Research Protocol

**Title:** Comparison of cardiovascular outcomes risk of romosozumab vs denosumab

Responsible parties

Study Lead:

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# Abstract

The purpose of this study is to describe the association between romosozumab and cardiovascular outcomes.

# Amendments and Updates

# Rationale and background

Romosozumab is a monoclonal antibody indicated for treating osteoporosis in postmenopausal women at risk of fractures. The ARCH study (Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk) found that the group receiving romosozumab had superior efficacy in preventing fractures compared to the alendronate group, with a 48% lower risk of vertebral fractures, a 38% lower risk of hip fractures, and a 19% lower risk of non-vertebral fractures. However, the romosozumab group also had a higher incidence of cardiac ischemic events and cerebrovascular events during the first year. It has been shown that romosozumab is beneficial for bone health, however several studies suggest that it worsens cardiovascular disease endpoints. By comparing romosozumab with denosumab, the other anti-osteoporosis medication, in this study, we aim to determine whether there is an association between romosozumab and cardiovascular outcomes.

# Aims and Objectives

This study is a multinational cohort study comparing the cardiovascular outcomes risk between romosozumab versus denosumab.

# Research Methods

## Study design

The study will be retrospective and observational and will compare the short-term risk of cardiovascular outcomes between romosozumab and denosumab. Data sources will be administrative claims or electronic health record (EHR) data across the OHDSI network.

## Study population

The target group consists of patients who romosozumab treatment and who meet the criteria below. Patients who denosumab and meet the criteria below are included in the comparator group.

Index rule defining the index date:

* Exposure to one of the treatments of interest for the first time in the person’s history on or after 2020-01-01.

Inclusion rules based on the index date:

* At least 50 years old on the index date and all days before

Exit rules defining the cohort end date:

* Event will persist until end of continuous observation, exit based on drug exposure to other osteoporosis medications

Table 1 Romosozumab Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 1511251 | romosozumab | Drug | FALSE | TRUE | FALSE |

Table 2 Denosumab Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40222444 | denosumab | Drug | FALSE | TRUE | FALSE |

Table 3 Anti-Osteoporosis (without romosuzmab) Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 1524674 | zoledronic acid | Drug | FALSE | TRUE | FALSE |
| 1578445 | tiludronate | Drug | FALSE | TRUE | FALSE |
| 1521987 | teriparatide | Drug | FALSE | TRUE | FALSE |
| 1436678 | tamoxifen | Drug | FALSE | TRUE | FALSE |
| 40222444 | denosumab | Drug | FALSE | TRUE | FALSE |
| 1516800 | risedronate | Drug | FALSE | TRUE | FALSE |
| 1513103 | raloxifene | Drug | FALSE | TRUE | FALSE |
| 1511646 | pamidronate | Drug | FALSE | TRUE | FALSE |
| 36850663 | LASOFOXIFENE | Drug | FALSE | TRUE | FALSE |
| 1512480 | ibandronate | Drug | FALSE | TRUE | FALSE |
| 1552929 | etidronate | Drug | FALSE | TRUE | FALSE |
| 44506794 | bazedoxifene | Drug | FALSE | TRUE | FALSE |
| 1557272 | alendronate | Drug | FALSE | TRUE | FALSE |
| 1594148 | abaloparatide | Drug | FALSE | TRUE | FALSE |

Table 4 Anti-Osteoporosis (without denosumab) Concept Set Definition

|  |  |  |  |  |  |
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| 1511251 | romosozumab | Drug | FALSE | TRUE | FALSE |
| 1516800 | risedronate | Drug | FALSE | TRUE | FALSE |
| 1513103 | raloxifene | Drug | FALSE | TRUE | FALSE |
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| 36850663 | LASOFOXIFENE | Drug | FALSE | TRUE | FALSE |
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| 1557272 | alendronate | Drug | FALSE | TRUE | FALSE |
| 1594148 | abaloparatide | Drug | FALSE | TRUE | FALSE |

### Outcomes

#### Primary outcome: Adjudicated CV event

Index rule defining the index date:

* Occurrence of death having any of the following criteria
  + At least 1 occurrence of acute myocardial infarction between 30 days before and 7 days after index start date
  + At least 1 occurrence of ischemic stroke between 30 days before and 7 days after index start date
  + At least 1 occurrence of intracranial bleed hemorrhagic stroke between 30 days before and 7 days after index start date
  + At least 1 occurrence of sudden cardiac death between 30 days before and 7 days after index start date
  + At least 1 occurrence of heart failure visited inpatient or ED between 30 days before and 7 days after index start date
  + At least 1 occurrence of peripheral artery disease without non-coronary revascularization history between 30 days before and 7 days after index start date
  + At least 1 occurrence of ischemic stroke between 30 days before and 7 days after index start date
  + At least 1 occurrence non-coronary revascularization between 30 days before and 7 days after index start date
* Occurrence of acute myocardial Infarction
* Occurrence of peripheral artery disease
* Occurrence of ischemic stroke
* Occurrence of heart failure
* Occurrence of non-coronary revascularization

