NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL (OP0004)

EUROPEAN NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY RELATED TO SERIOUS CARDIOVASCULAR EVENTS OF MYOCARDIAL INFARCTION AND STROKE, AND ALL-CAUSE MORTALITY FOR ROMOSOZUMAB BY THE EU-ADR ALLIANCE

Final Non-interventional PASS Protocol	15 November 2024

PASS INFORMATION

Title	European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke, and all-cause mortality for romosozumab by the EU-ADR Alliance
Protocol version identifier	4.0
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Medicinal product	Romosozumab (AMG 785; CDP7851)
Product reference	H0004465
Marketing authorization holder (MAH)	UCB Pharma S.A.
Joint PASS	Not applicable
Research question and objectives	The overarching objective of this study is to characterise the risk of serious cardiovascular (CV) events of myocardial infarction (MI) and stroke, and all-cause mortality, including CV death and arrhythmia associated with the use of romosozumab, in comparison with other available osteoporosis (OP) medications used in routine clinical practice in Europe
Countries of study	Denmark, Germany, Netherlands, Spain, and the UK
Authors	PPD

MARKETING AUTHORIZATION HOLDER

Marketing authorization holder (MAH)	UCB Pharma S.A. Allée de la Recherche 60 B-1070 Brussels Belgium
MAH contact person	PPD

DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully and understood this non-interventional PASS protocol and agree to conduct this non-interventional PASS as outlined in this protocol, as well as local laws and requirements.

I will ensure that all physicians and other staff members read and understand all aspects of this non-interventional PASS protocol.

I have received and have read all study-related information provided to me.

The objectives and content of this non-interventional PASS protocol as well as the results deriving from it will be treated confidentially and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB unless other agreements were made in a separate contract.

Investigator

_____	_____
Printed name	Date/signature

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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
BIPS	Leibniz Institute for Preventions Research and Epidemiology
BMI	body mass index
CI	confidence interval
CPR	Central Personal Register
CPRD	Clinical Practice Research Datalink
CUI	Concept Unique Identifier
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
GVP	Good Pharmacovigilance Practice
HbA1c	haemoglobin A1c
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, revision 9, clinical modification
ICD-10	International Classification of Diseases, revision 10
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICPC	International Classification of Primary Care
IPCI	Integrated Primary Care Information Project
IR	incidence rate
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
iv	intravenous

Abbreviation	Definition
LDL	low-density lipoprotein
LTD	long-term disease
MACE	major adverse cardiac event(s)
MAH	Marketing Authorization Holder
MI	myocardial infarction
NDR	National linked Danish Registries
OP	osteoporosis
ONS	Office for National Statistics
PAS	Post-Authorization Study
PASS	post-authorization safety study(ies)
PPV	positive predictive value
PV	pharmacovigilance
RMM	risk minimisation measure
RMP	Risk Management Plan
RRE	remote research environment
SCCS	self-controlled case series
SD	standard deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SmPC	Summary of Product Characteristics
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UMLS®	Unified Medical Language System®
WHO	World Health Organization

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Participating countries				
Data source CPRD (UK)	PPD			
Data source IPCI (NL)				
Data source SIDIAP (ES)				
Data source NDR (DK)				
Data source GePaRD (DE)				

Function	Name	Title	Affiliation	Address

CPRD=Clinical Practice Research Datalink; DE=Germany; DK=Denmark; ES=Spain; EU=European Union; GePaRD=German Pharmacoepidemiological Research Database; IPCI=Integrated Primary Care Information Project; MAH=Marketing Authorization Holder; NDR= National linked Danish Registries; NL=Netherlands; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària;

4 ABSTRACT

Title

European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke, and all-cause mortality 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 20070337 (FRAME) after 12 months of treatment. Serious CV events of MI and stroke are important identified risks in the European Union (EU)-Risk Management Plan (RMP). Cardiac arrhythmias have recently been classified as important potential risks in the EU-RMP, so an additional search strategy has been implemented to further analyses these events.

Research question and objectives

The overarching objective of this study is to characterise the risks of serious CV events of MI and stroke, all-cause mortality, including CV death, and arrhythmia associated with the use of romosozumab in comparison with other available osteoporosis (OP) medications used in routine clinical practice in Europe.

Specifically, the study will provide a further understanding of the following objectives:

- Objective 1: to assess the incidence rate (IR) of serious CV events (MI and stroke), and all-cause mortality, including CV death, and cardiac arrhythmia in romosozumab users in the indicated population in Europe as per the Summary of Product Characteristics (SmPC), and in cohorts of users of other OP medications who would also fulfil the indication/contraindications for romosozumab in Europe.
- Objective 2: to assess the IR of serious CV events (MI and stroke), all-cause mortality, including CV death, and cardiac arrhythmia in romosozumab users in the indicated population in Europe as per the SmPC and amongst users of other OP medications similar to the indicated population for romosozumab in Europe as per the SmPC, stratified by age, previous use of OP medications, and by prespecified key CV risk factors.

- Objective 3: to assess the comparative risk of CV events (MI and stroke), all-cause mortality, including CV death, and cardiac arrhythmia in romosozumab users in the indicated population in Europe as per the SmPC to users of ALN (active comparator) with similar baseline characteristics.

Study design

This will be a multi-national, multi-database cohort study of new users of romosozumab and new users of other OP medications. The study is expected to last 6 years (2020 to 2026).

Population

The study population comprises all women from the 6 participating databases from 5 European countries with severe OP who (i) are dispensed or prescribed an OP medication of interest for the first time (new user) during the study period, (ii) have been continuously registered in the data source for at least 12 months prior to the first recorded dispensing/prescription of the OP medication of interest, and (iii) are at least 50 years of age on the date of the first dispensing/prescription of the OP medication of interest. Women with a diagnosis of Paget's disease at any time before treatment initiation will be excluded.

New users will be followed for a maximum of 24 months from index therapy initiation (index date). Two follow-up periods will be included for the estimation of CV IRs: (i) an exposure-based follow-up period and (ii) a fixed (first exposure carried forward) follow-up period.

For the exposure-based analysis, patients will be followed until the first occurrence of the CV event of interest, discontinuation of the study drug of interest, switching or addition of any other OP medication (except calcium/vitamin D supplements), lost to follow-up, death, end of the 12 months after the index date (as per the romosozumab SmPC), or end of the study period/data extraction date. At the point of switching treatment, a patient is censored for that arm of the study in this analysis. For the fixed follow-up period, patients will be followed in their respective cohorts until the first occurrence of loss to follow-up, CV event of interest, death, or end of the study period. In this analysis, patients are followed for up to 24 months regardless of whether they stop treatment or switch to a new treatment.

Variables

The OP medications of interest include romosozumab and other OP medications, such as ALN (the primary active comparator), other oral bisphosphonates (ibandronate or risedronate at doses indicated for OP treatment), intravenous (iv) bisphosphonates (zoledronate at doses indicated for OP treatment), denosumab (at the dose indicated for OP treatment), and teriparatide.

Primary outcome is major adverse cardiac event(s) (MACE-2) (first occurrence of death [all-cause], MI, or stroke). Secondary outcomes are MI, stroke, death due to CV causes, all cause mortality, MACE-1 (first occurrence of death due to CV causes, MI or stroke), arrhythmia, and atrial fibrillation.

Values for other predefined covariates and potential confounding factors will be identified at cohort entry (index date) based on the patients' records in the previous 12 months (baseline period) and will include general patient characteristics, CV risk factors, markers of OP severity, and use of other medications, as described in detail in Section 9.3.3.

Data sources

This study will be conducted using routinely collected data from 3 different data sources that participate in the EU-ADR Alliance (the Integrated Primary Care Information Project [IPCI], the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP] and the National linked Danish Registries [NDR], from the Netherlands, Spain and Denmark, respectively), with the addition of databases from the UK (Clinical Practice Research Datalink [CPRD] GOLD and AURUM) and Germany (German Pharmacoepidemiological Research Database [GePaRD]). Patients from 5 European countries will provide heterogeneous and representative data on the safety of romosozumab, ensuring sufficient statistical power for the study.

Study size

Feasibility estimates demonstrate the capability of the consortium and the data sources to capture a sufficient sample of patients in each OP medication group. The number of romosozumab users and comparator users needed to obtain an alpha risk of 0.05 with 90% power in a 1:3 (romosozumab:comparator) matched cohort analysis for different scenarios of IR of CV events and hazard ratio (HR) were calculated. In the worst-case scenario of IRs of 2 per 100 person-years and a 2-fold relative increase in risk, 1,450 romosozumab users (and 4,350 users of the active comparator) would be required.

Data Analysis

The IRs of CV events of interest for each OP medication will be calculated for the 2 follow-up periods. IRs and 95% confidence intervals (CIs) of CV events of interest will be calculated for each study drug using a Poisson model.

For the fixed follow-up period, IRs of patients with CV events of interest will also be reported.

The CV event/s rates (as in objectives 1 and 2) for each study drug will be provided stratified by key CV risk factors. For objective 3 (the comparative safety analysis), the Cox regression model stratified by matched sets will be used to calculate HRs and 95% CIs for each safety endpoint (MI, stroke, MACE-1, arrhythmias, atrial fibrillation, and MACE-2).

Measures for reducing confounding by indication will be implemented, including propensity score matching as well as negative control outcome analyses, to identify unobserved confounding. If required, additional analyses will be conducted to assess the effects of potential biases related to insufficient control for confounding/channeling bias: (i) empirical calibration using negative control outcomes; (ii) self-controlled case series (SCCS), and (iii) instrumental variable analysis.

Milestones

Six-monthly reports will be submitted for the first 2 years, followed by annual reports for an additional 4 years, up to a total of 6 years. Upon the minimum sample size being reached, the comparative safety analysis will be conducted and reported as part of the next interim and/or final report/s. The study will continue to completion (6 years) even if the sample size is reached before the 6 years to allow variability and better precision in the estimates of IR and HR.

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.

