NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL (OP0005)

EUROPEAN NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY RELATED TO ADHERENCE TO THE RISK MINIMIZATION MEASURES FOR ROMOSOZUMAB BY THE EU-ADR ALLIANCE

Final Non-interventional PASS Protocol	18 Jun 2020

PASS INFORMATION

Title	European non-interventional post-authorization safety study related to adherence to the risk minimization measures for romosozumab by the EU-ADR Alliance
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Product reference	H0004465
Marketing authorization holder (MAH)	UCB Pharma S.A.
Joint PASS	Not applicable
Research question and objectives	The overarching objective is to evaluate adherence to the cardiovascular risk minimization measures for the use of romosozumab in Europe.
Countries of study	Denmark, France, Germany, Italy, Netherlands, Spain, and the UK
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MARKETING AUTHORIZATION HOLDER

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ALN	alendronate or alendronic acid
ARCH	Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CV	cardiovascular
DDD	defined daily dose
EMA	European Medicines Agency
EMR	electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FRAME	Fracture Study in Postmenopausal Women with Osteoporosis
GePaRD	German Pharmacoepidemiological Research Database
GP	general practitioner
HSD	Health Search Database
ICD-10	International Classification of Diseases, revision 10
ICPC	International Classification of Primary Care
IPCI	Integrated Primary Care Information Project
IR	incidence rate
IRB	institutional review board
iv	intravenous
LTD	long-term disease
MACE	major adverse cardiac event(s)
MAH	Marketing Authorization Holder
MI	myocardial infarction
MPR	medication possession ratio
OP	osteoporosis
PASS	post-authorization safety study(ies)
PMSI	Programme de médicalisation des systèmes d`information
PV	pharmacovigilance

Abbreviation	Definition
RRE	Remote Research Environment
RMM	risk minimization measure
RMP	Risk Management Plan
SD	standard deviation
SERM	selective estrogen receptor modulator
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SmPC	Summary of Product Characteristics
SNDS	Système National Des Données de Santé
UMLS®	Unified Medical Language System®
WHO	World Health Organization

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CEO=Chief Executive Officer; CPRD=Clinical Practice Research Datalink; DE=Germany; DK=Denmark; ES=Spain; EU=European Union; FR=France; GePaRD=German Pharmacoepidemiological Research Database; HSD=Health Search Database; IPCI=Integrated Primary Care Information Project; IT=Italy; MAH=Marketing Authorization Holder; NL=Netherlands; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; SIMG=Societá Italiana di Medicina Generale; SNDS=Système National Des Données de Santé

4 ABSTRACT

Title

European non-interventional post-authorization safety study (PASS) related to adherence to the risk minimization measures (RMMs) for romosozumab by the EU-ADR Alliance.

Rationale and background

An imbalance in the incidence of serious cardiovascular (CV) events, driven by events of myocardial infarction (MI) and stroke, was observed with romosozumab in the alendronate (ALN)-controlled study 20110142 (ARCH) after 12 months of treatment. No imbalance was observed in the placebo-controlled study 20070377 (FRAME) after 12 months of treatment.

Serious CV events of MI and stroke are determined an identified risk in the European Union (EU)-Risk Management Plan (RMP).

Research question and objectives

The overarching aim of this drug utilization PASS is to evaluate adherence to the CV RMMs for the use of romosozumab in Europe. To achieve this, utilization patterns and adherence to the contraindication of history of MI or stroke and the EU approved indication of severe osteoporosis (OP) in postmenopausal women at high risk of fracture, will be described amongst incident romosozumab users in routine clinical practice.

Specifically, the study objectives are:

1. To assess the prevalence and incidence of romosozumab use at the population level and the relative trends over time;
2. To characterize users of romosozumab and to evaluate compliance with the EU approved indication and contraindication (history of MI or stroke) as per the RMMs;
3. To describe prevalence and incidence of use of other OP medications and to characterize users, in order to provide context.

Study design

This will be a multi-national, multi-database cohort study conducted in 7 European countries, ie, EU-ADR Alliance data sources (UK, Netherlands, Spain, Italy and Denmark) and databases from France and Germany. The study period will cover 2020 to 2026.

Population

Adult women and men (18 years or older) registered for at least 12 months with each of the participating databases during the study period will be included for the population-level drug use estimation. New users of romosozumab (participants with a first dispensation/prescription for romosozumab without any use of this same drug in the previous year) and of other OP medications (participants with a first dispensation/prescription for another OP medication without any use of this same drug in the previous year) will be identified. For each medication, patients will be followed from the date of first prescription (index date) until cessation of current treatment (including switching to another OP medication) or end of current data collection.

Variables

The OP medications of interest include romosozumab and other OP medications, such as ALN, other oral bisphosphonates (ibandronate or risedronate at doses indicated for OP treatment), intravenous (iv) bisphosphonates (zoledronate and ibandronate at doses indicated for OP treatment), selective estrogen receptor modulators (SERMs) (raloxifene, bazedoxifene, and lasofoxifene at doses indicated for OP treatment), denosumab (at the dose indicated for OP treatment), and teriparatide.

Among romosozumab users, presence of contraindication will be defined as history of MI or stroke; presence of documented indication will be defined as history of fracture and female gender and age. Both indication and contraindication will be ascertained based on the patients' records before index date.

Other covariates will be identified at cohort entry (index date) based on the patients' records before index date, and will include general patient characteristics, markers of OP severity, and use of other medications.

Data sources

This study will be conducted using routinely collected data from different data sources that participate in the EU-ADR Alliance, with the addition of databases from the UK (Clinical Practice Research Datalink [CPRD] GOLD), Germany (German Pharmacoepidemiological Research Database [GePaRD]), and France (Système National Des Données de Santé [SNDS] database). Participants from 7 European countries will provide heterogeneous and representative data on the safety of romosozumab as well as ensuring sufficient statistical power for the study.

Study size

No minimum sample size will be required for this study since is descriptive in nature.

Data analysis

For romosozumab and other OP medications, the following measures will be calculated:

- Monthly *prevalence of use* will be calculated for each OP drug separately as the point prevalence of use of a particular drug on day 15 of each calendar month, where the numerator will be all users of the drug, and the denominator will be all eligible in the source population and registered in the database on that same day
- Monthly *incidence of use* will be calculated for each OP drug separately as the incidence rate (IR) of use of a particular drug, where the numerator will be all new users of the drug (ie, with no use of this same drug in the previous year) in a given calendar month, and the denominator will be person-months of people available in the dataset on a given calendar month, who were not users of the specific drug at the beginning of that calendar month and no use of this same drug in the previous year)

- Overall duration of treatment/persistence: number of days from index date to discontinuation as defined in Section 9.3.1. Kaplan-Meier plots will be used to depict persistence over time.
- Proportion persistent at 6, 12, 18, and 24 months: number (n) and percentage (%) of patients who complete a treatment duration (as defined above) of 6, 12, 18, and 24 months, respectively, will be reported.
- Switching: number (n) and percentage (%) of patients who switch to another OP medication as listed above after 6, 12, 18, and 24 months of starting their index treatment will be reported. Sankey plots will be used to depict treatment switching patterns.

