

**EU-RISK MANAGEMENT PLAN FOR EVENITY®
(ROMOSUZUMAB)**

90mg/mL Prefilled syringe or prefilled autoinjector/Pen

Version 3.0

Date: 21 Nov 2025

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ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 3.0

Data Lock Point (DLP) for this RMP: 15 Sep 2025

Date of final sign off: 21 Nov 2025

Rationale for submitting an updated RMP:

Update of the RMP to reflect the result of the EU-Postauthorization Safety Study (PASS) OP0006 which is submitted via a Type II variation.

Summary of significant changes in this RMP: The main changes to EU-RMP include updates to sections below:

Removal of details pertaining to OP0006 from Part III, Part V, Part VI, and Part VII Annex 3.

Deletion of OP0006 study details from the ongoing studies table and moving it to completed studies table in Part VII Annex 2.

Based on the evidence derived from OP0006 study and other sources, the EU-RMP is updated to remove the important potential risk of serious infections. Changes are reflected in Part II Module SVII, Part II SVIII, Part V, and Part VI.

Other changes:

To update the milestones for studies OP0004 and OP0005 under Part III and Annex 2 of the EU-RMP and general updates across the EU-RMP to align the date with the DLP of 15 Sep 2025.

Inclusion of updated OP0004 and OP0005 study protocols under Part VII Annex 3

Other RMP version under evaluation: Not applicable

Details of the currently approved RMP:

Version number: 2.2

Approved with procedure:
EMA/VR/0000245496

Date of approval (opinion date): 14 Feb 2025

Qualified Person for Pharmacovigilance (QPPV) name: Bart Teeuw

QPPV signature: Please see the electronic signature of the EEA QPPV or his deputy on the last page of this report.

LIST OF ABBREVIATIONS

ADR	adverse drug reaction
ADA	antidrug antibodies
AFF	atypical femoral fracture
BMD	bone mineral density
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CV	cardiovascular
DDD	defined daily dose
DCRI	Duke Clinical Research Institute
DLP	data lock point
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GePaRD	German Pharmacoepidemiological Research Database
HCP	healthcare professional
HR	hazard ratio
IPCI	Integrated Primary Care Information
MACE	major adverse cardiac events
MAH	marketing authorization holder
MI	myocardial infarction
MOP	male osteoporosis
NDR	National Diabetes Register
NHANES	National Health and Nutrition Examination Survey
ONJ	osteonecrosis of the jaw
PAC	patient alert card
PASS	postauthorization safety study
PG	prescriber guide
PIL	patient information leaflet
PMO	postmenopausal osteoporosis
PRAC	Pharmacovigilance Risk Assessment Committee
PSP	patient support program
PTH	parathyroid hormone
PV	pharmacovigilance
QM	once every month

QPPV	Qualified Person for Pharmacovigilance
RMM	risk minimization measures
RMP	risk management plan
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació a l'Atenció Primària
SMD	standard monthly dose
SmPC	summary of product characteristics
TIMI	Thrombolysis in Myocardial Infarction study group
WHO	World Health Organization

PART I PRODUCT OVERVIEW

Table Part I–1: Product overview

Active substance(s)	Romosozumab (AMG 785; CDP7851)
Pharmacotherapeutic group(s)	Drugs affecting bone structure and mineralization (M05BX06)
Marketing Authorization Holder	UCB Pharma S.A.
Medicinal products to which this RMP refers	Romosozumab
Invented name(s) in the EEA	EVENITY®
Marketing authorization procedure	Centralized procedure
Brief description of the product	Romosozumab is a humanized immunoglobulin G2 monoclonal antibody with high affinity and specificity for sclerostin. Romosozumab binds and inhibits sclerostin. Romosozumab increases bone formation due to the activation of bone lining cells, increased bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells. Additionally, romosozumab results in changes in expression of osteoclast mediators, thereby decreasing bone resorption. Together, this dual-effect of increasing bone formation and decreasing bone resorption results in rapid increases in trabecular and cortical bone mass, improvements in bone structure and strength, and fracture risk reduction. Romosozumab has an approximate molecular weight of 145kDa and is produced in a mammalian cell line (Chinese hamster ovary) by recombinant deoxyribonucleic acid technology.
Chemical class	
Summary of mode of action	
Important information about its composition	
Hyperlink to the Product Information	Module 1.3.1 SmPC, Labelling and Package Leaflet
Indication in the EEA	Current: Romosozumab is indicated in treatment of severe osteoporosis in postmenopausal women at high risk of fracture.
	Proposed: Not applicable