The following amendments have been made to the protocol:

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
1	13 Aug 2021	4, 7.1, 8, 9.1, 9.3.2, 9.3.3, 9.7, Appendix 3, Appendix 4	Inclusion of cardiac arrhythmia and Atrial Fibrillation as outcomes and relevant covariates. Also changes to required validations in line with additional outcomes.	Cardiac arrhythmia was requested by the EMA due to spontaneous reports. The analysis team decided to also include atrial fibrillation on the basis of past work with cardiac arrhythmia since (a) it is the most common type of cardiac arrhythmia and (b) it is usually the most accurately recorded type of cardiac arrhythmia in routinely collected data.
		9.2.4	Amendment of the definition of ‘severe osteoporosis’ inclusion	We are proposing to modify this definition in line with the current

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
			criteria from “fracture in the prior year” to “fracture up to 24 months prior to start of treatment”.	literature (severe osteoporosis is often classified as fracture in the past 24 months) to increase sample size.
		9.4	Incorporation of CPRD AURUM to list of our databases.	Inclusion of this dataset increases the likelihood of early identification of Romosozumab users and increases the sample size from UK data.
		4, 9.2.2, 12	Removal of monthly data reports of Romosozumab and the need for monthly data collection from the project.	We have removed the monthly updates of data since monthly updates are only available for CPRD GOLD and CPRD AURUM
		Global	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol
2	April 2023	N/A	N/A	Not implemented
3	May 2024	6	Milestones	Milestones dates have been updated
		9.2.4	Removal of the inclusion criterion “Severe OP, as identified by the presence of 1 or more fractures of any skeletal sites except face/skull/digit/s fractures recorded in the 2 years prior to therapy initiation”	September 2023 OP0004 interim report showed that a significant number of patients who started romosozumab did not present with a fracture in the 2 years prior to therapy initiation. This criterion is removed to not hinder the objective of the study and improve

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
				the power of this comparative study to identify risk of serious cardiovascular events.
		9.7.1.5	Addition of a sensitivity analysis	A sensitivity analysis is now added to assess the risk of cardiovascular (CV) events among patients with at least one fracture in the 2 years prior to therapy initiation. CV incidence rates and comparative safety analyses will be performed in this subgroup population.
		Global	Removal of SNDS database from all the related sections of the protocol	Marketing launch of romosozumab in France is delayed. Therefore, we do not expect to see any romosozumab users in this database until the end of the study.
		Global	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with the remainder of the protocol.
4	November 2024	Global	Removal of HSD database from all the related sections of the protocol	Due to a change in Italy's data privacy law, there will be no further updates to the database.
		4, 9.2.5	Removal of the exclusion criteria of cancer diagnosis	The September 2024 OP0004 interim report had reported a large proportion of patients

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
				treated with romosozumab who had a history of cancer and these patients were therefore excluded per eligibility criteria in force. The EVENITY EU label does not preclude use of the product (or other OP drugs in scope of this study) in patients with a history of cancer and removing this criterion would increase the population size and improve generalizability.
		9.3.3, 9.7.1.5	Addition of a sensitivity analysis and a covariate, history of cancer	A sensitivity analysis is now added to assess the risk of CV events among patients without a history of cancer prior to therapy initiation to assess any potential bias. Incidence rates of CV events and comparative safety analyses will be performed in this subgroup population. The covariate, history of cancer (any except basal cell skin cancer), will be identified from patient records.
		Global	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol.

6 MILESTONES

Milestone	Planned date*
Protocol submission to EMA	04 Feb 2020
Protocol approval by EMA	17 Sep 2020
Registration of the EU PAS register	30 Sep 2020
Start of data collection (first semester year 1)	01 Dec 2020
End of data collection (first semester year 1)	29 Jan 2021
Interim report 1 - explanatory features of dataset (first semester year 1)	31 Mar 2021
Start of data collection (second semester year 1)	14 May 2021
End of data collection (second semester year 1)	09 Jul 2021
Interim report 2 - explanatory features of dataset (second semester year 1)	30 Sep 2021
Start of data collection (first semester year 2)	01 Dec 2021
End of data collection (first semester year 2)	31 Jan 2022
Interim report 3 – explanatory features of dataset (first semester year 2)	31 Mar 2022
Start of data collection (second semester year 2)	29 May 2022
End of data collection (second semester year 2)	10 Jun 2022
Interim report 4 – explanatory features of dataset (second semester year 2)	19 Sep 2022
Start of data collection (year 3)	14 April 2023
End of data collection (year 3)	19 May 2023
Interim report 5–explanatory features of dataset	19 Sep 2023
Start of data collection (year 4)	02 May 2024
End of data collection (year 4)	01 Jul 2024
Interim report 6 – explanatory features of dataset	30 Sep 2024
Start of data collection (year 5)	02 May 2025
End of data collection (year 5)	30 Jun 2025
Interim report 7 – explanatory features of dataset and comparative safety analysis	30 Sep 2025
Start of data collection (year 6)	CCI [redacted]
End of data collection (year 6)	
Final report - comparative safety analysis	

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

7 RATIONALE AND BACKGROUND

7.1 Product

Romosozumab (Anatomical Therapeutic Chemical [ATC] code: CCI) 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 osteoporosis (OP) and previous fragility fracture/s, romosozumab followed by alendronate (ALN) showed superior efficacy to the 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 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 important 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 MACE (MACE1: 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.

In the meta-analysis of the full patient set from studies 20070337 (FRAME) and 20110142 (ARCH), the incidence of MACE-1 at 12 months was 1.3% (71/5621) in romosozumab-treated subjects vs 0.9% (51/5590) in controls, corresponding to an HR of 1.39 (95% CI: 0.97 to 2.00).

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 characterise the risk for serious CV safety events of MI and stroke, and all-cause mortality, including CV death, associated with the use of romosozumab in clinical practice compared with other available OP medications, a European multi-national, multi-database, comparative post-authorization safety study (PASS) will be conducted.

Since the approval of this study, a disproportionality signal for cardiac arrythmia events for romosozumab was identified in the Eudravigilance database. The EMA PRAC requested a signal assessment. On review of the analysis, the PRAC endorsed that limited data prevented a proper assessment to establish a potential causal relationship, but having considered all available data about cardiac arrhythmia, the PRAC recommended (procedure no: EMA/PRAC/265359/2021) to add cardiac arrhythmia as a new important risk in the list of safety concerns for romosozumab and endorsed the proposal of addition of an analysis of cardiac arrhythmias in this study.

7.2 Regulatory action

This EU CV 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 CV PASS, the PASS program encompasses a study aimed at describing romosozumab use and adherence to the indication and contraindication (Risk Minimisation Measure [RMM] PASS) and a comparative study addressing serious infections (Serious Infections PASS).

7.3 Previous observational studies

This will be the first PASS to describe the risk of serious CV events (MI and stroke) and all-cause mortality, including CV death and cardiac arrhythmia, among romosozumab users in clinical practice in Europe. Routine post marketing pharmacovigilance (PV) data are being collected in parallel in other regions of the world, including the US and Japan.

8 RESEARCH QUESTION AND OBJECTIVES

The overarching objective of this study is to characterise the risk of serious CV events of MI and stroke, and all-cause mortality, including CV death, and cardiac arrhythmia associated with the use of romosozumab, in comparison with other available OP medications used in routine clinical practice in Europe.

Specifically, the study will provide a further understanding of the following objectives:

- Objective 1: To assess the IR of serious CV events (MI and stroke), all-cause mortality, including CV death, and cardiac arrhythmia in romosozumab users in the indicated population in Europe as per the Summary of Product Characteristics (SmPC), and in cohorts of users of other OP medications who would also fulfil the indication/contraindications for romosozumab in Europe.
- Objective 2: To assess the IR of serious CV events (MI and stroke), all-cause mortality, including CV death, and cardiac arrhythmia in romosozumab users in the indicated population in Europe as per the SmPC and amongst users of other OP medications similar to the indicated population for romosozumab in Europe as per the SmPC, stratified by age, previous use of OP medications, and by prespecified key CV risk factors.
- Objective 3: To assess the comparative risk of CV events (MI and stroke), all-cause mortality including CV death, and cardiac arrhythmia in romosozumab users in the indicated population in Europe as per the SmPC to users of ALN (active comparator) with similar baseline characteristics.

9 RESEARCH METHODS

9.1 Study design

This will be a multi-national, multi-database cohort study of new users of romosozumab and new users of other OP medications. This is a state-of-the-art study design in pharmacoepidemiology as endorsed by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidelines on methodological standards (EMA/95098/2010, Rev 7).

- Objectives 1 and 2, as outlined in Section 8, will report IRs of serious CV events (MI, and stroke), all-cause mortality, including CV death, and cardiac arrhythmia in romosozumab users adherent to the indicated population in the SmPC and in patients receiving other OP medications, who would also be eligible for romosozumab as per the approved SmPC.
- For objective 3, a parallel cohort design will be used, matched on propensity scores, to compare the risk of serious CV events (MI and stroke), and all-cause mortality including CV death, and cardiac arrhythmia in new users of romosozumab, adherent to the indicated population per the SmPC, to new users of ALN who would also be eligible for romosozumab per the approved SmPC. This approach has been proposed and is widely accepted to minimise confounding, including confounding by indication in observational drug safety research (Joffe and Rosenbaum, 1999), and endorsed by ENCePP methodological guidelines for pharmacoepidemiology (EMA/95098/2010, Rev 7).

9.2 Setting

Patients from 5 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 utilised.

The EU-ADR Alliance, an alliance of academic research centers with expertise in pharmacoepidemiological research within Europe, will conduct this study. The EU-ADR Alliance was created to undertake PV studies and has worked on 7 drug safety projects, consolidating results from the datasets in the different participating countries. Data from the following 3 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 Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain and the National linked Danish Registries (NDR) from Denmark,.

Furthermore, with the aim of increasing the potential number of romosozumab users under study, and to maximise the representativeness of the study findings, 3 additional databases from 2 European countries, the UK (the Clinical Practice Research Database [CPRD] GOLD and AURUM) and Germany (the German Pharmacoepidemiological Research Database [GePar D]), have been integrated into the network and will be accessed through an existing collaboration agreement. From the UK, CPRD will be obtained through an existing license by the Marketing Authorization Holder (MAH). From Germany, GePaRD will provide access in collaboration with the Leibniz Institute for Preventions Research and Epidemiology (BIPS).

9.2.1 Source population

All women registered in 1 of the contributing data sources for at least 12 months, and included in 1 of the 6 participating databases (from 5 European countries) during the study period, will be eligible as source population.

9.2.2 Study period

Since the marketing authorization of romosozumab was granted in the EU on 09th December 2019, the study period started in 2020. The study period will end with the most recent version of data that is available within each of the databases at the end of the study. The study is expected to end 6 years after the study start date. Six-monthly- reports will be submitted for the first 2 years, followed by annual reports for an additional 4 years, up to a total of 6 years. Upon the minimum sample size being reached as set out in Section 9.5 , the comparative safety analysis will be conducted and reported as part of the next interim and/or final report/s. If the minimum sample size is reached before the 6-year study period, the study will continue until the end of the sixth year to increase variability and precision in the estimates of IR and HR.

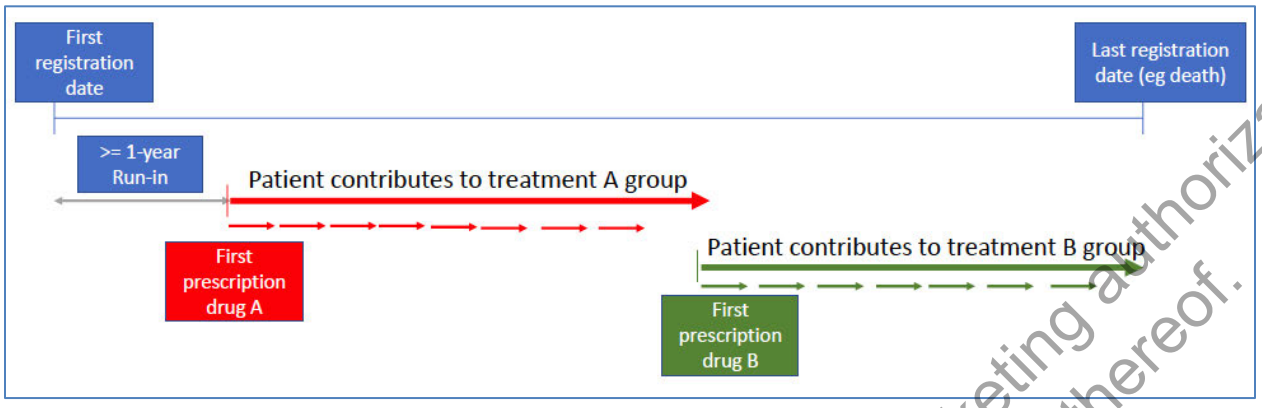
9.2.3 Study population

The study population represents the indicated population for romosozumab in Europe as per the SmPC and therefore comprises all women from the source population with severe OP who are first dispensed or prescribed an OP medication of interest (new user) during the study period. They will also have been continuously registered in the data source for at least 12 months prior to the first recorded dispensing/prescription of the OP medication of interest and are at least 50 years of age on the date of the first dispensing/prescription of the OP medication of interest.

