Romosozumab (ATC M05BX06)

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

Final report – Year 5 – M60

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Research questions and objectives	The overarching objective of this study is to monitor the potential risk of serious infection associated with the use of romosozumab in comparison with other available osteoporosis medications in routine clinical practice in Europe
Country (-is) of study	The Netherlands, Denmark, Spain, the United Kingdom, and Germany
Author	PPD

MARKETING AUTHORISATION HOLDER

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

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1 ABSTRACT

Title	**European non-interventional post-authorization safety study related to serious infections for romosozumab by the EU-ADR Alliance**
Keywords	Osteoporosis, serious infection events, COVID-19, epidemiology, electronic health records
Rationale and background	An imbalance in the incidence of serious adverse events (SAEs) of infections was observed in a placebo-controlled study, FRAME. Incidence of serious infections and infestations was 1.9% amongst romosozumab users and 1.3% amongst placebo users. The difference was mainly driven by cases of serious pneumonia (romosozumab 0.5% and placebo 0.3%). Serious infections (SIs) are considered an important potential risk in the European Union (EU)-Risk Management Plan (RMP) for romosozumab.
Research question and objectives	Overarching objective: to assess the risk of SI associated with the use of romosozumab in comparison with other routinely used osteoporosis (OP) medications in Europe. This final report addressed 3 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 SmPC, and in cohorts of users of other OP medications similar to the romosozumab indicated population in Europe as per the SmPC. • Objective 2: to assess the IR of SI and serious COVID-19 infection in subgroups of romosozumab users and amongst users of other OP medications 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 to users of alendronate with similar baseline characteristics.
Study design	A multi-national, multi-database cohort study of new users of romosozumab and other OP medications. For the comparative safety analysis, a propensity score-matched study design was used. The study period for this fifth and final report covered data extraction from January 2018 up until the most recent version of data that was available within each of the databases (between December 2022 to January 2025).
Setting	Population in routinely collected datasets in the Netherlands (IPCI), Denmark (NDR), Spain (SIDIAP), the United Kingdom (CPRD) and Germany (GePaRD) including primary care electronic health records, linked hospital inpatient data, and national registries.
Study patients and study size, including dropouts	Women aged ≥50 who were new users of an OP drug between January 2018 and January 2025. New users were those initiating a single OP drug during the study period, with no use of the same drug in the last year. Women with a history of myocardial infarction (MI), stroke, Paget's disease, SI in the prior 30 days, and cancer any time prior to OP treatment initiation were excluded. The minimum sample size needed to run the comparative safety analysis was pre-specified at 1,399 romosozumab users and 4,018 alendronate users using

	propensity score matching with 1:3 ratio. In this study, there were 1,887 eligible users of romosozumab and 311,058 eligible users of alendronate. After propensity score matching, 1,738 romosozumab users were matched to 4,632 alendronate users.
Variables and databases	This fifth and final report contains results from 6 databases: 3 that participate in the EU-ADR Alliance (IPCI, Netherlands; NDR, Denmark; and SIDIAP, Spain) plus 3 additional databases from 2 European countries, the UK (CPRD GOLD and CPRD Aurum) and Germany (GePaRD). The OP medications of interest included romosozumab, alendronate (primary active comparator), other oral bisphosphonates, intravenous bisphosphonates, denosumab, and teriparatide. The primary outcome was the incidence of SI (i.e., hospitalization due to serious infection). Secondary outcomes were death due to SI, serious COVID-19 infection leading to hospitalisation, and death due to COVID-19 infection. Covariates were assessed at cohort entry (index date) and included socio-demographics, comorbidity, medicines use, SI risk factors, markers of OP severity, and use of other medications. Incidence rates of the primary and secondary outcomes were stratified by age, prior use of OP medications, and history of SI events. For the comparative safety analysis, subgroup analysis was performed in patients with history of fracture in the two years prior or at any time before treatment. Negative control outcome (NCO) analysis assessed up to 71 outcomes that should not be associated with romosozumab. If more than 5% of NCOs were associated with romosozumab use, three further sensitivity analyses were performed: (1) empirical calibration of risk effect estimates, (2) instrumental variable analysis using physician preference as the instrumental variable, and (3) self-controlled case series (SCCS) comparing the incidence of SI in periods exposed and not exposed to romosozumab.
Results	A total of 1,887 eligible users of romosozumab were included. In total, across all databases there were 311,058 eligible users of alendronate, 59,595 oral bisphosphonate, 23,320 intravenous bisphosphonate, 70,640 denosumab, and 12,014 teriparatide. Across the databases, the median age at baseline ranged from 70.7 to 74.4 years for users of any OP drug. The median number of visits to the general practitioner in 1 year before index date ranged from 2 to 11, and number of prescriptions ranged from 3 to 8. OP diagnosis was recorded in 45% to 89% of patients, and 33% to 63% of patients had a previous fracture. Common comorbidities included hypertension (22% to 61%), hypercholesterolaemia (23% to 56%), and established cardiovascular (CV) disease (21% to 43%). In the year prior to treatment, immunosuppressants and systemic glucocorticoids were prescribed in 2.8% to 7.1% and 17% to 25% of patients, respectively. The IR of SI per 1,000 PY in romosozumab users ranged from 24.44 to 90.62; in alendronate users 47.88 to 124.60; in oral bisphosphonate users 36.51 to 135.56; in intravenous bisphosphonate users 79.10 to 115.54; in denosumab users 74.63 to 109.90; and in teriparatide users 62.50 to 177.26.

	There were no or fewer than 5 serious COVID-19 infection events amongst romosozumab users. The IRs of serious COVID-19 infection per 1,000 PY in alendronate users ranged 2.47 to 11.46; in oral bisphosphonate users 2.27 to 15.22; in intravenous bisphosphonate users 3.08 to 19.95; in denosumab users 3.81 to 13.29; and in teriparatide users 4.94 to 36.65. There were no deaths due to SI or serious COVID-19 infection in romosozumab users. Stratification of IR for SI by 5-year age bands showed that IR increased with older age, particularly after the age of 75. Stratification by history of SI showed that IR in all treatment groups was higher in patients with a recorded history of SI in the year before index date. IRs were similar between patients who did and did not have previous use of OP medications. Patterns of IRs stratified by SI risk factors were similar for serious COVID-19 infection. Prior to propensity score matching, across databases romosozumab and alendronate users had visible differences on several important risk factors for SI including age, recorded diagnosis of OP, history of fracture, record of prescription of other OP medications, immunosuppressants, or systemic glucocorticoids in the previous year. Propensity score matching created comparable treatment groups in terms of all observed covariates. Overall, 1,738 (92%) romosozumab users were matched to 4,632 alendronate users. Hazard ratios (HRs) for the primary outcome of SI after matching were estimated in 4 databases. There were no SI events in both treatment groups in IPCI (there were only 61 romosozumab and 160 alendronate users in this database in the matched cohorts). The HRs were 0.49 (95% confidence interval 0.20, 1.18) in NDR; 1.18 (0.69, 2.00) in SIDIAP; 0.98 (0.16, 5.87) in CPRD Aurum; and 1.31 (0.88, 1.95) in GePaRD. Pooling HRs across databases using meta-analysis (I^2 = 26.4% (95% CI 0%, 72.1%)) showed an overall HR 1.12 (95% CI 0.84, 1.51) in the fixed effects model and HR 1.07 (95% CI 0.73, 1.57) in the random effects model. Secondary outcome analysis of serious COVID-19 infection estimated HRs of 0.74 (0.10, 5.22) in NDR; 2.83 (0.42, 19.21) in SIDIAP; and 0.91 (0.15, 5.41) in GePaRD. Meta-analysis pooling the HRs across databases (I^2 = 0% (0%, 89.6%)) estimated an overall HR 1.23 (95% CI 0.41, 3.64). There were no events of death due to SI or serious COVID-19 infection in the matched cohorts in any of the databases. Similar patterns of SI and serious COVID-19 infection in the main analysis were observed for the two subgroup analyses of history of fracture in the prior 2 years, and history of fracture at any time prior to treatment initiation. NCO analyses found evidence of unmeasured confounding only in 1 database, GePaRD. Additional sensitivity analyses in GePaRD found risk estimates similar to the main analyses. Empirical calibration showed a calibrated HR of 1.21 (95% CI 0.81, 1.81) for SI, which was closer to the null value compared to the HR from the main analysis [HR 1.31 (0.88, 1.95)]. In SCCS, comparing risk of SI among romosozumab users in the

	period they were exposed to romosozumab vs. unexposed, the age-adjusted incidence rate ratio was 0.91 (0.54, 1.54).
Discussion	In this final report, 1,887 eligible romosozumab users were included, which provided the power to conduct the comparative safety analysis for SI outcome. The pooled meta-analysis showed no evidence of association between romosozumab use and the risks of SI and serious COVID-19 infection. Subgroup analyses in patients with a recent fracture or any fracture showed the same pattern. The differences observed between romosozumab and alendronate users in the general population of all 5 databases were removed after propensity score matching. NCO and other sensitivity analyses confirmed robustness of meta-analysis results for the main outcome of the study. Overall, this study shows that there is no evidence of increased risk of SI associated with romosozumab in patients with severe OP.
Marketing Authorization Holder	UCB Pharma S.A. Allée de la Recherche 60 B-1070 Brussels Belgium
Name(s) and Affiliation(s) of Principal Investigator(s)	PPD

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
ASMD	absolute standardised mean difference
ATC	Anatomical Therapeutic Chemical
BIPS	Leibniz Institute for Prevention Research and Epidemiology - BIPS
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CV	cardiovascular
DDD	defined daily dose
DENO	denosumab
EMA	European Medicines Agency

Abbreviation	Definition
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
HbA1c	haemoglobin A1c
HMA	Heads of Medicines Agencies
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, revision 9, clinical modification
ICD-10	International Classification of Diseases, revision 10
ICPC	International Classification of Primary Care
IPCI	Integrated Primary Care Information Project
IQR	interquartile Range
IR	incidence rate
IRR	incidence rate ratio
IV	intravenous
IV BP	intravenous bisphosphonate
LDL	low-density lipoprotein
MACE	major adverse cardiac event(s)
MAH	Marketing Authorization Holder
MI	myocardial infarction
NCO	negative control outcome
NDR	Nationwide Linked Danish Registry
OBP	oral bisphosphonate
OP	osteoporosis
ONS	Office for National Statistics
PAS	post-authorization study
PASS	post-authorization safety study(ies)
PS	propensity score
PY	person-years
PPV	positive predictive value
PV	pharmacovigilance
RMM	Risk Minimization Measure
RMP	Risk Management Plan
ROMO	romosozumab
RR	relative risk

Abbreviation	Definition
RRE	remote research environment
SAE	serious adverse event
SCCS	self-controlled case series
SD	standard deviation
SES	socioeconomic status
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
TERI	teriparatide
UMLS®	Unified Medical Language System®

3 INVESTIGATORS

Function	Name	Title	Affiliation	Address
Principal investigator (whole study & UK)	PPD			
Coordinating investigator (whole study & UK)				
Statistician (whole study & UK)				
Principal investigator (NL)				

Function	Name	Title	Affiliation	Address
Coordinating investigator (NL)	PPD			
Principal investigator (DK)				
Coordinating investigator (DK)				
Principal Investigator (ES)				
Coordinating investigator (ES)				
Principal Investigator (DE)				

4 OTHER RESPONSIBLE PARTIES

Function	Name	Title	Affiliation	Address
Study Coordinator (UK)	PPD			

Function	Name	Title	Affiliation	Address
Study co-Coordinator (UK)	PPD			
Study Manager (ES)				
Study Manager (ES)				
Information Technology Programming and Infrastructure				
EU Regulatory Lead - Contact Person (MAH)				
Real World Evidence Lead Scientist - Contact Person (MAH)				
Safety Lead - Contact Person (MAH)				
Participating countries				
Database CPRD (UK)	PPD			

Function	Name	Title	Affiliation	Address
Database IPCI (NL)	PPD			
Database SIDIAP (ES)				
Database NDR (DK)				
Database GePaRD (DE)				
Scientific Advisory Board				
Function	**Name**	**Title**	**Affliation**	**Address**
Scientific Advisor	PPD			
Scientific Advisor				
Scientific Advisor				
Scientific Advisor				
Scientific Advisor				

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; NL=Netherlands; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Registration of the EU PAS register	30 September 2020	25 June 2020	NA
Start of data collection	01 September 2020	01 September 2020	NA
End of data collection	CCI		
Interim report 1-explanatory features of dataset (first semester year 1)	30 September 2021	30 September 2021	NA
Interim report 2-explanatory features of dataset	30 September 2022	19 September 2022	NA
Interim report 3–explanatory features of dataset	30 September 2023	19 September 2023	NA
Interim report 4–explanatory features of dataset	30 September 2024	13 September 2024	NA
Final report of study results	17 December 2025		

EU=European Union; PAS=post-authorization study

6 AMENDMENTS AND UPDATES

The following amendments have been made to the protocol:

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
1	13 August 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 proposed 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.
		4, 9.2.2, 12	Removal of monthly data reports of romosozumab and the need for monthly data collection from the project.	Monthly updates are only available for CPRD GOLD and CPRD Aurum
		Global	Minor administrative, formatting, and typographical changes have been made.	Updated to provide clarity and be consistent with remainder of protocol.
2	April 2023	NA	NA	NA
3	October 2023	6	Milestones	Milestones dates have been revised
		9.2.4	Removal of the inclusion criterion "Severe OP, as identified by the presence of 1 or more fractures of any skeletal sites except face/skull/digit/s fractures recorded in the 2 years prior to therapy initiation"	September 2023 OP0006 interim report showed that a significant number of patients who started romosozumab did not present with a fracture in the 2 years prior to therapy initiation. This criterion is

				removed to not hinder the objective of the study and improve 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	Serious COVID-19 infection was separated 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. 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 CCI [redacted] OP0006 study.	In the third OP0006 interim report, 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 databases. These values are higher than the original assumptions for sample size calculations in the study protocol (1.0 to 2.5 per 100py). The needed sample size was

				recalculated 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 related sections of the protocol	It is not expected to see any romosozumab users in this database until the end of the study since the marketing launch of romosozumab in France is delayed.
		Global	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with the remainder of the protocol.
4	October 2025	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.
		Global	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol.

The following deviations from the protocol have been made:

Deviation number	Date	Section of protocol where deviation occurred	Details
1	June 2025	9.8.1.2.1.1	In propensity score matching, the clustering of patients within a matched set needs to be accounted for to obtain the correct 95% confidence interval for the risk effect estimate for romosozumab. The protocol stated this clustering would be accounted for using Cox regression models stratified by matched sets. Another method is to account for the clustering by incorporating matching weights with cluster-robust standard errors to account for the clustering. This method has been shown to estimate the marginal hazard ratio and has less bias in the effect estimates compared to the Cox regression models stratified by matched sets (1). Therefore, for this analysis the Cox regression model with robust standard errors was implemented.

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 (2, 3). Romosozumab was approved in the European Union (EU) and the UK in December 2019 for the treatment of severe osteoporosis (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.

In postmenopausal women with OP and previous fragility fractures, romosozumab followed by alendronate, showed superior efficacy to standard of care alendronate 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]).

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 OP safety analysis set, overall incidence of SAEs of infections was 1.9% in

romosozumab-treated participants and 1.3% in placebo-treated participants, with a relative risk (RR) of 1.49 (95% confidence interval (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 overall infections and no imbalance for adverse events of infections (serious and nonserious) in the alendronate-controlled study 20110142 (ARCH), in which the incidence of SAEs of infections was 2.3% in romosozumab -treated participants and 2.4% in alendronate -treated participants (RR=0.97; 95% CI: 0.65, 1.44) during the 12-month, double -blind period.

Based on the above observation, serious infections (SIs) were included in the EU-Risk Management Plan (RMP) for romosozumab as an important potential risk.

The aim of this study is to evaluate the real-world incidence of SIs and serious COVID-19 outcomes in romosozumab users across Europe, compared to users of other OP medications. This study is a European multi-national, multi-database, comparative post-authorization safety study (PASS).

7.2 Regulatory action

This EU SI PASS is part of a PASS program aimed at monitoring the safe use of romosozumab in the European population within the framework of a comprehensive RMP. In addition to the EU SI PASS, the PASS program encompasses a study aimed at describing romosozumab use and adherence to the indication and contraindication (Risk Minimization Measure [RMM] PASS) and a comparative study addressing cardiovascular safety (Cardiovascular [CV] PASS).

The study was entered in the EU PAS register on 30th of September 2020 and the protocol is available at the Heads of Medicines Agencies (HMA)-EMA Catalogue of real-word data studies [HMA-EMA RWE Study Catalogue], EU PAS number: EUPAS36001.

