NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL (OP0006)

EUROPEAN NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY RELATED TO SERIOUS INFECTIONS FOR ROMOSOZUMAB BY THE EU-ADR ALLIANCE

PUBLIC COPY
This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

Final Non-interventional PASS Protocol	15 November 2024

PASS INFORMATION

Title	European non-interventional post-authorization safety study related to serious infections for romosozumab by the EU-ADR Alliance
Protocol version identifier	4
Date of last version of protocol	19 July 2024
EU PAS register number	EUPAS36005
Active substance	Romosozumab
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 monitor the potential risk of serious infection (SI) 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, the Netherlands, Spain, and the UK
Authors	PPD

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

MARKETING AUTHORIZATION HOLDER

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

PUBLIC COPY
This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read 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

PUBLIC COPY
This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

1 TABLE OF CONTENTS

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

LIST OF TABLES

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

LIST OF FIGURES

PUBLIC COPY
This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ALN	alendronate or alendronic acid
AIDS	Acquired Immune Deficiency Syndrome
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
BMD	Bone Mineral Density
BMI	body mass index
BNF	British National Formulary
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
HIV	Human Immunodeficiency Virus Infection
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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

Abbreviation	Definition
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
iv	intravenous
LTD	long-term disease
MAH	Marketing Authorization Holder
MI	myocardial infarction
NDR	National linked Danish Registries
ONS	Office for National Statistics
OP	osteoporosis
PAS	Post-Authorization Study
PASS	post-authorization safety study(ies)
PPV	positive predictive value
PV	pharmacovigilance
RR	relative risk
RMM	risk minimisation measure
RMP	Risk Management Plan
RRE	Remote Research Environment
SAE	serious adverse event
SCCS	self-controlled case series
SD	standard deviation
SI	serious infection
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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

3 RESPONSIBLE PARTIES

Function	Name	Title	Affiliation	Address
Study Coordinator (UK)	PPD			

Function	Name	Title	Affiliation	Address
		PPD		
Study Manager (ES)	PPD			
Study Manager (ES)				
Information Technology Programming and Infrastructure				
Global Regulatory Lead - Contact Person (MAH)	PPD		UCB Biopharma SRL	Allée de la Recherche 60 B-1070 Brussels Belgium
Real World Evidence Lead Scientist - Contact Person (MAH)			UCB Biopharma SRL	Allée de la Recherche 60 B-1070 Brussels Belgium
Safety Lead Romosozumab - Contact Person (MAH)			UCB Biopharma SRL	Allée de la Recherche 60 B-1070 Brussels Belgium
Participating countries				
Data source CPRD (UK)	PPD			
Data source IPCI (NL)				
Data source SIDIAP (ES)				
Data source NDR (DK)				
Data source GePaRD (DE)				

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;

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

4 ABSTRACT

Title

European non-interventional post-authorization safety study related to serious infections for romosozumab by the EU-ADR Alliance.

Rationale and background

An imbalance in the incidence of serious adverse events (SAEs) of infections was observed in the 12-month Placebo-Controlled Osteoporosis Safety Analysis Set. This imbalance was not driven by a specific type of infection or causative micro-organism. No imbalance was observed in the alendronate (ALN)-controlled study 20110142 (ARCH). Given the imbalance of SAEs of infections in the pooled placebo-controlled studies, serious infection (SI) events were included in the European Union (EU)-Risk Management Plan (RMP) as an important potential risk associated with romosozumab treatment.

Research question and objectives

The overarching objective of this study is to monitor the potential risk of SI associated with the use of romosozumab in comparison with other available osteoporosis (OP) medications in routine clinical practice in Europe.

Specifically, the study will provide further understanding on the following objectives:

- Objective 1: to assess the incidence rate (IR) of SI and serious Covid-19 infection 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 similar to the romosozumab indicated population in Europe as per SmPC (i.e., who would also fulfil the indications/contraindications for romosozumab in Europe).
- Objective 2: to assess the IR of SI and serious Covid-19 infection in subgroups of 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, after stratification by age, previous use of OP medications, and by prespecified key SI risk factors.
- Objective 3: to compare the risk of SI and serious Covid-19 infection in romosozumab users in the indicated population in Europe as per the SmPC to the risk of SI seen amongst users of ALN similar to the indicated population for romosozumab in Europe as per the SmPC and with similar baseline characteristics.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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 5 years (2020 to 2025).

Population

The study population will comprise of all women from the 6 participating data sources 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 SI 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 SI 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 index date (as per the romosozumab SmPC), or end of the study period/data extraction date. For the fixed follow-up period, patients will be followed in their respective cohorts until the first occurrence of loss to follow-up, SI event of interest, death, or end of the study period.

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 SI leading to hospitalisation. Secondary outcomes are death due to SI, serious Covid-19 infection leading to hospitalisation and death due to Covid-19 infection. Death due to SI or Covid-19 infection will be defined as either of in-hospital death with a diagnosis of infection during the same admission/episode or recorded diagnosis of any infection/Covid-19 followed by death in the subsequent month.

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, SI risk factors, markers of OP severity, and use of other medications at baseline, as described in detail in Section 9.3.3.

Data sources

This document cannot be used to support any marketing authorization application and any extensions thereof.
PUBLIC COPY

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 2 databases from the UK (Clinical Practice Research Datalink [CPRD] GOLD & AURUM) and 1 from 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. A total of 5,357 patients (1,339 romosozumab users and 4,018 alendronate users) with one romosozumab user matched to three alendronate users, would detect a hazard ratio (HR) of 1.5 for SI, assuming a cumulative incidence rate of 5% of SI in the alendronate group, with an alpha level of 0.05, 90% power, and accounting for a dropout rate of 10%.

Data Analysis

The IRs of SI for each OP medication will be calculated for the 2 follow-up periods. IRs and 95% confidence intervals (CIs) of SI events of interest will be calculated for each study drug using a Poisson model. If there is overdispersion, a negative binomial model will be used instead.

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

The SI event/s rates (as in objectives 1 and 2) for each study drug will be provided stratified by key SI 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 (SI and Covid-19 infection leading to hospitalization, and SI and Covid-19 infection leading to death).