Table Part I–1: Product overview

Dosage in the EEA	Current: The recommended dose is 210mg romosozumab (administered as 2subcutaneous injections of 105mg each) once monthly for 12 months.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Romosozumab is supplied as a single-use prefilled syringe or prefilled autoinjector/pen containing 105mg romosozumab in 1.17mL solution (90mg/mL).
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

EEA=European Economic Area; RMP=Risk Management Plan

PART II SAFETY SPECIFICATION

Part II Module SI Epidemiology of the indication(s) and target population(s)

SI.1 Osteoporosis in postmenopausal women at high risk of fracture

SI.1.1 Incidence

Osteoporosis is a chronic disease identified by low bone mineral density (BMD) or presence of a fragility fracture. Due to the chronic and progressive nature of the disease, there are no good measures available to capture incidence; epidemiology is usually reported in form of prevalence estimates. Incidence of the disease is mainly described through its major consequence, osteoporosis-related fractures (Strom et al, 2011; Masi, 2008).

In the EU in 2000, 620,000 new hip fractures, 574,000 fractures of the forearm, 250,000 fractures at the proximal humerus and 620,000 clinical spine fractures were estimated to have occurred in women and men aged 50 years or older (Kanis et al, 2013)

SI.1.2 Prevalence

Postmenopausal osteoporosis (PMO) is common, with a reported prevalence of 15% to 38% of women 50 years and older, based on the World Health Organization (WHO) definition (Wade et al, 2014; Wright et al, 2014; Hernlund et al, 2013). Estimates from the USA, Europe, Australia, Canada, and Japan suggest that across these countries approximately 44 million women aged $\geq$ 50 years have PMO (Wade et al, 2014; Hernlund et al, 2013) and approximately 4.5 million suffer osteoporotic fractures annually (Hernlund et al, 2013; Wade et al, 2012; Burge et al, 2007).

Based on BMD measurements at the femoral neck or lumbar spine 2.5 standard deviations or more below the average BMD of the young, white, female population, the age-adjusted prevalence of osteoporosis in US women aged 50 years or older was estimated to be 15.4% in the National Health and Nutrition Examination Survey (NHANES), from 2005 to 2010 (Wright et al, 2014). The prevalence of osteoporosis, in Canadian women aged 50 years or older, as measured at the femoral neck or lumbar spine using the WHO criteria (2.5 standard deviations or more below young adult mean), was estimated to be 15.8% in a population based cohort study (Tenenhouse et al, 2000). In the EU, the overall prevalence of osteoporosis is estimated to be 22% in women aged 50 or older, based on a report prepared in collaboration with the International Osteoporosis Foundation and the European Federation of Pharmaceutical Industry Associations (Hernlund et al, 2013). Postmenopausal osteoporosis prevalence in Australia has also been estimated to be 22% when BMD assessments at both spine and total hip were considered (Wade et al, 2014).

SI.1.3 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease

All patients with PMO are women who have completed menopause. The prevalence of osteoporosis varies by age (increasing with age) and by ancestry (highest amongst European descent relative to Asian or African descent) (Cauley, 2011).

Women who have completed menopause are at risk for PMO. Risk factors for osteoporotic fracture for women include lower BMD, older age, history of previous fractures, parental history of hip fracture, glucocorticoid use, low body mass index, rheumatoid arthritis, current tobacco smoking, and high alcohol consumption (Cummings et al, 2006; Johnell et al, 2005; Siris et al, 2004; Kanis et al, 2001).

SI.1.4 The main existing treatment options

Main treatment options in PMO are:

- Calcium and vitamin D supplementation
- Parathyroid hormone (PTH) analogues
- Bisphosphonates
- Calcitonin
- Selective estrogen receptor modulator
- Receptor activator of nuclear factor kappa-B ligand inhibitor

SI.1.5 Natural history of postmenopausal osteoporosis in the untreated population, including mortality and morbidity

The lifetime risk of osteoporotic fracture overall is 40% to 42% among women in Western Europe and Australia, and approximately 50% among white women age 50 years and older in the USA (NOF, 2014; Office of the Surgeon General, 2004). The number of osteoporosis related fractures is projected to increase substantially as the world's population ages.

Lifetime risk of osteoporotic fracture in women ranges from 40% to 50% (NOF, 2014; Dennison et al, 2006). Hip fractures often result in disability and loss of independence (Cummings and Melton, 2002; Cree et al, 2000). Between 18% to 34% of patients may die within 12 months following hip fracture, with rates as high as 42% reported among long term care facility residents (Tajeu et al, 2014; Sawalha and Parker, 2012; Gutierrez et al, 2011; Roche et al, 2005; Parker et al, 2002). Patients with non-hip, non-vertebral fractures have been reported to have up to 24% excess risk of mortality in the first 5 years postfracture compared to age-adjusted mortality risk in the general population; approximately half of this increased risk has been attributed to the initial fracture, and the remainder attributed to the effect of subsequent fractures (Gosch et al, 2015; Bliuc et al, 2014). In addition, among men and women with vertebral fractures and those with non-hip, non-vertebral fractures, rapid bone loss has been independently associated with greater mortality risk (Bliuc et al, 2015a; Bliuc et al, 2015b).