OP medications of interest are romosozumab, ALN, other oral bisphosphonates (risedronate, ibandronate), intravenous bisphosphonate (zoledronate), denosumab, and teriparatide and will be identified through specific codes in dispensation or prescription records. To identify new users, no prior use of the same study drug during the previous 12-month baseline period will be allowed.

Study patients in each cohort will be followed from the date of the first dispensation or prescription of the index study drug during the study period, and for at least 1 year after registration in the data source. Analyses will be conducted using a time-varying exposure strategy, where patients who switch to another index treatment (i.e., to a different drug) over time contribute to the different index treatment arms/groups. This is represented 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.

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 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

New users of romosozumab, ALN, risedronate, ibandronate, zoledronate, denosumab, and teriparatide will be identified. To identify new users, no prior use of the same study drug (e.g., ALN) or the same drug class (e.g., bisphosphonates) during the previous 12-month baseline period will be allowed. Prescriptions/dispensations or claims for other study drugs, including other OP medications that are not of interest in the study, will be allowed during the baseline period in order to identify previously treated patients.

All the following inclusion criteria must be met for patients to enter the study:

- Women aged 50 years or older at the time of index therapy initiation (index date).
- At least 12 months of eligibility in the database before the index date with continuous enrolment.
- No use of the same drug during the 12 months prior to index date.

9.2.5 Exclusion criteria

The exclusion criteria are:

- Dispensation or prescription of more than 1 study drug starting on the same date (i.e., combination therapy).

- Patients with a diagnosis of Paget's disease at any time before the index date (i.e., treatment initiation).
- User/s of the same drug in the 12 months before the index date (or the same drug in combination with another therapy, e.g., alendronic acid and cholecalciferol (ATC [redacted]

As the study proposes to focus on the approved indicated population for romosozumab, patients not meeting the EU label criteria will be excluded from all analyses:

- Women below the age of 50 years.
- Patients meeting any of the study drug contraindications with respect to CV history (history of stroke or MI at any time before the index date).

9.2.6 Follow up

New users of OP medications will be followed for a maximum of 24 months from index date. Switching will be handled using a time-varying exposure strategy as depicted in Figure 1 above. Overlapping treatment with two or more OP medications (except calcium/vitamin D supplements) for >1 month will result in the censoring of the patient as reinitiation of a new treatment episode related to a previously prescribed treatment.

Two follow-up periods will be included for the estimation of CV IRs in each of the study drug cohorts separately; an exposure-based follow-up period and a fixed (first exposure carried forward) follow-up period.

For the exposure-based analysis, patients will be followed until the first occurrence of the CV event of interest, discontinuation of the study drug of interest, switching or addition of any other OP medication (except calcium/vitamin D supplements), loss to follow-up, death, end of the 12 months after index date (as per the romosozumab SmPC), or end of the study period/data extraction date. At the point of switching treatment, a patient is censored for that arm of the study in this analysis.

For the fixed follow-up period, patients will be followed in their respective cohorts until the first occurrence of loss to follow-up, CV event of interest, death, or end of the study period. This will be a maximum of 24 months following the index date, regardless of exposure status, cessation, addition of another OP medication, or switching. For the fixed follow-up analysis, the IR of CV events of interest will be reported at 6, 12, 18, and 24 months following the identified index dates for study drug initiation. In this analysis, patients are followed for up to 24 months regardless of whether they stop treatment or switch to a new treatment.

For the comparative safety analyses (objective 3), patient characteristics (i.e., confounders) will be reassessed, and propensity scores recalculated at the beginning of each treatment episode to minimise time-varying confounding. Each treatment episode will therefore be treated as a new exposure period.

9.3 Variables

9.3.1 Exposure

Exposure to OP medications in each data source will be assessed according to the ATC classification system or other country and data source-specific coding system used for recording.

Osteoporosis medications of interest include:

- Drug of interest
  - Romosozumab (ATC CCI
- Other OP medications, specifically:
  - Alendronate (ATC CCI (primary active comparator)
  - Other oral bisphosphonates (ibandronate [ATC CCI or risedronate [ATC CCI at the indicated doses for OP treatment.
  - iv bisphosphonates (zoledronate [ATC CCI at indicated doses for OP treatment.
  - Denosumab (ATC CCI at the indicated doses for OP treatment.
  - Teriparatide (ATC CCI

All of the OP medications listed above will be analysed for objectives 1 and 2 (see Section 8). Alendronate (ATC CCI will be the active comparator in the comparative safety analyses (objective 3).

Treatment duration

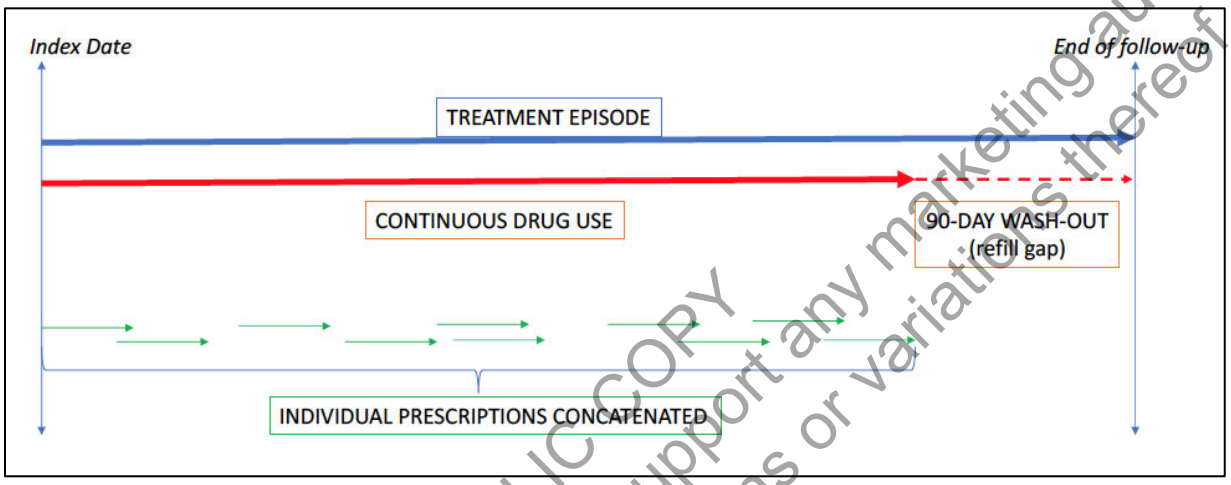
Exposure to a study drug will commence on the index date, i.e., the date of the first dispensation or prescription for the study drug or record for an office-based administration without any record of study drug use during the baseline period. The end of exposure will be defined as the date of the last prescription/dispensation/claim for the study drug plus the calculated number of exposure days provided in the last prescription/dispensation based on the dispensed strength, package size, and defined daily dose (DDD).

The recommended dose of romosozumab is 210mg (administered as 2 subcutaneous injections of 105mg each) once monthly for 12 months. Romosozumab 105mg solution for injection is delivered via a prefilled pen or prefilled syringe, each delivering 105mg of romosozumab in 1.17mL of solution (90mg/mL).

Based on the pharmacological profile of romosozumab, it is expected that the majority of romosozumab will be eliminated after 64 days, and the drug effect is diminished for a refill gap exceeding 3 months. Treatment gaps of ≤90 days between drug utilisation records for any of the study drugs will be allowed. This is consistent with previously published observational analyses focused on persistence with OP medications (Reyes et al, 2017).

Drug discontinuation will be defined as no dispensation/prescription during a 3-month period after the end of exposure, with the end of exposure estimated as the date of the last prescription plus the number of doses prescribed/dispensed in that last prescription. Stockpiling will not be considered (see Figure 2). Drug discontinuation will also be considered at the date when a concomitant second OP medication is added.

Figure 2: Construction of treatment episode/s for patient-level drug utilisation, incidence rate/s, and comparative safety study



Any subsequent claim associated with a study drug administration after the discontinuation of that same drug (for longer than the established refill gap) will be classified as treatment reinitiation and therefore excluded from all analyses.

Drug switching

Treatment switching will be handled as follows:

- For objectives 1 and 2, the analyses will be conducted at the treatment episode level as in Figure 2 above. For example, a user of denosumab who then switches to ALN will contribute first to the denosumab user, and then (after switching) to the ALN user cohort.
- For objective 3 (comparative safety), follow-up will start with the first prescription of either ALN or romosozumab, regardless of previous other OP drug use. For the exposure-based analysis, a switch from romosozumab or ALN to any other OP drug will result in censoring. In contrast, switching from ALN to romosozumab or from romosozumab to ALN will be handled as a time-varying exposure, just like in Objectives 1 and 2. For the fixed follow-up analysis, patients will be followed until first occurrence of loss to follow-up, CV event of interest, or death, 24 months after the start of treatment, or end of the study period regardless of switching treatment.

9.3.2 Outcomes

Primary outcome: MACE-2 (first occurrence of death [all cause including CV death], MI, or stroke)

Secondary outcomes:

- MI
- Stroke
- Death due to CV causes, i.e., MI or stroke
- All-cause mortality
- First occurrence of death (CV causes), MI, or stroke (MACE-1).
- Cardiac arrhythmias
- Atrial fibrillation

The definitions of the events listed above will be adapted based on previous work driven by the data partners and described below.

From the above-listed CV events, MACE-2 will be considered in the comparative analysis as the primary outcome while MI, stroke, MACE-1, cardiac arrhythmia, and atrial fibrillation will be considered as secondary outcomes.

Outcome identification and validation

The proposed code list/s or algorithm/s for the identification of MI, stroke, and arrhythmia are fully detailed in Appendix 3. The proposed study outcomes have been validated in the proposed databases previously as summarized in Table 1. Published work has shown very high validity of the coding of MI, with positive predictive values (PPVs) ranging from 75% to 100% within EU-ADR Alliance partners (Coloma et al, 2013). The lists developed and used in these validation studies performed as follows: International Classification of Diseases, revision 10 (ICD-10) codes (to be used by SIDIAP and NDR [Sundbøll et al, 2016]) had a PPV of 100%, while ICD, revision 9, clinical modification (ICD-9-CM) codes (used by NDR [Denmark]) had a PPV of 96.6% (95% CI: 93.2% to 99.9%); International Classification of Primary Care (ICPC) codes (used by IPCI [Netherlands]) had a PPV of 75% (95% CI: 67.4% to 82.6%). Database-specific validation studies have also been conducted, suggesting similar findings (Ramos et al, 2012; Madsen et al, 2003). Besides published estimates of the PPVs, the study will also consider the PPV assessment performed in the context of the other PASS by the data owners. As for GePaRD, MI has not yet been validated. A validation/plausibility assessment study will be completed during the course of the current PASS.

As for stroke, these diagnoses have been validated in Denmark, with a PPV ranging from 78% to 80% (Krarup et al, 2007). Furthermore, the study will build on the PPV assessment performed in

the context of other PASS by the data owners. Code lists used in these studies will be implemented in the proposed PASS. Stroke has been validated using "external rate" comparison methods in GePaRD (Schink et al, 2011).

Death is identified directly through linkage to administrative records or mortality registries in most of the proposed databases (CPRD through linkage to the Office of National Statistics (ONS); SIDIAP through linkage to the administrative database of national insurance; and NDR through the linkage to the Danish Mortality Register [Schmidt et al, 2014; Helweg-Larsen, 2011]), but not all (Table 1). Mortality has been previously validated in GePaRD and shown to be highly valid (PPV >97%) (Ohlmeier et al, 2016; Ohlmeier et al, 2015). All-cause mortality has been validated in IPCI (Netherlands) in the context of previous PASS.