For romosozumab users only, the following measures will be calculated:

- Prevalence of contraindications amongst new romosozumab users:
  - Initiation of romosozumab in men
  - History of MI in the year before romosozumab therapy initiation
  - History of MI at any time before romosozumab therapy initiation

  - History of stroke in the year before romosozumab therapy initiation
  - History of stroke at any time before romosozumab therapy initiation
  - History of MI or stroke in the year before romosozumab therapy initiation
  - History of MI or stroke at any time before romosozumab therapy initiation
- Prevalence of documented indication amongst new romosozumab users:
  - History of any fracture (except the face, skull and digits) in the year before romosozumab therapy initiation
  - History of major osteoporotic fracture (hip, spine, proximal humerus, or wrist/forearm) in the year before romosozumab therapy initiation
  - History of any fracture (except the face, skull and digits) at any time before romosozumab therapy initiation
  - History of major osteoporotic fracture (hip, spine, proximal humerus, or wrist/forearm) at any time before romosozumab therapy initiation

All these estimates will be calculated for each of the contributing databases separately. Estimates will be provided overall (for the whole source population) and stratified by sex (except for use in men), age (5-year bands) and calendar year.

Baseline characteristics of all users of romosozumab and of other OP medications, as well as of romosozumab users in each of the contraindication and restriction of indication groups, will be described.

Milestones

Interim reports will be generated monthly and submitted in the 6-monthly reports for the first 2 years followed by annual reports for an additional 4 years, up to a total of 6 years.

5 AMENDMENTS AND UPDATES

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, institutional review board (IRB)/independent ethics committee, regulatory authorities and local institutions (if required), prior to being implemented.

6 MILESTONES

Milestone	Planned date*
Protocol submission to EMA	04 Feb 2020
Protocol approval by EMA	
Registration of the EU PAS register	
Start of data collection (first semester year 1)	
End of data collection (first semester year 1)	
Interim report 1-explanatory features of dataset (first semester year 1)	
Start of data collection (second semester year 1)	
End of data collection (second semester year 1)	
Interim report 2-explanatory features of dataset (second semester year 1)	
Start of data collection (first semester year 2)	
End of data collection (first semester year 2)	
Interim report 3–explanatory features of dataset (first semester year 2)	
Start of data collection (second semester year 2)	
End of data collection (second semester year 2)	
Interim report 4–explanatory features of dataset (second semester year 2)	
Start of data collection (year 3)	
End of data collection (year 3)	
Interim report 5–explanatory features of dataset	
Start of data collection (year 4)	
End of data collection (year 4)	
Interim report 6–explanatory features of dataset	
Start of data collection (year 5)	
End of data collection (year 5)	
Interim report 7–explanatory features of dataset	
Start of data collection (year 6)	
End of data collection (year 6)	
Final report	

EMA=European Medicines Agency; EU=European Union; PAS=post-authorization study
* The dates for the milestones will be included after the protocol is approved by EMA.

7 RATIONALE AND BACKGROUND

7.1 Product

Romosozumab (Anatomical Therapeutic Chemical [ATC] code: M05BX06) is a bone-forming monoclonal antibody that binds to and inhibits sclerostin, with a dual effect of increasing bone formation and decreasing bone resorption (McClung et al, 2014; Padhi et al, 2011).

In postmenopausal women with OP and previous fragility fracture/s, romosozumab followed by ALN showed superior efficacy to standard of care ALN alone in reducing fracture risk (pivotal study 20110142 [ARCH]). Romosozumab was also superior to placebo in reducing fracture risk in postmenopausal women with OP (pivotal study 20070337 [FRAME]).

Romosozumab is indicated in the form of monthly injections for 12 months for the treatment of severe OP in postmenopausal women at high risk of fracture with the following contraindications: history of MI or stroke, hypersensitivity to the active substance (s) or to any of the excipients, and hypocalcaemia.

Serious CV events of MI and stroke were determined as an identified risk (by European Medicines Agency [EMA] and is included in the EU-RMP) associated with romosozumab treatment, based on an increased incidence of adjudicated CV events recorded in the active-comparator study 20110142 (ARCH). In this study, 2.0% (41 subjects) of romosozumab-treated subjects compared with 1.1% (22 subjects) of ALN-treated subjects experienced a major adverse cardiac event (MACE) (MACE-1: composite of CV death, MI, and stroke) in the first 12 months of the study. No imbalance in CV events was observed in the larger placebo-controlled study 20070337 (FRAME), where the incidence of MACE-1 was 0.8% in both the romosozumab-treated (30 subjects) and placebo-treated (29 subjects) groups at 12 months.

Nonclinical studies did not provide any supporting evidence for a causal relationship between romosozumab and the imbalance in CV events observed in 1 of the pivotal studies (20110142 [ARCH]).

To ensure a favorable benefit-risk balance of romosozumab in clinical practice, pharmacovigilance (PV) measures and RMMs have been established. These include an EU RMM PASS to monitor the adherence to RMMs contained in the Summary of Product Characteristics (SmPC), including prescriptions of romosozumab to the indicated population ie, postmenopausal women with severe OP at high risk of fracture without a history of MI or stroke.

7.2 Regulatory action

This EU RMM PASS is part of a PASS program aimed at monitoring the safe use of romosozumab in the European population within the framework of a comprehensive RMP. In addition to the EU RMM PASS, the PASS program encompasses studies aimed at assessing the incidence and comparative risk of CV events of MI and stroke, and all-cause mortality (CV PASS) and serious infections (Serious Infections PASS), respectively.

7.3 Previous observational studies

This will be the first PASS which will be initiated to evaluate adherence to the CV RMMs for the use of romosozumab in routine clinical practice in Europe. Routine postmarketing PV data are being collected in parallel in other regions of the world, including US and Japan.

8 RESEARCH QUESTION AND OBJECTIVES

The overarching aim of this drug utilization PASS is to evaluate adherence to the CV RMMs for the use of romosozumab in Europe. To achieve this, utilization patterns and adherence to contraindications and target indication will be described amongst incident romosozumab users in routine clinical practice.

Specifically, the study objectives are:

1. To assess the prevalence and incidence of romosozumab use at the population level and the relative trends over time;
2. To characterize users of romosozumab and to evaluate compliance with the EU approved indication and contraindication (history of MI or stroke) as per the RMMs
3. To describe prevalence and incidence of use of other OP medications and to characterize users, in order to provide context.

9 RESEARCH METHODS

9.1 Study design

This will be a multi-national, multi-database prospective cohort study. The study will include the entire source population/s for population-level drug use estimates and new users of romosozumab or new users of other OP medications for the characterization of patient-level drug utilization.

9.2 Setting

Participants from 7 European countries, including North, South and Central Europe, will be included. Data from primary care, secondary care, health registers, prescription/dispensation registers and claims will be utilized.

The EU-ADR Alliance, an alliance of academic research center with expertise in pharmacoepidemiological research within the EU, will conduct this study. The EU-ADR Alliance was created to undertake PV studies and have worked on 7 drug safety projects, consolidating results from the datasets in the different countries. Data from the following 5 current EU-ADR Alliance member electronic healthcare databases will be obtained for this study: the Integrated Primary Care Information Project (IPCI) from the Netherlands, the Health Search Database (HSD) from Italy, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain, the data linked from the population-based administrative and health registries in Denmark, and CPRD from the UK. The

latter will be obtained through an existing license by the Marketing Authorization Holder (MAH).

Furthermore, with the aim of increasing the potential number of romosozumab users under study, and to maximize the representativeness of the study findings, 2 additional databases from Germany and France have been integrated into the network and will be accessed through an existing collaboration agreement. From Germany, GePaRD will provide access in collaboration with the Leibniz Institute for Preventions Research and Epidemiology (BIPS). From France, the French nationwide healthcare data system (SNDS) with linkage from the national outpatients claims database (Système National d`Information Inter-Règimes de l`Assurance Maladie [SNIIRAM]), the hospital discharge summaries database (Programme de médicalisation des systèmes d`information [PMSI]) and the death registry (Centre d`épidemiologie sur les causes médicales de décès [CEpiDC]) will provide access in collaboration with the Bordeaux PharmacoEpi research platform in pharmacoepidemiology.