7.3 Previous observational studies

This is the first PASS conducted to study the risk of SI associated with the use of romosozumab under routine clinical practice in Europe. In addition, routine post-marketing pharmacovigilance (PV) data are being collected in EU and in other regions of the world, including the US and Japan and submitted to Health Authorities as part of safety reporting.

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 is provided further understanding on the following specific 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 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).

- 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 alendronate similar to the indicated population for romosozumab in Europe as per the SmPC and with similar baseline characteristics.

This final report presents findings for all three objectives.

9 RESEARCH METHODS

9.1 Study design

This was a multi-national, multi-database cohort study of new users of romosozumab and new users of other OP medications. For objective 3, a propensity score cohort study design was implemented.

9.2 Setting

Patients from 5 European countries were involved in this study. The study population was covered in databases from primary care, secondary care, health registers, prescription/dispensation registers and claims.

Data from the following 6 electronic healthcare databases from 5 European countries were 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, the National linked Danish Registries (NDR) from Denmark, Clinical Practice Research Datalink (CPRD) GOLD and Aurum from the UK, and the German Pharmacoepidemiological Research Database (GePaRD) from Germany.

9.2.1 Source population

All women registered in 1 of the contributing databases (from 5 European countries) for at least 12 months and identified during the study period, were eligible as the source population.

9.2.2 Study period

Since the marketing authorization of romosozumab was granted in Europe on the 9th of December 2019, the study began on the 1st of October 2020. Data were collected from 1st of January 2018. The data collection ended with the most recent version of data that was

available within each of the databases at the end of the study, that was between December 2022 and January 2025 (see Table 1 below).

Table 1: Dates of data availability for the final report

Database	Data extraction start date	Data extraction end date
IPCI	01 January 2018	31 December 2024
NDR	01 January 2018	31 December 2024
SIDIAP	01 January 2018	30 June 2024
CPRD GOLD	01 January 2018	31 January 2025
CPRD Aurum	01 January 2018	31 December 2024
GePaRD	01 January 2018	31 December 2022

IPCI: Integrated Primary Care Information Project; The Netherlands; NDR: Nationwide linked Danish registries, Denmark; SIDIAP: Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, Spain; CPRD: Clinical Practice Research Datalink, UK; GePaRD: German Pharmacoepidemiological Research Database, Germany.

9.3 Study Patients

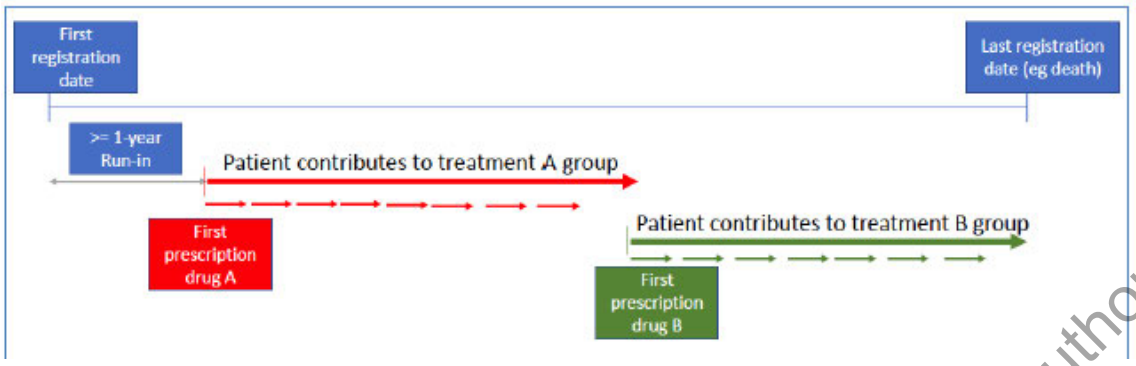
9.3.1 Study population

The study population comprised all post-menopausal women who received romosozumab within the indicated population in Europe as per the SmPC or other OP medications of interest for the first time during the study period (new users). Specific eligibility criteria were applied to all patients (see Section 9.3.2 and Section 9.3.3).

OP medications of interest were romosozumab (ROMO), alendronate (ALN), other oral bisphosphonate (OBP) (risedronate, ibandronate), intravenous bisphosphonate (IV BP) (zoledronate), denosumab (DENO) and teriparatide (TERI) and had been 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 was allowed.

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

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



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

Before the analysis was undertaken for this final report (see Milestones Section 5), the RMM and the label was checked.

9.3.2 Inclusion criteria

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

Patients had to meet all the following inclusion criteria to enter the study:

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

9.3.3 Exclusion criteria

The exclusion criteria were:

- Dispensation or prescription of more than 1 study drug starting on the same date (i.e., combination therapy).
- Patients with a diagnosis of cancer (any except basal cell skin cancer).
- Patients with a diagnosis or Paget's disease at any time before the index date.
- Users of the same drug in the 12 months before the index date (or the same drug in combination with another therapy e.g., alendronic acid and colecalciferol (ATC CCI))
- Patients with a history of SI in the 30 days before index date.

- Patients meeting the study drug contraindication with respect to CV contraindication (history of stroke or MI at any time before index date).

9.3.4 Follow-up

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

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

For the exposure-based follow-up period, patients were followed until first occurrence of the 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 therapy initiation (as per the romosozumab SmPC), or end of the study period/data extraction date. At the point of switching or discontinuation of the treatment, a patient was censored for that arm of the study in this analysis.

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

For the comparative safety analyses (objective 3), the exposure-based follow up was used.

9.4 Variables

9.4.1 Exposure

Exposure to OP medications in each database was assessed according to the ATC classification system or other country and database-specific coding system used for recording.

- Study drug of interest:
  - Romosozumab (ATC CCI [redacted]), one dose of 210mg administered as two injections of 105mg monthly
- Other OP medication. Comparator drugs:
  - Alendronate (ATC CCI [redacted]) (oral) 10mg once daily or 70mg once weekly
  - Other oral bisphosphonates at doses indicated for OP treatment
    - Ibandronate (ATC CCI [redacted]) 150mg once monthly
    - Risedronate (ATC CCI [redacted]) 5mg once daily or 35mg once weekly, or 75 mg two consecutive days each month

- Intravenous bisphosphonates at doses indicated for OP treatment
  - Zoledronate (ATC [redacted]) 5mg once a year
- Denosumab (ATC [redacted]) (subcutaneous) 60mg every 6 months
- Teriparatide (ATC [redacted]) (subcutaneous) 20µg once daily

All of the OP medications listed above were analysed for objectives 1 and 2 (see Section 8) in this report. Alendronate (ATC [redacted]) will be the active comparator in the comparative safety analyses (Objective 3).

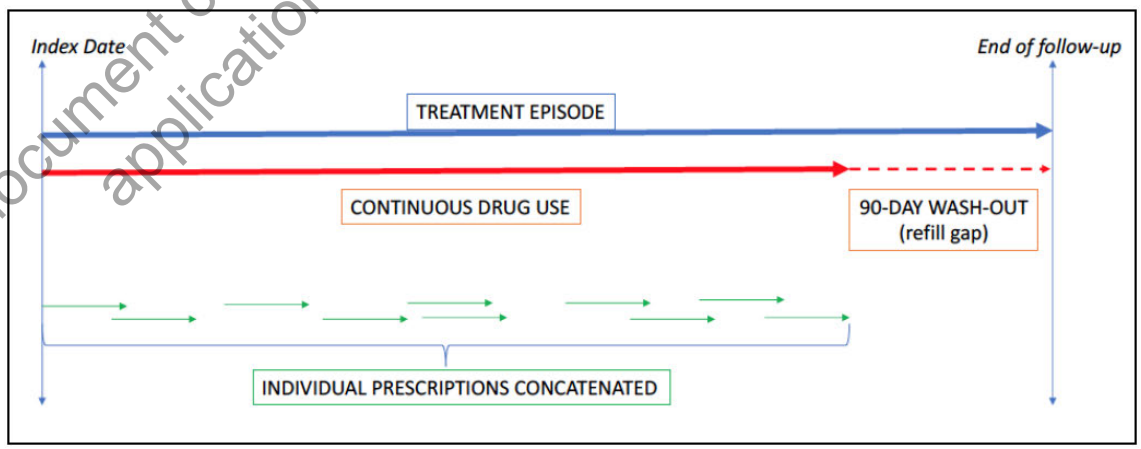
Treatment duration

Exposure (first dispensation or prescription) to a study drug commenced on the index date. The end of exposure was defined as the date of the last prescription/dispensation 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. Based on the pharmacological profile of romosozumab, it is expected that the majority of the effects of romosozumab are 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 was allowed. This is consistent with previously published observational analyses focused on persistence with OP medications (4).

Drug discontinuation was defined as no dispensation/prescription during a 3-month period after the end of exposure, with end of exposure estimated as the date of the last prescription plus the number of doses prescribed/dispensed in that last prescription. Stockpiling was considered (see Figure 2). Drug discontinuation was also considered at the date when a concomitant second OP medication was 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) was classified as treatment reinitiation and therefore excluded from all analyses.

Drug switching

Treatment switching for the exposure-based follow-up was handled as follows:

- For objectives 1 and 2, the analyses were conducted at the treatment episode level as in Figure 2 above. For example, a user of denosumab who then switched to alendronate contributed first to the denosumab user cohort, and then (after switching) to the alendronate user cohort.
- For objective 3 (comparative safety), follow-up started with the first prescription of either alendronate or romosozumab, regardless of previous other OP drug use. For the exposure-based analysis, a switch from romosozumab or alendronate to any other OP drug had resulted in censoring. In contrast, switching from alendronate to romosozumab or from romosozumab to alendronate will be handled as a time-varying exposure, just like in objectives 1 and 2.

9.4.2 Outcomes

Depending on the database, outcomes were identified in either hospital records, electronic primary care records or outpatient records. The outcome of death may be identified in linked death records. Further information about what information each database collects is provided in Section 9.5.

Primary outcome: SI associated with 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 validity:

Code validation for SI had been reported previously for CPRD (UK) and the Nationwide linked Danish Registers (Denmark). PPD (5) and colleagues conducted a validation study using the NDR database (DK) in 2014. For CPRD (UK), a number of validation studies had been reported on different types of specific infections including

tuberculosis (6, 7), impetigo, measles, rubella, scabies and viral illness (8) as well as urinary tract infection (8, 9), and respiratory infection (9). Table 2 gives an overview of the validity of outcomes.

Table 2: Overview of outcome validation available with references

Database	Validity of SI	Validity of death
NDR (DK)	Yes (5)	Yes (built in validation of civil registration system) (10)
IPCI (NL)	No	Yes[a]
SIDIAP (ES)	Yes[a]	Yes
GePaRD (DE)	Yes[a]	Yes (11, 12)
CPRD (UK)	Yes (7, 9)	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; 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 validation of SI has not previously been conducted, sample validation studies were done for databases where linkage to hospital data was available. Only cases that were confirmed during validation were included for the comparative safety analysis. Validation was conducted in Q2 2021 and Q2 2024 in parallel to the SI PASS study. Table 3 reports the most recent positive predictive value (PPV) for each database for SI.

In Q2 2021, validation of SI was performed in GePaRD, IPCI, and SIDIAP. In GePaRD, a random sample of 250 cases of the primary outcome were identified, yielding a PPV of 85.9%, indicating good validity. All case validation was performed for databases where hospitalisations were identified from free text (IPCI (NL)), which yielded PPV of 100%, however the number of outcomes was ≤10. For SIDIAP, all case validation was performed as the required number of patients to perform sample validation was not met. Validity of SI was poor with PPV of 43.1%; the poor validity may be explained by the medical doctor not including additional information within free text as this information may be included within hospital discharge letters (which researchers do not have access to).

In Q2 2024, all case validation of SI in SIDIAP was repeated. The validation algorithm was amended such that a SI recorded in hospital records were assumed to be definite cases. As the definition of the primary outcome required a record of SI in hospital records, by default all patients with a SI were assumed to be cases, thus the PPV was 100%.

In Q2 2025, sample validation of 250 patients with 293 SI events in IPCI was repeated due to a small number of events observed in the validation performed in 2021. The PPV for SI was 61.7%. As the PPV was less than 75%, all cases in the propensity score matched cohorts would be validated for the comparative safety analysis (Objective 3).

Table 3: PPV for SI in each database

	IPCI (NL)	SIDIAP (ES)	GePaRD (DE)
Serious infection	61.7[c]	100[b]	85.9[a]

DE=Germany; ES=Spain; GePaRD=German Pharmacoepidemiological Research Database; IPCI=Integrated Primary Care Information Project; NL=Netherlands; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària;
[a]validation conducted in Q2 2021; [b]validation performed in Q2 2024; [c]validation performed in Q2 2025.

9.4.3 Covariates (confounders and interaction terms)

9.4.3.1 Potential confounders

All covariates were identified at cohort entry (index date) based on the patients' records prior to study entry and were considered to be included as covariates in the proposed propensity score models, Section 9.9.3.1. Key confounders were identified a priori based on previous literature and recent research and are listed below. Previous analyses of primary care (13) and of health register data around Europe (14) have demonstrated the richness and detail of risk factors recorded in the proposed real-world databases. In addition, ongoing work by the Centre for Statistics in Medicine in Oxford has confirmed this for the indicated population of interest, i.e., women with OP and/or who initiate OP medication in clinical practice settings. The set of variables was grouped into 4 main categories: general patient characteristics, SI risk factors, markers of OP severity, and use of other medications. Different databases have access to different variables and/or proxies for each of the confounders listed below. Covariates were grouped into 4 categories.

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

  - BMI/obesity (most recent measure or diagnosis of obesity as recorded in the previous 5 years)
  - Smoking (most recent measure or diagnosis of smoking as recorded in the previous 5 years)
  - Alcohol drinking (most recent measure or diagnosis of alcoholism/alcohol drinking problems as recorded in the previous 5 years)
  - History of asthma
  - History of chronic obstructive pulmonary disease
  - History of any surgery in the year before index date
  - History of chronic kidney disease
  - 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 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 index date
  - History of eating disorder/s (anorexia nervosa, bulimia) at any time before 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 index date
  - Previous use of other OP medications (ATC CCI) in the year before index date: type, number of therapies, and DDDs prescribed
  - Previous use of prescribed vitamin D supplements (ATC CCI 5) in the year before index date
  - Previous use of prescribed calcium supplements (ATC CCI) in the year before index date
  - Previous use of prescribed calcium and vitamin D (concomitant) supplements (ATC CCI) in the year before index date

- Use of medications associated with low bone mineral density/OP as prescribed in the year before index date
- Use of other medication/s associated with fall/s and/or fracture/s as prescribed in the year before index date
- Number of recorded fall/s in the year before index date
- Estimated absolute 5-year fracture risk score based on the Garvan nomogram (15), recently tested by members of the EU-ADR Alliance
- Bone mineral density T-score recorded in the year before index date (if available) (Note: it will not be included in the propensity score due to probable confounding by indication)

- Use of other medications:
  - Use of any drugs: number of different ATC classes (ATC 4-digit groups) used in the year prior to index date
  - Use of any drugs: number of different ATC classes (ATC 4-digit groups) used in the year prior to cohort entry
  - 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 F)
  - Previous use of OP medications (ATC CCI) in the year prior to cohort entry
  - Number of ATC/BNF codes prescribed in the year before index date

9.5 Databases and measurement

This study was conducted using routinely collected data from 3 databases 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 provide representative clinical information as collected in routine clinical practice in different European healthcare settings.

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

Five countries from different European areas are included, to provide diverse and representative data on the safety of romosozumab, as well as to ensure sufficient statistical power for the study.

All analyses have been 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 European guidelines on the use of medical data for medical research and have been validated for pharmacoepidemiological research (16, 17). All of the contributing databases are listed under the HMA-EMA Catalogue of real-world databases.

Table 4 provides an overview of key elements of the 6 databases. The total number of persons actively registered in the source population of these 6 databases together was over 56 million.

Further details on each of these databases can be found in the EU PASS OP0006 Protocol.