As for cardiac arrhythmia, these diagnoses have been validated in Denmark with a PPV ranging from 80% to 95% [Sundbøll et al, 2016]; CPRD with a PPV of 93% [Hennessy et al, 2008]; IPCI with a PPV of 93%; and SIDIAP with a PPV ranging from 81.8% to 100%. Updated versions of code lists used in these studies will be implemented in the proposed PASS.

As for atrial fibrillation, these diagnoses have been validated in Denmark with a PPV ranging from 95% [Sundbøll et al, 2016]; CPRD with a PPV of 95% [Ruigómez et al, 2002]; IPCI with a PPV of 99% and SIDIAP with a PPV of 89%. Updated versions of code lists used in these studies will be implemented in the proposed PASS.

Table 1: Overview of outcome validation available with references

Database	Validity of MI	Validity of stroke	Validity of death	Validity of cardiac arrhythmia	Validity of atrial fibrillation
NDR (DK)	Yes (Sundbøll et al, 2016; Coloma et al, 2013)	Yes (Krarup et al, 2007; Frost and Vestergaard, 2004)	Yes (built in validation of civil registration system) (Madsen et al, 2003)	Yes (Sundbøll et al, 2016)	Yes (Sundbøll et al, 2016)
IPCI (NL)	Yes (Coloma et al, 2013; Preciosa et al, 2013)	Yes[a]	Yes[a]	Yes[a]	Yes[a]
SIDIAP (ES)	Yes (Ramos et al, 2012)	Yes[a]	Yes	Yes[a]	Yes[a]
GePaRD (DE)	No	No	Yes (Ohlmeier et al, 2016; Ohlmeier et al, 2015)	No	No

Table 1: Overview of outcome validation available with references

Database	Validity of MI	Validity of stroke	Validity of death	Validity of cardiac arrhythmia	Validity of atrial fibrillation
CPRD (UK)	Yes (Herrett et al, 2013)	Yes (Zhou et al, 2013)	Yes (specific death register)	Yes (Hennessy et al, 2008)	Yes (Ruigómez et al, 2002)

CPRD=Clinical Practice Research Datalink; DE=Germany; DK=Denmark; ES=Spain; GePaRD=German Pharmacoepidemiological Research Database; IPCI=Integrated Primary Care Information Project; MI=myocardial infarction; NDR= National linked Danish Registries; NL=Netherlands; PASS=post-authorization safety study(ies); SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

[a] Available from the data owner based on other PASS-related activity in partnership with EU-ADR Alliance.

Where validations have not been done or have shown a low PPV (<75%), the applicant in collaboration with the EU-ADR Alliance will conduct validation studies with a random sample of 250 cases per database. The validation studies will be implemented in parallel and will have no impact on the proposed study timelines. If this shows a low PPV (<75%), then all "potential" cases in the comparative safety analysis (objective 3) will be individually validated, and only confirmed ones will be included for analysis. This strategy has been implemented in similar PASS including EUPASS9117 (EU-ADR Alliance, 2017).

Details on the proposed validation studies are provided in Appendix 4.

9.3.3 Covariates (confounders and interaction terms)

9.3.3.1 Potential confounders

All covariates will be identified at cohort entry (index date) based on the patients' records in the previous 12 months (Baseline Period), and potentially included as covariates in the proposed propensity score models. Key confounders have been identified a priori based on previous literature and recent research and are listed below. The final list of confounders to be included in the propensity score equation will be identified during the estimation of propensity scores using a multivariable logistic regression equation (see details below).

The set of variables is grouped into 4 main categories: general patient characteristics, CV risk factors, markers of OP severity, and use of other medications. This list will be refined following

CCI

Preliminary findings from this work suggest great richness and granularity of recorded CV and fracture risk factors in the proposed databases: multivariable models result in the area under the curve receiver operator characteristics of about 70% for imminent fracture risk, and around 80% for short-term risk of MACE-2 amongst users of OP medications in clinical practice settings.

Beyond the lists below, the final detailed code lists will be provided once access to the study data is available.

It must be noted that different data sources will have access to different variables and/or proxies for each of the confounders listed below. It is expected that primary care records will have easier access and more granularity on clinical measurements (e.g., body mass index [BMI] or blood pressure), and laboratory values (e.g., haemoglobin A1c [HbA1c] or cholesterol levels in serum), whilst registers, hospital records, and claims data will have richer data on healthcare resource use (e.g., hospital contacts) and hospital treatments (e.g., surgical procedures or medical devices). Therefore, a combination of these will be used to capture as much detail as possible on each of the key risk factors below. Propensity scores will indeed be estimated for each data source separately to maximise the richness and granularity of each data source, and to capture as much information as possible on the key confounders prespecified below.

General characteristics (as measured at the index date or in the previous year):

- Socio-demographics: age, sex, socio-economic status (where available).
- Country of residence/database.
- Number of previous general practitioner (GP)/hospital contact/s.
- Number of ATC/British National Formulary codes (of any drug) prescribed.
- Charlson comorbidity index (most recent as recorded in the year before the index date).
- Other (selected) comorbidities:
  - Liver failure/disease.
- Most recent laboratory markers (as recorded in the year before the index date)
  - Serum creatinine.
  - Total cholesterol.
  - Low-density lipoprotein (LDL) cholesterol.
- Medical device use (as recorded in the year before the index date)
  - Devices connected with CV procedures.
  - Devices connected with fracture healing.
  - Devices connected with limited mobility.
- CV risk factors (not covered above):
  - BMI/obesity (most recent measure or diagnosis of obesity as recorded in the previous 5 years).
  - Smoking (most recent measure or diagnosis of smoking as recorded in the previous 5 years).

- Alcohol drinking (most recent measure or diagnosis of alcoholism/alcohol drinking problems as recorded in the previous 5 years).
- Hypertension: diagnosis recorded prior to the index date (Sundbøll et al, 2016); or 2 or more recorded measures of systolic blood pressure >140mmHg; or 2 or more measures of diastolic blood pressure >90mmHg in the year before the index date.
- Use of antihypertensive therapy/ies prescribed in the year before the index date: alpha blockers (ATC CCI), beta-blockers (ATC CCI), angiotensin-converting enzyme inhibitors (ATC CCI), angiotensin II inhibitors (ATC CCI), calcium channel blockers (ATC CCI).
- Type 2 diabetes mellitus: diagnosis recorded prior to index date; or 2 or more measures of HbA1c ≥6.5% in the year before the index date; or use of diabetes medication.
- Use of antidiabetes therapy/ies (ATC CCI) prescribed in the year before the index date.
- Hypercholesterolaemia/dyslipidaemia: diagnosis recorded prior to index date; or the presence of 1 or more measurements of the raised level of total cholesterol or LDL cholesterol in the year before the index date.
- Use of lipid-lowering drugs (ATC CCI) as prescribed in the year before the index date.
- History of chronic kidney disease: diagnosis recorded prior to index date; or 2 or more measurements of estimated glomerular filtration rate <60mL/min/1.73m^2 in the year before the index date.
- Previous history of ischaemic heart disease: number of events and time from the most recent event to the index date.
- Previous history of cardiac arrythmia: number of events and time from the most recent event to the index date.
- Previous history of cerebrovascular disease: number of events and time from the most recent event to the index date.
- Previous history of thromboembolism: number of events and time from the most recent event to the index date.
- Use of antithrombotic agents: low-dose aspirin (ATC PPD or clopidogrel (ATC CCI) in the year before the index date.
- Use of anticoagulants in the year prior to the index date: vitamin K antagonists (ATC CCI), heparins (ATC CCI), direct thrombin inhibitors (ATC CCI), or direct factor Xa inhibitors (ATC CCI).
- Use of cardiac therapies: antiarrhythmics, classes I and III (ATC CCI), digitalis glycosides (ATC CCI).
- Hypo- or hypercalcaemia based on laboratory measures or on diagnostic codes (e.g., E83.5 in ICD-10) in the year prior to index the date.

- Markers of disease severity (risk factors for OP/fractures):

- History of recorded OP at any time before the index date.
- History of previous fracture/s: site/s (hip, vertebral, major osteoporotic, other/s), number of fracture/s, and time from the most recent to the index date.
- History of rheumatoid arthritis at any time before the index date.
- History of eating disorder/s (anorexia nervosa, bulimia) at any time before the index date.
- History of cancer (any except basal cell skin cancer) at any time before the index date.
- Use of systemic glucocorticoids (ATC CCI): cumulative number of DDDs of prednisone equivalents prescribed in the year before the index date.
- Previous use of other OP medications (ATC CCI) in the year prior to the index date: type, number of therapies, and DDDs prescribed in the year before the index date.
- Previous use of prescribed vitamin D supplements (ATC CCI) in the year before the index date.
- Previous use of prescribed calcium supplements (ATC CCI) in the year prior to the index date.
- Previous use of prescribed calcium and vitamin D (concomitant) supplements (ATC CCI) in the year prior to the index date.
- Use of other medications associated with low bone mineral density/OP as prescribed in the year before the index date.
- Use of other medication/s associated with fall/s and/or fracture/s as prescribed in the year before the index date.
- Number of recorded fall/s in the year before the index date.
- Estimated absolute 5-year fracture risk, based on the Garvan nomogram (Bolland et al, 2011), recently tested by members of the EU-ADR Alliance.
- Bone mineral density T-score recorded in the year before the index date (if available) (Note: it will not be included in the propensity score due to probable confounding by indication).

- Use of other medications:

  Use of any drugs: number of different ATC classes (ATC 4-digit groups) used in the year prior to the index date.

  - Use of lipid-lowering agents (ATC CCI) in the year prior to the index date.
  - Use of oral antidiabetic agents (ATC CCI) in the year prior to the index date.

- Use of low-dose aspirin (ATC [redacted]) or clopidogrel (ATC [redacted]) in the year prior to the index date.
- Previous use of anticoagulants in the year prior to the index date: vitamin K antagonists (ATC [redacted]), heparins (ATC [redacted]), direct thrombin inhibitors (ATC [redacted]), direct factor Xa inhibitors (ATC [redacted]).
- Previous use of OP medications (ATC [redacted]) in the year prior to the index date.
- Previous use of systemic glucocorticoids (ATC [redacted]) in the year prior to the index date.
- Polypharmacy: use of, for example, 5 or more medications from different therapeutic classes (5 different ATC 4-digit groups) in the year prior to the index date.

9.3.3.2 Interaction/stratification terms

The CV event/s rates of MI, stroke, cardiac arrhythmia, and atrial fibrillation (as in objectives 1 and 2) will be provided stratified by key CV risk factors.

The IRs of CV events of interest of MI, stroke, cardiac arrhythmia and atrial fibrillation will be calculated based on the two follow-up periods (exposure-based and fixed, as described in Section 9.2.6) for each of the study cohorts. In accordance with the secondary objectives, stratification will be conducted based on the following baseline characteristics of each of the study cohorts:

- Age (on the index date), stratified by database-specific 5-year age bands..
- Prior use of OP medication: defined as at least one dispensation or claim for an OP medication other than the study drug during the baseline period.
- Previous history of "minor" CV events (transient ischaemic attack/angina).
- Previous history of peripheral artery disease.
- Previous history of type 1 or type 2 diabetes mellitus.
- Previous history of hypertension.
- Previous history of hypercholesterolaemia.
- Previous history of cardiac arrhythmia.