Measures for reducing confounding by indication will be implemented including propensity score matching as well as negative control outcomes 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

Annual reports will be submitted for 5 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 (5 years) even if the sample size is reached before the 5 years to allow variability and better precision in the estimates of IR and HR.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

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	9.2.4	Amendment of the definition of 'severe osteoporosis' inclusion criteria from "fracture in the prior year" to "fracture up to 24 months prior to start of treatment".	We are proposing to modify this definition in line with the current 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.
		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	October 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	September 2023 OP0006 interim report showed that a significant number of patients who started

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
			fractures of any skeletal sites except face/skull/digit/s fractures recorded in the 2 years prior to therapy initiation"	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 the power of this comparative study to identify risk of serious infection.
		9.7.1.5	Addition of sensitivity analyses	A sensitivity analysis is now added to assess the risk of serious infection among patients with at least one fracture in the 2 years prior to therapy initiation. Incidence rate of serious infection and comparative safety analyses will be performed in this subgroup population.
		9.3.2	Incorporation of serious Covid-19 infection to the list of secondary outcomes and all related sections of the protocol	We separated serious Covid-19 infection as a secondary outcome to this study. Member of the Science Advisory Board recommended to separate Covid-19 from the other infections as this infection is different from the others.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
				Two additional secondary outcomes have been added to this study: 1. Serious Covid-19 infections leading to hospitalisation, and 2. Death due to Covid-19 infection.
		9.5	Re-calculation the needed sample size considering new IRs data from previous interim reports of the ongoing op0006 study.	In the OP0006 interim report of September 2023, results showed that IRs of the primary outcome (SI leading to hospitalisation) amongst alendronate users ranged from 5 to 13 per 100 person-years in validated data sources. These values are higher than the original assumptions for sample size calculations in the study protocol (1.0 to 2.5 per 100py). We have now re-calculated the needed sample size considering an IR of 5 per 100py (literature review and lowest observed rates in any country) and target HR value of 1.5 (from romosozumab clinical studies).
		Global	Removal of SNDS database from all the	Marketing launch of romosozumab in France

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
			related sections of the protocol	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 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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
		9.3.3, 9.7.1.5	Addition of a sensitivity analysis	A sensitivity analysis is now added to assess the risk of serious infection among patients without a history of cancer prior to therapy initiation to assess any potential bias. Incidence rates of serious infection 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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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 (year 1)	14 May 2021
End of data collection (year 1)	09 Jul 2021
Interim report 1-explanatory features of dataset	30 Sep 2021
Start of data collection (year 2)	29 May 2022
End of data collection (year 2)	10 Jun 2022
Interim report 2-explanatory features of dataset	19 Sep 2022
Start of data collection (year 3)	14 April 2023
End of data collection (year 3)	19 May 2023
Interim report 3–explanatory features of dataset	19 Sep 2023
Start of data collection (year 4)	26 May 2024
End of data collection (year 4)	24 Jun 2024
Interim report 4–explanatory features of dataset	19 Sep 2024
Start of data collection (year 5)	01 May 2025
End of data collection (year 5)	01 Jul 2025
Final report	30 Sep 2025

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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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 myocardial infarction (MI) or stroke, hypersensitivity to the active substance(s) or to any of the excipients, and hypocalcaemia.

An imbalance in the incidence of serious adverse events (SAEs) of infections was observed in the pooled placebo-controlled studies. In the 12-month Placebo-Controlled Osteoporosis Safety Analysis Set, overall incidence of SAEs of infections was 1.9% in romosozumab-treated subjects and 1.3% in placebo-treated subjects, with a relative risk (RR) of 1.49 (95% CI: 1.04, 2.13). This treatment difference was not driven by a specific type of infection or causative microorganism. Of note, no imbalance was observed for adverse events of infections (serious and nonserious), either in pooled placebo-controlled studies or the ALN-controlled study 20110142 (ARCH). In the latter, the incidence of SIs was 2.3% in romosozumab-treated subjects and 2.4% in ALN-treated subjects (RR=0.97; 95% CI: 0.65, 1.44) during the 12 month, Double-Blind Period.

Based on the above observation, SIs were included in the EU-RMP for romosozumab as an important potential risk.

To evaluate the risk of SIs associated with the use of romosozumab in routine clinical practice compared with other available OP medications, a European multi-national, multi-database, comparative post-authorization safety study (PASS) will be conducted.

7.2 Regulatory action

This EU SI PASS is part of a PASS program aimed at monitoring the safe use of romosozumab in European populations within the framework of a comprehensive RMP. In addition to the EU SI PASS, the PASS program encompasses a study on the use of romosozumab and adherence to indication and contraindication as per the approved the Summary of Product Characteristics (SmPC) (Risk Minimisation Measure [RMM] PASS), and a cardiovascular (CV) comparative safety study (CV PASS).

7.3 Previous observational studies

This will be the first PASS conducted to study the risk of SI associated with the use of romosozumab under routine 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 monitor the potential risk of SI associated with the use of romosozumab in comparison with other available OP medications in routine clinical practice in Europe.

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

- Objective 1: to assess the IR of SI and serious Covid-19 infection in romosozumab users in the indicated population in Europe as per the SmPC, and in cohorts of users of other OP medications similar to the romosozumab indicated population in Europe as per the SmPC (i.e., who would also fulfil the indications/contraindications for romosozumab in Europe).

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
PUBLIC COPY

- Objective 2: to assess the IR of SI and serious Covid-19 infection in subgroups of 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, after stratification by age, previous use of OP medications, and by prespecified key SI risk factors.
- Objective 3: to compare the risk of SI and serious Covid-19 infection in romosozumab users in the indicated population in Europe as per the SmPC to the risk of SI seen amongst users of ALN similar to the indicated population for romosozumab in Europe as per the SmPC and 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 (European Medicines Agency [EMA]/95098/2010, Rev 7).

- Objectives 1 and 2, as outlined in Section 8, will report IRs of SI events and serious Covid-19 infection (hospitalisation or death due to SI and Covid-19) in new users of romosozumab adherent to the indicated population of 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 and will compare the risk of SI events and serious Covid-19 infection (hospitalisation or death due to SI and Covid-19) in new users of romosozumab adherent to the indicated population defined in the SmPC, compared to new users of ALN with similar baseline characteristics.