Table 4: Overview of the study databases

Country	Netherlands	UK	Denmark	Spain	Germany
Name of the database	IPCI	CPRD	NDR	SIDIAP	GePaRD
Type of database	MR	MR	ADM	MR	ADM
# active patients (millions)	1.2	2.9 for GOLD & 16.1 for Aurum	5.8	5.8	25
Age categories	All	All	All	≥15 years	All
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Date death	Yes	Yes	Yes	Yes	Yes
Prescriptions					
Outpatient treatment/s	Yes (specialist incomplete)	Yes (specialist incomplete)	Yes	Yes (specialist incomplete)	Yes
Coding of drugs	ATC	BNF/Multilex	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes	No
Outcomes					
Hospitalizations	Yes	Yes (60%)	Yes	Yes	Yes
Outpatient diagnoses	Yes	Yes	Yes (hospital outpatient)	Yes	Yes
Coding of disease	ICPC	READ / SNOMED	ICD-10	ICD-10-CM	ICD-10-GM
Cause of death	SI death identified from patient records	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; ONS=Office for National Statistics; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

9.6 Study size

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 – 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 PY of follow-up ranged from 5.4 to 13.2 per 100 PY (Table 5). 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 100 PY).

Table 5: Incidence of SI 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 (18, 19) as well as IRs observed in this study.

The targeted hazard ratio (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 100 PY 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).

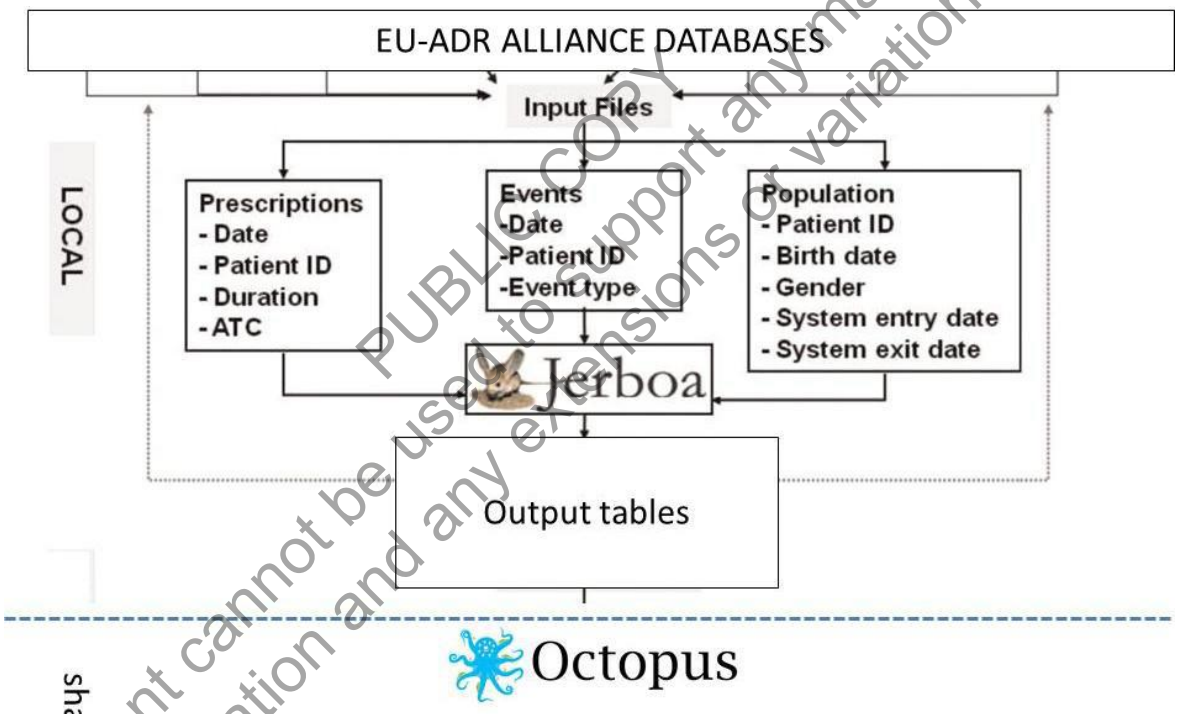
9.7 Bias

Details of selection bias due to missing data (Section 9.9.3.1), information bias from misclassification (Section 11.2), and confounding (Section 9.9.3.1) have been described elsewhere. Further details on each of these type of biases can be found in the EU PASS OP0006 Protocol.

9.8 Data management

The EU-ADR Alliance works in a federated manner: data extraction and elaboration were done locally; pooling of aggregated data was done on a remote research environment (RRE) (see Figure 3 for overview). Below the data standardisation for SIDIAP, CPRD, IPCI data is described. The same input files were used by NDR and GePaRD with data extraction, elaboration and analysis undertaken in SAS in their local environment in line with local governance.

Figure 3: Model for data sharing and elaboration



9.8.1 Data elaboration

A standardised Jerboa© tool was created by Erasmus MC to create the study specific output tables for the databases IPCI, SIDIAP, and CPRD. This was double coded in Jerboa (JAVA) and SAS (version 9.2). The SAS code was used for databases not kept on the RRE (NDR and GePaRD).

A study-specific folder on the central Octopus RRE for secure access by members was used to analyse the output provided by Jerboa© for data from SIDIAP, CPRD and IPCI.

Data from NDR and GePaRD were analysed in the country of origin on their own local or national servers using scripts provided by the University of Oxford.

These output files contained only anonymised de-identifiable data that were shared in the RRE where members had a secure and restricted access and where data was analysed. Stata (version 17) and R (version 4.3.3) was used for post-processing of data. All final results of all countries were stored on the RRE, for NDR and GePaRD these were after values <5 had been removed.

9.8.2 Harmonisation of data extraction

All events/outcomes have been ascertained using a list of agreed ICD (Denmark, Germany, and Spain), ICPC (the Netherlands), READ (UK-CPRD GOLD) codes and READ2/SNOMED/local EMIS® (UK-CPRD Aurum). These were mapped to an additional database from Germany to their respective terminologies. The proposed lists of codes have been previously created and were validated for a previous study [EUPASS9117 (20)] following a number of steps:

- Clinical definition
- Preliminary list of concept identifiers using Unified Medical Language System® (UMLS®) Metathesaurus Browser
- Addition of codes found after 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 databases. As coding might change over time, relevant codes might be updated during the course of the project. Harmonisation of these code lists is taking 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).

Further details of this process can be found in the EU PASS OP0006 protocol.

9.9 Statistical methods

Small cell counts (numbers <5) were masked as required by local regulations.

9.9.1 Data analysis of the descriptive study component

Patient characteristics assessed at the index date were described for users of each OP medication and users of any OP medication. For continuous covariates the mean (standard deviation) and median (interquartile range) were presented. For binary and categorical covariates, the number (percentage) was presented.

9.9.2 Incidence rates

For the analysis which determines the IR of each event of interest for each OP medication, the following calculations were performed.

- Scenario 1: exposure-based follow-up

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

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

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

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

IRs and 95% CIs were calculated for each study drug cohort (as defined in Section 9.4.1 using a Poisson model. The IR was reported for prespecified intervals of 6, 12, 18, and 24 months after treatment indexes in Scenario 2.

9.9.2.1 Stratified incidence rates

Where there were 5 or more number of events, the IRs were stratified by key SI risk factors. Stratification had been conducted based on the following baseline characteristics of each of the OP drug 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.
- History of SI events in the year prior to index date.

9.9.3 Comparative safety analyses

9.9.3.1 Propensity score matching

Propensity scores represent the probability that a given patient will receive the drug of interest (romosozumab) based on their baseline demographics and clinical characteristics specified in Section 9.4.3. This probability was estimated using a multivariable logistic regression model.

Propensity score matching reduces confounding by indication by producing comparable groups of patients in terms of observed confounders. It was expected that romosozumab users would have high fracture risk as per the proposed label. Key features to be added in the propensity score model therefore included predictors of fracture as well as SI risk factors.

All the identified risk factors were considered for inclusion in the logistic regression for propensity score estimation provided there were at least 5 counts amongst romosozumab users to prevent model separation. For covariates with missing data (for example the Garvan fracture risk score and socioeconomic status), to allow estimation of the propensity score in patients with missing covariate data, a separate category was created indicating whether the data was missing. Patients with missing data for the covariates 'current smoker' and 'heavy alcohol drinker' were assumed to be 'not current smoker' and 'not heavy alcohol drinker', respectively.

Romosozumab was launched in Germany in March 2020; UK in November 2020; Denmark in March 2020; the Netherlands in March 2021, and Spain in September 2022. For each database, prescriptions for alendronate were excluded in the years prior to launch of romosozumab prior to propensity score matching.

Nearest neighbour matching without replacement was performed. Patients using romosozumab were matched to up to 3 users of alendronate with a caliper width of 0.20 standard deviations (SDs) on the logit of the propensity score (21). 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. Not all romosozumab users would have been matched to 3 alendronate users therefore matching weights was used to account for the differential weights of the matched alendronate users for analyses performed in the propensity score matched cohorts (22). The total number of romosozumab users and alendronate users after propensity score matching was reported alongside with the effective sample size. The effective sample size is a measure of the size of a hypothetical unweighted sample with approximately the same precision as a weighted sample. The effective sample size will always be less than or equal to the propensity score matched sample size, reflecting the loss in precision due to using the weights (23).

Balance between the propensity-matched cohorts was checked using absolute standardised mean differences (ASMD). A difference of ≥0.1 would show that a variable was imbalanced between romosozumab users and alendronate users. In this scenario, the propensity score model was respecified, re-estimated the propensity scores, and the balance was rechecked. Should this strategy fail, double adjustment (i.e., further adjustment for imbalanced variables) for any potential imbalances after matching, as recommended by Tri-Long Nguyen et al (24). The distribution of the propensity score will also be compared between romosozumab users and alendronate users.

If the validity of outcomes had PPV less than 75%, outcomes were adjudicated in the propensity score matched cohorts prior to fitting the Cox regression model (Section 9.4.2).

9.9.3.2 Survival analysis

Cox regression models were used to calculate HRs and 95% CIs for each of the safety events according to drug exposure in the propensity-matched cohorts. The models accounted for the matching weights and cluster-robust standard errors for the HRs that were calculated.

Should an association between romosozumab use and death (SI or COVID-19 infection) be identified (in either direction), cause-specific hazards from competing risk analyses would be calculated to assess the risk of the primary outcome of SI.

The proportionality of hazards was tested in all the Cox regression models by plotting log plots of the Nelson-Aalen estimates. Alternative models would be considered in case of nonproportionality of hazards.

9.9.3.3 Meta-analysis

The pooled estimates of the HR of SI for the databases were calculated using the random or fixed effects model depending on heterogeneity detected using an I^2 threshold of >40% (25).

9.9.4 Measures proposed to account for unobserved confounding

9.9.4.1 Subgroup analysis in patients with clinically severe osteoporosis

The feasibility of a subgroup analysis in patients with clinically severe OP (bone mineral density [BMD] T-score <-2.5 and a fracture recorded in the year prior to start of treatment) was 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 would be performed in patients with clinically severe OP to complement the comparative safety of romosozumab.

9.9.4.2 Negative control outcomes

Cox regression models were 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, but it is assumed to share the same confounding structure as the outcome of interest. The negative controls to be used in this analysis were agreed with academic clinicians and provided in advance before comparative analyses were conducted. The negative control outcome was assessed if there was at least 1 event in both treatment groups. A preliminary and non-exhaustive list of potential negative control outcomes are listed here for illustrative purposes with the full list stated in Appendix, Section 1:

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

Should the Cox regression analysis of more than 5% of the negative controls produce significant results, 3 additional analyses would be conducted to assess the effects of potential biases related to insufficient control for confounding/channelling bias on the risk effect estimate for SI: (i) empirical calibration using negative control outcomes; (ii)

self-controlled case series analyses (SCCS), and (iii) instrumental variable analysis for the primary outcome, SI.

9.9.4.3 Empirical calibration using negative control outcomes.

The obtained estimates from the analyses above would be used to empirically calibrate the HRs obtained from the main propensity-matched analysis, as proposed by Schuemie et al (26). This would provide a readjusted risk estimate of SI after accounting for unobserved confounding.

9.9.4.4 Self-controlled case series (SCCS)

A SCCS would be undertaken. This method would only use data for the cases (i.e., patients who have had the primary outcome, SI) and assess whether there was an elevated risk during time windows of exposure to romosozumab compared to time windows of no exposure (27). The SCCS controls for all time fixed confounders, including unobserved ones by being a within person design i.e., a patient's comparator is themself. Unadjusted and age-adjusted incidence rate ratio would be estimated.

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

9.9.4.5 Instrumental variable analysis

Instrumental variable analyses based on physician prescription preference would 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 (romosozumab) would be estimated using the previous 10, 20, and 50 prescriptions of OP medications (either romosozumab or alendronate) at the prescriber level. Falsification tests would be used as diagnostics for the testable assumptions (28):

- an association between the instrument (physician prescription preference) and the actual exposure would be tested using logistic regression modelling and calculating the F statistic.
- the expected lack of association between the instrument (physician prescription preference) and all the available confounders would be tested by measuring the ASMD.

The risk effect estimate would be calculated if the association between the instrument and exposure was strong and there was no imbalance (ASMD <0.1) between the measured confounders and the instrument.

9.9.5 Subgroup analysis

To account for potential differences in risk of safety events between patients with or without prior fractures, subgroup analyses were performed in 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.

9.10 Quality control

This study has been designed, implemented and reported in accordance with the guidelines for good pharmacoepidemiology practices of the International Society for Pharmacoepidemiology (29), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (30), and with the ethical principles laid down in the Declaration of Helsinki.

This study adheres to the methods guidance of a "European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the "ENCePP Code of Conduct" (31).

All programs were programmed according to agreed coding standards and validated by double programming or source code review with the second programmer involvement. STATA version 17 (StataCorp, College Station, Texas, USA) and R (version 4.3.3, the R Foundation for Statistical Computing) was used for statistical analysis.

10 RESULTS

10.1 Study patients

The total number of romosozumab users across all databases was 2,505 (921 in GePaRD, 608 in NDR, 567 in SIDIAP, 310 in CPRD Aurum, and 99 in IPCI), as shown in Table 6. There were no romosozumab users in CPRD GOLD.

Among romosozumab users, the most common reason for exclusion was a documented history of a cancer diagnosis at any time prior to initiation (range from 14.1% in IPCI to 22.6% in CPRD Aurum).

After applying inclusion/exclusion criteria, there was a total of 1,887 eligible users of romosozumab across all databases (661 in GePaRD, 504 in NDR, 423 in SIDIAP, 225 in CPRD Aurum, and 74 in IPCI).

Table 6: Eligible romosozumab cohort by database

Exclusion	IPCI (NL)	NDR (DK)	SIDIAP (ES)	CPRD Aurum (UK)	GePaRD (DE)	Total
Patients with a prescription or administration and at least 1 year naïve	**99**	**608**	**567**	**310**	**921**	**2,505**
Male	<5	6 (1.0%)	9 (1.6%)	5 (1.6)	13 (1.4%)	NC
Age <50	0	[b]	<5	<5	18 (2.0%)	NC
Concomitant OP medication	<5	[b]	0	<5	<5	NC
History of cancer	14 (14.1%)	97 (16.0%)	109 (19.2%)	70 (22.6%)	187 (20.3%)	477 (19.0%)
History of Paget's	[a]	0	<5	0	<5	NC
History of MI	<5	0	<5	<5	15 (1.6%)	NC

Exclusion	IPCI (NL)	NDR (DK)	SIDIAP (ES)	CPRD Aurum (UK)	GePaRD (DE)	Total
History of stroke	<5	<5	13 (2.3%)	<5	22 (2.4%)	NC
History of infection in 30 days prior	<5	<5	6 (1.1%)	0	<5	NC
Eligible for inclusion in the study	**74 (74.7%)**	**504 (82.9%)**	**423 (74.6%)**	**225 (72.6%)**	**661 (71.8%)**	**1,887 (75.3%)**

CPRD=Clinical Practice Research Datalink; DE=Germany; DK=Denmark; ES=Spain; GePaRD=German Pharmacoepidemiological Research Database; IPCI=Integrated Primary Care Information Project; MI=myocardial infarction; NL=Netherlands; OP=osteoporosis [medication]; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària;
<5 = cell count is <5. The true number is masked for data protection reasons.
NC: not calculated due to number of events <5
[a] There is no disease code for Paget available for IPCI.
[b] Incorporated into identification of patients with history of cancer (n<5).

The number of patients with a prescription for an OP medication and the number eligible for inclusion is detailed per database in Table 7. The number of patients meeting the exclusion criteria for each database is shown in Appendix 1, Section 2.

In total across all databases, 52.5% (n=311,058) alendronate users, 53.4% (n=59,595) oral bisphosphonate users, 31.5% (n=23,320) intravenous bisphosphonate users, 49.7% (n=70,640) denosumab users, and 64.4% (n=12,014) teriparatide users met the eligibility criteria.