Further stratification variables will be defined to capture all relevant CV risk factors if requested and in agreement with the regulatory authorities.

9.4 Data sources

This study will be conducted using routinely collected data from 3 data sources that participate in the EU-ADR Alliance (IPCI, SIDIAP, and NDR from the Netherlands, Spain, and Denmark, respectively), with the addition of 2 databases from the UK (CPRD GOLD & CPRD AURUM) and 1 from Germany (GePaRD).

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 utilisation, and their experience in previous multi-database studies on both drug utilisation and safety.

Five countries from different European areas are included, to provide heterogeneous and representative data on the safety of romosozumab, as well as ensure 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 (Vlug et al, 1999). All of the contributing data sources are listed under the ENCePP resources database (ENCePP Resources Database, 2019).

The confirmed participating databases will be IPCI (Netherlands), NDR (Denmark), and SIDIAP (Spain), all of which form part of the stable structure of the EU-ADR Alliance, and additionally, CPRD GOLD & AURUM (UK) and GePaRD (Germany). Table 2 provides an overview of the key elements of these databases. The total number of persons actively registered in the source population of these 6 databases together was more than 54.4 million in 2016.

Table 2 Overview of the considered databases

Country	Netherlands	UK	Denmark	Spain	Germany
Name of the database	IPCI	CPRD GOLD &AURUM	NDR	SIDIAP	GePaRD
Type of database	MR	MR	ADM	MR	ADM
# active patients (millions)	1.2	16.6 3.2/13.4	5.8	5.8	25
Age categories	All	All	All	>15 years	All
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Date death	Yes	Yes	Yes	Yes	Yes
Prescriptions					
Outpatient treatment/s	Yes (specialist incomplete)	Yes (specialist incomplete)	Yes	Yes (specialist incomplete)	Yes
Coding of drugs	ATC	BNF/Multilex	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes	No
Outcomes					
Hospitalizations	Yes	Yes (60%)	Yes	Yes (30%)	Yes
Outpatient diagnoses	Yes	Yes	Yes (hospital outpatient)	Yes	Yes (hospital outpatient)
Coding of disease	ICPC	READ/SNOMED CT	ICD-10	ICD-10 (ICD-9 for hospital diagnoses)	ICD-10_GM
Cause of death	No	From linked ONS death data (60%)	Yes (lag 2 years)	No	No

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; 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; NDR= National linked Danish Registries; ONS=Office for National Statistics; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària SNOMED CT=Systematized Nomenclature of Medicine Clinical Terms.

9.4.1 IPCI, the NETHERLANDS

In 1992, the IPCI database was started by the Department of Medical Informatics of the Erasmus University Medical Centre. 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 diagnoses 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. 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.

9.4.2 NDR, 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) comprises dispensing data from community pharmacies and contains information on the 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 to 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.

9.4.3 SIDIAP, 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 electronic medical records (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 7.5 million population of Catalonia) from 274 primary care practices with 3,414 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 ICD-10 codes and structured forms designed for the collection of variables relevant to 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 Committees.

9.4.4 CPRD GOLD & AURUM, the UK

The UK patients' data will be sourced from CPRD (both GOLD and AURUM).

CPRD (former GPRD) comprises computerised 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 (GOLD), and SNOMED codes (AURUM)), 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 database 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 60 million patients (20 million GOLD, 40 million AURUM), including over 16.6 million currently registered patients (3.2 million GOLD, 13.4 million AURUM) which is considered to be representative of the UK population.

9.4.5 GePaRD, GERMANY

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 database 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 hospitals. 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 utilisation 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 utilisation 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.

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 April and June, Table 3 shows how frequently and at what time of the year each data source is updated.

Table 3: 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
NDR (DK)	Yearly	May	End (31 Dec) the previous year
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; GePaRD=German Pharmacopidemiological Research Database; GP=general practitioner; IPCI=Integrated Primary Care Information Project; M=month; NDR=Nationwide linked Danish registries; NL=Netherlands; Q=quarter; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.
Note: Any changes to prescribing practice reflected in the databases may affect the results regarding bisphosphonates.

9.5 Study size

Since this study will be undertaken using routinely collected data, all patients meeting the eligibility criteria previously described will be included. Table 4 illustrates the feasibility counts including the number of incident users of each OP medication available in each of the contributing databases in the EU-ADR Alliance, GePaRD and CPRD GOLD in 2016. These can be used to inform the availability of propensity-matched active comparator (ALN) and that of romosozumab users, which could potentially be similar to more advanced/costly therapies, such as teriparatide.

Although romosozumab is obviously not represented, market uptake is expected to be at least as high as teriparatide, probably not initially, but in subsequent years. As can be seen in Table 4 , approximately 2,322 users of teriparatide have been identified in the contributing databases in the year 2016.

Table 4: Target population for the descriptive and drug utilisation sections of the proposed PASS - Numbers of new users of OP medications in 2016 in contributing databases

	NDR (DK)	IPCI (NL)	SIDIAP (ES)	GePaRD (DE)	CPRD GOLD (UK)	TOTAL
ALN (ATC [redacted])	15,000	2,108	11,508	8,622	7,852	45,090

	NDR (DK)	IPCI (NL)	SIDIAP (ES)	GePaRD (DE)	CPRD GOLD (UK)	TOTAL
All oral bisphosphonates (CCI [redacted])	15,100	2,529	11,690	12,221	8,645	50,185
Zoledronate (ATC CCI [redacted])	6,800	112	-	165	62	7,139
Denosumab (ATC CCI [redacted])	2,100	529	4,364	2,356	410	9,759
Teriparatide (ATC CCI [redacted])	680	25	1,551	55	11	2,322

These figures demonstrate the capabilities of the proposed consortium and data sources to capture a sufficient sample of patients in the considered study drug groups. Based on the above feasibility, we suggest that iv therapies (e.g., zoledronate) will not be identified in the proposed study. Consequently, this observation will not impact the romosozumab sample as romosozumab will be commercialised as a subcutaneous preparation, similar to denosumab or teriparatide, which are well represented in the table above.

It is expected that all of the contributing databases will reliably collect information on the proposed CV events of MI and stroke, as these will most likely lead to hospital admissions. Both primary and secondary care databases will therefore be able to identify all of the proposed outcomes. The three primary care databases with linkage to hospital inpatient data (SIDIAP and CPRD GOLD and AURUM) will be useful to confirm the outcomes and perform any sensitivity analyses on hospital records data if needed. Previous validation studies have demonstrated the validity and completeness of these outcomes in the chosen data sources. For more details about the outcome ascertainment algorithms and their validity, refer to Section 9.6.

Since romosozumab has yet to be launched in all participating countries, the sample size needed has been calculated by considering different levels of assumed IRs of CV events, instead of using power. Table 5 shows the number of romosozumab users and comparator users needed to obtain an alpha risk of 0.05 with 90% power in a 1:3 (romosozumab:comparator) matched cohort analysis for different scenarios of incidence of CV events and HR.

The range of incidence of CV events has been defined based on a review of published literature and on ad hoc analysis of Swedish Health Data. The results of this analysis showed a range from 0.5 to 3.0 per 100 person-years.

The range of HR has been defined based on results from CV safety data from studies 20070337 (FRAME) and 20110142 (ARCH). These results show a potential excess risk of CV death, MI, or stroke (MACE-1 outcome) in romosozumab-treated patients with the magnitude ranging from 1.0 (equal risk) to 2.0 (HR=1.39 [95% CI: 0.97 to 2.00]). The study will thus be powered to provide additional confidence that, in those patients who received romosozumab on the label, there

is no greater risk than that already characterised by this result and to demonstrate noninferiority using a margin of 2.0.

The number of patients needed will increase with decreasing incidence of the safety event and with decreasing HR. Although all patients eligible in the proposed data sources will be included, the natural consequence of this is that lower-risk scenarios will result in a delayed conclusion of the study. Conversely, high-risk scenarios defined by high incidence of CV events and high attributable risk would result in a swift analysis: indeed, the scenario of IRs of 2 per 100 person-years and a 2-fold relative increase in risk would only require 1,450 romosozumab users (and 4,350 users of the active comparator).

Table 5: Sample size needed under different scenarios of incidence and HR, with matching 1:3 (romo:comp)

Assumed incidence*	0.5		1		1.5		2	
HR (upper limit 95% CI)	Romo	Comp	Romo	Comp	Romo	Comp	Romo	Comp
2.0	5,850	17,550	2,950	8,850	1,950	5,850	1,450	4,350
1.8	8,150	24,450	4,100	12,300	2,700	8,100	2,050	6,150
1.6	12,700	38,100	6,350	19,050	4,250	12,750	3,200	9,600
1.5	17,050	51,150	8,550	25,650	5,700	17,100	4,250	12,750
1.4	24,750	74,250	12,400	37,200	8,250	24,750	6,200	18,600
1.3	40,750	122,250	20,400	61,200	13,600	40,800	10,200	30,600
1.2	84,300	252,900	42,150	126,450	28,100	84,300	21,100	63,300

CI=confidence interval; Comp=comparator; CV=cardiovascular; HR=hazard ratio; Romo=romosozumab
Note: This table shows the number of romo and comp users needed to obtain an alpha risk of 0.05 with 90% power in a 1:3 (romo:comp) matched cohort analysis for different scenarios of incidence of CV events and HR, where the true risk is 1.0 and 0% dropout.
* Per 100 person-years.

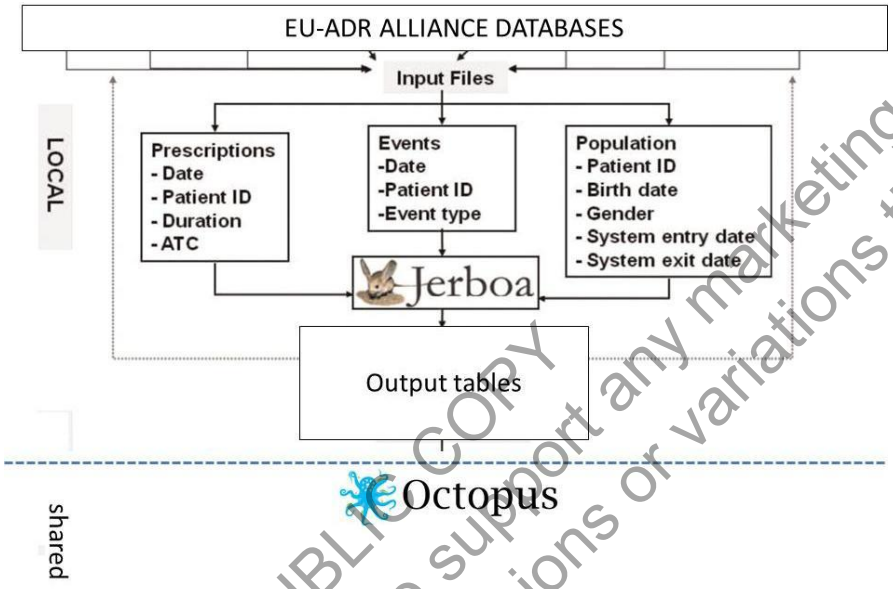
The calculation of the expected time to achieve sample size was based on:

- The anticipated timing of the different commercial launches in each European country.
- The number of patients expected from each country assessed using an evaluation of epidemiologic data, number of patients currently treated post fracture and the number of patients treated with the anabolic agent teriparatide.
- The assumption that local reimbursement criteria will allow the use of romosozumab in the indicated population.

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 in 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 one 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 harmonisation 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, Germany, and Spain), ICPC (Netherlands), READ and SNOMED (UK) codes. These will be mapped to an additional data source from Germany and its respective terminologies.