9.2.1 Source population

All patients registered for at least 12 months, with 1 of the 7 participating databases during the study period, will be eligible and included for the population-level drug use estimation.

9.2.2 Study period

Since the marketing authorization of romosozumab was granted in the EU on 09 Dec 2019, the study period is expected to begin early in 2020. The study period will end with the most recent version of data that is available within each of the databases for the annual reports, with a maximum of 6 waves of data, corresponding to 6 years of data.

9.2.3 Study population

The study population for this study comprises:

Population-level drug utilization: The whole source adult population (aged 18 years or older) for each of the contributing databases will be used as the denominator for the proposed population-based drug utilization analyses.

Patient-level drug utilization: As for the patient-level drug utilization, patient characterization and unadjusted IR analyses, the following patients will be included:

1. All new users of romosozumab: registered patients for at least 1 year in 1 of the contributing databases who receives prescription/s or dispensation/s of romosozumab for the first time (ie, with no use of this same drug in the previous year) and are 18 years of age or older. The date of that first prescription/dispensation will be used as the index date for all analyses.
2. All new users of other OP medications: new users (with a 1-year washout and at least 1 year of data available in 1 of the contributing databases and starting therapy at 18 years of age or older) of other OP medications available in the market at the time of romosozumab market launch will be included. Further details about inclusion and exclusion are available in Section 9.2.4 and Section 9.2.5. The date of the first prescription for a given drug will be used as the index date. Six other OP treatment cohorts will be included and analyzed separately:

- ALN
- Other oral bisphosphonates (ibandronate or risedronate at doses indicated for OP treatment)
- iv bisphosphonates (zoledronate and ibandronate at doses indicated for OP treatment), where hospital therapy data are available
- SERMs (raloxifene, bazedoxifene, and lasofoxifene at doses indicated for OP treatment)
- Denosumab (at the dose indicated for OP treatment)
- Teriparatide

All drug utilization analyses will be conducted at the treatment episode level, where a patient can contribute multiple times if he/she switches OP therapies over time.

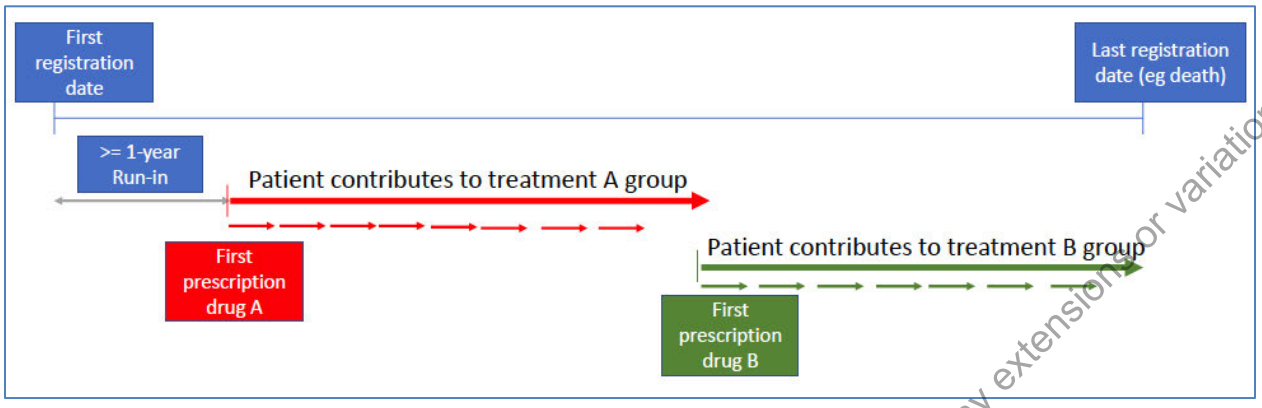
Before the analysis is undertaken for each report, the RMM label used in each country will be checked. Should any country deviate from the EU-wide RMM, including but not limited to SmPC and RMMs, this will be reported to the EMA and the impact of this change will be discussed in the report.

9.2.4 Inclusion criteria

Population-level drug utilization: All patients registered in the study databases in the study period and with at least 1 year of follow-up available since registration will be included in the population-level drug utilization analyses.

Patient-level drug utilization: New users of romosozumab, ALN, risedronate, ibandronate (both at doses indicated for OP treatment), raloxifene, bazedoxifene, lasofoxifene (at doses indicated for OP treatment), iv bisphosphonates (at doses indicated for OP treatment), denosumab (at the dose indicated for OP treatment), and teriparatide will be identified and included for patient-level drug utilization analyses. In order to identify new users, no prior use of the same study drug during the previous 12-month period will be allowed. Prescriptions/dispensations or claims for other study drugs during the Baseline Period will be allowed in order to identify patients previously treated patients. Patients may be included in different treatment cohorts if they switch treatment/s, and analyses will be performed at the treatment episode level. This is depicted in Figure 1.

Figure 1: Representation of patient eligibility and follow-up into different treatment cohorts



Note: "First prescription drug A" is the index date for a patient during exposure to drug A, and "First prescription drug B" is then the index date for the same patient when exposed to drug B.

The following inclusion criteria must be met:

- Adult women and men (18 years or older)
- At least 12 months of eligibility before the first index date in 1 of the included EU-ADR Alliance data sources and databases from France and Germany.
- No prior use of the same study drug during the previous 12-month Baseline Period (dispensations/claims for other study drugs during the Baseline Period will be allowed).

9.2.5 Exclusion criteria

No additional exclusion criteria apply.

9.2.6 Follow up

For each medication, patients will be followed from the date of first prescription (index date) until cessation of current treatment (including switching to another OP medication), death, end of enrollment in database, or end of current data collection.

9.3 Variables

9.3.1 Exposure

Cohorts of OP medication initiators will be identified and analyzed separately to include:

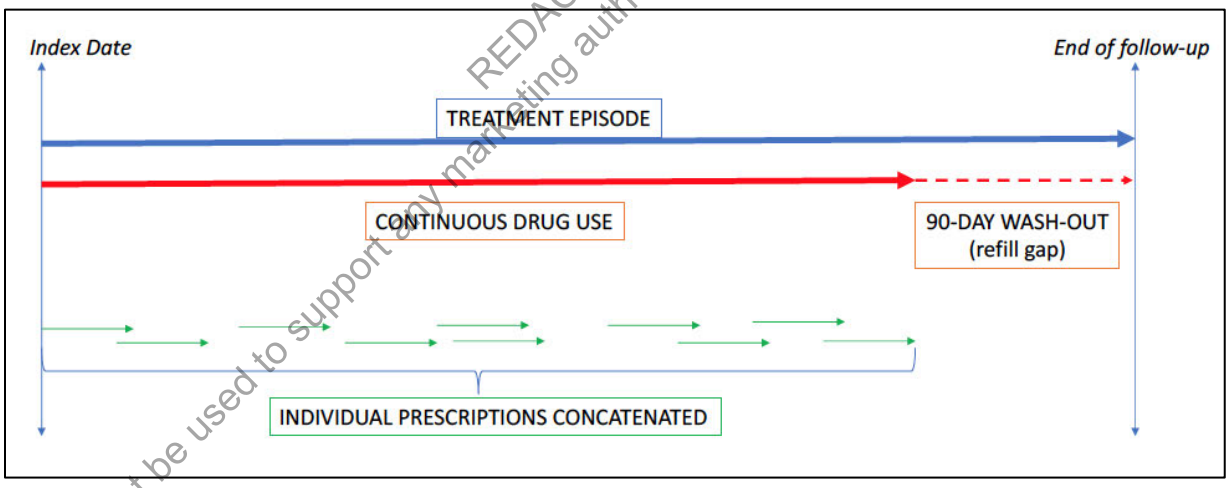
- Romosozumab
- ALN (ATC M05BA04)
- Other oral bisphosphonates (ibandronate [ATC M05BA06] or risedronate [ATC M05BA07]) at doses indicated for OP treatment
- Zoledronate (ATC M05BA08) or ibandronate [ATC M05BA06] at doses indicated for OP treatment