Exit rules defining the cohort end date:

* Allowance for 1-day offset from index date

#### Primary outcome: MACE

Index rule defining the index date:

* Occurrence of acute myocardial Infarction
* Occurrence of ischemic stroke
* Occurrence of death having any of the following criteria
  + At least 1 occurrence of acute myocardial infarction between 30 days before and 7 days after index start date
  + At least 1 occurrence of ischemic stroke between 30 days before and 7 days after index start date
  + At least 1 occurrence of intracranial bleed hemorrhagic stroke between 30 days before and 7 days after index start date
  + At least 1 occurrence of sudden cardiac death between 30 days before and 7 days after index start date
  + At least 1 occurrence of heart failure visited inpatient or ED between 30 days before and 7 days after index start date

Exit rules defining the cohort end date:

* Allowance for 1-day offset from index date

#### Secondary outcome: Acute myocardial Infarction

Index rule defining the index date:

* Occurrence of acute myocardial Infarction

Exit rules defining the cohort end date:

* Allowance for 1-day offset from index date

#### Secondary outcome: Heart failure

Index rule defining the index date:

* Occurrence of heart failure visited inpatient or ED

Exit rules defining the cohort end date:

* Allowance for 1-day offsets from index date

#### Secondary outcome: Ischemic stroke

Index rule defining the index date:

* Occurrence of ischemic stroke

Exit rules defining the cohort end date:

* Allowance for 1-day offsets from index date

#### Secondary outcome: Non-coronary revascularization

Index rule defining the index date:

* Occurrence of non-coronary revascularization

Exit rules defining the cohort end date:

* Allowance for 1-day offsets from index date

#### Secondary outcome: Peripheral artery disease

Index rule defining the index date:

* Occurrence of peripheral artery disease without non-coronary revascularization history

Exit rules defining the cohort end date:

* Allowance for 1-day offsets from index date

#### Secondary outcome: Sudden cardiac death

Index rule defining the index date:

* Occurrence of sudden cardiac death

Exit rules defining the cohort end date:

* Allowance for 1-day offsets from index date

#### Negative controls outcome

A total of 161 concepts were selected as negative controls that were not associated with bisphosphonates and denosumab.

Table 25 Negative controls outcomes

|  |  |
| --- | --- |
| Concept ID | Concept Name |
| 376707 | Acute conjunctivitis |
| 433753 | Alcohol abuse |
| 257007 | Allergic rhinitis |
| 76725 | Anal fissure |
| 380094 | Carpal tunnel syndrome |
| 4260364 | Choledochal cyst |
| 255573 | Chronic obstructive lung disease |
| 134438 | Contact dermatitis |
| 78619 | Contusion of knee |
| 378752 | Corneal opacity |
| 201606 | Crohn's disease |
| 133228 | Dental caries |
| 134681 | Diffuse spasm of esophagus |
| 432251 | Disease caused by parasite |
| 378161 | Disorder of ear |
| 139057 | Disorder of oral soft tissues |
| 138225 | Disorder of sebaceous gland |
| 443530 | Hematochezia |
| 440329 | Herpes zoster without complication |
| 441788 | Human papilloma virus infection |
| 374375 | Impacted cerumen |
| 139099 | Ingrowing nail |
| 436962 | Insomnia |
| 201322 | Internal hemorrhoids without complication |
| 132466 | Lumbar sprain |
| 255891 | Lupus erythematosus |
| 4103703 | Melena |
| 440385 | Obstructive hydrocephalus |
| 438130 | Opioid abuse |
| 380733 | Otalgia |
| 372328 | Otitis media |
| 4002650 | Plantar fasciitis |
| 373478 | Presbyopia |
| 438688 | Sarcoidosis |
| 372409 | Sciatica |
| 73562 | Solitary sacroiliitis |
| 438252 | Spontaneous ecchymosis |
| 133141 | Tinea pedis |
| 435315 | Torsion of testis |
| 376707 | Acute conjunctivitis |
| 433753 | Alcohol abuse |
| 257007 | Allergic rhinitis |
| 76725 | Anal fissure |
| 380094 | Carpal tunnel syndrome |
| 4260364 | Choledochal cyst |
| 255573 | Chronic obstructive lung disease |
| 134438 | Contact dermatitis |
| 78619 | Contusion of knee |
| 378752 | Corneal opacity |
| 201606 | Crohn's disease |
| 133228 | Dental caries |
| 134681 | Diffuse spasm of esophagus |
| 432251 | Disease caused by parasite |
| 378161 | Disorder of ear |
| 139057 | Disorder of oral soft tissues |
| 138225 | Disorder of sebaceous gland |
| 443530 | Hematochezia |
| 440329 | Herpes zoster without complication |
| 441788 | Human papilloma virus infection |
| 374375 | Impacted cerumen |
| 139099 | Ingrowing nail |
| 436962 | Insomnia |
| 201322 | Internal hemorrhoids without complication |
| 132466 | Lumbar sprain |
| 255891 | Lupus erythematosus |
| 4103703 | Melena |
| 440385 | Obstructive hydrocephalus |
| 438130 | Opioid abuse |
| 380733 | Otalgia |
| 372328 | Otitis media |
| 4002650 | Plantar fasciitis |
| 373478 | Presbyopia |
| 438688 | Sarcoidosis |
| 372409 | Sciatica |
| 73562 | Solitary sacroiliitis |
| 438252 | Spontaneous ecchymosis |
| 133141 | Tinea pedis |
| 435315 | Torsion of testis |