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

- Clinical definition.
- Preliminary list of concept identifiers using Unified Medical Language System® (UMLS®) Metathesaurus Browser.

- Addition of codes found after a literature review of validated lists of codes for each of the study outcomes in each of the databases.
- 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 project. Harmonisation 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 source (Germany) 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, i.e., standardised patient, drug, and event files linkable via a patient unique identifier.

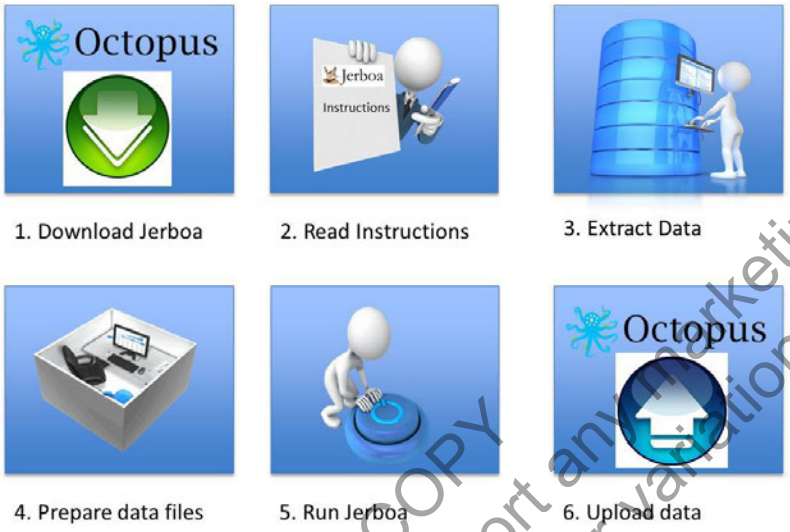
9.6.4 Benchmarking of incidence rates of events

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 maximises the involvement of the data providers in the study by utilising their knowledge of the characteristics and the process underlying the data collection.

After completion of harmonisation, 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



9.6.5 Data elaboration

A standardised 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.

9.6.6 Missing data

Since the underlying data represent attended medical care, it is assumed that the absence of information on 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 the index date, and assume patients are not smokers or heavy drinkers otherwise. This will help harmonise with hospital EMRs/administrative databases where no measurement of smoking/drinking is available.

9.6.7 Data sharing

A study-specific folder on the central Octopus RRE will be used to analyse the output provided by Jerboa©. These output files will contain only anonymised de-identified data that will be shared in the RRE where members will have secure and restricted access and where data will be

analysed. SAS, version 9.4, will be used for post-processing of data. Small cell counts will be masked as required by local regulations.

The German and Danish data cannot be shared in the RRE and will therefore be analysed 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 proposed comparative safety analysis aims to assess whether in women with severe OP at high risk for fracture and no history of MI or stroke (as per proposed SmPC), treatment with romosozumab is associated with an increased risk of CV events of MI, stroke and cardiac arrhythmia, and all-cause mortality compared to users of ALN similar to the indicated population for romosozumab in Europe as per the SmPC and with similar baseline characteristics.

Numerous previous studies, including some conducted by the EU-ADR Alliance in a similar indication and with similar outcomes (EUPASS9117), have demonstrated the feasibility and [redacted] 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

9.7.1.1 Data analysis of the descriptive study component

9.7.1.1.1 CV incidence rates

For the analysis which determines the IR of each CV event of interest for each OP medication, the following calculations will be performed. In the case of Scenario 2 (see below), the IRs of patients with CV events of interest will be reported as well.

- Scenario 1: follow-up per drug exposure

  $$\text{IR of CV events of interest} = \frac{\text{number of new events among patients in the study drug cohort}}{\text{number of exposed person} - \text{years at risk for the study drug cohort}}$$

- Scenario 2: follow-up per first exposure carried forward

  $$\text{IR of CV events of interest} = \frac{\text{number of events among patients in the study drug cohort}}{\text{number of exposed person} - \text{years at risk for the study drug cohort}}$$

$$\text{IR of patients with CV events of interest} = \frac{\text{number of patients with a new event of interest in the study drug cohort}}{\text{number of exposed person} - \text{years at risk for the study drug cohort}}$$

IRs and 95% CIs will be calculated for each study drug cohort (as defined in Section 9.3.1) using a Poisson model. If there is overdispersion, a negative binomial model will be used instead. The IR will be reported for prespecified intervals of 6, 12, 18, and 24 months after treatment indexes in Scenario 2. These rates will be presented and reported annually, and the number of patients and person-years at risk will be cumulative, such that the CV IRs reported after the first year following launch will include both newly identified patients in addition to all patients identified in earlier years.

9.7.1.1.2 Stratified CV incidence rates

For each study drug exposure cohort, the CV IRs and 95% CIs will be stratified by the variables presented in Section 9.3.3.2.

9.7.1.2 Comparative safety analyses

9.7.1.2.1 Propensity score matching

Propensity scores represent the probability that a given patient will receive the drug of interest (romosozumab) based on her baseline demographics and clinical characteristics specified in Section 9.3.3. This probability will be estimated using a multivariable logistic regression equation.

Propensity score matching reduces confounding by indication by producing comparable groups of patients in terms of observed confounders. In the proposed study, it is expected that romosozumab users will have a high fracture risk and very low prevalence of previous major CV events (MI/stroke), as per the proposed label. Key features to be added in the propensity score equation will therefore include predictors of fracture as well as CV risk factors. Previous analyses of primary care (Hippisley-Cox et al, 2017) and of health register data around Europe (Rubin et al, 2018) have demonstrated the richness and detail of risk factors recorded in the proposed real-world data sources. In addition, CCI [redacted] CCI

Patients using romosozumab will be matched to up to 3 users of ALN with a caliper width of 0.20 standard deviations (SDs) on the logit of the propensity score (Austin, 2011). Caliper matching is a strategy where only romosozumab users with "comparable" matches are kept in the analysis, whilst those with matched controls outside of the pre-established level of SD are excluded to minimise confounding. This is state of the art methodology to minimise confounding by indication in pharmacoepidemiology and has been shown to replicate findings from randomized controlled trials in different settings (Strauss et al, 2019), including CV studies (Dahabreh et al, 2012). An active comparator new user study design approach will be used (Lund et al, 2015).

The balance between the propensity-matched cohorts will be checked using absolute standardised mean differences. A difference ≥0.1 will show that a variable is unmatched between romosozumab users and the comparison OP medication. In this scenario, the propensity score model will be respecified and re-estimated and the balance will be rechecked. Should this strategy fail,

double-adjustment (i.e., further adjustment for imbalanced variables) to adjust for any potential imbalances after matching) will be carried out, as recommended by Nguyen et al (2017).

9.7.1.2.2 Survival analysis

Cox regression models stratified by matched sets will be used to calculate HRs and 95% CIs for each of the safety endpoints (MI, stroke, cardiac arrhythmia, atrial fibrillation, MACE-1, and MACE-2) according to drug exposure in the propensity-matched cohorts. The outcomes of death and CV death will also be analysed using Cox regression to check for competing risks. These analyses will be conducted "per treatment episode" as described above.

Should an association between romosozumab use and primary outcome (MACE-2) be identified (in either direction), cause-specific hazards from competing risk analyses will be calculated to assess the risk of the secondary outcomes of MI and stroke (Austin et al, 2016).

The proportionality of hazards will be tested in all the Cox regression models by plotting log-plots of the Nelson-Aalen estimates. Alternative models will be used in case of non-proportionality of hazards.

9.7.1.3 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% (Higgins et. al., 2022).

9.7.1.4 Measures proposed to account for unobserved confounding

9.7.1.4.1 Subgroup analysis in patients with clinically severe osteoporosis

The feasibility of a subgroup analysis in patients with clinically severe osteoporosis (BMD T-score <-2.5 and a fracture recorded in the year prior to starting of treatment) will be evaluated through the assessment of the number of patients treated with romosozumab and ALN with a BMD measurement in the 12 months prior to treatment commencement. Should sufficient patients meet this criterion, a subgroup analysis will be performed in patients with clinically severe osteoporosis to complement the comparative safety of romosozumab.

9.7.1.4.2 Negative control outcomes

Cox regression models stratified by matched sets will also be used to calculate HRs and 95% CIs for a prespecified list of negative control outcomes. The definition of a negative control outcome is an outcome upon which the treatment and comparator are not expected to have an effect. The negative controls to be used in this analysis will be agreed upon with academic clinicians and provided in advance before comparative analyses are conducted. A preliminary and non-exhaustive list of potential negative control outcomes is reported here for illustrative purposes:

- Ingrown nail
- Hernia repair surgery
- Inguinal hernia
- Road traffic accident
- Shoulder tendonitis/rotator cuff disease
- Carpal tunnel syndrome
- Appendicitis surgery

Should the Cox regression analysis of more than 5% of the negative controls produce significant results, 3 additional analyses will be conducted to assess the effects of potential biases related to insufficient control for confounding/channeling bias: (i) empirical calibration using negative control outcomes; (ii) SCCS, and (iii) instrumental variable analysis.

9.7.1.4.3 Empirical calibration using negative control outcomes

The obtained estimates from the analyses above will be used to empirically calibrate the HRs obtained from the primary propensity-matched analysis, as proposed by Schuemie et al (2018). This will provide a readjusted risk estimate of comparative CV safety after accounting for unobserved confounding.

9.7.1.4.4 Self-controlled case series analysis (SCCS)

A self-controlled case series analyses (SCCS) will be undertaken. This method uses data only for the cases (i.e., patients who have had an outcome) and assesses whether there is an elevated risk during time windows of exposure to the drug of interest (Petersen et al, 2016). The SCCS controls for all-time fixed confounders, including unobserved ones.

Whilst this analysis does not assess at the whole population level, it will determine where the patient's outcome was more likely to occur before or after treatment and may support results found in the Cox regression.

9.7.1.4.5 Instrumental variable analysis

Instrumental variable analyses based on physician prescription preference will be used. Under certain assumptions, instrumental variable analyses can account for residual confounding related to unmeasured variables. Instrumental variable analyses rely on the existence of an instrument, a variable that is strongly associated with the exposure of interest, but not associated with patient confounders and not directly associated with the outcome. Physician prescription preference has been shown to be useful in the study of CV drug safety using observational routinely collected data (Uddin et al, 2016). Physician preference for the use of the study drug (i.e., romosozumab)

will be estimated using the previous 10, 20, and 50 prescriptions of OP medications at the prescriber level. Falsification tests will be used as diagnostics for the testable assumptions (Ali et al, 2014): 1) an association between the instrument (physician prescription preference) and the actual exposure will be tested using logistic regression modelling; and 2) the expected lack of association between the instrument and all the available confounders will be tested by measuring the standardised mean difference vs the estimated physician prescription preference.

9.7.1.5 Sensitivity analysis

To account for potential differences in CV risk between patients with or without prior recent fractures, we will perform a sensitivity analysis only including patients with at least one fracture in the 2 years prior to the therapy initiation. Another sensitivity analysis will also be performed by only including patients without history of cancer (any except basal cell skin cancer).

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 a second programmer's 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.

9.9.1 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 the active consent of patients. Therefore, lack of participation is not an issue. Selection bias might however arise if data are missing for some confounders (e.g., smoking or BMI) if the analyses are limited to a complete case. This will be avoided by binarizing as "current smoker" or "heavy alcohol drinker" where measurement data are available in primary care databases or based on the existence/absence of a record of smoker or alcohol addiction diagnoses in all the proposed data sources.