As shown in Appendix 1, Section 2, in each database the common reasons to be excluded across prescriptions for alendronate, oral bisphosphonate, intravenous bisphosphonate, denosumab, and teriparatide were:

- History of cancer
  - IPCI: range 11.2% to 16.3%
  - NDR: range 5.2% to 44.4%
  - SIDIAP: range 10.2% to 16.6%
  - CPRD GOLD: range 0% to 17.6%
  - CPRD Aurum: range 16.1% to 23.1%
  - GePaRD: range 11.6% to 24.5%
- Being male
  - IPCI: range 11.9% to 23.9%
  - NDR: range 10.1% to 31.5%
  - SIDIAP: range 11.0% to 13.9%
  - CPRD GOLD: range 6.1% to 18.4%
  - CPRD Aurum: range 8.6% to 20.4%
  - GePaRD: range 10.3% to 18.2%

The percentage of patients excluded with a history of infection in the last 30 days varied across databases. Within each database, across OP medications, a maximum of 2.6% were

excluded in IPCI; 0.6% in NDR; 1.3% in SIDIAP; 1.0% in CPRD GOLD; 2.0% in CPRD Aurum; and 0.3% in GePaRD (details in Appendix 1, Section 2).

Table 7: Number (%) of eligible users of OP medications across databases

		IPCI (NL)	NDR (DK)	SIDIAP (ES)	CPRD GOLD (UK)	CPRD Aurum (UK)	GePaRD (DE)	Total
ROMO	**Patients with a prescription or administration in hospital**	99	608	567	0	310	921	2,505
	Eligible for inclusion in the study	74 (74.7%)	504 (82.9%)	423 (74.6%)	0	225 (72.6%)	661 (71.8%)	**1,887** (75.3%)
ALN	**Patients with a prescription or administration in hospital**	21,617	135,584	97,902	6,921	206,722	123,671	592,417
	Eligible for inclusion in the study	8,915 (41.2%)	79,123 (58.4%)	60,080 (61.4%)	2,839 (41.0%)	86,485 (41.8%)	73,616 (59.5%)	**311,058** (52.5%)
OBP	**Patients with a prescription or administration in hospital**	6,928	6,674	19,689	897	42,492	34,989	111,669
	Eligible for inclusion in the study	2,785 (40.2%)	3,829 (57.4%)	12,469 (63.3%)	404 (45.0%)	19,634 (46.2%)	20,474 (58.5%)	**59,595** (53.4%)
IV BP	**Patients with a prescription or administration in hospital**	586	62294	0	6	4,199	7,049	74,134
	Eligible for inclusion in the study	296 (50.5%)	17,622 (28.3%)	0	5 (83.3%)	1,936 (46.1%)	3,461 (49.1%)	**23,320** (31.5%)
DENO	**Patients with a prescription or administration in hospital**	3,745	31,333	39,630	213	21,880	45,428	142,229
	Eligible for inclusion in the study	1,592 (42.5%)	12,925 (41.3%)	21,051 (53.1%)	119 (55.9%)	9,582 (43.8%)	25,371 (55.8%)	**70,640** (49.7%)
TERI	**Patients with a prescription or administration in hospital**	295	4,107	10,395	0	967	2,890	18,654
	Eligible for inclusion in the study	173 (58.6%)	2,576 (62.7%)	6,925 (66.6%)	0	587 (60.7%)	1,753 (60.7%)	**12,014** (64.4%)

ALN = alendronate; CPRD=Clinical Practice Research Datalink; DE=Germany; DENO = denosumab; DK=Denmark; ES=Spain; GePaRD=German Pharmacoepidemiological Research Database; IPCI=Integrated Primary Care Information Project; IVBP = intravenous bisphosphonate; MI=myocardial infarction; NL=Netherlands; OBP = oral bisphosphonate; OP=osteoporosis [medication]; ROMO=romosozumab; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; TERI = teriparatide.

10.2 Characteristics of patients

A summary of key characteristics of all eligible users of any OP medications is shown per database, in Table 8 below.

Across the databases and for users of any OP medication, the median age ranged from 70.7 to 74.4 years, median number of visits to the GP was 2 to 11, and median number of prescriptions was 3 to 8. OP diagnosis was recorded in 45% to 89% of patients, and 33% to 63% of patients had previous fracture. Common comorbidities included hypertension (22% to 61%), hypercholesterolaemia (23% to 56%), and established CV disease (21% to 43%).

Patient characteristics for each OP drug and across all OP drugs in each database are fully detailed in Appendix 1, Section 3.

Table 8: Summary characteristics of eligible users of osteoporosis medications from each database

Variable	IPCI	NDR	SIDIAP	CPRD GOLD	CPRD AURUM	GePaRD
Number of patients	13,835	116,579	100,948	3,367	118,449	125,336
Age: Median (IQR)	71.90 (64.10 - 79.00)	71.00 (64.00 - 78.00)	70.70 (62.90 - 78.50)	73.80 (65.70 - 80.80)	74.40 (66.00 - 81.20)	74.00 (66.00 - 80.00)
General practice visits in the prior year: Median (IQR)	2.00 (0.00 - 4.00)	NA	7.00 (3.00 - 12.00)	11.00 (6.00 - 19.00)	10.00 (6.00 - 16.00)	4.00 (0.00 - 6.00)
Number of prescriptions (ATC4) in prior year: Median (IQR)	7.00 (4.00 - 11.00)	3.00 (2.00 - 5.00)	8.00 (5.00 - 12.00)	NA	NA	5.00 (1.00 - 8.00)
Systemic glucocorticoids	3,196 (23%)	19,959 (17%)	16,938 (17%)	849 (25%)	27,136 (23%)	27,902 (22%)
Osteoporosis	7,372 (53%)	63,740 (55%)	59,160 (59%)	1,512 (45%)	61,668 (52%)	111,846 (89%)
Fracture	6,582 (48%)	57,693 (49%)	45,971 (46%)	1,815 (54%)	75,035 (63%)	40,930 (33%)
Fracture in prior two years	4,269 (31%)	34,511 (30%)	26,590 (26%)	1,091 (33%)	48,821 (41%)	21,461 (17%)
Arrhythmia	1,625 (12%)	11,807 (10%)	13,507 (13%)	402 (12%)	16,047 (14%)	34,564 (28%)
Atrial fibrillation/flutter	1,173 (8.5%)	7,997 (6.9%)	6,689 (6.6%)	284 (8.4%)	10,992 (9.3%)	5,656 (4.5%)
Heart failure	616 (4.5%)	2,519 (2.2%)	5,391 (5.3%)	146 (4.3%)	6,419 (5.4%)	23,303 (19%)
Established cardiovascular disease^	4,244 (31%)	24,473 (21%)	21,559 (21%)	873 (26%)	32,104 (27%)	54,058 (43%)
Cerebrovascular disease*	714 (5.2%)	2,505 (2.1%)	1,888 (1.9%)	103 (3.1%)	3,109 (2.6%)	3,586 (2.9%)
Hypercholesterolemia	3,207 (23%)	49,890 (43%)	38,997 (39%)	952 (28%)	39,156 (33%)	70,696 (56%)
Hypertension	6,003 (43%)	25,285 (22%)	45,325 (45%)	1,654 (49%)	58,943 (50%)	76,856 (61%)
Diabetes (Type 1, type 2 or secondary)	1,584 (11%)	9,232 (7.9%)	12,210 (12%)	378 (11%)	15,719 (13%)	8,248 (6.6%)
Chronic obstructive pulmonary disease	1,525 (11%)	10,009 (8.6%)	5,595 (5.5%)	442 (13%)	15,267 (13%)	21,798 (17%)

Variable	IPCI	NDR	SIDIAP	CPRD GOLD	CPRD AURUM	GePaRD
Charlson comorbidity score						
0	5,052 (37%)	94,812 (81%)	26,942 (27%)	647 (19%)	20,808 (18%)	56,521 (45%)
1	235 (1.7%)	17,600 (15%)	1,712 (1.7%)	157 (4.7%)	4,283 (3.6%)	33,449 (27%)
2	7,451 (54%)	2,366 (2.0%)	59,185 (59%)	1,625 (48%)	54,974 (46%)	17,482 (14%)
3	1,014 (7.3%)	1,151 (1.0%)	9,283 (9.2%)	690 (20%)	27,494 (23%)	9,411 (7.5%)
≥4	83 (0.6%)	650 (0.6%)	3,826 (3.8%)	248 (7.4%)	10,890 (9.2%)	8,473 (6.8%)
Garvan fracture risk - weight based: Median (IQR)	12.00 (7.20 - 22.10)	NA	11.40 (6.70 - 24.80)	12.50 (7.30 - 23.70)	14.10 (8.00 - 28.30)	NA
Missing	3,373	116,579	12,224	50	9,357	125,336

IQR=Interquartile range; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
NA = variable not available in the database.
^Includes angina, atherosclerosis, atrial fibrillation.
*Includes cerebral ischaemia and transient ischaemic attack.

10.3 Incidence of events

This section reports results of IRs of events in patients using different OP medications.

10.3.1 Exposure-based analysis

10.3.1.1 Primary outcome

In the exposure-based analysis, the IR of SI per 1,000 PY (with 95% CI) are reported in Table 9. The full results (total number of PY, events and IRs) for each OP medication in each database are reported in Appendix 1, Section 4.

Across the databases, the IR of SI in romosozumab users ranged from 24.44 (95% CI 8.97, 53.2) to 90.62 (57.45, 135.98). In alendronate users, the IR of SI ranged from 47.88 (45.95, 49.88) to 124.6 (108.85, 141.99). The IRs of SI among users of other OP medications ranged from 36.51 (32.8, 40.53) to 177.26 (122.02, 248.94).

10.3.1.2 Secondary outcomes

The IR per 1,000 PY of death due to SI for each OP drug per database is documented in Table 10. Amongst romosozumab users, there were no events of death due to SI across all databases.

The IR of serious COVID-19 infection per 1,000 PY is documented in Table 11. There were fewer than 5 serious COVID-19 infection events amongst romosozumab users in NDR, SIDIAP, and GePaRD and 0 events in CPRD Aurum and IPCI. For the IRs of serious COVID-19 infections in alendronate and other OP medication users, refer to Table 11.

No events of death due to serious COVID-19 infection were observed amongst romosozumab users. For the IRs of death due to serious COVID-19 infections amongst alendronate and other OP users, refer to Table 12.

Table 9: Incidence rate per 1,000 PY of SI events for each osteoporotic drug

Database	ROMO	ALN	OBP	IV BP	DENO	TERI
IPCI	<5	[a]	[a]	[a]	[a]	[a]
NDR	24.44 (8.97, 53.2)	53.34 (51.54, 55.18)	44.89 (37.25, 53.64)	86.79 (82.15, 91.63)	76.00 (70.87, 81.4)	62.50 (52.44, 73.93)
SIDIAP	90.62 (57.45, 135.98)	47.88 (45.95, 49.88)	36.51 (32.8, 40.53)	NA	74.63 (70.52, 78.91)	84.44 (76.67, 92.79)
CPRD Aurum	<5	95.72 (93.23, 98.26)	93.33 (87.97, 98.93)	115.54 (99.14, 133.87)	109.9 (102.54, 117.65)	177.26 (122.02, 248.94)
GePaRD	86.82 (61.13, 119.67)	94.96 (92.17, 97.83)	80.72 (75.94, 85.71)	79.10 (69.03, 90.21)	102.56 (98.19, 107.06)	143.74 (123.4, 166.48)
CPRD GOLD	NA	124.6 (108.85, 141.99)	135.56 (92.72, 191.37)	<5	99.26 (45.39, 188.43)	NA

ALN=alendronate; DENO=denosumab; IVBP=intravenous bisphosphate; OBP=oral bisphosphonate; ROMO=romosozumab; SI=serious infection; TERI=teriparatide;
IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
NA = there were no users of this drug.
[a] For the IPCI database, SI was not validated for users of alendronate, oral bisphosphonate, intravenous bisphosphonate, denosumab and teriparatide in the general population of identified patients. After propensity score matching, SI was validated for all alendronate users before confirming them in the matched control group.

Table 10: Incidence rate per 1,000 PY of death due to SI events for each osteoporotic drug

Database	ROMO	ALN	OBP	IV BP	DENO	TERI
IPCI	0 (0, 0)	[a]	[a]	[a]	[a]	[a]
NDR	0 (0, 0)	3.41 (2.97, 3.89)	4.38 (2.26, 7.65)	8.11 (6.76, 9.64)	7.30 (5.8, 9.07)	4.48 (2.15, 8.24)
SIDIAP	0 (0, 0)	3.4 (2.91, 3.96)	1.94 (1.17, 3.02)	NA	8.85 (7.5, 10.38)	5.46 (3.66, 7.84)
CPRD Aurum	0 (0, 0)	10.41 (9.61, 11.25)	12.2 (10.34, 14.29)	17.91 (11.99, 25.71)	16.17 (13.48, 19.23)	<5
GePaRD	0 (0, 0)	3.35 (2.85, 3.91)	1.90 (1.24, 2.79)	1.71 (0.55, 3.99)	3.38 (2.65, 4.26)	6.02 (2.6, 11.87)
CPRD GOLD	NA	13.22 (8.55, 19.51)	24.18 (8.88, 52.64)	0 (0, 0)	<5	NA

ALN=alendronate; DENO=denosumab; IVBP=intravenous bisphosphate; OBP=oral bisphosphonate; ROMO=romosozumab; SI=serious infection; TERI=teriparatide; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
NA = there were no users of this drug.
[a] For the IPCI database, death due to SI was not validated for users of alendronate, oral bisphosphonate, intravenous bisphosphonate, denosumab and teriparatide in the general population of identified patients. After propensity score matching, death due to SI was validated for all alendronate users before confirming them in the matched control group.

Table 11: Incidence rate per 1,000 PY of serious COVID-19 infection events for each osteoporotic drug

Database	ROMO	ALN	OBP	IV BP	DENO	TERI
IPCI	0 (0, 0)	[a]	[a]	[a]	[a]	[a]
NDR	<5	3.95 (3.48, 4.47)	<5	4.48 (3.49, 5.65)	5.51 (4.22, 7.08)	4.94 (2.47, 8.84)
SIDIAP	<5	7.41 (6.67, 8.22)	6.64 (5.13, 8.46)	NA	9.88 (8.45, 11.5)	12.49 (9.66, 15.89)
CPRD Aurum	0 (0, 0)	11.46 (10.62, 12.34)	15.22 (13.13, 17.54)	19.95 (13.65, 28.16)	13.29 (10.86, 16.1)	36.65 (14.74, 75.52)
GePaRD	<5	2.47 (2.05, 2.96)	2.27 (1.54, 3.22)	3.08 (1.41, 5.85)	3.81 (3.03, 4.74)	<5
CPRD GOLD	NA	7.94 (4.45, 13.1)	<5	0 (0, 0)	<5	NA

ALN=alendronate; DENO=denosumab; IVBP=intravenous bisphosphate; OBP=oral bisphosphonate; ROMO=romosozumab; SI=serious infection; TERI=teriparatide ; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
NA = there were no users of this drug.
[a] For the IPCI database, serious COVID-19 infection was not validated for all users of alendronate, oral bisphosphonate, intravenous bisphosphonate, denosumab and teriparatide in the general population of identified patients. After propensity score matching, serious COVID-19 infection was validated for all alendronate users before confirming them in the matched control group.

Table 12: Incidence rate per 1,000 PY of death due to serious COVID-19 infection events for each osteoporotic drug

Database	ROMO	ALN	OBP	IV BP	DENO	TERI
IPCI	0 (0, 0)	[a]	[a]	[a]	[a]	[a]
NDR	0 (0, 0)	0.22 (0.12, 0.37)	0 (0, 0)	0.45 (0.18, 0.92)	0.63 (0.25, 1.3)	0 (0, 0)
SIDIAP	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)
CPRD Aurum	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
GePaRD	0 (0, 0)	0.23 (0.12, 0.41)	0 (0, 0)	0 (0, 0)	0.38 (0.16, 0.74)	<5
CPRD GOLD	NA	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA

ALN=alendronate; DENO=denosumab; IVBP=intravenous bisphosphate; OBP=oral bisphosphonate; ROMO=romosozumab; SI=serious infection; TERI=teriparatide; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
NA = there were no users of this drug.
[a] For the IPCI database, death due to serious COVID-19 infection was not validated for all users of alendronate, oral bisphosphonate, intravenous bisphosphonate, denosumab and teriparatide in the general population of identified patients. After propensity score matching, death due to serious COVID-19 infection was validated for all alendronate users before confirming them in the matched control group.

10.3.1.3 Incidence of SI events stratified by key risk factors

Stratification of incidence of SI events was performed for users of each OP medication provided there were 5 or more events in each stratum for the exposure-based analysis. Stratifications were performed by age (5-year bands), history of OP medication and history of SI in the year prior to index date. Results are illustrated in Appendix 1, Section 4.