- SERMs (raloxifene [ATC G03XC01], bazedoxifene [ATC G03XC02], or lasofoxifene [ATC G03XC03]) at doses indicated for OP treatment
- Denosumab (ATC M05BX04) at the dose indicated for OP treatment
- Teriparatide (ATC H05AA02)

Exposure assessment

Exposure to a study drug will commence on the date of the first dispensation for the study drug (considering the group of drugs in the case of other oral bisphosphonates) in the pharmacy database or a record for an office-based administration of the study drug without any record of study drug use during the Baseline Period. The end of drug exposure will be defined as the date of the last prescription or dispensation or claim for the study drug plus the calculated number of exposure days provided in the last prescription or dispensation based on the dispensed strength, package size and defined daily dose (DDD). In line with observational analyses focused on persistence and compliance with OP medications, treatment gaps of ≤3 months between drug utilization records for the study drug will be allowed (see Figure 2). A refill gap exceeding 3 months will be considered as a definition of therapy cessation/discontinuation. Drug discontinuation will therefore be defined as the last date of exposure to a study drug plus an additional 3 months (in line with the treatment gap). Sensitivity analyses using 1- and 6-month gaps will be used. Stockpiling will be dismissed.

Figure 2: Construction of treatment episode/s for patient-level drug utilization and incidence rate/s



Drug switching will be considered if a patient switches from 1 study drug to another OP medication, or when a concomitant second OP medication is added. Treatment switches will be handled as follows:

- A switch to another OP medication will be considered a drug discontinuation of the first drug unless an overlap of 3 months or more is seen. A switch from 1 oral bisphosphonate to another bisphosphonate in the "other bisphosphonate" drug cohort will not be considered as drug switching or discontinuation.Any subsequent claim associated with the index/same drug after drug discontinuation (ie, after no prescription/dispensation for the prespecified refill

gap) or switching will be dismissed, as only the first treatment episode with a given drug will be considered.

After study drug discontinuation, a patient may initiate another OP medication. All analyses will be conducted at the treatment episode level as demonstrated in Figure 2 above. The same patient will therefore be eligible to contribute to different drug cohorts if they switch treatments during the study period.

9.3.2 Outcomes

9.3.2.1 Population-level measures of drug utilization

The following measures will be estimated using the whole source population/s from each of the contributing databases as a denominator.

For romosozumab and other OP medications:

- Monthly *prevalence of use* will be calculated for each OP drug separately as the point prevalence of use of a particular drug on day 15 of each calendar month, where the numerator will be all users of the drug, and the denominator will be all eligible in the source population and registered in the database on that same day (see note below).
- Monthly *incidence of use* will be calculated for each OP drug separately as the IR of use of a particular drug, where the numerator will be all new users of the drug (ie, with no use of this same drug in the previous year) in a given calendar month, and the denominator will be person-months of people available in the dataset on that given calendar month, who were not users of the specific drug at the beginning of that calendar month and no use of this same drug in the previous year) (see note below).

These estimates will be calculated for each of the contributing databases separately. Estimates will be provided overall (for the whole source population) and stratified by sex, age (5-year bands) and calendar year.

Note: For France, the denominators will be estimated using counts provided by IN-SEE (French annual demographic statistics) as access to the entire source data is not allowed.

9.3.2.2 Patient-level drug utilization measures

The following estimates will be reported for each of the 7 OP treatment cohorts:

- Overall duration of treatment/persistence: number of days from index date to discontinuation as defined above. Kaplan-Meier plots will be used to depict persistence over time.
- Proportion persistent at 6, 12, 18, and 24 months: number (n) and percentage (%) of patients who complete a treatment duration (as defined above) of 6, 12, 18, and 24 months, respectively, will be reported.
- Switching: number (n) and percentage (%) of patients who switch to another OP medication as listed above after 6, 12, 18, and 24 months of starting their index treatment will be reported. Sankey plots will be used to depict treatment switching patterns.

In addition, the following will be calculated only for romosozumab users:

- Prevalence of contraindications amongst new romosozumab users:
  - Initiation of romosozumab in men
  - History of MI in the year before romosozumab therapy initiation
  - History of MI at any time before romosozumab therapy initiation
  - History of stroke in the year before romosozumab therapy initiation
  - History of stroke at any time before romosozumab therapy initiation
  - History of MI or stroke in the year before romosozumab therapy initiation
  - History of MI or stroke at any time before romosozumab therapy initiation
- Prevalence of documented indication amongst new romosozumab users:
  - History of any fracture (except the face, skull and digits) in the year before romosozumab therapy initiation
  - History of major osteoporotic fracture (hip, spine, proximal humerus, or wrist/forearm) in the year before romosozumab therapy initiation
  - History of any fracture (except the face, skull and digits) at any time before romosozumab therapy initiation
  - History of major osteoporotic fracture (hip, spine, proximal humerus, or wrist/forearm) at any time before romosozumab therapy initiation

All these estimates will be calculated for each of the contributing databases separately. Estimates will be provided overall (for the whole source population) and stratified by sex (except for use in men), age (5-year bands) and calendar year.

9.3.2.3 Specific drug utilization measures for romosozumab users

The metrics below will focus on the romosozumab cohort only. Per the SmPC, a single complete course of treatment will include 12 doses of romosozumab administered at monthly intervals (using 2 subcutaneous injections to deliver each dose) for a total duration of 12 months plus allowed treatment gap:

- Compliance with romosozumab:
  - where compliance corresponds to the determination of the medication possession ratio (MPR). This measure refers to the quantity of medication that is in a patient's possession for consumption over an observed period of time. The consumed medication will be tracked within each database with the medication prescription record. The consumed medication data over 12 months will be contrasted with the recommended dose of 12 x 2 injections over the treatment course of romosozumab to calculate the MPR.
  - Number (n) and percentage (%) of patients who discontinuation before the recommended treatment duration (12 months)

All these estimates will be calculated for each of the contributing databases separately. Estimates will be provided overall (for the whole source population) and stratified by sex (except for use in men), age (5-year bands) and calendar year.

Patient characteristics

Baseline characteristics of all users of romosozumab and of other OP medications, as well as of romosozumab users in each of the contraindication and restriction of indication groups, will be described. Baseline characteristics will include the following:

- General characteristics:
  - Socio-demographics: age, sex, socio-economic status (where available)*
  - Country of residence or database
  - Number of previous general practitioner (GP)/hospital contact/s in the year before index date
  - Number of different ATC/British National Formulary codes prescribed in the year before index date
  - Charlson comorbidity index (most recent as recorded in the year before index date)
  - Body mass index (BMI)/obesity (most recent as recorded in the previous 5 years)*
  - Current smoking (most recent as recorded in the previous 5 years)*
  - Heavy alcohol drinking (most recent as recorded in the previous 5 years)*

*NOTE: only available for primary care electronic medical record (EMR) databases and/or for a subset of the population.

