and history of osteoporosis medication use (denosumab, teriparatide, alendronate, zolendronate). Availability was also provided for the clinical covariates of interest: BMI, blood pressure, blood glucose, HbA1C, LDL-C, HDL-C, and triglycerides (see Table 1 below for details).Based on these feasibility results and the confirmed linkage method between Medicare and PCORnet (see response to question #11 for details), we will include these three PCORnet CDRN sites. .

Table 1. Availability of Biometric Data in Post-menopausal Women Under Medicare Coverage in PCORnet

	PATH (N=90,043)	Mid-South (N=279,449)	OneFlorida (N=135,218)
BMI	96.73%	69.30%	76.96%
Blood pressure	97.57%	71.31%	77.60%
Blood glucose	79.76%	64.70%	65.89%
HbA1C	17.82%	26.02%	30.28%
LDL-C	52.88%	42.06%	46.34%
HDL-C	58.69%	42.54%	41.48%
Triglycerides	41.86%	41.46%	42.19%

Section: 8.4

Add: Amgen continues to evaluate with Optum the possibility and proposed linkage methods for Medicare – Optum EHR data. If feasible, we may consider adding this as an amendment to study 20190205 in the future.

Section: 8.5

Table 2. Sample Size Estimation for Study Drugs in Study 20190205 in the Primary and Secondary Datasets

	Primary dataset		Secondary dataset	
	Medicare	Optum	Medicare-PCORnet linked	Optum claims - EHR linked
Romosozumab	30,706	4,862	3,887	876
Denosumab	204,706	32,414	25,911	5,842
PTH analogs	44,927	11,036	7,168	1,604
Zolendronate	114,099	22,648	18,257	5,187
Oral BPs[a]	557,099	134,451	88,886	74,307

[a] Alendronate, risedronate and ibandronate

Section: 8.6.2

Add: The current study will link Medicare claims with PCORnet through the following methods and steps:

1. The CMS Chronic Condition Data Warehouse (CCW) has the ability to extract data from Medicare research identifiable files at the individual beneficiary level using finder files. See the CMS CCW Finder File Encryption Policy guidance document, page 2, https://www2.ccwdata.org/web/guest/request-data for information on the different finder file types.
2. The participating PCORnet Clinical Data Research Networks (CDRNs) sites will identify patients and prepare finder files using social security numbers (SSN) or Medicare Health Insurance Claim (HIC) identifiers for linkage of all patients meeting inclusion criteria.
3. A single finder file at each PCORnet data mart will be paired with the corresponding PCORnet patient ID and will be submitted by each data mart directly to the Centers for Medicare and Medicaid Services (CMS) for matching claims data.

See below figures for details of data flow between PCORnet Data Marts and CMS VRDC.

Optum's Integrated Claims-Clinical dataset combines adjudicated claims data with Optum's Electronic Health Record (EHR) data. Optum's longitudinal EHR clinical repository from Optum Analytics is derived from more than 50 healthcare provider organizations in the United States, that includes more than 700 hospitals and 7000 clinics, treating more than 100 million patients receiving care in the United States. Optum's Integrated Claims-EHR dataset is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum® and customer data use agreements. The Integrated dataset, which uses both salting and cryptographic hashing, links both claims and clinical data for approximately 24 million matched individuals. Only three, high-probability matching levels are accepted: 1) Social Security Number + Date of Birth + Last Name + First Name; 2) Social Security Number + Date of Birth; and 3) Date of Birth + Last Name + First Name + State + Zip code. If multiple matches are found, those matches are excluded. Standardized cleaning is performed on both the claims and EHR data to maximize the likelihood of matching (eg, invalid zip codes or social security numbers are discarded). The performance characteristics of the linkage is not currently available but is expected to be highly accurate since it mostly relies on SSN and there are standard QC process as described above

Section: 8.7.1.1

Remove: “due in September 2020, analysis will be completed in April 2020”

Rationale: The study start date is pending on USFDA’s agreement on final protocol. The original plan is not applicable now.

Section: 8.7.2.2

Add: There could be two types of missingness: 1) the physician ordered the test but the result was missing in the supplemental EHR, or 2) the test was never ordered. Using specific HCPCS/CPT codes in the claims data (primary data source), we can evaluate whether or not a patient had a test ordered. Conditional on patients having tests done as indicated via the claims data, we may or may not get the test results in the supplemental EHR data.

It is possible to construct multivariable logistic regression models to evaluate the association between patient baseline characteristics available in the claims and the two types of missingness noted above. However, we consider this kind of analysis as exploratory given it is not easy to make inferences about patient characteristics based on whether the lab results are available or not. A retrospective study using secondary data is less likely to be fit-for-purpose for this topic.

Section: 8.7.2.4.1

Given that biometric data will only be available in a subset of the study population identified from the primary dataset, the propensity score model will be built based on all claims-based variables as described in protocol section 8.3.3.

Four pairwise 1:1 PS-matching will be conducted in the primary dataset: 1) romosozumab vs. denosumab; 2) romosozumab vs. PTH analog; 3) romosozumab vs. zolendronate; 4) romosozumab vs. oral BPs. Pre- and post-matching balance of potential confounders between exposure groups will be described and visualized by calculating SMD, with meaningful imbalance set at >0.1. Although not included in the final PS model, the balance of biometric variables will be described as SMDs in the subset of the PS matched population with biometric data available. This method and process has been described and adopted in a recent USFDA-sponsored real-world study using similar datasets (Patorno, Schneeweiss et al. 2019).

Section: 8.7.2.5

Add: Two sensitivity analyses are planned for the current study:

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-months look back window will be adopted to assess all covariates specified in protocol section 8.3.3 for both primary and secondary analysis.
2. To evaluate the representativeness of the secondary (claims-EHR linked) dataset through following process:
    I. If there were n_i number of individuals in the claims-EHR linked subset for exposure group i [subcutaneous romosozumab, subcutaneous denosumab, parathyroid hormone analog (subcutaneous teriparatide or abaloparatide), intra-venous zolendronate, or oral bisphosphonates (alendronate, risedronate, ibandronate)]
    II. Obtain a bootstrap (sampling with replacement) sample size n_i from the claims data for each exposure group.
    III. Calculate the standardized mean difference (SMD) between the bootstrap sample and the claims-EHR linked subset for each exposure group for claims-based variables
    IV. Repeat this process at least 1000 times to obtain 1000 SMDs for each covariate and exposure group.
    V. Generate a box plot of the SMDs by each covariate.

    This process should inform whether on average, there were any major differences between the linked sample and a sample that was selected randomly among those in the claims data.

Results for sensitivity analysis will be provided in the final report.