Stratified IRs for SI and serious COVID-19 infection for each OP drug per database are presented in Appendix 1, Section 4. Across databases and OP medications, IR of SI was found to increase with age, and had increased rapidly in ages older than 75 years. Patients with a history of SI were at an increased risk of SI. The IRs were similar between patients with and without a history of OP medication. Similar patterns were also observed for serious COVID-19 infection.

10.3.2 Fixed-follow up analysis

In the fixed follow-up analysis, patients were considered as exposed to the medication regardless of whether they stopped or switched to an alternative OP medicine. In these results, two analyses were undertaken: the events-based analysis and the person-based analysis specified in Section 9.9.2. IRs per 1,000 PY were calculated in 0-5.9, 6-11.9, 12-17.9, and 18-24 months post treatment initiation.

The IRs with 95% CI for the person-based analysis for the primary outcome of SI are presented in Table 13. The full results (number of patients with events, total number of PY and IR) and events-based analysis are presented in Appendix 1, Section 5.

10.3.2.1 Primary outcome

In romosozumab users, across databases and time windows the IR for SI ranged from 0 to 98.78 (65.64, 142.77).

In alendronate users, the IR for SI ranged from 46.65 (44.04, 49.38) to 102.53 (99.46, 105.67). In all other OP medications (oral bisphosphonate, intravenous bisphosphonate, denosumab and teriparatide), IRs ranged from 33.77 (28.67, 39.53) to 186.78 (80.64, 368.04) across databases Table 13.

10.3.2.2 Secondary outcomes

Amongst romosozumab users, there were no events of death due to SI or serious COVID-19 infection across the databases.

There were no events or fewer than 5 events of serious COVID-19 infection across all other databases. For other OP drugs, refer to Appendix 1, Section 5.

Table 13: Person-based incidence rate (95% CI) per 1,000 PY of SI based on the fixed follow-up for each osteoporotic drug

Database	Drug	0-5.9 months	6-11.9 months	12-17.9 months	18-24 months
IPCI	**ROMO**	<5	0 (0, 0)	0 (0, 0)	0 (0, 0)
	ALN	a	a	a	a
	OBP	a	a	a	a
	IV BP	a	a	a	a
	DENO	a	a	a	a
	TERI	a	a	a	a
NDR	**ROMO**	21.03 (6.83, 49.08)	61.02 (31.53, 106.59)	57.57 (26.32, 109.28)	<5
	ALN	57.08 (54.71, 59.53)	58.06 (55.54, 60.66)	61.28 (58.55, 64.1)	62.23 (59.3, 65.26)
	OBP	50.89 (41.12, 62.27)	46.59 (36.88, 58.06)	53.81 (42.92, 66.62)	47.54 (36.85, 60.38)
	IV BP	98.34 (91.72, 105.31)	83.25 (76.78, 90.12)	97.16 (89.73, 105.05)	96.41 (88.5, 104.84)
	DENO	84.52 (77.39, 92.13)	76.66 (69.41, 84.46)	85.53 (77.29, 94.4)	83.62 (74.8, 93.19)
	TERI	71.65 (57.62, 88.07)	70.89 (56.38, 87.99)	72.96 (57.67, 91.05)	86.25 (68.79, 106.78)
SIDIAP	**ROMO**	79.25 (43.33, 132.97)	98.5 (49.17, 176.24)	<5	0 (0, 0)
	ALN	52.86 (50.22, 55.59)	46.65 (44.04, 49.38)	50.29 (47.42, 53.28)	52.28 (49.16, 55.55)
	OBP	38.17 (33.36, 43.49)	40.44 (35.18, 46.27)	33.77 (28.67, 39.53)	36.34 (30.61, 42.83)
	DENO	78.99 (73.56, 84.73)	77.71 (71.98, 83.76)	70.77 (65, 76.92)	78.57 (72.05, 85.51)
	TERI	89.17 (79.15, 100.11)	85.24 (74.79, 96.73)	79.87 (69.11, 91.84)	87.21 (75.1, 100.72)
CPRD Aurum	**ROMO**	<5	<5	0 (0, 0)	<5
	ALN	102.53 (99.46, 105.67)	93.03 (89.94, 96.21)	88.32 (85.13, 91.61)	88.8 (85.38, 92.33)
	OBP	102.41 (96.05, 109.08)	82.46 (76.48, 88.77)	69.32 (63.58, 75.44)	69.47 (63.33, 76.04)
	IV BP	127.66 (105.31, 153.36)	123.02 (99.05, 151.05)	119.32 (93.36, 150.27)	127.95 (98.32, 163.7)
	DENO	109.55 (100.13, 119.61)	118.74 (108.29, 129.92)	123.74 (112.37, 135.95)	101.66 (90.61, 113.69)

Database	Drug	0-5.9 months	6-11.9 months	12-17.9 months	18-24 months
	TERI	170.99 (126.08, 226.71)	133.72 (92.04, 187.79)	70.17 (39.27, 115.74)	138.6 (89.69, 204.6)
GePaRD	**ROMO**	98.78 (65.64, 142.77)	56.07 (27.99, 100.33)	64.52 (27.86, 127.13)	<5
	ALN	99.28 (95.99, 102.66)	67.53 (64.64, 70.51)	55.23 (52.45, 58.11)	52.6 (49.68, 55.64)
	OBP	85.8 (80.07, 91.83)	65.75 (60.43, 71.41)	51.8 (46.78, 57.21)	48.56 (43.31, 54.27)
	IV BP	77.79 (64.7, 92.75)	70.19 (56.65, 85.98)	59.7 (46.27, 75.82)	43 (30.72, 58.55)
	DENO	111.31 (105.4, 117.46)	77.82 (72.53, 83.39)	69.92 (64.53, 75.65)	59.89 (54.44, 65.75)
	TERI	163.99 (137.4, 194.22)	97.71 (76.17, 123.46)	65.05 (46.68, 88.24)	41.21 (25.83, 62.39)
CPRD GOLD	**ALN**	132.59 (113.62, 153.82)	124.12 (103.78, 147.29)	118.32 (95.84, 144.49)	108.68 (83.7, 138.78)
	OBP	145.55 (95.92, 211.77)	133.18 (80.19, 207.98)	64.42 (25.9, 132.72)	<5
	IV BP	0 (0, 0)	<5	<5	0 (0, 0)
	DENO	<5	186.78 (80.64, 368.04)	<5	<5

ROMO=romosozumab; ALN=alendronate; OBP=oral bisphosphonate; IV BP=intravenous bisphosphonate; DENO=denosumab; SI=serious infection; TERI=teriparatide; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
[a] For the IPCI database, SI was not validated for users of alendronate, oral bisphosphonate, intravenous bisphosphonate, denosumab and teriparatide in the general population of identified patients. After propensity score matching, SI was validated for all alendronate users before confirming them in the matched control group.

10.4 Comparative safety analysis

There were a total of 1,887 users of eligible romosozumab users. This met the requirement that at least 1,399 romosozumab users were needed to perform the comparative safety analysis (Section 9.6).

The next sections present the comparability of the propensity score matching between romosozumab and alendronate users (Section 10.4.1), the results of the comparative safety analysis for the primary outcome of SI (Section 10.4.2) and the secondary outcome of serious COVID-19 infection (Section 10.4.3), and results from the subgroup analyses (Section 10.4.4).

There were no events of death due to SI or death due to serious COVID-19 infection in the propensity score matched cohorts, therefore no analysis was conducted for these outcomes.

10.4.1 Comparability of romosozumab and alendronate matched cohorts

The propensity score models were fitted in each database separately and the estimated coefficients from the models are shown in Appendix 1, Section 6. Table 14 shows the number of romosozumab and alendronate users before and after propensity score matching. Prior to propensity score matching, across the five databases there were a total of 1,887 users of romosozumab and 308,219 users of alendronate. After propensity score matching, there were a total of 1,738 (92.1%) romosozumab users and 4,632 (1.5%) alendronate users in the matched cohorts, which was used for the comparative safety analysis.

The total effective sample size of 1,738 romosozumab users and 4,085 alendronate users was an indication of the number of patients contributing to the analysis after using matching weights and has the same level of precision as the propensity score matched cohorts. The effective sample size exceeds the number of romosozumab and alendronate users required based on the sample size calculation (Section 9.6).

Table 14: Number of romosozumab and alendronate users before and after propensity score matching

Database	Before PS matching		After PS matching		Effective sample size after PS matching*	
	ROMO	ALN	ROMO	ALN	ROMO	ALN
IPCI	74	8,915	61 (82.4%)	160 (1.8%)	61	140
NDR	504	79,123	465 (92.3%)	1,191 (1.6%)	465	992
SIDIAP	423	60,080	400 (94.6%)	1,086 (1.8%)	400	978
CPRD Aurum	225	86,485	176 (78.2%)	470 (0.5%)	176	404
GePaRD	661	73,616	636 (96.2%)	1,725 (2.3%)	636	1,571
Total	1,887	308,219	1,738 (92.1%)	4,632 (1.5%)	1,738	4,085

ALN=alendronate; PS=propensity score; ROMO=romosozumab; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
*The effective sample size is a measure of the size of a hypothetical unweighted sample with approximately the same precision as a weighted sample i.e. the propensity score matched sample. The effective sample size will always be less than or equal to the propensity score matched sample size, reflecting the loss in precision due to using the weights.

A total of 149 romosozumab users were not included in the propensity score matched cohorts. Jitter plots were used to describe the distribution of the propensity score in the unmatched and matched cohorts (Appendix 1, Section 7). These plots show that the unmatched romosozumab users had propensity scores that had no overlap with the propensity scores amongst unmatched alendronate users.

For all databases, the distribution of the propensity scores before and after matching is illustrated using histograms (Appendix 1, Section 8). These plots show that prior to matching the propensity score distribution between the romosozumab and alendronate groups differed, with most alendronate users having a propensity score less than 0.2. However, after matching the propensity score distribution became similar between romosozumab and alendronate users.

Prior to matching, across databases romosozumab users had median age of 68 to 74 years whereas alendronate users had median age of 69.7 to 73.8 years. The median weight-based Garvan fracture risk score ranged from 12.5 to 28.5 in romosozumab users vs. 10.2 to 12.8 in alendronate users. In romosozumab users, the prevalence of recorded diagnoses of OP was 78% to 100% vs. 42% to 86% in alendronate users; fracture in the last two years was 27% to 91% in romosozumab users vs. 23% to 41% in alendronate users. The full list of patient characteristics before matching is detailed in Appendix 1, Section 3.

In the propensity score matched cohorts, weighted means and proportions of selected covariates included in the propensity score models are described in Table 15. In each database, propensity score matching had created groups of users of romosozumab and users of alendronate with similar baseline characteristics. The full list of covariates after matching are described in Appendix 1, Section 9.

Table 15: Patient characteristics in the propensity score matched romosozumab and alendronate cohorts

	IPCI		NDR		SIDIAP		CPRD Aurum		GePaRD	
Covariate entered in the PS model	**ROMO**	**ALN**	**ROMO**	**ALN**	**ROMO**	**ALN**	**ROMO**	**ALN**	**ROMO**	**ALN**
Age (mean (SD))	70.76 (8.68)	70.87 (10.45)	68.71 (8.41)	68.76 (9.52)	73.14 (8.82)	73.18 (10.47)	70.45 (7.41)	70.63 (9.7)	70.19 (9.17)	70.29 (9.55)
Charlson comorbidity score = 0 (%)	52.5%	52.2%	87.7%	87.8%	21%	23.1%	18.8%	18.7%	48.4%	48.4%
Charlson comorbidity score ≥4 (%)	0%	1.4%	0.6%	0.5%	3%	3.3%	4%	3.5%	5.8%	5.6%
Number of general practice visits in the prior year (mean (SD))	3.13 (1.55)	3.28 (1.77)	NA	NA	9.89 (7.52)	9.64 (7.15)	13.03 (8.99)	13.34 (10.37)	3.81 (3.68)	3.9 (3.79)
Garvan fracture risk - weight based (mean (SD))	13.5 (18.4)	15.2 (16.98)	NA	NA	29.61 (23.1)	30.17 (24.6)	23.7 (19.5)	23.82 (20.53)	NA	NA
Arrhythmia (%)	11.5%	10.9%	4.5%	4.1%	15%	15.9%	8%	7.4%	21.4%	22.5%
Atrial fibrillation/flutter (%)	NA	NA	1.7%	1.1%	5.2%	5.5%	4%	4.1%	3.6%	3.7%
Cerebrovascular disease (%)*	NA	NA	1.1%	1.3%	1.5%	1.5%	NA	NA	1.3%	0.7%
Chronic obstructive pulmonary disease (%)	9.8%	9%	4.7%	4.3%	10.8%	10.7%	14.8%	12.3%	15.1%	14%
Established cardiovascular disease (%)^	24.6%	22.4%	9.7%	9.1%	23%	24.3%	17%	18.7%	34.1%	34.3%
Diabetes (Type 1, type 2 or secondary) (%)	8.2%	7.1%	4.7%	4.7%	8.5%	9.4%	8%	9.8%	3.9%	4%
No fracture history (%)	41%	37.2%	3.4%	2.2%	21.5%	20.1%	7.4%	7.6%	51.7%	49.3%
Fracture history in prior two years (%)	27.9%	29.2%	90.5%	92.3%	49.2%	49.4%	72.2%	71.5%	25.6%	26.9%
Fracture history (ever) (%)	31.1%	33.6%	6%	5.5%	29.2%	30.5%	20.5%	20.9%	22.6%	23.8%
Hypercholesterolaemia (%)	16.4%	15.3%	57.8%	56.8%	41%	42.7%	21.6%	20.7%	49.4%	49.2%
Hypertension (%)	26.2%	27.3%	15.1%	13.7%	43.8%	43.2%	33%	34.8%	50.5%	51.8%
Infection (%)	21.3%	25.1%	NA	NA	33%	32.4%	14.8%	16.6%	24.7%	23.1%
Osteoporosis (%)	75.4%	72.1%	99.8%	100%	89.2%	90%	90.9%	91.6%	97.6%	97.5%
Serious infection (%)	NA	NA	5.2%	5.4%	5.8%	5.2%	6.8%	5.9%	2.4%	2.4%

	IPCI		NDR		SIDIAP		CPRD Aurum		GePaRD	
Covariate entered in the PS model	**ROMO**	**ALN**	**ROMO**	**ALN**	**ROMO**	**ALN**	**ROMO**	**ALN**	**ROMO**	**ALN**
Systemic glucocorticoids (%)	26.2%	25.1%	7.1%	7.8%	19.5%	17.9%	17%	16.7%	22.3%	22.1%
Number of prescriptions in prior year (mean (SD))	9.16 (4.14)	9.28 (5.3)	3.43 (2.39)	3.37 (2.28)	10.11 (5.74)	9.95 (5.44)	NA	NA	2.43 (3.86)	2.55 (3.6)

ALN=alendronate; BP=bisphosphonates; NSAIDs=Non-steroidal anti-inflammatory drugs; PS=propensity score; ROMO=romosozumab; SD=Standard deviation; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
NA = variable not included in the propensity score model, either it was unavailable in the database or the number of counts was <5 amongst romosozumab users.
^Includes angina, atherosclerosis, atrial fibrillation.
*Includes cerebral ischaemia and transient ischaemic attack.

The comparability of patient characteristics between romosozumab users and alendronate users was assessed using absolute standardised mean differences (ASMD), with differences larger than 0.1 deemed to be considered as imbalanced between treatment groups. Table 16 shows the number of covariates entered in the propensity score model and the number of imbalanced covariates remaining in the propensity score matched cohorts. The number of covariates entered in the propensity score model for each database ranged from 41 covariates in IPCI to 70 covariates in SIDIAP. No relevant differences with an ASMD ≥0.1 persisted after propensity score matching for any covariate in NDR, SIDIAP, CPRD Aurum, and GePaRD.

Only the IPCI database had 8 imbalanced covariates remaining in the propensity score matched cohorts, which would most likely be due to its small population size. These covariates were adjusted for in the survival model in risk effect estimation.

The balance plots illustrating the ASMD before and after matching are shown in Appendix 1, Section 10.