SI.1.6 Important co-morbidities

Table Part II–1: Summary of epidemiology of important comorbidities in the target PMO population

Cardiovascular disease	
Incidence/prevalence	In placebo arms of clinical trials of selective estrogen receptor modulators in women with PMO, the cumulative incidence of cardiovascular events was approximately 3% to 4% over 4 to 5 years (Ensrud et al, 2010; Tanko et al, 2005). In Denmark among women aged 60 to 85 years, there was a higher prevalence of cardiovascular disease (aortic calcification and acute events) in women with vertebral fracture compared with women with non-vertebral fracture (7.4% vs 3.6%, $p = 0.02$; 4.3% in the combined group) (Bagger et al, 2007). In population-based studies of women with PMO, incidence rates per 1000 person-years range between approximately 2 and 13 for myocardial infarction (MI), and between approximately 16 and 38 for stroke, depending on patient demographics and risk factors (Cooper et al, 2014; Abrahamsen et al, 2014; Kang et al, 2013; Chen et al, 2013).
Mortality	In the placebo arm of a clinical trial in women with PMO, cardiovascular death was reported at 2.18 per 1000 person years (Ensrud et al, 2010). In another clinical trial in women with PMO, death due to stroke was reported in 0.3% of participants in the placebo arm over a 3-year period (Black et al, 2007). In a large, population-based study from the UK of women using anti-osteoporosis treatment, the incidence rate of cardiovascular death was 14.66 per 1000 person-years (Cooper et al, 2014).
Malignancy	
Incidence/prevalence	Incidence rate of malignancy (all cancers combined) was 20.7 per 1000 person years (95% CI = 19.5, 22.0) in women age ranging from 55 to 89 years with PMO enrolled in a US integrated healthcare system (calculated using 2004 through 2009 data from electronic health records). In this study, women with PMO had decreased incidence of ovarian, uterine, colorectal, and liver cancers and increased incidence of lung cancer, breast cancer, and multiple myeloma, compared with women in the nonosteoporosis cohort (O'Malley et al, 2014). The incidence rates of most other cancers were similar between the 2 cohorts. In Danish women aged ≥ 70 years hospitalized for osteoporosis, the risk of cancer was less than the rate in the general population of women in the same age group (standardized incidence rate [SIR] = 0.91, 95% CI = 0.87, 0.96) (McGlynn et al, 2008). Women with osteoporosis < 70 years old were found to have increased cancer risk compared with the general population of women in that age group (SIR = 1.11, 95% CI = 1.04, 1.19). Swedish studies have reported reduced risk of overall cancer, as well as breast and gynecologic cancers in women after a distal forearm fracture (Olsson and Hagglund, 1992), or hip fracture (Persson et al, 1994).
Mortality	In Swedish patients hospitalized for osteoporosis (mostly women), death due to malignant tumors was lower than expected as compared with the general population (30 cases observed vs 40.41 expected) (Olsson and Hagglund, 1992).

Table Part II–1: Summary of epidemiology of important comorbidities in the target PMO population

Infection	
Incidence/prevalence	A study of postmenopausal women enrolled in a US integrated healthcare system reported that the incidence rates of several common infections (calculated using 2004 through 2009 data from electronic health records) were higher in women with osteoporosis than without. There were no differences in sepsis rates compared with women in the non-osteoporosis cohort. Incidence rates per 1000 person years in women with osteoporosis: bronchitis 55 (95% CI = 53.0, 57.2) versus 29.8 (95% CI = 28.3, 31.3) in women without osteoporosis; influenza 2.5 (95% CI = 2.1, 2.9) versus 1.5 (95% CI = 1.2, 1.8) in women without osteoporosis; pneumonia 21.4 (95% CI = 20.2, 22.7) versus 13.1 (95% CI = 12.2, 14.1) in women without osteoporosis; gastroenteritis 5.1 (95% CI = 4.5, 5.7) versus 4.4 (95% CI = 3.8, 4.9) in women without osteoporosis; and sepsis 4.2 (95% CI = 3.7, 4.8) vs 4.2 (95% CI = 3.7, 4.8) in women without osteoporosis (O'Malley et al, 2014). In a randomized clinical trial in 2352 women with PMO, the subject incidence of infections in placebo-treated subjects was 53.9% over 18 months (Greenspan et al, 2007). In a randomized 36-month study of 447 women with PMO, the subject incidence of upper respiratory tract infections, influenza, infectious gastroenteritis, and dental process infection in placebo-treated subjects (n = 504) was 31.1%, 14.4%, 7.0%, and 7.0%, respectively (US Food and Drug Administration, 1997).
Mortality	Information on mortality due to infection in women with PMO is not readily available.
Osteoarthritis	
Incidence/prevalence	Results from a study of postmenopausal women enrolled in a US integrated healthcare system, which evaluated rates of comorbidities in women with and without osteoporosis using 2004 to 2009 data, suggested that the incidence rate of osteoarthritis (OA) was higher in women with osteoporosis than without. The study reported that the incidence rates per 1000 person-years of 'osteoarthritis + arthralgia' were 59.9 (95% CI = 57.6, 62.2) among women with osteoporosis and 47.0 (95% CI = 45.0, 49.1) among women without osteoporosis. The incidence rates per 1000 person-years of 'osteoarthrosis + spinal osteoarthritis' were 63.0 (95% CI = 60.7, 65.4) among women with osteoporosis and 48.5 (95% CI = 46.5, 50.6) among women without osteoporosis (O'Malley et al, 2014).
Mortality	Information on mortality associated with OA among women with PMO is not readily available.