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 center 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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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 [GePaRD]), 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 for at least 12 months, with 1 of the 6 participating data sources (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 at the most recent version of data that is available within each of the databases at the end of the study, expected 5 years after the study start date. Annual reports will be submitted for a total of 5 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 following interim and/or final report/s. If the minimum sample size is reached before the end of the 5-year study period, the study will continue until the end of the study period 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, will comprise of all women from the source population with severe OP who are dispensed or prescribed an OP medication of interest for the first time (new users) 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.

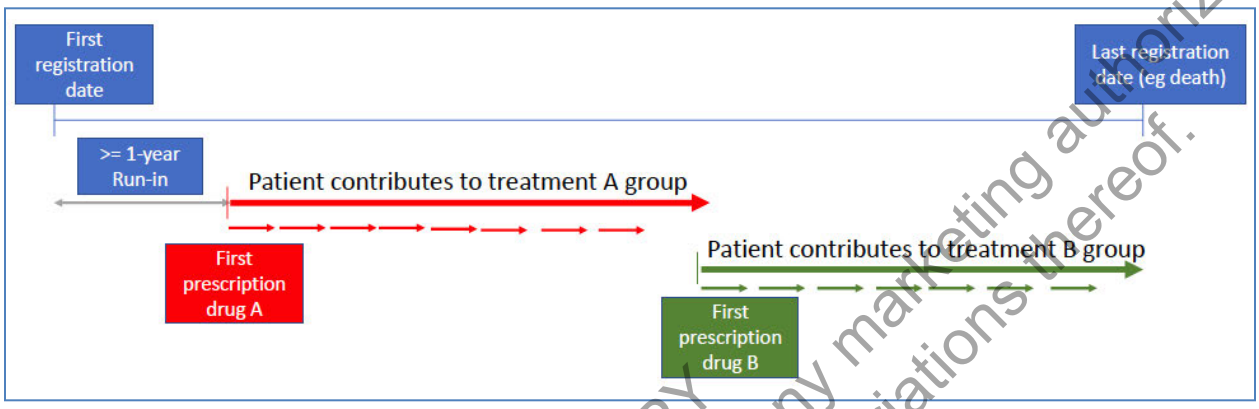
OP medications of interest are romosozumab, ALN, other oral bisphosphonates (risedronate, ibandronate), intravenous bisphosphonate (zoledronate), denosumab, and teriparatide and will be identified through specific codes in dispensation or prescription records. To identify new users, no prior use of the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

The date of the first dispensation or prescription within the study period that qualifies the user as a new user of 1 of the study drugs will be defined as the index date. Analyses will be conducted using a time-varying exposure strategy, where patients who switch to another index treatment

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

(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 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 enrollment.
- No prior use of the same drug (or drug class) during the 12 months prior to index date.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

9.2.5 Exclusion criteria

The exclusion criteria include:

- Dispensing, claim, or prescription of more than 1 study drug on the same date (i.e., combination therapy).
- Patients with a diagnosis Paget's disease at any time before the index date (i.e., treatment initiation).
- User/s of the same drug/drug class in the year before the index date (or the same drug in combination with another therapy, e.g., alendronic acid and cholecalciferol (ATC CCI [redacted])).
- Patients with a history of SI in the 30 days before the index date.

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

- 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 drugs (except calcium/vitamin D supplements) for >1 month will result in the censoring of the patient, as will reinitiation of a new treatment episode related to a previously prescribed treatment.

Two follow-up periods will be included for the estimation of SI 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 SI 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, or end of the 12 months after the index date. The total follow-up period is designed to cover a 12-month, post-initiation period in line with romosozumab administration per the SmPC.

For the fixed follow-up period, the patients will be followed in their respective cohorts until the first occurrence of loss to follow-up, SI events 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 (except calcium/vitamin D supplements) or switching. For the fixed follow-up analysis, the IR of SI events of interest will be reported at 6, 12, 18 and 24 months following the identified index dates for study drug initiation.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

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:
  - ALN (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 the 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).

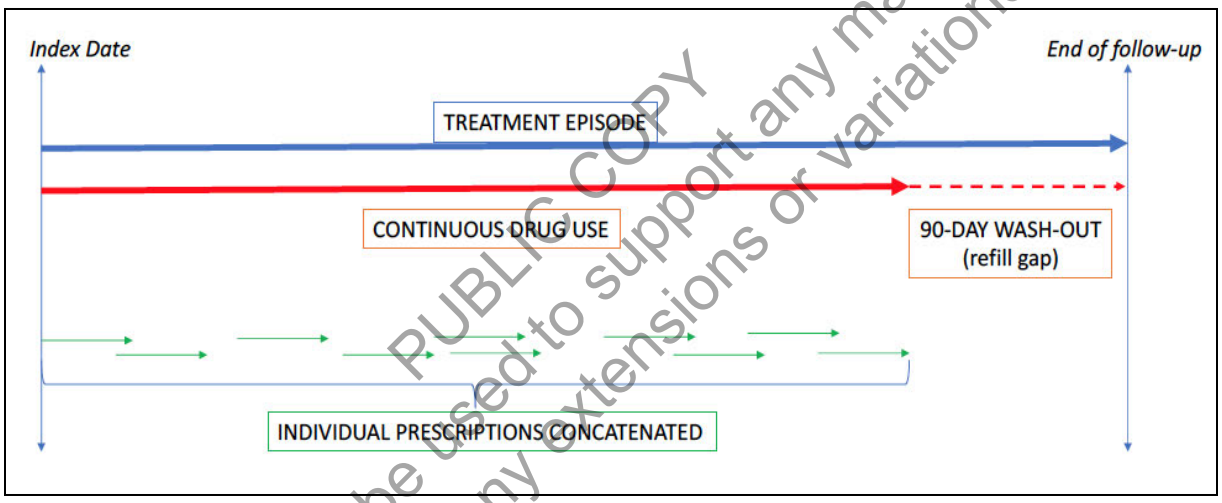
The recommended dose of romosozumab is 210mg (administered as 2 subcutaneous injections of 105mg each) once monthly for 12 months. Romosozumab 105mg solution for injection is delivered via a prefilled pen or prefilled syringe, each delivering 105mg of romosozumab in 1.17mL of solution (90mg/mL).

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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 switches 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. A switch from romosozumab or ALN to any other OP drug will result in censoring. In contrast, switching from ALN

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

to romosozumab or from romosozumab to ALN will be handled as a time-varying exposure, just like in objectives 1 and 2.