Table 16: Imbalanced covariates after propensity score matching

Database	Number of covariates entered in the PS model	Number of imbalanced covariates after PS matching	Imbalanced covariates after matching (ASMD)*
IPCI	41	8 (19.5%)	Charlson comorbidity score of 2 (0.1108) Charlson comorbidity score of ≥4 (0.1183) Charlson comorbidity score of 3 (0.1524) Missing Garvan fracture risk (weight-based) score (0.1783) Lipid lowering drugs (0.1604) Antiarrhythmic drugs (0.1524) Beta blockers (0.1593) Current smoker (0.1848)
NDR	59	0	
SIDIAP	70	0	
CPRD Aurum	66	0	
GePaRD	69	0	

PS=propensity score; ASMD=absolute standardised mean difference; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
*Imbalanced covariates were adjusted for in the Cox regression model in risk effect estimation.

10.4.2 Comparative safety analysis for the primary outcome

The risk of SI (primary outcome) was compared between users of romosozumab and users of alendronate in the propensity score matched cohorts. Weighted IRs per 1,000 PY are presented in Table 17. There were no events in both treatment groups in IPCI. In romosozumab users the IR ranged from 0 to 91.27. In alendronate users the IR ranged from 0 to 77.93.

The proportional hazards assumption was assessed using log-log plots as shown in Appendix 1, Section 11. There was no obvious violation of the proportional hazards assumption in any of the databases. Cause-specific hazards from competing risk analyses were not performed as no events of death due to SI or serious COVID-19 infection were observed in any cohort.

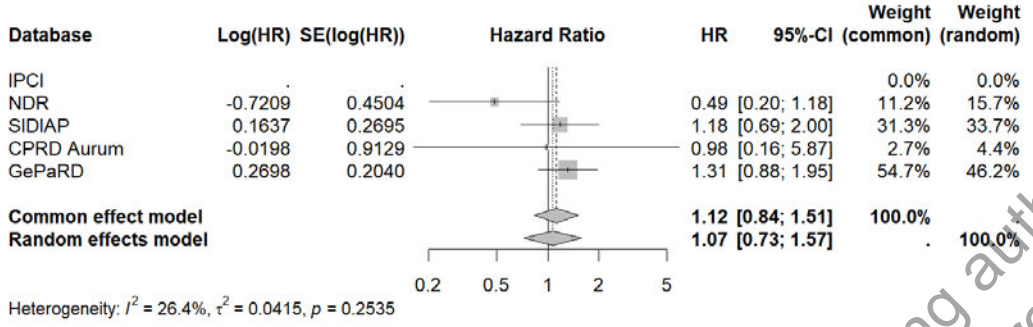
Table 17: Incidence rates of SI in romosozumab users compared to alendronate users in the propensity score matched cohorts

Database	Incidence rate (95% CI)	
	ROMO	ALN
IPCI	0 (0, 0)	0 (0, 0)
NDR	27.10 (11.27, 55.86)	55.37 (41.29, 72.79)
SIDIAP	91.27 (58.82, 135.69)	77.93 (58.39, 102.03)
CPRD Aurum	*	24.54 (10.38, 49.96)
GePaRD	87.47 (62.27, 119.68)	67.79 (52.69, 85.94)

ALN=alendronate; CI=confidence interval; ROMO=romosozumab; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
*fewer than 5 events thus incidence rate was not reported.

We used common- and random effects meta-analysis to pool the database specific HRs to obtain an overall HR. Figure 4 illustrates that the heterogeneity across databases was low with an I^2 of 26.4% (95% CI: 0.0%, 72.1%). The pooled estimated risk of SI in romosozumab users was not significantly different from alendronate users in both conservative fixed/common effects model: HR 1.12 (95% CI: 0.84, 1.51) and random effects model: HR 1.07 (0.73, 1.57). In each database, the estimated 95% confidence interval of the hazard ratio included the null value of 1 and ranged from 0.49 to 1.31.

Figure 4: Forest plot showing the meta-analysis of hazard ratio estimates for the overall risk of SI associated with romosozumab compared to alendronate in the propensity score matched cohorts



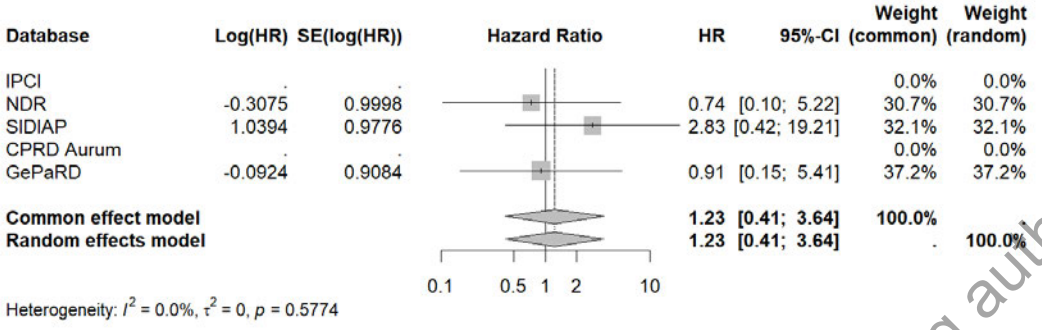
CI=confidence interval; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany; HR: hazard ratio; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SE: standard error; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, Spain;
No events in IPCI hence the HR was not calculated.

10.4.3 Comparative safety analysis for the secondary outcomes

There were no events of death due to SI or serious COVID-19 infection in the propensity score matched cohorts in any of the databases. Therefore, the risk effect estimates could not be derived for these outcomes. There were events of serious COVID-19 infection in the propensity score matched cohorts and its risk effect estimates are reported below.

In IPCI (both treatment groups) and CPRD Aurum (romosozumab users), there were no events of serious COVID-19 infection. The other three databases had <5 patients with serious COVID-19 infection in each treatment group. Figure 5 shows the forest plot of the results from the meta-analysis pooling the database specific HRs across 3 databases. Overall, the pooled estimated risk of serious COVID-19 infection in romosozumab users was not significantly different from alendronate users: HR 1.23 (95% CI: 0.41, 3.64). There was little heterogeneity across databases (I^2 of 0% [95% CI: 0.0%, 89.6%]). In each database, the estimated 95% confidence interval of the HR included the null value of 1 and ranged from 0.74 to 2.83.

Figure 5: Forest plot showing the meta-analysis of the hazard ratio estimates for the overall risk of serious COVID-19 infection associated with romosozumab compared to alendronate in the propensity score matched cohorts



CI=confidence interval; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany; HR: hazard ratio; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SE: standard error; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain;
No events in IPCI hence HR was not calculated.

10.4.4 Subgroup analyses

The feasibility of a subgroup analysis in patients with clinically severe OP (bone mineral density [BMD] T-score <-2.5 and a fracture recorded in the year prior to start of treatment) was assessed. However, this subgroup analysis was not performed due to limited sample size. In CPRD Aurum there were no romosozumab users with clinically severe OP. There were <5 and 7 romosozumab users with clinically severe OP in IPCI and SIDIAP, respectively. The BMD T-score was not recorded in NDR and GePaRD, precluding this subgroup analysis.

Subgroup analyses were performed in patients with a history of fracture in the 2 years and at any time prior to treatment. Separate propensity score models to perform matching was performed for each of these patient populations.

The next sections present the comparability of the propensity score matching between romosozumab and alendronate users (Section 10.4.4.1), the results of the comparative safety analysis for the primary outcome of SI (Section 10.4.4.2) and the secondary outcome of serious COVID-19 infection (Section 10.4.4.3) in these patient populations.

10.4.4.1 Subgroup analysis in patients with a history of fracture: Comparability of romosozumab and alendronate matched cohorts

Table 18 states the number of romosozumab users and alendronate users before and after propensity score matching for each subgroup analysis.

In patients with a history of fracture in the 2 years prior to treatment, from a total of 1,047 romosozumab users, 89% (n=934) were included in the propensity score matched cohorts.

In patients with a history of fracture at any time prior to treatment, in total 92% (n=1,292) of romosozumab users were included in the propensity score matched cohorts.

Table 18: Subgroup analysis in patients with a history of fracture: Number of romosozumab and alendronate users before and after propensity score matching

	Before PS matching		After PS matching		Effective sample size after PS matching	
	ROMO	**ALN**	**ROMO**	**ALN**	**ROMO**	**ALN**
History of fracture in the 2 years prior to treatment						
IPCI	24	2,832	16 (66.7%)	36 (1.3%)	16	30
NDR	460	18,428	429 (93.3%)	1,072 (5.8%)	429	901
SIDIAP	220	14,759	201 (91.4%)	499 (3.4%)	201	419
CPRD Aurum	166	34,891	129 (77.7%)	338 (1.0%)	129	284
GePaRD	177	13,407	159 (89.8%)	430 (3.2%)	159	382
Total	**1,047**	**84,317**	**934 (89.2%)**	**2,375 (2.8%)**	**934**	**2,017**
History of fracture at any time prior to treatment						
IPCI	47	4,021	35 (74.5%)	86 (2.1%)	35	70
NDR	488	34,018	454 (93.0%)	1,173 (3.4%)	454	990
SIDIAP	337	24,559	323 (95.8%)	845 (3.4%)	323	715
CPRD Aurum	212	52,017	173 (81.6%)	452 (0.9%)	173	381
GePaRD	328	23,580	307 (93.6%)	828 (3.5%)	307	733
Total	**1,412**	**138,195**	**1,292 (91.5%)**	**3,384 (2.4%)**	**1,292**	**2,889**

ALN=alendronate; PS=propensity score; ROMO=romosozumab; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.

For each subgroup analysis, the estimated coefficients from the propensity score model and patient characteristics in the propensity score matched cohorts is in Appendix 1, Sections 12 and 13.

Comparability of treatment groups is described in Table 19. In the matched cohorts, in patients with a history of fracture in the prior 2 years, there was imbalance in IPCI with 12 covariates with ASMD ≥0.1. In SIDIAP and CPRD Aurum, there were 1 (1.6%) and 4 (6.8%) covariates with ASMD ≥0.1, respectively. NDR and GePaRD achieved balance for all covariates included in the propensity score model. Imbalanced covariates were adjusted for in the survival models for IPCI, SIDIAP and CPRD Aurum.

In the matched cohorts, in patients with a history of fracture at any time before OP treatment initiation, there were 14 covariates exceeding ASMD ≥0.1 in IPCI. Imbalanced covariates were adjusted for in the survival model. In CPRD Aurum, there was 1 (1.8%) imbalanced covariate however, adjusting for this covariate in the survival model prevented converging this model successfully, and therefore it was removed from analysis. In SIDIAP, NDR, and GePaRD balance was achieved for all covariates. Plots of the ASMD before and after matching is illustrated in Appendix 1, Sections 12 and 13.

Across all subgroup analyses and databases, the distribution of the propensity score in romosozumab users and alendronate users in the matched cohorts were similar (Appendix 1, Sections 12 and 13).

Table 19: Subgroup analysis in patients with a history of fracture: Imbalanced covariates between users of romosozumab and alendronate after propensity score matching

	History of fracture in the 2 years prior to treatment		History of fracture at any time prior to treatment	
Database	**Number of imbalanced covariates from all covariates entered in the PS model**	**Imbalanced covariates after PS matching (ASMD)***	**Number of imbalanced covariates from all covariates in the PS model**	**Imbalanced covariates after PS matching (ASMD)***
IPCI	12/24 (50%)	Charlson comorbidity score = 0 (0.1250) Charlson comorbidity score ≥4 (0.3128) Osteoporosis (0.2565) Vitamin D or calcium (0.1882) Age (0.1183) Number of general practice visits (0.1104) Systemic glucocorticoids (0.3136) Opioids (0.1375) Beta-blockers (0.1146) Hypertension (0.1105) Anti-hypertensives (0.4090) Infection (0.2292)	14/35 (40%)	Age (0.1680) Hypertension (0.1090) Number of prescriptions (0.2242) Inhaled glucocorticoids (0.1427) Opioid (0.1261) Diabetes (0.1699) Weight-based Garvan fracture risk (0.1501) ACE inhibitor (0.1978) Angiotensin II inhibitor (0.1855) Hyperlipidaemia (0.2178) Cardiovascular disease (0.1041) Anti-hypertensives (0.1638) Charlson comorbidity score = 1 (0.1320) Charlson comorbidity score = 3 (0.1536)
NDR	0/55		0/55	
SIDIAP	1/62 (1.6%)	Year of index prescription = 2023 (0.1096)	0/68	
CPRD Aurum	4/59 (6.8%)	Age (0.1124) Weight-based Garvan fracture risk (0.1231) Arrhythmia (0.1154) Serious infection (0.1162)	1/57 (1.8%)	Charlson comorbidity score = 0 (0.1105)
GePaRD	0/63 (%)		0/67	

ASMD=absolute standardised mean difference; PS=propensity score; NSAIDS=non-steroidal anti-inflammatory drugs; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany. *Imbalanced covariates were adjusted for in the Cox regression model in risk effect estimation.

10.4.4.2 Subgroup analysis in patients with a history of fracture: Comparative safety analysis for the primary outcome

The IR of SI in romosozumab users and alendronate users for each subgroup is shown in Table 20. The risk of SI in romosozumab users compared to alendronate users is illustrated in Figure 6 (patients with history of fracture in the prior two years) and Figure 7 (patients with a history of fracture at any time).

There were no events of SI in IPCI in both treatment groups and <5 events amongst romosozumab users in CPRD Aurum for both subgroup analyses. In patients with a history of fracture in the 2 years prior to treatment, the IR ranged from 0 to 108.48 amongst romosozumab users and 0 to 103.64 amongst alendronate users. In patients with a history of fracture at any time, the IR ranged from 0 to 96.19 amongst romosozumab users and 0 to 95.03 amongst alendronate users.

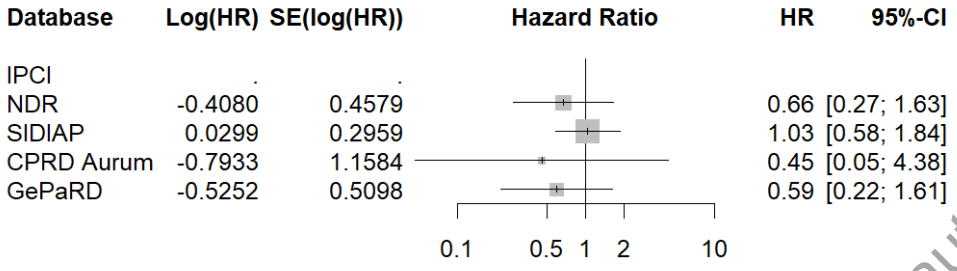
Overall, the risk of SI was not significantly different between romosozumab users and alendronate users in any of databases for each subgroup analysis. The CIs of the risk effect estimates in the subgroup analyses overlapped with the main analysis (Section 10.4.2) suggesting the risk effect does not change in these subgroups of patients.

Table 20: Subgroup analysis in patients with a history of fracture: Incidence rates of SI in romosozumab users compared to alendronate users in the propensity score matched cohorts

Database	Incidence rate (95% CI)	
	ROMO	ALN
History of fracture in the 2 years prior to treatment		
IPCI	0 (0, 0)	0 (0, 0)
NDR	28.98 (12.05, 59.75)	48.86 (35.17, 66.25)
SIDIAP	108.48 (62.12, 177.15)	103.64 (71.98, 144.82)
CPRD Aurum	*	46.94 (22.47, 87.65)
GePaRD	48.13 (18.25, 105.49)	87.24 (55.16, 131.73)
History of fracture at any time prior to treatment		
IPCI	0 (0, 0)	0 (0, 0)
NDR	27.86 (11.58, 57.42)	46.32 (33.46, 62.59)
SIDIAP	94.15 (58.58, 144)	66.46 (46.84, 91.73)
CPRD Aurum	*	34.73 (16.6, 64.9)
GePaRD	96.19 (59.85, 147.12)	95.03 (69.63, 126.85)

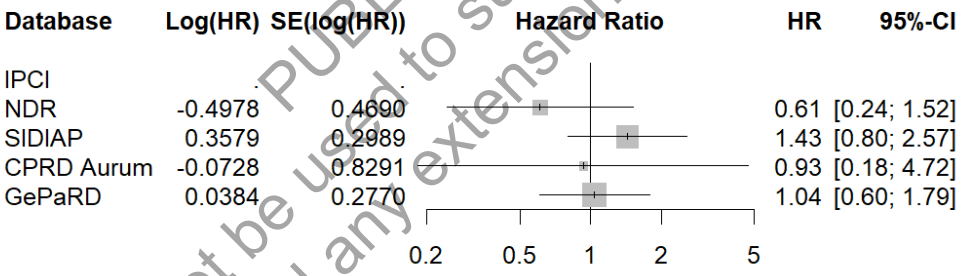
ALN=alendronate; CI=confidence interval; ROMO=romosozumab; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.
*fewer than 5 events thus incidence rate was not reported.