CI=confidence interval; MI=myocardial infarction; OA=osteoarthritis; PMO=postmenopausal osteoporosis; SIR=standardized incidence rate

Part II Module SII Nonclinical part of the safety specification

Key safety findings from nonclinical studies and relevance to human usage are presented in [Table Part II–2](#). There were no nonclinical safety concerns identified during the development of romosozumab that would prohibit the intended use in the targeted population.

Table Part II–2: Summary of important nonclinical findings

Study Type	Key Safety Finding	Relevance to Human Usage
General toxicity	Toxicology studies of romosozumab in rats and monkeys at exposures up to 37 and 90 times higher, respectively, than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison) demonstrated romosozumab-mediated effects were either a direct or indirect consequence of the intended primary pharmacological effects on bone (increased bone formation and bone mass). Indirect consequences of the effects on bone included minor increases or decreases in serum phosphorus and minor decreases in serum calcium, red cell and platelet number. In growing rats administered a rodent surrogate sclerostin antibody at pharmacologically active doses, a transient increase in longitudinal growth rate predicted to result in < 1% increase in bone length was observed. In 8-week old growing rats dosed with 50mg/kg/weekly romosozumab for 6 months resulting in exposures up to 19 times higher than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison), there was no effect on femur length. No histologic alterations in the growth plate were observed in rats and monkeys in chronic toxicology studies at exposures up to 37 and 90 times higher, respectively, than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison). In bone safety studies in ovariectomized rats and monkeys, once-weekly treatment with romosozumab for 12 months increased bone formation and decreased bone resorption. The resulting increase in bone mass and improvements in cortical bone geometry and cancellous bone microarchitecture was associated with increased bone strength at exposures from 0.5 to 21 times higher than the systemic exposure observed in	Romosozumab is contraindicated in patients with hypocalcemia. The relevance of the small increase in bone length in rat is unknown. Effects on longitudinal bone growth and hyperostosis would be a theoretical concern in pediatric subjects. Pediatric studies are ongoing as per pediatric investigation plan.

Table Part II–2: Summary of important nonclinical findings

Study Type	Key Safety Finding	Relevance to Human Usage
	humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison). Bone tissue was of normal or improved quality with no evidence of mineralization defects, accumulation of osteoid, or woven bone. In nonclinical toxicity studies of romosozumab, hyperostosis or macroscopically thickened long bones and skull was observed in rats. Partial recovery of the bone finding was observed upon cessation of romosozumab. There were no adverse consequences of these bone findings at exposures 37 to 90 times the exposures being investigated clinically. In a study of lifetime romosozumab administration in rats, macroscopic findings of thickened bone were observed with extended duration of treatment at approximately equivalent systemic clinical exposures. In a rat model of ONJ, using ligature-induced periodontitis, animals treated with a sclerostin antibody lost less periodontal bone at sites with periodontitis and showed no radiographic or histologic signs of ONJ.	
Developmental toxicity	Reproductive and developmental effects of romosozumab were assessed in preliminary and definitive embryo-fetal development (EFD) studies, a combined fertility and EFD study, and a pre- and postnatal development study in the rat at doses up to 300mg/kg/week. Across all EFD development studies, romosozumab-related effects were limited to a slight increase in the incidence of reduced ventral processes on the sixth cervical vertebrae at exposures at least 30 times higher than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison). This variation represents a slight developmental delay, confirmed by its absence postnatally, in a skeletal process not found in humans. At exposures at least 30 times higher than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison), skeletal abnormalities (including syndactyly and	Animal studies are not always predictive of the human response. There are no adequate and well-controlled studies of romosozumab in pregnant women. Currently, romosozumab is indicated in postmenopausal women. In the rat, the sixth cervical vertebrae variation was considered species-specific and not relevant to human. The findings of syndactyly and polydactyly were not replicated in other studies with substantially higher maternal and fetal exposures. Syndactyly occurs at a high incidence in sclerosteosis but does not occur in patients heterozygous for the genetic mutation. Romosozumab is