9.3.2 Outcomes

Primary outcome: SI leading to hospitalisation.

Secondary outcomes

- Death due to SI, operationalised as either of:
  - In-hospital death with a diagnosis of infection during the same admission/episode.
  - Recorded diagnosis of any infection followed by death in the subsequent month.
- Serious Covid-19 infection leading to hospitalisation.
- Death due to serious Covid-19 infection, operationalised as either of:
  - In-hospital death with a diagnosis of Covid-19 infection during the same admission/episode.
  - Recorded diagnosis of Covid-19 infection followed by death in the subsequent month.

Outcome identification and validation

The proposed code list/s or algorithm/s for the identification of SI are fully detailed in Appendix 3. No validation has yet been undertaken for the outcomes of "serious infection leading to hospitalization" (Holland-Bill et al, 2014) and "serious infection requiring intravenous antimicrobial therapy" hence, validation studies will be required.

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); and SIDIAP through linkage to the administrative database of national insurance; NDR through the linkage to the Danish Mortality Register [Schmidt et al, 2014; Helweg-Larsen, 2011]) (see Table 1). Mortality has been previously validated in GePaRD and shown to be highly valid (positive predictive value [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.

Table 1: Overview of outcome validation available with references

Database	Validity of SI	Validity of death
NDR (DK)	Yes	Yes (built in validation of civil registration system) (Madsen et al, 2003)
IPCI (NL)	No	Yes[a]

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

Table 1: Overview of outcome validation available with references

Database	Validity of SI	Validity of death
SIDIAP (ES)	No	Yes
GePaRD (DE)	No	Yes (Ohlmeier et al, 2016; Ohlmeier et al, 2015)
CPRD (UK)	Yes	Yes (specific death register)

CPRD=Clinical Practice Research Datalink; DE=Germany; DK=Denmark; ES=Spain; GePaRD=German Pharmacoepidemiological Research Database; IPCI=Integrated Primary Care Information Project; NDR= National linked Danish Registries; NL=Netherlands; PASS=post-authorization safety study(ies); SI=serious infection; 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 of the proposed study timelines. If this shows a low PPV (<75%), then all "potential" cases in the comparative safety analysis will be individually validated, and only confirmed ones will be included for analysis. This strategy has been recently implemented in similar PASS including EUPASS9117 (EU-ADR Alliance, 2017).

Details of 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 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, SI risk factors, markers of OP severity, and use of other medications at baseline. This list will be refined following CCI

CCI

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]), and

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

laboratory values, whilst registers, hospital records and claims data will have richer data on healthcare resource use (e.g., hospital contacts), 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:
  - Socio-demographics: age, sex, socio-economic status (where available).
  - Country of residence/database.
  - Number of previous general practitioner (GP)/hospital contact/s in the year before the index date.
  - Number of ATC/British National Formulary (BNF) codes prescribed in the year before the index date.
  - Charlson comorbidity index (most recent as recorded in the year before the index date).
  - Other (selected) comorbidities:
    - Liver failure/disease.
  - Laboratory markers
    - White blood cell counts (total and subtypes as available).
    - Serum creatinine.
    - 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.
- SI risk factors - A final list will be defined with feedback from clinicians with expertise in the management of serious infectious disease. A preliminary list is provided here:
  - BMI/obesity (as recorded in previous year).
  - Smoking (as recorded in previous year).
  - Alcohol drinking (as recorded in previous year).
  - History of asthma.
  - History of chronic obstructive pulmonary disease.
  - History of any surgery in the year before the index date.
  - History of chronic kidney disease.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

  - History of liver failure/liver disease.
  - History of immunodeficiencies.
  - History of human immunodeficiency virus infection (HIV) and/or acquired immune deficiency syndrome (AIDS).
  - Previous history of SI events.
- Markers of disease severity (risk factors for OP/fractures):
  - History of recorded OP at any time before the index date.
  - History of previous OP medication/s use.
  - History of previous fracture/s: site/s (hip, vertebral, major osteoporotic, other/s), number of fracture/s, and time from most recent to index date.
  - History of rheumatoid arthritis at any time before 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 inhaled respiratory glucocorticoids (ATC CCI).
  - 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 before the index date: type, number of therapies, and DDDs prescribed.
  - 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 before the index date.
  - Previous use of prescribed calcium and vitamin D (concomitant) supplements (ATC CCI) in the year before the index date.
  - Use of 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 score based on the Garvan nomogram (Bolland et al, 2011), recently tested by members of the EU-ADR Alliance.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

  - Bone mineral density T-score recorded in the year before the index date (if available) (Note: not to be included in the propensity score due to probable confounding by indication).

- Use of other medications at baseline:
  - Use of any drugs: number of different ATC classes (ATC 4-digit groups) used in the year prior to cohort entry.
  - Use of antineoplastic agents (ATC CCI).
  - Use of immunosuppressants (ATC CCI).
  - Use of lipid-lowering agents (ATC CCI) at cohort entry.
  - Use of oral antidiabetic agents (ATC CCI) at cohort entry.
  - Use of antihypertensive drugs in the year prior to cohort entry: alpha blockers (ATC CCI), beta-blockers (ATC CCI), angiotensin-converting enzyme inhibitors (ATC CCI), angiotensin II inhibitors (ATC CCI), calcium channel blockers (ATC CCI).
  - Use of low-dose aspirin (ATC CCI) or clopidogrel (ATC CCI) in the year prior to cohort entry.
  - Previous use of anticoagulants in the year prior to cohort entry: vitamin K antagonists (ATC CCI), heparins (ATC CCI), direct thrombin inhibitors (ATC CCI), direct factor Xa inhibitors (ATC CCI).
  - Previous use of OP medications (ATC CCI) in the year prior to cohort entry.
  - Polypharmacy: use of, for example, 5 or more medications from different therapeutic classes in the year prior to cohort entry.
  - Number of ATC/BNF codes prescribed in the year before the index date.

9.3.3.2 Interaction/stratification terms

The SI event/s rates (as in objectives 1 and 2) will be provided stratified by key SI risk factors.

The IRs of SI events of interest 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: Prior OP medication use will be defined by at least 1 prescription/dispensation or claim for an OP medication other than the study drug during the baseline period.
- Previous history (prior year) of SI events.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

Further stratification variables will be defined to capture all relevant SI 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 different 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, in order to provide heterogeneous and representative data on the safety of romosozumab as well as ensuring sufficient statistical power for the study.