9.9.2 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 to non-compliance. Hence, an overestimate of the utilisation 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 (<90, 90, and 180 days) will be used to define treatment episode duration.

Lack of recording (i.e., incompleteness) of safety events may lead to misclassification of the safety endpoints. However, previous work has shown very high validity of the coding of MI and stroke, with PPVs ranging from 75% to 100% within EU-ADR Alliance partners (Coloma et al, 2013). Cardiovascular death has been validated as part of a recent EU PASS: in those databases where no mortality registry data are available, an algorithm combining death date and medical records will be used, and so identified events will be manually validated using free text review.

Validation of the outcomes in all datasets has previously been addressed in Section 9.3.2.

9.9.3 Confounding

Due to the observational design chosen, causality in the observed associations will not be established. Instead, associations between drug use and risks will be assessed. As confounding by indication (with romosozumab users more likely to suffer more severe OP and less likely to be at risk of CV events) will likely produce differences in baseline characteristics between romosozumab and ALN users, the study will use several methods to deal with confounding:

- Restriction: comparative studies will be conducted only in persons in line with the EU label to restrict the population to those who would be prescribed romosozumab according to the label (i.e., ALN users with a history of MI or stroke will be excluded).
- Matching: for the comparative studies, the study will use propensity score matching to minimise confounding related to all observed confounders.
- Adjustment: the study will adjust for all covariates that remain imbalanced (standardised mean difference >0.1) after propensity score matching.
- Sensitivity analysis: negative control outcome analyses will be used to identify any residual unobserved confounding in the propensity-matching analyses. If this analysis suggests the presence of relevant unresolved confounding, then 3 additional analyses will be used to minimise the impact of any resulting bias, including empirical calibration, SCCS, and instrumental variable analyses. These are detailed in the previous section (Section 9.7.1.1.2).

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 International Council for Harmonisation (ICH) guideline of Pharmacovigilance Planning (ICH, 2004)

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

For this study, patients from 5 different European countries will process individual data as collected in national electronic health record databases in compliance with all applicable national and European regulations 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 the 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 the 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 to 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 the 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 the 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 interim and final reports in aggregate tables.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim reports of descriptive statistics about the uptake and safety of romosozumab (i.e., IR of CV events of MI and stroke) will be generated (6 monthly for the first 2 years followed by yearly for the remaining 4 years, up to a total of 6 years) and reviewed. These reports will be submitted to EMA. The interim report in year 5, in addition to the descriptive statistics, will include interim comparative safety analysis results.

Further, 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.

13 REFERENCES (AVAILABLE UPON REQUEST)

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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
3	Appendix 3	28 Jan 2020	List of Diagnosis and Medication Codes
4	Appendix 4	28 Jan 2020	Validation Process for Study Outcomes

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))	☒	☐	☐	9.7.1
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
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	9.3.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	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)	☒	☐	☐	9.3.3.2

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?	☒	☐	☐	9.3.3
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?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.1.1.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.1.1.2
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?	☒	☐	☐	9.9

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).	☒	☐	☐	9.7.1.1.2
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: _____

APPENDIX 3. LIST OF DIAGNOSIS AND MEDICATION CODES

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
Myocardial infarction	Cardiac infarction	I22*	--	--	--
	Cardiac infarction	I21*	--	--	--
	Acute myocardial infarction	I21*	410*	G30z.	K75
	Acute myocardial infarction, unspecified	I21.9	410.9	--	--
	Myocardial infarction (acute) NOS	I21.3	410	--	--
	Acute myocardial infarction, unspecified site, episode of care unspecified	--	410.90	--	--
	AMI NOS, unspecified	--	410.90	--	--
	Acute myocardial infarction sub endocardial infarction	--	410.7	--	--
	Old myocardial infarction #	I25.2	412	G32..00	
	Healed myocardial infarction #	--	--	G32..11	--
	Subsequent/recurrent myocardial infarction	I22	--	G35..	--
	Subsequent myocardial infarction of unspecified site	I22.9	--	Gyu36	--
	Subsequent myocardial infarction of other sites	I22.8	--	Gyu35, G353.	--
	Subsequent myocardial infarction of anterior wall	I22.0	--	G350.	--
	Subsequent myocardial infarction of inferior wall	I22.1	--	G351.]	--
	Subsequent acute sub endocardial myocardial infarction	I22.2	--	--	--
	Subsequent non transmural myocardial infarction NOS	I22.2	--	--	--
	Subsequent myocardial infarction (acute) NOS	I22.9	--	--	--
	Re-infarction of myocardium	--	--	G35..	--
	Acute sub endocardial myocardial infarction	I21.4	--	--	--

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Acute myocardial infarction sub endocardial infarction, episode of care unspecified	--	410.70	--	--
	Non transmural myocardial infarction	I21.4	--	--	--
	Acute myocardial infarction, of antero lateral wall	--	410.0	G300.	--
	Acute antero septal myocardial infarction	--	--	G3011	--
	Acute inferior myocardial infarction	--	410.4	G308.00	--
	Acute myocardial infarction, true posterior wall infarction	--	410.6	--	--
	True posterior myocardial infarction	--	--	G306.	--
	Acute myocardial infarction, of inferoposterior wall	--	410.3	G303.]	--
	Other specified anterior myocardial infarction	--	--	G301.]	--
	Acute transmural myocardial infarction of unspecified site	I21.3	--	Gyu34, G30X.00	--
	Acute transmural myocardial infarction of anterior wall	I21.0, 122.0	--	--	--
	Acute transmural myocardial infarction of inferior wall	I21.1, I21.19, 122.1	--	--	--
	Acute transmural myocardial infarction of other sites	I21.2, I21.29, 122.8	--	--	--
	ECG: old myocardial infarction #	--	--	3232.	--
	Anterior myocard. infarct NOS	--	410.8	G301z	--
	Other acute myocardial infarct	--	--	G30y.	--
	Other acute myocardial inf. NOS	--	--	G30yz	--
	Inferior myocard. infarct NOS	--	--	G308.	--
	Acute myocardial infarction, of infero lateral wall	--	410.2	G302.	--

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Acute lateral myocardial infarction	--	410.5	--	--
	Lateral myocardial infarct NOS	--	--	G305.]	--
	Acute widespread myocardial infarction	--	--	X200S	--
	Acute posterior myocardial infarction	--	410.60, 410.61, 401.62	--	--
	Posterior myocard. infarct NOS	--	--	G304.]	--
	Silent myocardial infarct [#]	--	--	G30..17	--
	ECG: myocardial infarction	--	--	323..	--
	ECG: myocardial infarct NOS	--	--	323Z.	--
	Postoperative sub endocardial myocardial infarction	--	--	G384.00	--
	Postoperative myocardial infarction	--	--	G38z.00	--
	Acute anterior myocardial infarction	--	410.1		--
	Acute Q wave myocard infarct	--	--	G309.00	--
	Acute myocardial infarction sub endocardial infarction	--	410.71, 410.72	--	--
	Non-Q wave myocardial infarction NOS	I21.4, I22.2	--	--	--
	Non-ST elevation (NSTEMI) myocardial infarction	I21.4, I22.2	--	--	--
	History of MI [#]	--	--	14A3.00, 14A4.00, 14AH.00, 14AT.00	K76.02
	Diabetes mellitus insulin-glucose infuse acute myocardial infarct	--	--	889A.00	--
Stroke	Stroke, not specified as hemorrhage or	I64	--	--	--
	Stroke NOS	I63.9	--	--	K90
	Non-traumatic subarachnoidal bleeding	I60	430	G60..	--

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Intracerebral haemorrhage	I61	431	G61..	--
	Cerebrovascular accident (CVA)	--	--	G66..13	--
	Stroke and cerebrovascular accident unspecified	--	--	G66..00	--
	Stroke NOS	--	--	G66..12	--
	Sequelae of stroke, not specified as hemorrhage or infarction [b]	I69	--	Gyu6C	--
	Brain stem stroke syndrome	G46.3	--	G663.	--
	Cerebellar stroke syndrome	G46.4	--	G664.	--
	Other and unspecified intracranial haemorrhage	I62	432*	G62..00, G62z.00	--
	Cerebral infarction	I63	--	G64.	--
	Personal history of stroke [#]	--	--	ZV125	--
	Sequelae of stroke NOS [#]	I69.3	--	--	--
	H/O: Stroke [§]	--	--	14A7.00, 14A7.11, 14A7.12, 14AK.00	--
	Cerebral infarct due to thrombosis of precerebral arteries	--	433.*1	G63y00	--
	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits [#]	Z86.73	V12.54	--	--
	Management/monitoring of stroke	--	--	661M700, 661N700, 662e.00, 662e.11, 662M.00, 662M100, 662M200, 662o.00, 9Om..00, 9Om0.00, 9Om1.00, 9Om2.00, 9Om3.00, 9Om4.00	--
	Delivery of rehabilitation for stroke	--	--	7P24200	--

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Stroke referral, Seen in stroke clinic	--	--	8HBJ.00, 8HTQ.00, 8IEC.00, 9N0p.00	--
	Quality indicators stroke	--	--	9h2..00, 9h21.00, 9h22.00	--
	Sequelae of cerebral infarction	--	--	G683.00	--
	Sequelae of stroke, not specified as haemorrhage or infarction #	--	438*	G68X.00/Gyu6C00	--
	Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries	--	433.*1	G6W..00/Gyu6300	--
	Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries		434.*1	G6X..00/Gyu6G00	
	[X] Other cerebral infarction	--	--	Gyu6400	--
	[X] Occlusion and stenosis of other cerebral arteries	--	--	Gyu6600	--
	Discharge from stroke service	--	--	ZLEP.00	--
	Hemiplegia and hemiparesis	--	--		--
	Acute, but ill-defined, cerebrovascular disease	--	436.*		--
All arrhyth-mia	Atrioventricular and left bundle-branch block	I44			
	Atrioventricular block first degree	I44.0	426.11		K84.02
	Atrioventricular block second degree	I44.1	426.10		
	Atrioventricular block complete	I44.2	426.0		
	Other and unspecified atrioventricular block	I44.3	426.1*		
	Other and unspecified fascicular block	I44.6			
	Long QT syndrome	I45.81	426.82		K84.07

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Paroxysmal tachycardia	I47	427.2		
	Re-entry ventricular arrhythmia	I47.0			
	Ventricular tachycardia	I47.2			
	Paroxysmal tachycardia, unspecified	I47.9			K79
	Atrial fibrillation and flutter	I48	427.3*		K78
	Persistent atrial fibrillation	I48.1	427.31		
	Chronic atrial fibrillation	I48.2	427.31		
	Typical atrial flutter	I48.3			
	Atypical atrial flutter	I48.4			
	Unspecified atrial fibrillation and atrial flutter	I48.9			
	Unspecified atrial flutter	I48.92			
	Ventricular fibrillation and flutter	I49.0	427.4*		
	Atrial premature depolarization	I49.1			
	Junctional premature depolarization	I49.2			
	Ventricular premature depolarization	I49.3			
	Other and unspecified premature depolarization	I49.4			
	Other premature depolarization	I49.49			
	Sick sinus syndrome	I49.5			K80.03
	Cardiac arrhythmia, unspecified	I49.9			
	Paroxysmal ventricular tachycardia		427.1		
	WPW-Syndrome				K84.01
	Paroxysmal atrial fibrillation			G573200	