Figure 6: Subgroup analysis in patients with history of fracture in the 2 years prior to treatment: Forest plot of the hazard ratio estimates of SI associated with romosozumab compared to alendronate in the propensity score matched cohorts



CI=confidence interval; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany; HR: hazard ratio; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SE: standard error; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain;
No events in IPCI hence HR was not calculated.

Figure 7: Subgroup analysis in patients with history of fracture at any time prior to treatment: Forest plot of the hazard ratio estimates of SI associated with romosozumab compared to alendronate in the propensity score matched cohorts

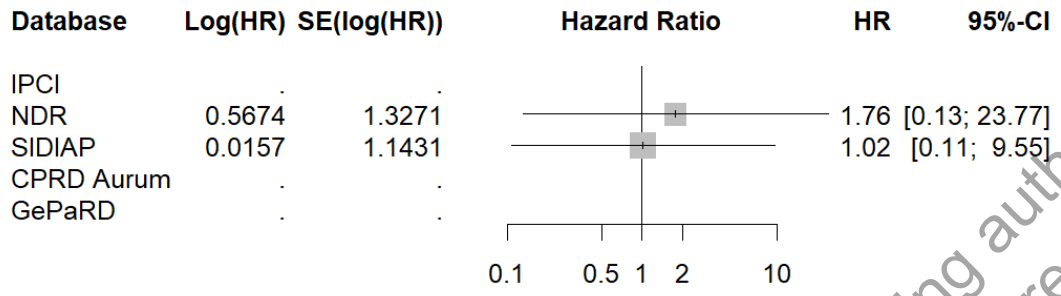


CI=confidence interval; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany; HR: hazard ratio; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SE: standard error; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain;
No events in IPCI hence HR was not calculated.

10.4.4.3 Subgroup analysis in patients with a history of fracture: Comparative safety analysis for the secondary outcomes

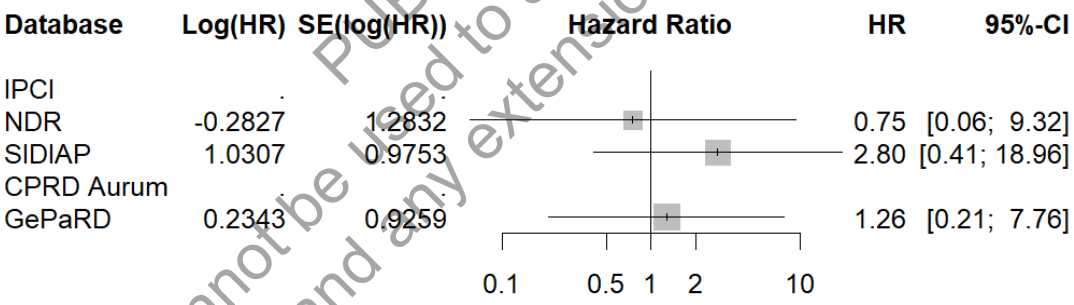
The risk of serious COVID-19 infection was not significantly different between romosozumab and alendronate users in patients with a history of fracture in the 2 years prior with an estimated HR of 1.02 and 1.76 in SIDIAP and NDR respectively (Figure 8); and in patients with a history of fracture at any time with HR ranging from 0.75 to 2.80 across 3 databases (Figure 9).

Figure 8: Subgroup analysis in patients with history of fracture in the 2 years prior to treatment: Forest plot of the hazard ratio estimates of serious COVID-19 infection associated with romosozumab compared to alendronate in the propensity score matched cohorts



CI=confidence interval; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany; HR: hazard ratio; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SE=standard error; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain;
No events in IPCI, CPRD Aurum, and GePaRD hence HR was not calculated.

Figure 9: Subgroup analysis in patients with history of fracture at any time prior to treatment: Forest plot of the hazard ratio estimates of serious COVID-19 infection associated with romosozumab compared to alendronate in the propensity score matched cohorts



CI=confidence interval; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany; HR: hazard ratio; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SE=standard error; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain;
No events in IPCI and CPRD Aurum hence HR was not calculated.

10.5 Assessment of reliability and validity of comparative safety analysis

This section will report the robustness of comparative safety analysis against unmeasured confounding. Results of the NCO analysis are reported in Section 10.5.1. If the NCO analysis indicated presence of unmeasured confounding in any database, further sensitivity analyses of empirical calibration (Section 10.5.1.1), SCCS (Section 10.5.1.2), and instrumental variable analysis (Section 10.5.1.3) are reported.

10.5.1 Negative control outcome (NCO) analysis

The association between romosozumab and up to 71 NCOs was estimated in the propensity score matched cohorts for each database. The definition of a NCO is an outcome upon which the treatment and comparator are not expected to have an effect (for example ingrown nail), but it is assumed to share the same confounding structure as the outcome of interest (Section 9.9.4.2). The complete list of NCOs is provided in Appendix 1, Section 1. Table 21 shows the total number of NCOs available for assessment in each database and the number of them associated with romosozumab use. The estimated association between romosozumab and NCOs are shown in Appendix 1, Section 14.

The only study suggesting unobserved confounding was GePaRD, in which 3 (10.7%) NCOs were positively associated with romosozumab use: hyperkeratosis [log HR 0.85 (95% CI: 0.18, 1.52)], verruca [log HR 1.22 (95% CI: 0.15, 2.30)] and urgent desire of stool [log HR 0.88 (95% CI: 0.09, 1.67)]. As more than 5% of assessable NCOs were statistically significant, three sensitivity analyses (empirical calibration, self-controlled case series, and instrumental variable analysis) were performed only in this database.

Table 21: Number of assessable negative control outcomes associated with romosozumab use in the propensity score matched cohorts

Database	Number of assessable NCOs	Number (%) of NCOs associated with romosozumab use
IPCI	4	0
NDR	4	0
SIDIAP	8	0
CPRD Aurum	1	0
GePaRD	28	3 (10.7%)

NCO=negative control outcome; IPCI=Integrated Primary Care Information Project, the Netherlands; NDR=Nationwide Linked Danish Registry, Denmark; SIDIAP=Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; Spain; CPRD=Clinical Practice Research Datalink, United Kingdom; GePaRD=German Pharmacoepidemiological Research Database, Germany.

10.5.1.1 Empirical calibration in GePaRD

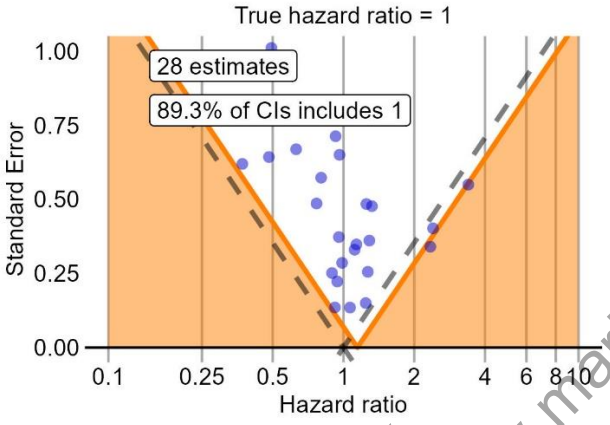
The estimated risk effect estimates performed in GePaRD may have systematic error due to unobserved confounding. Therefore, the risk effect estimates were calibrated. The distribution of the estimated log HRs for NCOs appeared evenly on either side of the null value of 0 (Appendix 1, Section 14.5). Figure 10 shows the 28 estimated HRs from the NCOs plotted against their standard error.

Assuming that the true effect was 1, before calibration the area above the dashed line shows that 25 (89.3%) NCOs have their 95% CI including the true null value of 1. After calibration, there were only 2 estimates below the orange area, meaning 26 (92.8%) of NCOs have their calibrated 95% CI including the true null value.

Since the distribution of the NCOs contained more NCOs with point estimate above 1, the empirical calibration adjusted for this bias. Hence, the calibrated HR for romosozumab on risk of SI was 1.21 (95% CI 0.81, 1.81) which was closer to the null value compared to the HR obtained from the main (uncalibrated) analysis [HR 1.31

(0.88, 1.95)]. This confirms that main conclusions of this study (i.e. no significant differences between the primary outcome of SI in romosozumab vs. alendronate patients) were not affected by the unobserved confounding in the GePaRD database.

Figure 10: Effect size estimates for negative control outcomes before and after calibration in the propensity score matched cohorts



Blue dots indicate the negative control outcomes, area below the grey dashed line indicate confidence intervals excluding 1, area below the orange line indicate calibrated confidence intervals excluding 1.

10.5.1.2 Self-controlled case series (SCCS) in GePaRD

There were 72 (11%) romosozumab users in GePaRD who had 123 SI events in total. The incidence rate ratio (IRR) for SCCS compared periods when the patient was exposed to romosozumab to periods when the same patient was not exposed to romosozumab. The unadjusted and age-adjusted IRRs are shown in Table 22. Both the unadjusted and age-adjusted estimates were close to the null, and included 1 in their confidence intervals, suggesting no differential risk of SI during exposure to romosozumab compared to unexposed time.

Table 22: Within patient comparison of the risk of SI in periods exposed and unexposed to romosozumab from the SCCS analysis

	Unadjusted incidence rate ratio	Age-adjusted incidence rate ratio
Exposed to romosozumab vs unexposed	0.95 (0.58, 1.53)	0.91 (0.54, 1.54)

We also verified the assumptions of SCCS analysis. The assumption that the event was uncommon or events were independent was determined by first counting the number of times the patient had a SI. A total of 51 (71%) patients had more than one SI event (Table 23). The SCCS was then repeated restricting analysis to the first event. The unadjusted IRR was 1.08 (0.57, 2.06) whereas the age-adjusted IRR was 1.14 (0.55, 2.34).

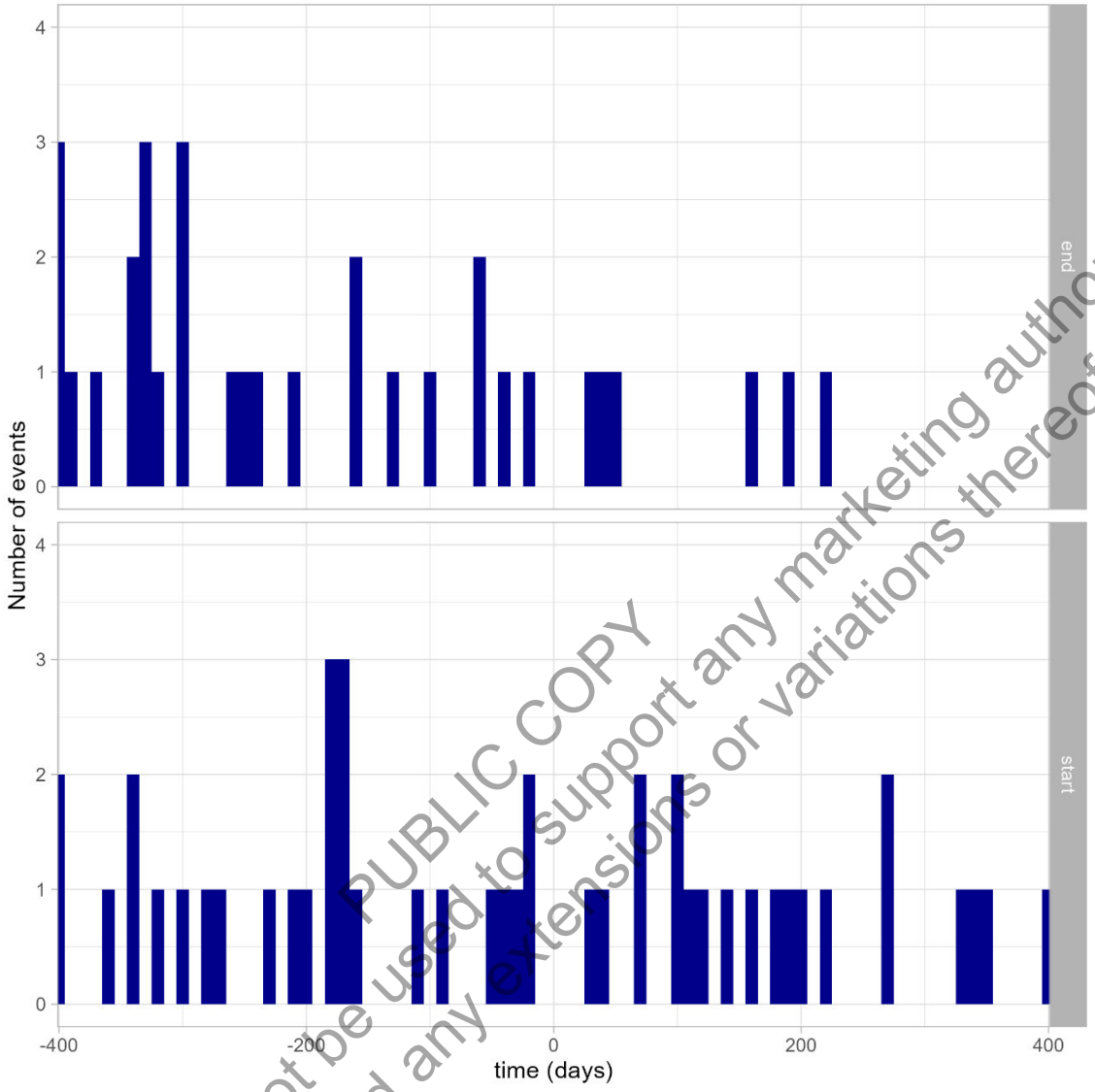
Table 23: Number of repeat SI in the SCCS analysis

Number of serious infections	N (%)
1	72 (100)
2	16 (22.2)
3	9 (12.5)
4	7 (9.7)
5 or more	19 (26.4)

The assumption that SI events did not influence the length of observation period due to death was quantified by first calculating the number of deaths. The SCCS was repeated in 68 patients who did not die during the observation period. The unadjusted IRR was 0.90 (0.51, 1.58) whereas the age-adjusted IRR was 0.84 (0.45, 1.55).

The assumption that SI events did not influence the probability of romosozumab exposure was assessed by examining the distribution of SI events in relation to time of romosozumab initiation and end (Figure 11). There were no obvious trends that SI increased or decreased the probability of romosozumab exposure as there were no clear peaks in the histogram.

Figure 11: Distribution of start and end dates of SI events before and after initiation of romosozumab in the SCCS analysis



10.5.1.3 Instrumental variable analysis in GePaRD

Using the cohort of patients prescribed romosozumab or alendronate, physician preference for the use of romosozumab was estimated by calculating the proportion of romosozumab prescriptions in the previous 10, 20, and 50 prescriptions. Alendronate users prior to 2021 were excluded as there were no romosozumab users at that time. The first 10, 20, and 50 prescriptions for each physician were then excluded from analysis respectively. The eligible number of patients is described in Table 24.

Table 24: Number of eligible patients for the instrumental variable analysis

Physician prescription preference for romosozumab (IV variable) in the last:	ROMO N=661	ALN N=73,616
10 previous prescriptions	225 (34.0%)	37,594 (51.1%)
20 previous prescriptions	146 (22.1%)	33,944 (46.1%)
50 previous prescriptions	82 (12.4%)	32,230 (43.8%)

ALN=alendronate; IV=instrumental variable; ROMO=romosozumab.

The assumption that the association between the physician preference instrumental variable and romosozumab needs to be strong was assessed by calculating the odds ratio and the F-statistic (Table 25). The association was the strongest between the physician preference for romosozumab in the 10 previous prescriptions and romosozumab use with an odds ratio of 2.10. The association between physician preference for romosozumab in the previous 20 and 50 prescriptions and romosozumab use was not strong with an odds ratio of 1.47 and 1.15 respectively, despite highly significant F-statistics that rejected the null hypothesis of a weak instrument.

Table 25: Association between instrumental variable and romosozumab use

IV	Odds ratio (95% CI)	F-statistic
10 previous prescriptions	2.10 (1.94, 2.26)	1485.86 (p<0.001)
20 previous prescriptions	1.47 (1.41, 1.55)	645.908 (p<0.001)
50 previous prescriptions	1.15 (1.11, 1.18)	87.626 (p<0.001)

IV=Instrumental variable; CI=confidence interval.

The assumption of lack of association between the instrumental variable and confounding was assessed using ASMD for covariates in the database (Appendix 1, Section 15). For each instrumental variable, the percentage of covariates with ASMD ≥0.1 was 21% (10 previous prescriptions), 24% (20 previous prescriptions), and 55% (50 previous prescriptions). Imbalanced covariates included strong confounders such as age, socioeconomic status, or hospital visits in the previous year. Thus, the assumption of no association between the instrumental variables and measured potential confounders was not met. No other instrumental variable could be identified in the database and, therefore, no instrumental variable analysis was performed.