All analyses will be conducted in a federated manner using the tools previously validated and tested in several 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), the 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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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
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
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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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 healthcare 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 3414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in EMRs, comprehensive demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes.

Health professionals gather this information using International Classification of Diseases, revision 10 (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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

9.4.4 CPRD GOLD & AURUM, the UK

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

The 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 hospital. The acceptability of GePaRD for pharmacoepidemiological research has been assessed methodologically as well as by validation studies (Ohlmeier et al, 2016; Ohlmeier et al, 2015; Ohlmeier et al, 2014; Pigeot and Ahrens, 2008). Recently, GePaRD has been used for various types of pharmacoepidemiological studies including drug 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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

(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) GOLD & AURUM	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= National 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, for each of these databases, all patients meeting the eligibility criteria previously described will be included in the analysis.

For more details about the outcome ascertainment algorithms and their validity, refer to Section 9.6 and Appendix 4 Validation process for study outcomes.

In this amended protocol, the needed number of romosozumab users and comparator users were calculated based on the assumption that the background level of incidence rate (IR) of SI events in this population is around 5 per 100 person-years (py), which is the lowest of the observed rates through analyses of observational data in scope of this study. Indeed, the analysis of the 3 databases (NDR, CPRD and GePaRD) from previous OP0006 interim report (interim report #3 –

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

Year 3 – M36, submission date 19th September 2023) for the validated primary outcome (SI) showed that the IRs of SI in alendronate users (comparator) with documented 2-year history of fracture based on 23,941 person-years of follow-up ranged from 5.4 to 13.2 per 100py (Table 4). For this sample size calculation, we used the lowest bound of 95% CI for the NDR database (cohort reporting lowest IR) as the assumed IR (i.e., IR=5 per 100py).

Table 4: Incidence of Serious Infection based on the exposure-based analysis reported in this study for alendronate users by database.

Database (country)	Person-year (PY)	N	IR per 100 PY (95% CI)
NDR (DK)	8,097.67	441	5.4 (5.0 - 6.0)
CPRD AURUM (UK)	10,818.02	1,045	9.7 (9.1 - 10.3)
GePaRD (DE)	5025.47	665	13.2 (12.2 - 14.3)

CPRD=Clinical Practice Research Datalink; DE=Germany; DK=Denmark; GePaRD=German Pharmacoepidemiological Research Database; NDR= National linked Danish Registries

Estimates of background rates of SI from observational data were prioritized ahead of those available from romosozumab clinical studies that, as expected were much lower. Indeed, there are several reasons why IR values derived from the clinical studies of romosozumab would be less suitable for the exercise. First, generally there are inherent differences in population characteristics between patients enrolled in randomised controlled trials and those observed in post-marketing real-world studies. Secondly, the COVID-19 pandemic (which happened after romosozumab clinical studies) had an important impact on incidence of SI deaths and hospitalisations and affect the rate of SI in this study. As expected, IR estimates from romosozumab clinical studies were much lower than the published literature in the general population (Theilacker et al. 2021, Yang et al. 2022) as well as IRs observed in this study.

The targeted HR to be detected was set at 1.5 based on the observation from the study 20070337 (FRAME), although not statistically significant. It should be noted that this observation was not made in study 20110142 [ARCH], which included a more similar romosozumab label population. Therefore, the conservative approach was taken to use the only observed risk in any population in order to answer whether the observed HR of 1.5 was purely a chance finding, given limited power in that study to be conclusive.

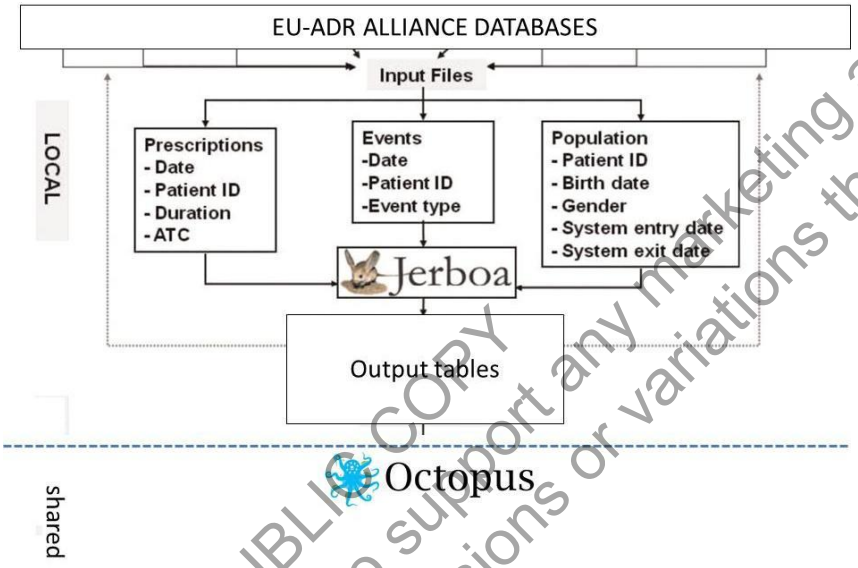
To achieve 90% power with an alpha risk of 0.05 to identify HR=1.5 with IR=5 per 100py of SI, and expected dropout of 10%, this study needs 1,339 romosozumab users and 4,018 alendronate users (1:3 matched controls) (Barthel et. al. 2006).

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

9.6 Data management

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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

- 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.

9.6.3.1 Benchmarking of incidence rates of events

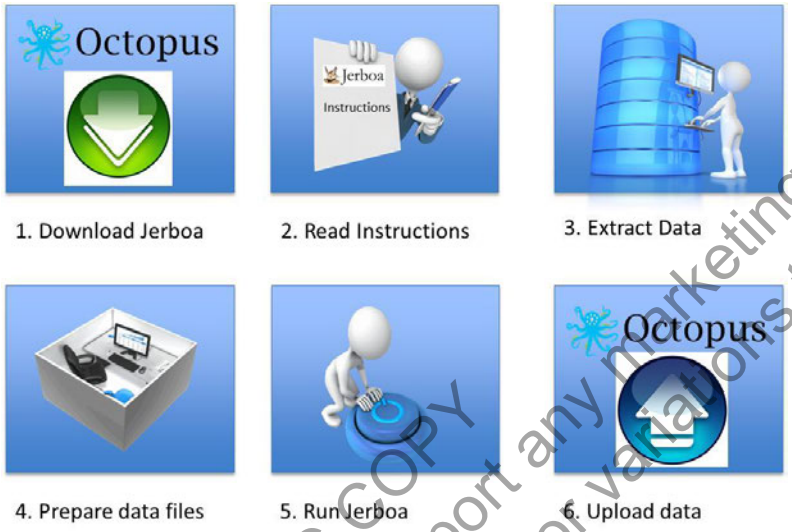
For each endpoint and covariate, database-specific IRs will be benchmarked using Jerboa©; scripts will be generated by Erasmus MC. The observed IRs are compared with IRs estimated from previous database studies and literature. Outliers are identified and further investigated in an iterative manner.