Table Part II–2: Summary of important nonclinical findings

Study Type	Key Safety Finding	Relevance to Human Usage
	polydactyly) were seen in 1 of 75 litters across the 4 studies. These findings were not seen at higher systemic exposures in the combined fertility and EFD study, and pre- and post-natal development studies. There were no adverse effects on postnatal growth and development.	not intended to completely inhibit sclerostin and thus the risk for malformations of developing digits in the human fetus is low following romosozumab exposure, further reduced by the timing of digit formation in the first trimester in humans when placental transfer of immunoglobulins is limited.
Reproductive toxicity	Romosozumab had no effects on fertility in male and female rats at doses up to 300mg/kg (100 times the clinical dose). No effects were noted in reproductive organs in rats and cynomolgus monkeys dosed with romosozumab in chronic toxicology studies at exposures up to 37 and 90 times higher than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison), respectively.	Animal studies are not always predictive of the human response. There are no adequate and well-controlled studies of romosozumab in women of childbearing potential to assess fertility, or to evaluate effects on male fertility. Currently, romosozumab is indicated in postmenopausal women.
Genotoxicity	Romosozumab is a monoclonal antibody (mAb) made up of natural amino acids and contains no inorganic linkers, synthetic organic linkers or other non-protein portions. Monoclonal antibodies also do not gain access to the cytoplasm or nucleus of cells and therefore do not directly interact with DNA, alter DNA integrity or influence the cell cycle. Hence genotoxicity studies are not required for mAbs and have not been conducted.	Not applicable
Carcinogenicity	In a carcinogenicity study, doses up to 50mg/kg/week were administered to male and female Sprague Dawley rats from 8 weeks of age for up to 98 weeks. These doses resulted in systemic exposures that were up to 19 times higher than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison). Romosozumab caused a dose-dependent increase in bone mass with macroscopic bone thickening at all doses. There were no effects of romosozumab on mortality or tumor incidence in male or female rats.	Animal studies are not always predictive of the human response. Based on nonclinical data and a carcinogenicity risk assessment, romosozumab would not pose a carcinogenic risk to humans.

Table Part II–2: Summary of important nonclinical findings

Study Type	Key Safety Finding	Relevance to Human Usage
Safety pharmacology		
Cardiovascular	Romosozumab administration was not associated with adverse cardiovascular effects in conscious telemetry instrumented cynomolgus monkeys administered a single intravenous (iv) dose followed by a 14-day observation period at AUC and maximum serum concentration (C_{max}) exposure margins approximately 30- and 188-fold, respectively, to systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab. There were no romosozumab-related electrocardiographic or blood pressure changes in the 1-month and 6-month repeat dose toxicology studies in monkeys at doses up to 300mg/kg iv. In rats and monkeys administered romosozumab for 6 months at exposures up to 37 and 90 times higher, respectively, than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison), there were no effects on hemostasis or coagulation parameters and no evidence of vascular abnormalities or mineralization. In adult ovariectomized monkeys, there was no radiographic evidence of aortic mineralization following once-weekly treatment with romosozumab for 12 months at exposures 21 times higher than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison). In rats administered romosozumab for up to 98 weeks at exposures up to 19 times higher than the systemic exposure observed in humans following a monthly SC dose of 210mg romosozumab (based on AUC comparison), there was no exacerbation of age-related vascular calcification or ectopic ossification. An in vitro human platelet activation study showed that romosozumab did not cause platelet activation. In the human coronary artery ring assay, there were no effects of romosozumab or sclerostin on vasoconstriction. Sclerostin expression was assessed in human atherosclerotic plaques in endarterectomy samples	Animal studies are not always predictive of the human response. The majority of the nonclinical pharmacology and toxicology studies were conducted in animals without underlying vascular disease. However, 2 nonclinical studies were conducted in diseased or disease-like tissues. There was no evidence that inhibition of sclerostin was associated with atheroprogession in a mouse model of atherosclerosis and no evidence that the absence of sclerostin in human atherosclerotic plaques was associated with a prior history of arterial disease or in subsequent major adverse cardiac events (MACE). It is also not associated with acute vasoconstriction of human arterial rings. The current nonclinical data showed no evidence of a plausible mechanistic link between sclerostin inhibition and MACE. The nonclinical data is further supported by human genetic data indicating a lack of association between genes associated with an increased cardiovascular risk in human subjects with loss of function mutations of the <i>SOST</i> gene.