- Markers of disease severity (risk factors for OP/fractures):
  - History of recorded OP at any time before therapy initiation
  - History of previous fracture/s: site/s (hip, vertebral, major osteoporotic, other/s), number of fracture/s, and time from most recent to index date
  - History of rheumatoid arthritis at any time before therapy initiation
  - History of eating disorder/s (anorexia nervosa, bulimia) at any time before therapy initiation
  - Use of systemic glucocorticoids (ATC H02AB) in the year before index date
  - History of established CV disease
  - History of stroke
  - History of MI
  - History of coronary revascularization and other arterial revascularization procedures
  - History of peripheral arterial disease

- History of peripheral vascular disease
- History of hypercholesterolaemia
- History of hyperlipidaemia
- History of hypertension
- History of diabetes
- History of thromboembolic events
- History of chronic kidney disease
- Estimated renal function
- Charlson comorbidity index
- Behavior (this information is available only in EMR databases and usually in a subset of the population in the database)
  - Smoking
  - Alcohol
  - BMI
- Previous use of other OP medications (ATC M05B, ATC M05B, ATC G03XC01, ATC G03XC02, ATC G03XC03, ATC H05AA02) in the year prior to index date/: type, number of therapies, and DDDs prescribed
- Previous use of prescribed vitamin D supplements (ATC A11CC01, A11CC03, A11CC04, A11CC05, A11CC06, A11CC20, and A11CC55) in the year before index date
- Previous use of prescribed calcium supplements (ATC A12AA01, A12AA02, A12AA03, A12AA04, A12AA05, A12AA06, A12AA07, A12AA08, A12AA09, A12AA10, A12AA11, A12AA12, A12AA13, A12AA20, and A12AA30) in the year before index date.
- Previous use of prescribed calcium and vitamin D (concomitant) supplements (ATC A12AX) in the year before index date.
- History of recorded fall/s in the year before index date (if available)
- Bone mineral density T-score recorded in the year before index date (if available)

- Use of other medications in the year before index date:
  - Polypharmacy: number (n) and percentage (%) of patients with 5 or more different ATC prescribed or dispensed
  - Use of lipid-lowering agents (ATC C10)
  - Use of oral antidiabetic agents (ATC A10B)

- Use of antihypertensive drugs: alpha blockers (ATC C02CA), beta-blockers (ATC C07), angiotensin-converting enzyme inhibitors (ATC C09A/C09B), angiotensin II inhibitors (ATC C09C/C09D), calcium channel blockers (ATC C08C)
- Use of low-dose aspirin <150mg/day (ATC B01AC06) or clopidogrel (ATC B01AC04)
- Previous use of anticoagulants: vitamin K antagonists (ATC B01AA), heparins (ATC B01AB), direct thrombin inhibitors (ATC B01AE), direct factor Xa inhibitors (ATC B01AF)

9.4 Data sources

This study will be conducted using routinely collected data from different data sources that participate in the EU-ADR Alliance, with the addition of databases from the UK (CPRD GOLD), Germany (GePaRD), and France (SNDS).

These databases will provide representative clinical information as collected in routine clinical practice in different European healthcare settings.

The proposed databases have been selected based on their geographic location, the availability of longitudinal population-based data on drug utilization, and their experience in previous multi-database studies on both drug utilization and safety.

Seven countries from different European areas are included, in order to provide heterogeneous and representative data on the safety of romosozumab, as well as ensuring sufficient statistical power for the study.

All analyses will be conducted in a federated manner using the tools previously validated and tested in a number of PASS completed by the EU-ADR Alliance.

All of the chosen databases comply with EU guidelines on the use of medical data for medical research and have been validated for pharmacoepidemiological research (Cazzola et al, 2011; Vlug et al, 1999). All of the contributing data sources are listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database (ENCePP Resources Database, 2019).

The confirmed participating databases will be HSD (Italy), IPCI (Netherlands), the nationwide linked Danish registries (Denmark), and SIDIAP (Spain), all of which form part of the stable structure of the EU-ADR Alliance, and additionally, CPRD (UK), GePaRD (Germany) and SNDS (France). Table 1 provides an overview of key elements of these databases. The total number of persons actively registered in the source population of these 7 databases together was in excess of 95 million in 2016.

Table 1: Overview of the considered databases

Country	Netherlands	UK	Denmark	Italy	Spain	Germany	France
Name of the database	IPCI	CPRD	Nationwide linked Danish registries	HSD-Thales	SIDIAP	GePaRD	SNDS
Type of database	MR	MR	ADM	MR	MR	ADM	ADM
# active patients (millions)	1.2	5	5.8	1.5	5.8	25	66
Age categories	All	All	All	>15 years	>15 years	All	All
Date in	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes	Yes	No
Date death	Yes	Yes	Yes	Yes	Yes	Yes	Yes (mm/yyyy)
Prescriptions							
Outpatient treatment/s	Yes (specialist incomplete)	Yes (specialist incomplete)	Yes	Yes (specialist incomplete)	Yes (specialist incomplete)	Yes	Yes (dates of prescription and dispensing)
Coding of drugs	ATC	BNF/Multilex	ATC	ATC	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes (incomplete)	Yes	No	Number of units and dosage dispensed
Outcomes							
Hospitalizations	Yes	Yes (60%)	Yes	Yes	Yes (30%)	Yes	Yes
Outpatient diagnoses	Yes	Yes	Yes (hospital outpatient)	Yes	Yes	Yes (hospital outpatient)	No

Table 1: Overview of the considered databases

Country	Netherlands	UK	Denmark	Italy	Spain	Germany	France
Coding of disease	ICPC	READ	ICD-10	ICD-9-CM	ICD-10 (ICD-9 for hospital diagnoses)	ICD-10_GM	ICD-10
Cause of death	No	From linked ONS death data (60%)	Yes (lag 2 years)	No	No	No	Yes, with a 2-to 4-year lag (only for 2013-2015 at present)

ADM=administrative; ATC=Anatomical Therapeutic Chemical; BNF=British National Formulary; CM=clinical modification; CPRD=Clinical Practice Research Datalink; GePaRD=German Pharmacoepidemiological Research Database; GM=German modification; HSD=Health Search Database; ICD=International Classification of Diseases; ICD-10=ICD, revision 10; ICD-9=ICD, revision 9; ICPC=International Classification of Primary Care; IPCI=Integrated Primary Care Information Project; MR=medical records; ONS=Office for National Statistics; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; SNDS=Système National Des Données de Santé

IPCI DATABASE-NETHERLANDS

In 1992, the IPCI was started by the Department of Medical Informatics of the Erasmus University Medical Centre. The IPCI is a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs throughout the Netherlands, who voluntarily chose to supply data to the database. Collaborating practices are located throughout the Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and gender. In the Netherlands, all citizens are registered with a GP practice, which forms the point of care and acts as a gatekeeper in a 2-way exchange of information with secondary care. The medical records of each patient can therefore be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care.

The IPCI database is representative of the Dutch population regarding age and gender (Voordouw et al, 2004).

The database contains information on about 2.5 million patients. This is the cumulative number of patients who have ever been part of the dynamic cohort of registered patients. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses but diagnoses and complaints can also be entered as free text. Prescription data such as product name, quantity prescribed, dosage regimen, strength and indication are entered into the computer (Vlug et al, 1999). The National Database of Drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the ATC classification scheme recommended by the World Health Organization (WHO, 2019). Approval needs to be obtained for each study from the governance board.