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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

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



PUBLIC COPY
This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

9.6.4 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.

9.6.5 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.

9.6.6 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 anonymized de-identified data that will be

shared in the RRE where members will have a secure and restricted access and where data will be 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 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 SI 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 similar indication and with similar outcomes (EUPASS9117), have demonstrated the feasibility and robustness of the proposed multi-database multinational real world comparative safety approach (EU-ADR Alliance, 2017). All analyses will be double-coded in 2 different statistical packages by 2 different statisticians at Oxford before sharing analytical programs with the different partners for analysis.

9.7.1 Statistical elements

9.7.1.1 Data analysis of the descriptive study component

9.7.1.1.1 SI incidence rates

For the analysis which determines the IR of each SI 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 SI events of interest will be reported as well.

- Scenario 1: follow-up per drug exposure

  IR of SI 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.

  IR of SI events of interest

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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

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

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 SI 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 SI incidence rates

For each study drug exposure cohort, the SI IRs and 95% CIs will be stratified by the variables presented above 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 as per the proposed label. Key features to be added in the propensity score equation will therefore include predictors of fracture as well as SI 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

CCI [redacted]

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

This document cannot be used to support any marketing authorization
PUBLIC COPY
or any extensions or variations thereof.

randomized controlled trials in different settings (Strauss et al, 2019). 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 SI safety endpoints (hospitalization, death due to infection) according to drug exposure in the propensity-matched cohorts. These analyses will be conducted "per treatment episode" as described above.

Should an association between romosozumab use and death (all cause or SI) be identified (in either direction), cause-specific hazards from competing risk analyses will be calculated to assess the risk of the primary outcome of hospitalization due to SI (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 (bone mineral density [BMD] T-score <-2.5 and a fracture recorded in the year prior to start 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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

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 with academic clinicians and provided in advance before comparative analyses are conducted. A preliminary and non-exhaustive list of potential negative control outcomes is listed here for illustrative purposes:

- Hernia repair surgery
- Inguinal hernia
- Road traffic accident
- Shoulder tendonitis/rotator cuff disease
- Knee osteoarthritis
- Hand osteoarthritis

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/channelling 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 SI safety after accounting for unobserved confounding.

9.7.1.4.4 Self-controlled case series analysis (SCCS)

A 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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

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 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 SI risk between patients with or without prior fractures, we will perform a sensitivity analysis only including patients with at least one fracture in the 2 years prior to the therapy initiation as well as in patients with at least one fracture at any time before therapy initiation. IRs of SI outcomes will be reported for this population in different countries and comparative safety analysis will be performed after achieving minimum sample size required in this population (see section 9.5). 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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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.

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 most likely to suffer more severe OP) will likely produce differences in baseline characteristics between romosozumab and other drug users, the study will use several methods to deal with confounding:

- Restriction: comparative studies will be conducted only in persons in line with the label to restrict the population to those who would be prescribed romosozumab according to the label.
- 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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

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 regulation as well as with ethical and regulatory issues including those on privacy.

All of the databases used in this study are already used for pharmacoepidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with 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).

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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).

All the identified adverse events related to the study outcomes will be summarized in the interim and final study report, which will consist 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 incidence and risk of SI associated with the use of romosozumab in comparison with other available OP medications will be provided in yearly increments. An interim comparative report will be submitted in year 3 after the beginning of the study and the final study report in year 4 after the beginning of the study.

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

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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

13 REFERENCES (AVAILABLE UPON REQUEST)

Aberra FN, Stettler N, Brensinger C, Lichtenstein GR, Lewis JD. Risk for active tuberculosis in inflammatory bowel disease patients. Clin Gastrolenterology and Hepatology. 2007;5(9):1070-5.

Ali MS, Uddin MJ, Groenwold RH, Pestman WR, Belitser SV, Hoes AW, et al. Quantitative falsification of instrumental variables assumption using balance measures. Epidemiol. 2014;25(5):770-2.

Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016;133(6):601-9.

Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10(2):150-61.

Barthel FM, Babiker A, Royston P, Parmar MK. Evaluation of sample size and power for multi-arm survival trials allowing for non-uniform accrual, non-proportional hazards, loss to follow-up and cross-over. Stat Med. 2006 Aug 15;25(15):2521-42.

Bolland MJ, Siu AT, Mason BH, Horne AM, Ames RW, Grey AB, et al. Evaluation of the FRAX and Garvan fracture risk calculators in older women. J Bone Miner Res. 2011;26(2):420-7.

De Wilde S, Carey IM, Bremner SA, Richards, N, Hilton SR, Strachan DP, et al. A comparison of the recording of 30 common childhood conditions in the Doctor's Independent Network and General Practice Research Databases. Health Stat Q. 2004:2:21-30.

EMA/813938/2011, Rev 3: Guideline of good pharmacovigilance practices (GVP). Module VIII – post-authorisation safety studies (Revision 3) (EMA). 2017. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf. Accessed on 25 Jan 2020.

EMA/95098/2010, Rev 7: Guide on methodological standards in pharmacoepidemiology (Revision 7). The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). 2010. Available from: http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideonMethStandardsinPE_Rev7.pdf. Accessed on 25 Jan 2020.

EU-ADR Alliance. European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance: RMM Analyses (part of Final Report). 23 Nov 2017. Available from: http://www.encepp.eu/encepp/openAttachment/studyResult/23300. Accessed on 25 Jan 2020.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP Resources Database. 2019. Available from: www.encepp.eu/encepp/resourcesDatabase.jsp. Accessed on 25 Jan 2020.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct. For scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies (Revision 4). 2018. Available from:

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

http://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct.pdf. Accessed on 25 Jan 2020.