Table Part II–2: Summary of important nonclinical findings

Study Type	Key Safety Finding	Relevance to Human Usage
	of carotid and femoral arteries. Immunohistochemical staining revealed sclerostin expression was absent in the majority of plaques. When present, expression was restricted to the deeper parts of the plaque/vessel wall and decreased in intensity compared with normal aorta. Sclerostin was not expressed in the superficial region of the plaque, ie, cap or endothelial cells and thus was not in locations that are relevant to plaque stability. The absence of sclerostin in the plaques did not correlate with a prior history of arterial disease or subsequent MACE. A study in ApoE mice revealed sclerostin antibody at exposures predicted to be 4-fold greater than clinical exposure at 210mg QM based on AUC did not increase total or mineralized plaque volume and had no effect on transcriptional and histologic changes in aortic atherosclerotic plaques or on circulating inflammatory cytokines. Public databases of Genome Wide Association Study (GWAS) results were examined to test for association of common SNPs near <i>SOST</i> that are associated with levels of <i>SOST</i> RNA expression and bone mineral density with risk of stroke or myocardial infarction. The major allele C of SNP rs2741856 is associated with lower expression of <i>SOST</i> in aorta and tibial artery and decreased risk of osteoporosis and fracture with no detectable effect on the risk of stroke or myocardial infarction.	

ApoE=apolipoprotein; AUC=area under the curve; Cmax=maximum serum concentration; DNA=deoxyribonucleic acid; EFD=embryo-fetal development; GWAS=Genome Wide Association Study; iv=intravenous; mAB=monoclonal antibody; MACE=major adverse cardiac events; ONJ=osteonecrosis of the jaw; QM=once every month; RNA=ribonucleic acid; SC=subcutaneous(ly); SNP=single nucleotide polymorphism

Other toxicity-related information or data

No additional nonclinical data are required for different patient populations.

Part II Module SIII Clinical trial exposure

Table Part II–3 presents the total study participant exposure to romosozumab in clinical trials by indication and duration.

Table Part II–3: Total exposure to romosozumab in clinical trials by indication and duration (Safety Analysis Set)

	Exposure to romosozumab by duration					Total n (sp-yrs)
	≤ 1 month n (sp-yrs)	> 1 month - ≤ 6 months n (sp-yrs)	> 6 month - ≤ 12 months n (sp-yrs)	> 12 month - ≤ 24 months n (sp-yrs)	> 24 months n (sp-yrs)	
Phase 1	40 (1.2)	905 (209.2)	0 (0.0)	0 (0)	0 (0)	945 (210.4)
PMO	160 (8.8)	714 (255.7)	5666 (5659.6)	101 (178.3)	139 (410.2)	6780 (6512.6)
MOP	0 (0)	7 (2.0)	153 (152.3)	3 (3.5)	0 (0)	163 (157.8)
FH	23 (0.9)	55 (16.3)	424 (422.7)	29 (34.1)	0 (0)	531 (474.1)
Total	223 (11.0)	1681 (483.2)	6243 (6234.6)	133 (215.9)	139 (410.2)	8419 (7354.9)

FH=fracture healing; MOP=men with osteoporosis; PMO=postmenopausal osteoporosis (includes postmenopausal women with low BMD);

Phase I=Phase I studies with population including healthy volunteers, postmenopausal women and patients with renal impairment.

n=number of study participants exposed to romosozumab; sp-years=total study participant-years of follow-up.

Data from ongoing and completed studies as of 22 May 2018. Romosozumab exposure for ongoing study 20150242 is based on unblinded treatment data from the primary analysis (data cutoff date of 12 Feb 2018) and for ongoing open-label study 20150120 is based on snapshot taken on 22 May 2018.

Study participant-years of exposure to a study treatment is counted from the first dose date to the earliest of the end of treatment period, or the last on-study evaluation up to the data snapshot date. For a study participant who switches treatment across study periods, study participant-year exposure is calculated in the periods at which the study treatment is received. Off-treatment safety follow-up periods do not contribute to exposure calculation.

Safety Analysis Set includes study participant who received at least 1 dose of investigational product.