11 DISCUSSION

This PASS (OP0006) is the first to evaluate the real-world incidence of SI and serious COVID-19 in romosozumab users across Europe, compared to other OP medications. The findings suggest that romosozumab does not confer a significantly increased risk of SI or serious COVID-19 infection compared to alendronate users. Other secondary outcomes (mortality due to SI or serious COVID-19 infection) could not be assessed due to absence of these outcomes in romosozumab users.

The key results section below discusses comparative safety analysis findings as well as observations related to incidence of SI across medications and databases.

11.1 Key results

Comparative safety analysis

Across databases, prior to propensity score matching, several large differences in patient characteristics were observed between romosozumab and alendronate users. Across databases, between 41% to 61% of romosozumab users had history of other OP medications in the previous year before starting treatment compared to between 1.4% and 9.4% in alendronate users, as alendronate is commonly prescribed as first line therapy.

The high percentage of patients with a diagnosis of OP (78% to 100% in romosozumab vs. 42% to 86% in alendronate users) as well as higher percentage with history of fracture in the prior two years of treatment initiation (27% to 91% vs. 18% to 41%) suggest higher risk of osteoporotic fracture in romosozumab users. Cardiovascular risk factors (e.g., established CV disease, antihypertensive use, and lipid-lowering drug use) and other comorbidities were observed to be different between romosozumab and alendronate cohorts in most databases. Therefore, propensity score matching (as planned in the protocol) was needed to adjust for potential differences between comparing cohorts.

Propensity score matching was applied to all users of romosozumab and alendronate (main analysis) and within 2 subgroups: patients with a history of fracture in the prior two years, and history of fracture at any time prior to treatment initiation. The subgroup analysis of clinically severe OP was not performed as there were insufficient number of romosozumab users with a BMD T-score data in databases.

In the main analysis, 1,738 (92%) romosozumab users were matched to 4,632 alendronate users. Propensity score matching was successful in achieving comparable groups of romosozumab and alendronate users on a wide range of confounding variables and SI risk factors in 4 databases as opposed to the starting population. For example, the difference between OP diagnosis and history of fracture in the romosozumab and alendronate groups was reduced to 0.1-3.3% and 0.4-2.5%, respectively, in the matched cohorts.

In the propensity score matched cohorts, the estimated HR within each database did not indicate any association between romosozumab use and risk of SI. Pooling HRs from 4 databases using meta-analysis, the fixed-effects meta-analytic estimate [HR: 1.12 (95% CI 0.84, 1.51)] showed no evidence of increased risk of SI in romosozumab users as compared to alendronate users.

Subgroup analyses in patients with 2-year or any history of fracture showed similar pattern to the main analysis. This suggests that the risk of SI is not increased in romosozumab irrespective of their baseline severity of OP.

Among secondary outcomes, only the risk of serious COVID-19 infection could be evaluated in three databases. Meta-analysis pooling the estimated HRs showed no evidence of increased risk of serious COVID-19 infection in romosozumab users as compared to alendronate users [HR: 1.23 (95% CI 0.41, 3.64)]. Similarly, within the subgroup analyses (patients with 2-year or any history of fracture), the risk effect

estimates did not differ to the main analysis. There were no reports of death due to SI or serious COVID-19 infection in romosozumab users in any of the databases.

To address potential unobserved confounding (even after propensity score matching), the association between romosozumab and negative control outcomes (NCOs) was assessed. Only in GePaRD there were significant number of NCOs associated with romosozumab use. Therefore, further sensitivity analyses to assess the impact of unmeasured confounding were performed. Empirical calibration showed a calibrated HR of 1.21 (95% CI 0.81, 1.81), which was closer to the null compared to the uncalibrated HR in GePaRD [1.31 (0.88, 1.95)]. Comparing the risk of SI in exposed vs. unexposed periods among romosozumab users showed an age-adjusted IRR of 0.91 (0.54, 1.54), suggesting no increased risk of SI during romosozumab treatment.

Incidence rates of SI events

IRs of SI events were calculated in unmatched users of OP medications based on two types of follow-up, exposure-based (while on treatment) and fixed follow-up, where the outcome identification was carried forward regardless of treatment continuation.

In exposure-based analysis and across the databases, the IR of SI in romosozumab users ranged between 24.4 and 90.6 per 1,000 PY. The corresponding range was 47.9 to 124.6 in alendronate users and 36.5 to 177.3 in users of other OP medications. In SIDIAP, the IR of SI in romosozumab users [90.6 (57.4, 136.0) per 1,000 PY] was significantly higher than alendronate users [47.9 (45.9, 49.9)] and oral bisphosphonate users [36.5 (32.8, 40.5)]. However, this can be related to general differences between these user populations (e.g., alendronate and other bisphosphonate users in SIDIAP were on average about 4 years younger than romosozumab users). This was confirmed after propensity score matching as the differences were not significant in matched populations [91.3 (58.8, 135.7) in romosozumab vs. 77.9 (58.4, 102.0) in alendronate users].

The small number (zero or fewer than 5) of serious COVID-19 infection events or death due to SI or serious COVID-19 infection in romosozumab users did not allow calculation of IRs in this population for any secondary outcome. Amongst alendronate users, the IR of serious COVID-19 infection ranged from 2.5 to 11.5 per 1,000 PY. This range was 0 to 36.6 among users of other OP medications. In alendronate users, the IRs of death due to SI or due to serious COVID-19 infection ranged from 3.3 to 13.2 and 0 to 0.2, respectively. The corresponding IR ranges among users of other OP medications were 1.7 to 24.2 and 0 to 0.6, respectively.

Fixed follow-up analysis showed similar IRs to exposure-based analysis, with overlapping confidence intervals.

Overall, the IRs observed in this study are in line with the recent epidemiological studies in European populations. Although we could not find any specific study that looks into combination of SI outcomes (similar to this study), triangulating recent European evidence suggests that the overall incidence of SIs leading to hospitalisation in geriatric adults is about 1.3 to 2.5 per 1,000 PY for community-dwelling older adults (≥65 years), and higher in institutionalised long-term–care populations (32-36).

11.2 Limitations

Our study has several limitations. Misclassification in the exposures (OP medications) and study outcomes (SIs) is possible given the real-world nature of the databases. Relevant primarily to IPCI and CPRD, primary care prescriptions are not necessarily equivalent to the actual dispensing or intake of the therapies in osteoporosis patients (as care for these patients may be provided by specialised settings). A study conducted in Spain showed a 20% adherence to alendronate in primary care data linked to prescription and pharmacy dispensation records (37). However, our analyses calculating IRs of events based on index exposure (i.e. 'on treatment') and dismissing compliance showed similar findings suggesting little impact of such misclassification in these data.

IRs in this report are crude rather than age adjusted (given the pre-specified age range for patients), and rates may not be representative of the population at large (due to potential differences between eligible patients and general population). However, all databases used in this study have been shown to be representative of the source population from which the data originate (38-43). In some instances, the IRs had wide CIs as the calculation of IR was based on a small number of events.

The observational nature of this study makes it vulnerable to confounding by indication due to differential use of medicines according to baseline fracture risk. Whilst the history of fracture in the last two years prior to the index date is used as a proxy for baseline fracture risk in the sensitivity analysis, this does not necessarily account for the full differential risk of fracture and other outcomes (including safety events) between patients. Across databases the percentage of patients with a diagnosis of OP varied significantly. This is expected as some countries require physicians to report the diagnosis codes before prescription of treatments for osteoporosis. However, we chose a new user cohort design, considered the best option for the estimation of drug effects in pharmacoepidemiology according to current relevant ENCePP methodological guidelines (44). By excluding prevalent users and starting follow-up of drug users at the time of their first prescription, we avoided selection bias resulting from the depletion of susceptible patients (45). Unlike more computationally efficient designs such as case-control studies, this cohort design allowed us to calculate IRs, which are essential for comparative safety analyses. Similar analyses based on routinely collected data from real-world practice have been shown to accurately replicate RCT findings (46). In addition, restriction to a subpopulation of OP medicine/s users compliant with the conditions of use of romosozumab made these cohorts more homogeneous and likely better balanced in terms of relevant confounders like fracture or SI risk factors.

In the comparative safety analysis, residual confounding could be a concern. Over 70 potential confounding variables and SI risk factors were included in the propensity score calculation models. However, the number of covariates to include were restricted by the number of romosozumab users, particularly in the smaller databases. Inclusion of all covariates had caused model separation where certain covariate patterns led to the estimation of PS of 0 and 1. This is problematic as these patients would not be included in the propensity score matched cohorts. Therefore, covariates with small counts were excluded. It should be noted that achieving balance in the smallest database (IPCI) was not possible due to the small number of romosozumab users, and therefore, some residual confounding may have remained.

Heterogeneity between databases was low [I^2=26%] but had wide CIs, with the higher bound reaching up to 72%. This does not mean that the study sample was homogenous,

it could rather be attributed to the low number of events, estimated HRs were in opposite directions with wide confidence intervals of the individual databases, and the estimated I^2 may be biased and imprecise in small-meta-analyses (47).

To assess whether any potential residual confounding is remaining in any of the databases, we utilised the robust approach of negative control outcomes (NCO). There was no sign of residual confounding in 4 out of 5 databases (including IPCI). In the largest database (GePaRD), analysis of 28 NCOs showed evidence of potential residual confounding. We mitigated this by performing additional sensitivity analyses in GePaRD, which all showed similar results to the main analysis.

Matching weights were used to account for variable ratio matching of a romosozumab user with up to three alendronate users. Consequently, the weighting reduces the precision within the propensity score matched cohorts. The effective sample size in the propensity score matched cohorts was calculated and represents the size of a hypothetical unweighted cohort that has the same amount of information as the weighted cohort. In the main analysis, the effective sample size was 1,738 romosozumab users and 4,085 alendronate users across 5 databases. The sample size calculation required 1,399 romosozumab users and 4,018 alendronate users to have 90% power to detect a HR of 1.5 suggesting the analysis was sufficiently powered. However, not all databases had contributed to the meta-analysis due to no events resulting in a smaller number of alendronate users that were required. All the subgroup analyses were underpowered, and the precision of some estimates were low.

Several pre-planned analyses could not be performed due to low number of outcome events (especially in romosozumab users). The risk of secondary outcomes of death due to SI or COVID-19 infection in romosozumab users could not be evaluated as there were no events. The subgroup analysis of clinically severe OP was not performed as the BMD T-score was not available in NDR and GePaRD, and it was mostly missing from other databases as it is not part of routine medical care especially in the primary care settings.

11.2.1 Limitations specific to this report

No bisphosphonates in fixed combination with calcium/vitamin D were included for the definition of exposure drug classes. While potentially some prescriptions including drugs defining exposure could have been missed, these preparations are typically prescribed rarely compared to plain bisphosphonate preparations.

No distinction could be made between the use of ibandronate for other oral bisphosphonates and intravenous bisphosphonates as the same ATC code was used, hence the intravenous bisphosphonate group did not include the ATC code for ibandronate in this report.

11.2.2 Database specific limitations

11.2.2.1 IPCI, the Netherlands

IPCI records provide info on prescribed rather than dispensed medications. Finally, due to nature of the database (i.e., primary care settings), information about secondary care visits, hospitalisations, and prescriptions (e.g., zoledronate) could be underreported.

11.2.2.2 NDR, Denmark

Whilst the NDR database contains comprehensive information about secondary care visits and dispensed medication, there is a lack of information about measurements (such as alcohol use, smoking and BMI) and medication dosage. Hence some patients may be misclassified in some variables (such as history of hypertension) due to the lack of measurement. Furthermore, due to the lack of primary care records, diagnoses typically made in primary care are unlikely to be recorded in a secondary care encounter or hospital settings, and so are likely to be underreported. Romosozumab is administered only in hospitals, and the current data system primarily relies on nurse and secretary reporting the date of administration. Some medications may be indicated in the treatment of more than one disease. IV BP is used in the treatment of OP and cancer with differing doses. Therefore, there may be misclassification in identifying IV BP users, although patients with a diagnosis code for cancer were excluded.

There may be underreporting in prescriptions, however, a recent study found that 96.6% of medication administration time recorded by investigators observing registered nurses during dayshifts matched the records in the regional registry (48).

11.2.2.3 SIDIAP, Spain

Due to nature of the database, information about secondary care prescriptions (e.g., zoledronate) could be underreported.

11.2.2.4 CPRD, UK

Many of the original practices in CPRD GOLD are no longer using the same software and have stopped providing data to CPRD GOLD, potentially explaining the small sample size. However, in this study we are using a second CPRD database named CPRD Aurum which contains information on a larger number of current patients. Due to the nature of the database, information about secondary care prescriptions (e.g., zoledronate, romosozumab, teriparatide) could be underreported. The duration of treatment of medications started in secondary care such as romosozumab could be underestimated as the GPs typically only record the initial prescription and not subsequent follow up by the specialists.

11.2.2.5 GePaRD, Germany

There are limitations inherent to the use of claims data. This includes the lack of information on lifestyle factors, results of laboratory and diagnostic tests (e.g., bone density), frailty, the severity of diseases, cause of death, most medication in the inpatient setting and OTC medication. Other lifestyle habits such as smoking and alcohol use are based on ICD-10 GM diagnoses and thus limited to severe cases. Particularly in the outpatient setting, miscoding or unspecific coding of diseases may occur, i.e., algorithms combining different types of information are typically applied to define cases. Furthermore, information on the prescribed daily dose is not available in GePaRD; the dose and intended duration had to be estimated. Moreover, the socioeconomic status (SES) is based on the German Index of Socioeconomic deprivation, which is a district-level measure of the SES and should be interpreted with caution as misclassification of the SES on person level can occur.

In Germany, outpatient diagnoses and procedures are reimbursed quarterly and thus do not have an exact date. However, BIPS has created an algorithm that match these diagnoses and procedures to the respective outpatient service codes, for which an exact date is available (for persons with a single contact with the diagnosing/treating physician). For diagnoses and procedures that cannot be matched to a single physician contact, diagnoses are set to the middle of the quarter. Of note, quarterly dates are only used for a subset of outpatient diagnoses and procedures, which were mainly used for covariates.

11.3 Interpretation

There was a total of 1,887 eligible romosozumab users across 5 databases. The IRs of SI before matching ranged across databases from 24.4 to 90.6 per 1,000 PY in romosozumab users, and 36.5 to 177.3 per 1,000 PY in users of other OP medications. Variability observed in IRs across databases are in line with other epidemiological studies given the real-world nature of the databases. As expected, rates increased with age and history of previous SI.

In the comparative safety analysis, propensity score models generally performed well, matching romosozumab users to alendronate users with similar characteristics. This reduced selection bias and confounding by indication. The findings from the negative control outcomes analysis which investigated the presence of unobserved confounding showed that the propensity score models were robust for most databases.

Findings from the comparative safety analysis showed no significant difference in risk of SI between romosozumab and alendronate users. The subgroup analyses showed similar patterns in higher risk populations (patients with 2-year or any history of fractures before treatment). Same observation was made for serious COVID-19 infections. However, there were no events of death due to SI or COVID-19 which precluded analysis for other secondary outcomes.

11.4 Generalisability

Previous studies have shown the representativeness of the contributing databases to the general population (49–54). Therefore, results of this study can be generalised to wider population of European patients receiving romosozumab and other OP medications in real-world clinical settings.

12 CONCLUSION

This non-interventional post-authorisation safety study provided real-world evidence on the safety of romosozumab with regards to SI as used according to the EU label and in selected subgroups of patients. The study was powered to compare incident cases of SI (any infection associated with a hospitalisation) between romosozumab users and comparator (alendronate users). Meta-analysis of the results from 5 databases across Europe showed no significant differences between these groups. Further subgroup analysis in patients with a recent or any fracture history showed similar patterns.

There was no significant difference in incidence of serious COVID-19 infection between romosozumab and alendronate users. There was no death related to SI or COVID-19 infection recorded in romosozumab users. Advanced methods of propensity score

matching and negative control outcome analysis were utilised to account for any observed and unobserved confounding.

Overall, this study showed no increased risk of SI or serious COVID-19 infection among romosozumab users as compared to alendronate users.

13 LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	01	18/11/2025	op0006 Additional information
2	02	18/11/2025	Code lists for events_extrac7
3	03	18/11/2025	Code lists for prescriptions: ATC_extrac7
4	04	18/11/2025	Measurement definitions_extrac7
5	05	18/11/2025	IPCI
6	06	18/11/2025	NDR
7	07	18/11/2025	SIDIAP
8	08	18/11/2025	CPRD GOLD
9	09	18/11/2025	CPRD Aurum
10	10	18/11/2025	GePaRD

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