García-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inform Prim Care. 2011;19(3):135-45.

Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health. 2011;39(Suppl 7):26-9.

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 Cochrane, 2022. Available from: www.training.cochrane.org/handbook.

Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357:j2099.

Holland-Bill L, Xu H, Sorensen HT, Acquavella J, Svaerke C, Gammelager H, et al. Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish National Registry of Patients. Ann Epidemiol. 2014;24(8):593-7.

International Council for Harmonisation (ICH). Guideline of Pharmacovigilance Planning. Technical Requirements for Registration of Pharmaceuticals for Human Use (E2E). 2004. Available from: https://database.ich.org/sites/default/files/E2E_Guideline.pdf. Accessed on 25 Jan 2020.

International Society of Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP) (Revision 3). Jun 2015. Available from: https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Accessed on 25 Jan 2020.

Jick SS, Lieberman ES, Rahman MU, Choi HK. Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Care & Research. 2006;55(1):19-26.

Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: Historical foundations and contemporary application. Curr Epidemiol Rep. 2015;2(4):221-8.

Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: A comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol. 2003;56(2):124-30.

McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med. 2014;370(5):412-20.

Nguyen TL, Collins GS, Spence J, Daurès JP, Devereaux PJ, Landais P, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol. 2017;17(1):78.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof
PUBLIC COPY

Ohlmeier C, Langner I, Garbe E, Riedel O. Validating mortality in the German Pharmacoepidemiological Research Database (GePaRD) against a mortality registry. Pharmacoepidemiol Drug Saf. 2016;25(7):778-84.

Ohlmeier C, Langner I, Hillebrand K, Schmedt N, Mikolajczyk R, Riedel O, et al. Mortality in the German Pharmacoepidemiological Research Database (GePaRD) compared to national data in Germany: results from a validation study. BMC Public Health. 2015;15:570.

Ohlmeier C, Frick J, Prütz F, Lampert T, Ziese T, Mikolajczyk R, et al. Use of routine data from statutory health insurances for federal health monitoring purposes. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2014;57(4):464-72.

Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. J Bone Miner Res. 2011;26(1):19-26.

Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:i4515.

Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf. 2008;17(3):215-23.

Pottegård A, Schmidt SA, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: The Danish National Prescription Registry. Int J Epidemiol. 2017;46(3):798-798f.

Reyes C, Tebe C, Martinez-Laguna D, Ali M, Soria-Castro A, Carbonell C, et al. One and two-year persistence with different anti-osteoporosis medications: a retrospective cohort study. Osteoporos Int. 2017;28(10):2997-3004.

Rubin KH, Möller S, Holmberg T, Bliddal M, Søndergaard J, Abrahamsen B. A new Fracture Risk Assessment Tool (FREM) based on public health registries. J Bone Miner Res. 2018;33(11):1967-79.

Schink T, Kollhorst B, Varas Lorenzo C, Arfè A, Herings R, Lucchi S, et al. Risk of ischemic stroke and the use of individual non-steroidal anti-inflammatory drugs: A multi-country European database study within the SOS Project. PLoS One. 2018;13(9):e0203362.

Schink T, Holstiege J, Kowalzik F, Zepp F, Garbe E. Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination. Vaccine. 2014;32(6):645-50.

Schmedt N, Kollhorst B, Enders D, Jobski K, Krappweis J, Garbe E, et al. Comparative risk of death in older adults treated with antipsychotics: A population-based cohort study. Eur Neuropsychopharmacol. 2016a;26(9):1390-400.

Schmedt N, Jobski K, Kollhorst B, Krappweis J, Rüther E, Schink T, et al. Treatment patterns and characteristics of older antipsychotic users in Germany. Int Clin Psychopharmacol. 2016b;31(3):159-69.

Schmidt M, Schmidt SA, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019;11:563-91.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, quality, and research potential. Clin Epidemiol. 2015;7:449-90.

Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-9.

Schuemie MJ, Hripcsak G, Ryan PB, Madigan D, Suchard MA. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. Proc Natl Acad Sci USA. 2018;115(11):2571-7.

Strauss V, Prats-Uribe A, Berencsi K, Carr A, Judge A, Silman A, et al. Propensity score stratification and inverse probability weighting compared to surgical randomized clinical trial results in device epidemiology. Pharmacoepidemiol Drug Saf. 2019;28(Suppl 2):79.

Theilacker C, Sprenger R, Leverkus F, Walker J, Häckl D, von Eiff C, Schiffner-Rohe J. Population-based incidence and mortality of community-acquired pneumonia in Germany. PLoS One 2021;16(6):e0253118.

Van Staa TP, Abenhaim L. The quality if information recorded on a UK database of primary care records: A study of hospitalization due to hypoglycemia and other conditions. Pharamacoepidemiol Drug Saf. 1994;3(1):15-21.

Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: The IPCI Project. Methods Inf Med. 1999;38(4-5):339-44.

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbrouche JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9.

Voordouw AC, Sturkenboom MC, Dieleman JP, Stijnen T, Smith DJ, van der Lei J, et al. Annual revaccination against influenza and mortality risk in community-dwelling elderly persons. JAMA. 2004;292(17):2089-95.

Wentzell N, Schink T, Haug U, Ulrich S; Niemeyer M, Mikolajczyk R. Optimizing an algorithm for the identification and classification of pregnancy outcomes in German claims data. Pharmacoepidemiol Drug Saf. 2018;27(9):1005-10.

World Health Organization Collaborating Centre for Drug Statistics Methodology. ACT/DDD Index 2019. Available from: https://www.whocc.no/atc_ddd_index/. Accessed on 25 Jan 2020.

Yang X, Chen H, Zheng Y, Qu S, Wang H, Yi F. Disease burden and long-term trends of urinary tract infections: A worldwide report. Front Public Health 2022:10:888205

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

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 Codes for Study Outcomes
4	Appendix 4	28 Jan 2020	Validation Process for Study Outcomes

PUBLIC COPY
This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

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:

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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

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

Comments:

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

Comments:

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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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

This document cannot be used to support any marketing authorization application or any extensions or variations thereof. PUBLIC COPY

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:

This document is PUBLIC COPY. It cannot be used to support any marketing authorization application and any extensions or variations thereof.