Exposure categories are defined as: ≤ 1 month: study participants with ≤ 30.4375 days of exposure; >1 month - ≤ 6 months: study participants with >30.4375 and ≤ 213 days of exposure; >6 months - ≤ 12 months: study participants with >213 and ≤ 396 days of exposure; >12 months - ≤ 24 months: study participants with >396 days and ≤ 765 days of exposure; >24 months: study participants with > 765 days of exposure

Program: /userdata/stat/amg785/safety/RMP/analysis/2019_crmp/tables/program/t-exposure-dur.sas

Output: t100-05-001-exposure-dur.rtf (Date Generated: 22MAY2019:22:47:48) Source Data: rmp2018.adsl

Total study participant exposure is presented by age group and gender, and dose level and indication in Table Part II–4 and Table Part II–5 respectively, and by race/ethnicity group in Table Part II–6.

Table Part II–4: Total exposure to romosozumab in clinical trials by indication, age group, and gender (Safety Analysis Set)

	18 to 64 years n (sp-yrs)	65 to 74 years n (sp-yrs)	75 to 84 years n (sp-yrs)	≥ 85 years n (sp-yrs)
Male				
Phase 1	381 (86.5)	13 (1.9)	2 (0.5)	0 (0)

Table Part II–4: Total exposure to romosozumab in clinical trials by indication, age group, and gender (Safety Analysis Set)

	18 to 64 years n (sp-yrs)	65 to 74 years n (sp-yrs)	75 to 84 years n (sp-yrs)	≥ 85 years n (sp-yrs)
PMO	0 (0)	0 (0)	0 (0)	0 (0)
MOP	31 (30.6)	62 (61.9)	65 (60.2)	5 (5.2)
FH	218 (203.2)	30 (25.3)	29 (26.6)	13 (9.1)
Total male	630 (320.3)	105 (89.0)	96 (87.3)	18 (14.3)
Female				
Phase 1	465 (103.7)	63 (13.4)	21 (4.4)	0 (0)
PMO	1374 (1372.4)	2966 (2882.4)	2152 (2002.2)	288 (255.5)
MOP	0 (0)	0 (0)	0 (0)	0 (0)
FH	95 (89.6)	39 (34.7)	64 (51.7)	43 (33.9)
Total female	1934 (1565.7)	3068 (2930.5)	2237 (2058.4)	331 (289.5)

FH=fracture healing; MOP=men with osteoporosis; PMO=postmenopausal osteoporosis (includes postmenopausal women with low BMD); n=number of study participants exposed to romosozumab; sp-years=total study participant-years of follow-up.

Phase I=Phase I studies with population including healthy volunteers, postmenopausal women and patients with renal impairment.

Data from ongoing and completed studies as of 22 May 2018. Romosozumab exposure for ongoing study 20150242 is based on unblinded treatment data from the primary analysis (data cutoff date of 12 Feb 2018) and for ongoing open-label study 20150120 is based on snapshot taken on 22 May 2018.

Study participant-years of exposure to a study treatment is counted from the first dose date to the earliest of the end of treatment period, or the last on-study evaluation up to the data snapshot date. For a study participant who switches treatment across study periods, study participant-year exposure is calculated in the periods at which the study treatment is received. Off-treatment safety follow-up periods do not contribute to exposure calculation. Safety Analysis Set includes study participants who received at least 1 dose of investigational product.

Program: /userdata/stat/amg785/safety/RMP/analysis/2018_crmp/tables/program/t-exposure-age-gender.sas

Output: t14-05-002-exposure-age-gender.rtf (Date Generated: 04JUN2018:11:20:13) Source Data: adam.adsl

Table Part II–5: Exposure to romosozumab in clinical trials by dose level and indication (Safety Analysis Set)

	Exposure to romosozumab in days					Study participant exposure to romosozumab				
	Average dose/month					Average dose/month				
	<70mg n (mean)	70mg n (mean)	140mg n (mean)	210mg n (mean)	>210mg n (mean)	<70mg n (sp-yrs)	70mg n (sp-yrs)	140mg n (sp-yrs)	210mg n (sp-yrs)	>210mg n (sp-yrs)
Phase 1	23 (41.4)	11 (57.2)	62 (93.6)	790 (79.7)	59 (110.3)	23 (2.6)	11 (1.7)	62 (15.9)	790 (172.4)	59 (17.8)
PMO	26 (555.0)	139 (543.7)	216 (639.9)	6399 (336.1)	0 (0)	26 (39.5)	139 (206.9)	216 (378.4)	6399 (5887.7)	0 (0)
MOP	0 (0)	0 (0)	0 (0)	163 (353.7)	0 (0)	0 (0)	0 (0)	0 (0)	163 (157.8)	0 (0)
FH	0 (0)	83 (340.8)	85 (300.0)	107 (321.1)	256 (332.1)	0 (0)	83 (77.4)	85 (69.8)	107 (94.1)	256 (232.8)
Total	49 (313.9)	233 (448.5)	363 (467.0)	7459 (309.1)	315 (290.5)	49 (42.1)	233 (286.1)	363 (464.1)	7459 (6312.0)	315 (250.6)

FH=fracture healing; MOP=men with osteoporosis; PMO=postmenopausal osteoporosis (includes postmenopausal women with low BMD);

Phase I=Phase I studies with population including healthy volunteers, postmenopausal women and patients with renal impairment.

n=number of study participants exposed to romosozumab; sp-yrs=total study participant-yr of follow-up.