# Data Analysis Plan

## Population Level Estimation

#### Covariates for Propensity scores

The types of baseline covariates used to fit the propensity score model will be:

* demographics
  + Age group (5-year bands)
  + Index Year
* Condition Aggregation
  + In prior 365d
* Drug Aggregation
  + In prior 365d
* Charlson Index
* Dcsi
* CHADS2
* CHA*2*DS*2*VASc

The concepts which composed of cohort definition of target or comparator excluded from the propensity score model.

#### Data Analysis Plan

##### **Calculation of time at risk**

Two time-at-risk period will be used:

* Intent-to-treat (1Y): Starting 1 days after treatment initiation and stopping at the 365 days.
* Intent-to-treat (3Y): Starting 1 days after treatment initiation and stopping at the 1095 days.

Incidence rates will be computed for outcome in time at risk group.

##### **Model specification**

we compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model. Incidence rates will be computed for each outcome in each exposure group.

###### Statistical model

Propensity score Adjustment will be:

* 1:1 PS matching: One-to-one matching will be performed. A caliper of 0.2 times the standard deviation of the propensity score distribution
* PS stratification: The target cohort and comparator cohorts will be stratified into ten quantiles of the PS distribution.

Outcome Model Settings will be:

* Cox proportional hazards model will be used to estimate the risk of outcome between target and comparator cohorts.

##### **Analysis to Perform**

The following comparative analysis will be performed:

* 1 comparison:
  + Romosozumab users (Target) vs Denosumab users (Comparator)
* 5 outcomes:
  + Adjudicated CV event
  + MACE
  + Heart Failure
  + Stroke
  + Peripheral artery disease
  + Non-coronary revascularization
  + Sudden cardiac death
* 3 time-at-risk:
  + Intent-to-treatment (1Y)
  + Intent-to-treatment (3Y)
* One model: Cox-regression after 1:1 PS matching

#### Output

|  |  |
| --- | --- |
| Output | Description |
| Propensity score distribution Plot | The propensity score distribution for both cohorts after matching will be provided. |
| Propensity model | The propensity model will show the table that reports the covariates selected from propensity score models, with associated coefficients. |
| Covariate Balance Scatter Plot | Covariate Balance Scatter Plot will show the absolute standardized difference of mean before and after propensity score matching. |
| Attrition diagram | Attrition diagram will show the counts to meet the various inclusion and exclusion criteria, and loss due to matching. |
| Kaplan-Meier plot | Kaplan-Meier plot will display the survival over time in both cohorts. |
| Population characteristics table | A table which lists some select population characteristics before and after matching will be created. |
| Outcome models | The summarized report will be provided from outcome models. It will report the hazards ration, associated 95% confidence interval, the number of persons, amount of time-at-risk, and number outcome in both cohorts. |

# Strengths and Limitations of the Research Methods

## Strength

* PS matching and outcome model allow balancing on many baselines potential confounders.

## Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or mis-specified confounders.

# Protection of Human Subjects

In this study, we will use only de-identified data from CDM. The results of study will be aggregated and will not identify individual subjects.

# Plans for Disseminating and Communicating Study Results

# Reference