HSD - ITALY

The Italian partner for the study will use the HSD, a longitudinal observational database that is representative of the Italian general population. The HSD was established in 1998 by the Italian College of General Practitioners (Filippi et al, 2005). The HSD contains data from computer-based patient records from a selected group of GPs covering a total of 1.5 million patients located throughout Italy. These GPs voluntarily agreed to collect data for the database and attend specified training courses. The database includes information on the age, gender, and identification of the patient and GP registration information, which is linked to prescription information, clinical events and diagnoses, hospital admission, and causes of death. All diagnoses are coded according to International Classification of Diseases, revision 9, clinical modification. Drug names are coded according to the ATC classification system (WHO, 2019). To be included in the study, GPs must have provided data for at least 1 year and meet standard quality criteria pertaining to levels of coding, prevalence of well-known diseases, and mortality rates (Cricelli et al, 2003). The HSD has been used as a data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care (Cazzola et al, 2011). Approval for use of data is obtained from the Italian College of General Practitioners for each study.

NATIONWIDE LINKED DANISH REGISTRIES - DENMARK

The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to GPs and hospitals, and partial reimbursement for prescribed medications

(Schmidt et al, 2019). Accurate linkage of all registries at the individual level is possible in Denmark using the unique Central Personal Register (CPR) number assigned to each Danish citizen at birth and to residents upon immigration (Schmidt et al, 2014). Data available on these patients can be linked to all registries. Dispensing data, recorded in the Danish National Prescription Registry (Pottegård et al, 2017) comprise of dispensing data from community pharmacies and contains information on name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data can be linked to the Danish National Patient Registry, which comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures (Schmidt et al, 2015). These databases have been used in numerous studies and are proven valid for pharmacoepidemiological research. The study must be announced at the governance committee. All registries will be accessed on per-protocol basis at the servers of the data custodians: Danish Health Data Board or Statistics Denmark.

SIDIAP DATABASE - SPAIN

The GPs play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. The SIDIAP database comprises of EMRs of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.8 million patients (over 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices with 3414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in EMRs, comprehensive demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes.

Health professionals gather this information using the International Classification of Diseases, revision 10 (ICD-10) codes and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, BMI, tobacco and alcohol use, blood pressure measurements, and blood and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. Recent reports have shown the SIDIAP data to be useful for epidemiological research (García-Gil Mdel et al, 2011).

Studies performed using SIDIAP data require previous approval by both the Scientific and the Ethics Committee.

CPRD GOLD - UK

The UK patients' data will be sourced from CPRD.

The CPRD (former GPRD) comprises of computerized records of all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, medication prescription data (coded using Gemscript codes), clinical events (coded using READ codes), specialist referrals, hospital admissions and their major outcomes in a sample of UK

patients. The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration.

Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Patients with records showing ill-defined or non-continuous follow up, and missing or inconsistent registration information are excluded during this process. The CPRD aims to obtain data from the earliest possible data points meeting "Up to Standard" (corresponding to the date when data meet specified data entry and quality criteria in GP practices signed up to CPRD). After this date, the practice is considered to have recorded continuous data of sufficiently high quality for use in research.

Data are available for over 20 million patients, including over 5.2 million currently registered patients which is considered to be representative of the UK population.

GePaRD - GERMANY

The GePaRD consists of claims data from 4 German statutory health insurance providers covering approximately 25 million individuals throughout Germany. Cross-sectionally, GePaRD covers about 15 million individuals, which represents approximately 17% of the German population of 82 million inhabitants.

The GePaRD contains individual level information on demographic characteristics, hospitalizations (including admission diagnoses, main discharge diagnoses, and reason for discharge including death), outpatient physician visits, and outpatient drug dispensations for reimbursed products. While exact dates are provided for hospitalizations and outpatient drug dispensations, only the year and quarter are known for outpatient diagnoses. Drugs that are purchased over the counter are not contained in the database. With a few exceptions the same applies to medication administered in hospital. The acceptability of GePaRD for pharmacoepidemiological research has been assessed methodologically as well as by validation studies (Ohlmeier et al, 2016; Ohlmeier et al, 2015; Ohlmeier et al, 2014; Pigeot and Ahrens, 2008). Recently, GePaRD has been used for various types of pharmacoepidemiological studies including drug utilization studies and studies investigating the risks of drugs or vaccines (Schink et al, 2018; Schmedt et al, 2016a; Schmedt et al, 2016b; Schink et al, 2014).

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal (Social) Insurance Office and the Senator for Science, Health, and Consumer Protection in Bremen as the responsible authorities, approved the use of GePaRD data for this study. Informed consent for studies based on GePaRD is not required by law, and according to the Ethics Committee of the University of Bremen, these studies are exempt from IRB review.

SNDS DATABASE - FRANCE

The SNDS database is the French nationwide healthcare insurance system database with individual anonymous information on all reimbursed outpatient claims linked to the national PMSI and the national death registry, using a unique national pseudonymized identifier. It currently includes 98.8% of the French population, more than 66 million persons from birth (or immigration) to death (or emigration), even if a patient changes occupation or retires.

The SNDS contains individual pseudonymized information on the following (Bezin et al, 2017; Tuppin et al, 2010):

- General characteristics: gender, year of birth, affiliation scheme, area of residence; deprivation status (CMU-c);
- Date of death for those concerned and (very soon) cause of death;
- Long-term disease (LTD, or ALD in French, and associated ICD-10 codes) with starting and ending dates. The LTD is mainly concerned with costly chronic diseases. The LTD registration is obtained at the request of a patient's practitioner and validated by the health insurance system physician. Once registered, patients receive full (ie, 100%) reimbursement for expenditure related to the LTD. The LTD information is specific for the diagnosis (very low risk of false positives), but not sensitive because not all patients with the disease are registered and benefit from LTD;
- Outpatient reimbursed healthcare expenditures: visits, medical procedures, nursing acts, physiotherapy, medical images, laboratory tests, drugs, medical devices, transport, sick leave with prescriber and professional caregiver information (medical or paramedical specialty, private/public practice), dates (prescription and dispensing), associated costs, and codes (but not the medical indication nor result);
- Hospital discharge summaries from the PMSI: ICD-10 diagnosis codes (primary, linked and associated diagnosis) for all private and public medical, obstetric and surgery hospitalizations, with the date and duration of hospitalization, medical procedures, and cost coding system, as well as most of the new costly drugs. The hospital discharge summary includes each department summary (eg, intensive care, then cardiology, then surgery). Primary diagnosis is the health problem that motivated the admission to the hospital. This is determined at hospital discharge. For patients hospitalized successively in several medical units, the primary diagnosis of the hospitalization, as well as all medical unit primary diagnoses, are generally taken into account to define the occurrence of an outcome in a pharmacoepidemiology study. A linked diagnosis can exist only if the primary diagnosis is a care procedure with a code Z of the ICD-10 classification (eg, chemotherapy session) for a chronic or LTD. It indicates the pathology at the origin of the care procedure.
- Nonhospital data are updated every month and hospital discharge summaries yearly at end of third quarter (Q3) for the previous year. Access to SNDS is regulated and needs approval from the National Institute of Health Data (Institut National Des Données de Santé [INDS]) and French data protection commission (Commission Nationale de l'Informatique et des Libertés [CNIL]).

Timing of data updates for the participating data sources

Different data sources update their data at different times of the year, with some datasets updating the information more frequently than others. To explain why data will be collected only between Apr and Jun, Table 2 shows how frequently and at what time of the year each data source is updated.