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

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

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: _____

PUBLIC COPY
This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

APPENDIX 3. LIST OF DIAGNOSIS CODES FOR STUDY OUTCOMES

A recent study has validated the coding of hospital diagnosis for infection with high PPV in Denmark (Holland-Bill et al, 2014).

The list of infection types included, and the ICD-10 codes used to identify them are detailed here:

Specific infection types	Broad infection types	Diagnostic codes according to the Danish version of the ICD-10
Pneumonia	Respiratory tract infection	J139, J151, J152, J157, J159, J180, J181
Other respiratory tract infection	Respiratory tract infection	J189, B599, J019, J039, J209, J320
Intestinal infection	Intestinal infection	A047, A099, B962, K122, K350, K359, K570, J573, K610, K611, K612, K810, K811
Cellulitis or erysipelas	Skin infection	N469, L030, L031, L038, L089
Other skin infection	Skin infection	L021, L022, L029, H620
Bladder infection	Urinary tract infection	N300, N309
Kidney infection	Urinary tract infection	N109, N151
Other urinary tract infection	Urinary tract infection	N390
Endocarditis	Endocarditis	I330
Meningitis	Intracranial infection	B003
Bacteremia	Bacteremia	A499, N499A
Sepsis	Sepsis	A408, A409, A410, A412, A415, A418, A419, B377
Osteomyelitis	Bone/joint infection	M860
Septic arthritis	Bone/joint infection	M009
Tuberculosis	Tuberculosis	A169, A180
Aspergillosis	Aspergillosis	B440
Other	Other	B370, B378, K122, H031, H702

ICD-10=International Classification of Diseases, revision 10

Serious infections will be identified in all the contributing databases as any of the above codes (or equivalent mapped code/s) for infection associated with a hospital admission and/or resulting in mortality. This results in 3 possible outcomes that will be included for analyses in the main study:

- Serious infection diagnosis leading to hospital admission (primary outcome). This will be defined as the presence of 1 of the conditions above recorded as part of the diagnoses recorded in a hospital admission where hospital or claims data are available. Where linked hospital or claim records are not available (IPCI [Netherlands]), the above diagnoses will be identified from primary care records, and free text reviewed for all such potential cases to identify those with evidence of a related hospital admission.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY

- In-hospital death with a diagnosis of infection during the same admission (secondary outcome). This will be defined as the presence of 1 of the conditions above recorded as part of the diagnoses recorded during a hospital admission that resulted in an in-hospital death. Where linked hospital or claim records are not available (IPCI [Netherlands]), the outcome below (#3) will be used instead.
- Recorded diagnosis of any infection in either primary or secondary care/hospital records, followed by death in the subsequent month (secondary outcome). The diagnosis of any infection in any patient clinical data (primary or secondary care records or claims) followed by death in the subsequent month will be identified.

PUBLIC COPY
This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

APPENDIX 4. VALIDATION PROCESS FOR STUDY OUTCOMES

Validation studies will be conducted for the study outcome, ie, SI/s for all databases except CPRD (UK) and the nationwide linked Danish registers. The results from validation studies from Denmark have been reported previously (Holland-Bill et al, 2014).

As for CPRD (UK), a number of validation studies have been reported on different types of specific infections.

First author	Year of publication	Journal/Reference	Specific infection type validated
Aberra	2007	Clinical Gastroenterol and Hepatol 5: 1070-1075	Tuberculosis
De Wilde	2004	Health Statistics Quarterly 22: 21	Impetigo
De Wilde	2004	Health Statistics Quarterly 22: 21	Measles
De Wilde	2004	Health Statistics Quarterly 22: 21	Rubella
De Wilde	2004	Health Statistics Quarterly 22: 21	Scabies
De Wilde	2004	Health Statistics Quarterly 22: 21	Urinary tract infection
De Wilde	2004	Health Statistics Quarterly 22: 21	Viral illness
Jick	2006	Arthritis and rheumatism 55(1): 19-26	Tuberculosis
Van Staa	1994	Pharmacoepidemiology and Drug Safety 3: 15-21	Urinary tract infection
Van Staa	1994	Pharmacoepidemiology and Drug Safety 3: 15-21	Respiratory infection

None of them have previously validated the diagnosis of infection or serious/hospital infection.

Serious infections are defined for the proposed studies as a combination of 1 or more infection codes with either evidence of a hospital admission or a related death.

- Hospital admissions will be identified using linked data in SIDIAP (Spain) (linked to loco-regional hospital admissions data in the so called Conjunto Mínimo de Datos [CMBD] database), CPRD (UK) (linked to English national hospital admissions data in the Hospital Episode Statistics [HES] Admitted Patient Care database), national health registers in Denmark, and claims GePaRD (Germany), and therefore, do not need validation.
- Databases with no linkage to either hospital or claims data (IPCI [Netherlands]) will review free text for all potential cases for comparative safety analysis (amongst eligible users of romosozumab or ALN in the study period) to identify related hospital admissions for the identification of potential cases. Medical charts, hospital letters and any other documents available will be reviewed by medical students and/or medical doctor.
- Finally, death has either been previously validated or will be validated as part of the concomitant CV PASS.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.
PUBLIC COPY

Therefore, it is the diagnosis of infection/s that needs validation. Sample validation studies of 250 cases will be needed from all the contributing databases except NDR (Denmark) and CPRD (UK).

For all others, validations in primary care databases (SIDIAP and IPCI) will be based on free text review of the individual cases. Primary care charts and any related documents (eg, specialist letters, referrals) will be reviewed by clinically trained validators using prespecified algorithms.

As for validations in GePaRD (Germany), a combination of plausibility of diagnoses and case reviews will be used as recently described (Wentzell et al, 2018). This 2-step process consists of the following stages:

- Plausibility" of diagnoses: Characterisation of potential "case" patients (eg, regarding age, sex, risk factors, comorbidity), and assessment of related diagnostic procedures, treatment/s initiated, follow-up, and outcome/s (eg, duration of hospitalization, mortality).
- External validation: the proposed (and refined as based on information from 1) case ascertainment algorithm/s are applied to external data where case review is possible (eg, from academic collaborating hospitals). Case verification will be based on information from the hospital records, and PPVs calculated for the algorithm used in GePaRD.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof. PUBLIC COPY