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Atrial fibrillation			G573000	
	Atrial flutter			G573100	
	Atrial fibrillation and flutter			G573.00	
	ECG: atrial fibrillation			3272.00	
	ECG: atrial flutter			3273.00	
	Implant intravenous pacemaker for atrial fibrillation			7936A00	
	Atrial fibrillation and flutter NOS			G573z00	
	Non-rheumatic atrial fibrillation			G573300	
	Perc transluminal ablation of atrial wall for atrial flutter			793M100	
	Perc translum ablat conduct sys heart for atrial flutter NEC			793M300	
	Persistent atrial fibrillation			G573500	
	Permanent atrial fibrillation			G573400	
	Paroxysmal atrial flutter			G573600	
	H/O: atrial fibrillation §			14AN.00	
	Atrial fibrillation resolved #			212R.00	
	Atrial fibrillation annual review #			6A9..00	
	History of atrial flutter §			14AR.00	
	Heart block			G56..12	
	Complete atrioventricular block			G560.00	
	Third degree atrioventricular block			G560.11	
	Atrioventricular block unspecified			G561000	
	First degree atrioventricular block			G561100	

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Second degree atrioventricular block			G561400	
	Atrioventricular block NOS			G561z00	
	Left bundle branch block			G562.11	
	Left anterior fascicular block			G562000	
	Left posterior fascicular block			G562100	
	Left bundle branch hemiblock NOS			G562z00	
	Other bundle branch block			G565.00	
	Bundle branch block unspecified			G565000	
	Other bundle branch block NOS			G565z00	
	Other heart block			G566.00	
	Interventricular block NOS			G566100	
	Other heart block NOS			G566z00	
	Atrioventricular dissociation			G56y100	
	Cardiac dysrhythmias			G57..00	
	Cardiac arrhythmias			G57..11	
	Ventricular tachycardia			G571.11	
	Paroxysmal tachycardia unspecified			G572.00	
	Essential paroxysmal tachycardia			G572000	
	Bouveret-Hoffmann syndrome			G572100	
	Paroxysmal tachycardia NOS			G572z00	
	Paroxysmal atrial fibrillation			G573200	
	Persistent atrial fibrillation			G573500	

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Chronic atrial fibrillation			G573700	
	Typical atrial flutter			G573800	
	Atypical atrial flutter			G573900	
	Atrial premature depolarization			G576300	
	Junctional premature depolarization			G576400	
	Ventricular premature depolarization			G576500	
	Other cardiac dysrhythmias			G57y.00	
	Sick sinus syndrome			G57y300	
	Supraventricular tachycardia NOS			G57y900	
	Re-entry ventricular arrhythmia			G57yA00	
	Other cardiac dysrhythmia NOS			G57yz00	
	Cardiac dysrhythmia NOS			G57z.00	
	[X]Other specified cardiac arrhythmias			Gyu5a00	
	[X]Other and unspecified atrioventricular block			Gyu5U00	
	[X]Other and unspecified fascicular block			Gyu5V00	
	[X]Other specified heart block			Gyu5X00	
Atrial fibrilla-tion	Atrial fibrillation and flutter	I48	427.3*		K78
	Persistent atrial fibrillation	I48.1	427.31		
	Chronic atrial fibrillation	I48.2	427.31		
	Typical atrial flutter	I48.3			
	Atypical atrial flutter	I48.4			
	Unspecified atrial fibrillation and atrial flutter	I48.9			

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	Unspecified atrial flutter	I48.92			
	Paroxysmal atrial fibrillation			G573200	
	Persistent atrial fibrillation			G573500	
	Chronic atrial fibrillation			G573700	
	Typical atrial flutter			G573800	
	Atypical atrial flutter			G573900	
	Atrial fibrillation and flutter NOS			G573z00	
	Non-rheumatic atrial fibrillation			G573300	
	Perc transluminal ablation of atrial wall for atrial flutter			793M100	
	Perc translum ablat conduct sys heart for atrial flutter NEC			793M300	
	Persistent atrial fibrillation			G573500	
	Permanent atrial fibrillation			G573400	
	Paroxysmal atrial flutter			G573600	
	H/O: atrial fibrillation §			14AN.00	
	Atrial fibrillation resolved #			212R.00	
	Atrial fibrillation annual review #			6A9..00	
	History of atrial flutter §			14AR.00	
	Paroxysmal atrial fibrillation			G573200	
	Atrial fibrillation			G573000	
	Atrial flutter			G573100	
	Atrial fibrillation and flutter			G573.00	
	ECG: atrial fibrillation			3272.00	

Study Outcome	Terms	ICD10	ICD-9-CM	READ codes	ICPC
	ECG: atrial flutter			3273.00	
	Implant intravenous pacemaker for atrial fibrillation			7936A00	

AMI=acute myocardial infarction; ECG=electrocardiogram; H/O=history of; ICD-9-CM=International Classification of Diseases, revision 9, clinical modification; ICD-10=International Classification of Diseases, revision 10; ICPC=International Classification of Primary Care; MI=myocardial infarction; NOS=not otherwise specified

* Includes subcodes.

[#] Not for an acute event; will only be considered for stroke and arrhythmia as underlying comorbidity.

[§] History of. Not to be used for the identification of incidence events.

APPENDIX 4. VALIDATION PROCESS FOR STUDY OUTCOMES

Validation studies will be conducted for each of the study outcomes. A sample of 250 eligible cases will be sampled from the study cohorts for previously unvalidated outcomes. All cases for Objective 3 (amongst eligible users of romosozumab or ALN in the study period) will be individually validated for outcomes where a PPV <75% has been previously demonstrated.

The following table summarizes previous validation studies and the results for each of the contributing data sources.

	MI	Stroke	All-cause death	CV death	Cardiac arrhythmia	Atrial fibrillation
SIDIAP (ES)	91.3%	75.7%	>90%	53.1%	82-100%	89%
CPRD (UK)	92.2%[a]	90%[b]	NA	NA	93%	95%
IPCI (NL)	75% (best case) 46.5% (worst case)	89.7%	NAP	38%	93%	99%
NDR (DK)	>95%	>97%	NA	NA	80-95%	95%
GePaRD (DE)			>83%[c]			

CPRD=Clinical Practice Research Datalink; CV=cardiovasctilar; DE=Germany; DK=Denmark; ES=Spain; GePaRD=German Pharmacoepidemiological Research Database; IPCI=Integrated Primary Care Information Project; IT=Italy; MI=myocardial infarction; NL=Netherlands; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària;

Note: NA=Validation not necessary as information is obtained directly from mortality records.

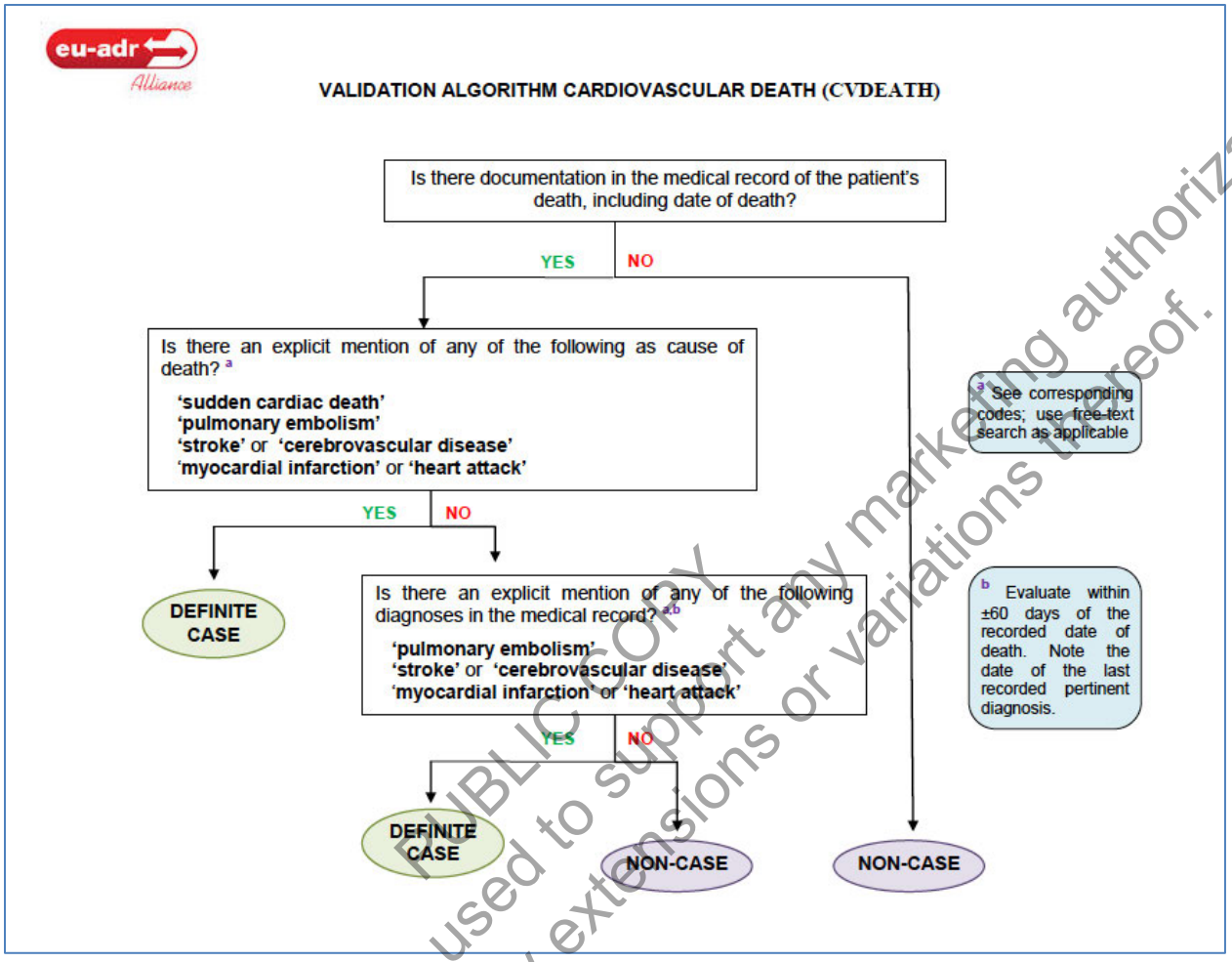
Note: NAP: Information on death in IPCI is provided by the GP as 1 of the reasons why a patient left the practice. In addition, by means of Natural Language Processing, additional searches for mortality are done each time a new dataset is released to pick up additional deaths. Specificity is 100% - Sensitivity might be lower but there is no gold standard to validate missing deaths in the database.

[a] Herrett et al, 2013
[b] Andersohn et al, 2006
[c] Ohlmeier et al, 2016

As shown, sample validation studies of 250 cases will be needed for MI, stroke, CV death, cardiac arrhythmia, and atrial fibrillation in GePaRD.

In addition, all eligible cases of CV death in the study cohorts for objective 3 in SIDIAP and IPCI, as well as all cases of MI in IPCI will need individual validation before they are included in the proposed comparative safety analyses.

All validations in primary care databases (SIDIAP and IPCI) will be based on free text reviews of the individual cases. Primary care charts and any related documents (e.g., specialist letters, referrals) will be reviewed by clinically trained validators using prespecified algorithms. The proposed algorithm for the validation of CV death is provided as an example below. Similar algorithms will be designed and used for the validation of all-cause mortality in IPCI.



The validation of cases in GePaRD will be performed based on a review of samples of individual case profiles, that is, all information (e.g., diagnoses, dispensations, procedures, hospitalized time) of the cases around the time of death will be reviewed by a medical expert. The same validation algorithm will be used, if necessary, some adaptions will be made according to the differences in the available information.