Table 2: Overview of the timing of data updates from participating data sources

Data source (Country)	Periodicity of updates	Time of the year when updates are released	Data availability for each update
SIDIAP (ES)	Yearly	Apr-May	End (31 Dec) of previous calendar year
IPCI (NL)	Yearly (twice is possible)	Apr-May	Variable as GPs provide not all at same time
CPRD (UK)	Monthly (linkage irregularly)	Every month	Variable as GPs provide not all at same time
HSD (IT)	Every 6 months	Jun and Dec	End of previous calendar year (in Jun); up to Jun in Dec
Nationwide linked Danish registries (DK)	Yearly	May	End (31 Dec) the previous year
SNDS (FR)	Monthly (outpatient data)	Outpatient data: every month with a 6-month lag to be 98% complete in the database, and 2 years to be 100% complete.	Outpatient data: until month M-6
	Yearly (inpatient data)	Inpatient data: year N-1 loaded in Sep-Oct of year N	Inpatient data: all outpatient stays ended year N-1
GePaRD (DE)	Yearly	Q2/Q3	31 Dec of the second-to-last year (eg, 2017 date are available in Q3 2019)

CPRD=Clinical Practice Research Datalink; DE=Germany; DK=Denmark; ES=Spain; FR=France; GePaRD=German Pharmacopidemiological Research Database; GP=general practitioner; HSD=Health Search Database; IPCI=Integrated Primary Care Information Project; IT=Italy; M=month; NL=Netherlands; Q=quarter; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; SNDS=Système National Des Données de Santé

Note: Any changes to prescribing practice reflected in the databases may affect the results regarding bisphosphonates.

9.5 Study size

In order to provide robust estimates, the projected precision based on expected prevalence of CV contraindications of interest (MI/stroke) for this study according to the patient population size was assessed. Hypothetical levels of incidence and prevalence of the considered patient groups (compliance to contraindication and restriction of indication) and the associated precision based on different sample size levels are presented in Table 3. It was concluded that a total of 1,000 romosozumab users will provide sufficient precision for the estimation of the prevalence of CV contraindications (MI or stroke) even in scenarios with low prevalence of <0.5%. Obviously, precision will improve in scenarios with higher prevalence of contraindications, but these are not expected in the current study and based on previous experience with CV contraindications for other OP medications (Berencsi et al, 2019).

Table 3: Overview of scenarios of prevalence levels and associated accuracy

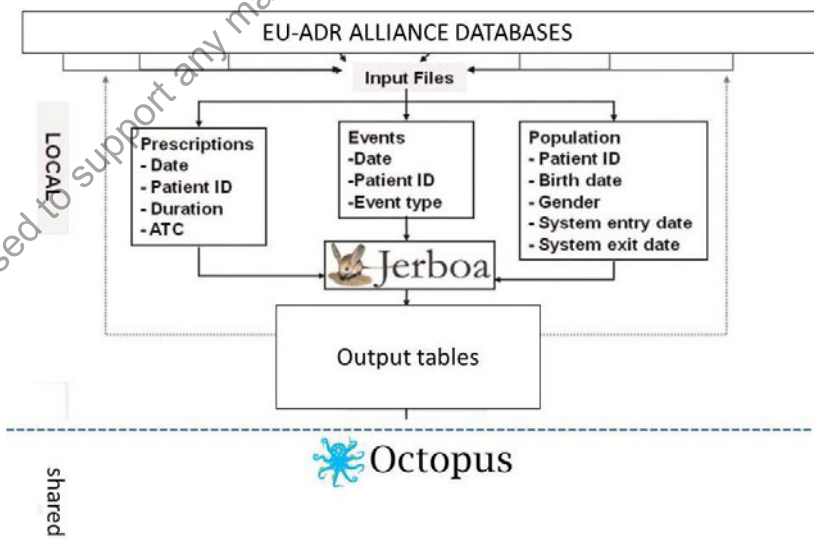
Sample size (N)		Estimated prevalence of MI/stroke					
		0.20%	**0.50%**	**1%**	**2%**	**5%**	**10%**
1000	Precision	0.28%	0.44%	0.62%	0.87%	1.35%	1.86%
	95% CI	0 to 0.48%	0.06% to 0.94%	0.38% to 1.62%	1.13% to 2.87%	3.65% to 6.35%	8.14% to 11.86%
2000	Precision	0.20%	0.31%	0.44%	0.61%	0.96%	1.31%
	95% CI	0% to 0.4%	0.19% to 0.81%	0.56% to 1.44%	1.39% to 2.61%	4.04% to 5.96%	8.69% to 11.31%
3000	Precision	0.16%	0.25%	0.36%	0.50%	0.78%	1.07%
	95% CI	0.04% to 0.36%	0.25% to 0.75%	0.64% to 1.36%	1.50% to 2.50%	4.22% to 5.78%	8.93% to 11.07%
4000	Precision	0.14%	0.22%	0.31%	0.43%	0.68%	0.93%
	95% CI	0.06% to 0.34%	0.28% to 0.72%	0.69% to 1.31%	1.57% to 2.43%	4.32% to 5.68%	9.07% to 10.93%

CI=confidence interval; MI=myocardial infarction

9.6 Data management

The EU-ADR Alliance works in a federated manner: data extraction and elaboration are done locally, and pooling of aggregated data is done on a remote research environment (RRE) (see Figure 3 for overview).

Figure 3: Model for data sharing and elaboration



ATC=Anatomical Therapeutic Chemical; ID=identifier

Due to the different database characteristics and coding schemes, it is not possible to use 1 single data extraction algorithm for all the databases. To reconcile differences across terminologies, a shared semantic foundation will be built for the definition of events under study using the recently developed CodeMappe. A multi-step and iterative process for the harmonization of event data will be set up.

The sequential steps of this process are briefly described below:

All events/outcomes have been ascertained using a list of agreed ICD (Denmark, France, Germany, Italy, and Spain), ICPC (Netherlands) and READ (UK) codes. These will be mapped to additional data sources from Germany and France and their respective terminologies.

The proposed lists of codes have been previously created and were validated for a previous study [EUPASS9117] following a number of steps:

1. Clinical definition;
2. Preliminary list of concept identifiers using Unified Medical Language System® (UMLS®) Metathesaurus Browser;
3. Addition of codes found after literature review of validated lists of codes for each of the study outcomes in each of the databases; and
4. Consensus with academic partners involved in the management and analysis of each of the data sources. As coding might change over time, relevant codes might be updated during the course of the project. Harmonization of these code lists will take place between databases by comparison of population-based age and sex specific IRs, according to standard quality assurance procedures in the EU-ADR Alliance (see below).

The sets of codes proposed based on these principles and used in previous studies will be further discussed with each of the academic partners and mapped to the newly incorporated data sources (Germany and France) during the first months of the study and before data extraction.

9.6.1 Identification of UMLS concepts

A UMLS concept is identified by a Concept Unique Identifier (CUI) and describes a single medical notion that can be expressed using different synonyms (terms). For each event, a medical definition will be created and, based on such a definition, relevant UMLS concepts are identified and projected into the database-specific terminologies. In addition, for those databases where free text is available, the labels of the codes are considered for free text search of the events.

9.6.2 Definition of data extraction algorithm

Based on the relevant diagnostic codes and key words (for free text search), a data extraction algorithm will be constructed for each event based on the consensus of the data providers. This data extraction algorithm will then be implemented by all databases.

9.6.3 Event data extraction

Subsequently, each database extracts data locally and transforms them into a simple common data model, ie, standardized patient, drug, and event files linkable via a patient unique identifier.

9.6.3.1 Benchmarking of incidence rates of events

For each endpoint and covariate, database-specific IRs will be benchmarked using Jerboa©; scripts will be generated by Erasmus MC. The observed IRs are compared with IRs estimated from previous database studies and literature. Outliers are identified and further investigated in an iterative manner.

This multi-step process has been used successfully in several other European multi-database projects. It maximizes the involvement of the data providers in the study by utilizing their knowledge on the characteristics and the process underlying the data collection.

After completion of harmonization, output tables for calculation and analysis of study endpoints will be created by the local data processors using the following steps (see Figure 4).

Figure 4: Process to be followed by local data processors

9.6.4 Data elaboration

A standardized Jerboa© script and instructions will be created by Erasmus MC to create the study-specific output tables. This will be developed in Jerboa (JAVA) by Erasmus MC and double-coded independently in SAS (version 9.4) by Aarhus. Either of these 2 versions will be used to "curate" the extracted data in the different databases.

9.6.5 Missing data

Since the underlying data represent attended medical care, it is assumed that absence of information of clinical events means absence of that condition. Lack of information on smoking, and alcohol use may occur, but this is unlikely differential. These will be binarized as "current smoker" or "heavy alcohol drinker" where data available suggests this in the year before index

date, and assume participants are not smokers or heavy drinkers otherwise. This will help harmonize with hospital EMRs/administrative databases where no measurement of smoking/drinking is available.

9.6.6 Data sharing

A study-specific folder on the central Octopus RRE will be used to analyze the output provided by Jerboa©. These output files will contain only anonymized de-identified data that will be shared in the RRE where members will have a secure and restricted access and where data will be analyzed. SAS, version 9.4, will be used for post-processing of data. Small cell counts will be masked as required by local regulations.

The French and Danish data cannot be shared in the RRE and will therefore be analyzed locally after transformation using Jerboa© and/or the equivalent (double-coded) SAS script. Findings will then be pooled in a meta-analysis.

9.7 Data analysis

The main statistics are described below and will be detailed further in the corresponding statistical analysis plan prepared after approval of the protocol.

Numerous previous studies conducted by the EU-ADR Alliance have demonstrated the feasibility and robustness of the proposed multi-database multinational real-world comparative safety approach (EU-ADR Alliance, 2017). All analyses will be double-coded in 2 different statistical packages by 2 different statisticians at Oxford before sharing analytical programs with the different partners for analysis.

9.7.1 Statistical elements

Categorical data will be presented as counts (n) and proportions (%) with 95% confidence intervals (CIs). The 95% CIs will be calculated using either the normal or Poisson distribution.

Continuous data will be presented as number of observations (n), number of patients with missing information, means and standard deviations (SDs) (where data is normally distributed) and medians and inter-quartile ranges (where data is skewed).

Analyses will be undertaken for the overall eligible population and stratified by gender and presence/absence of contraindications, where applicable.

9.7.1.1 Drug utilization and characterization of drug users

First, population-level measures of drug utilization will be estimated for each of the study drugs separately. Monthly prevalence/incidence of use overall and after stratification will be estimated, and 95% CIs estimated assuming a Poisson distribution. Secular trends/graphs will be plotted, where x axis is calendar month/year, and y axis is monthly prevalence/incidence of use of each of the study drugs.

For patient-level drug utilization patterns, duration of treatment will be reported as median (inter-quartile range) and persistence, switching and reinitiation will be reported as numbers and percentages (n [%]) of each of the drug cohorts separately. Kaplan-Meier plots will be used to depict persistence, whilst Sankey graphs will be plotted to illustrate treatment patterns/switching over time.

Characteristics of the different cohorts will be described for all potential covariates included in Section 9.3 using quantitative measures (mean [SD], median [inter-quartile range]) or n (%) for each of the individual features.

Meta-analysis

The pooled estimates of the IR for the databases will be calculated using the random or fixed effects model depending on heterogeneity detected using an I^2 threshold of >40%.

9.8 Quality control

This study has been designed and shall be implemented and reported in accordance with the Guidelines for good pharmacoepidemiology practices of the International Society for Pharmacoepidemiology (ISPE, 2015), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al, 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a "European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the "ENCePP Code of Conduct" (2018).

All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement.

STATA version 15.1 (StataCorp, College Station, Texas, USA) and R (version 3.2.3, the R Foundation for Statistical Computing) will be used for statistical analysis.

9.9 Limitations of the research methods

This study is non-interventional and as such has several important limitations.

Selection bias

Selection bias is not an issue in this study since the study is based on electronic health care records and does not require active consent of participants. Therefore, lack of participation is not an issue. Selection bias might however arise if data are missing for some confounders (eg, smoking or BMI) if the analyses are limited to a complete case. This will be avoided by using methodologies to include all participants regardless of the availability of information on particular confounders.

Information bias

Information bias may occur by not measuring correctly exposure, outcomes, or covariates.

With regards to exposure, misclassification may occur due to the patient not fulfilling the prescription (primary nonadherence) or in relation with noncompliance. Hence, an overestimate of utilization of romosozumab and other OP medications can happen, which would potentially lead to non-differential misclassification.

In parallel, misspecification of the risk window based on the construction of treatment episodes could lead to information bias. The effect of such potential misspecification will be addressed in sensitivity analyses where different refill gaps (30 vs 180 days) will be used to define treatment episode duration.

Furthermore, direct information about the indication for treatment is not available in all databases. Hence, a drug may appear to be "off label" when it is in fact being used on label but not adequately documented in the utilized data source.

As the study is based on coded information recorded by healthcare providers, incorrect coding is a source of information bias.

9.10 Other aspects

Not applicable

10 PROTECTION OF HUMAN SUBJECTS

This PASS is a non-interventional (observational) study in compliance with the definition of non-interventional study provided in the 2017 Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – post-authorisation safety studies, revision 3 (EMA/813938/2011, Rev 3, 2017) and in the ICH guideline of Pharmacovigilance Planning (ICH, 2004)

This PASS will use secondary data collection and does not pose any risks for patients.

For this study, participants from 7 different European member states will process individual data as collected in national electronic health record databases in compliance with all applicable national and European regulation as well as with ethical and regulatory issues including those on privacy.

All of the databases used in this study are already used for pharmacoepidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable data with less information that will be pooled across databases.

The output files will be stored in a central RRE held by Erasmus MC. These output files do not contain any data that allow identification of patients included in the study. In fact, each record is completely anonymous and does not contain any identifier key. Starting from this, the RRE implements further security measures in order to ensure a high level of stored data protection, according with the article 34 of legislative decree 196/2003 and article 22 of Regulation (EC) 45/2001.

The PASS will be registered in the ENCePP EU Post-Authorization Study (PAS) Register.

In addition, a scientific advisory committee consisting of external experts will be constituted to guarantee scientific soundness of the study and also to follow-up on the progress and the appropriate conduct of the study. The members of the scientific advisory committee will be involved in review of the data and preparation of the reports (yearly and final).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

According to the most recent guidelines for good PV practice (EMA/813938/2011, Rev. 3) there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases), which consists of fully de-identified data. Therefore, it is not possible to assess the causality of individual cases.

There will be no reporting of adverse events/reactions for this study. The study outcomes will be provided in the study reports in aggregate tables.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim reports of descriptive statistics about the uptake and drug utilization will be generated monthly and reviewed. These monthly reports will be submitted once every 6 months to EMA for the first 2 years, followed by annual reports for an additional 4 years, up to a total of 6 years.

In addition, dissemination activities will be undertaken including articles in scientific journals and presentations at conferences. Publications will be developed according to UCB policies and authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines.

In order to allow national competent authorities to review the results and interpretations to be published in advance, the MAH will communicate with the Agency and the competent authorities of the Member States where the product is authorized, the final manuscript of the article within 2 weeks after first acceptance for publication.

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APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Appendix 1	28 Jan 2020	List of Stand-Alone Documents
2	Appendix 2	28 Jan 2020	ENCEPP Checklist for Study Protocols

APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

The final timelines will depend on the date of the protocol approval

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7 & 8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or sub-group to whom the study results are intended to be generalised)	☒	☐	☐	9.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.3
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.3
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.4 and 9.2.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.2.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.1
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6.5
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.3.1

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	10

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	5.5
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

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

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____