Data from ongoing and completed studies as of 22 May 2018. Romosozumab exposure for ongoing study 20150242 is based on unblinded treatment data from the primary analysis (data cutoff date of 12 Feb 2018) and for ongoing open-label study 20150120 is based on snapshot taken on 22 May 2018.

Study participant-years of exposure to a study treatment is counted from the first dose date to the earliest of the end of treatment period, or the last on-study evaluation up to the data snapshot date. For a study participant who switches treatment across study periods, study participant-year exposure is calculated in the periods at which the study treatment is received. Off-treatment safety follow-up periods do not contribute to exposure calculation.

For study participants whose dosing frequency is not QM or Q3M, 1 month is considered as comprised of 4 weeks. For study participants in study 20060221 who receive Q2W dose, average dose/month = average (sum(dose1, dose2), sum(dose3, dose4)). For studies 20062017 and 20080394, average dose/month = sum(doses)*4 / treatment duration (wks.) for durations ≥ 4 weeks; else average dose/month = sum(doses) for treatment duration of < 4 weeks. For study participants in study 20060326, Q3M dose is converted to QM dose as Q3M/3 before calculating the average. Average monthly doses ≥ 70mg and < 105mg are counted in 70mg column; average monthly doses ≥ 105mg and <175mg are counted in 140mg column; average monthly doses ≥ 175mg and ≤ 210mg are counted in 210mg column.

Safety Analysis Set includes study participants who received at least 1 dose of investigational product.

Program: /userdata/stat/amg785/safety/RMP/analysis/2018_crmp/tables/program/t-exposure-dose.sas

Output: t14-05-003-exposure-dose.rtf (Date Generated: 04JUN2018:11:08:16) Source Data: adam.adsl, adam.dose

Table Part II–6: Total exposure to romosozumab in clinical trials by race/ethnic group and indication (Safety Analysis Set)

	White n (sp-yrs)	Black or African American n (sp-yrs)	Hispanic or Latino n (sp-yrs)	Asian n (sp-yrs)	American Indian or Alaska Native n (sp-yrs)	Native Hawaiian or Pacific Islander n (sp-yrs)	Other n (sp-yrs)	Total n (sp-yrs)
Phase 1	682 (154.7)	115 (24.8)	66 (14.5)	61 (12.2)	5 (0.9)	3 (0.5)	13 (2.7)	945 (210.4)
PMO	4359 (4142.0)	99 (99.3)	39 (82.0)	789 (739.5)	72 (69.1)	1 (3.1)	1421 (1377.5)	6780 (6512.6)
MOP	120 (115.2)	1 (1.0)	0 (0)	18 (18.0)	0 (0)	0 (0)	24 (23.6)	163 (157.8)
FH	412 (364.4)	7 (5.8)	9 (5.6)	102 (97.3)	0 (0)	0 (0)	1 (1.0)	531 (474.1)
Total	5573 (4776.3)	222 (130.9)	114 (102.1)	970 (867.1)	77 (70.0)	4 (3.7)	1459 (1404.9)	8419 (7354.9)

PMO=postmenopausal osteoporosis (includes postmenopausal women with low BMD); MOP=men with osteoporosis; FH=fracture healing;

Phase I=Phase I studies with population including healthy volunteers, postmenopausal women and patients with renal impairment.

n=number of study participants exposed to romosozumab; sp-years = total study participant-years of follow-up.

Data from ongoing and completed studies as of 22 May 2018. Romosozumab exposure for ongoing study 20150242 is based on unblinded treatment data from the primary analysis (data cutoff date of 12 Feb 2018) and for ongoing open-label study 20150120 is based on snapshot taken on 22 May 2018.

Study participant-years of exposure to a study treatment is counted from the first dose date to the earliest of the end of treatment period, or the last on-study evaluation up to the data snapshot date. For a study participant who switches treatment across study periods, study participant-year exposure is calculated in the periods at which the study treatment is received. Off-treatment safety follow-up periods do not contribute to exposure calculation.

Safety Analysis Set includes study participants who received at least 1 dose of investigational product.

Program: /userdata/stat/amg785/safety/RMP/analysis/2018_crmp/tables/program/t-exposure-race-ethnic.sas

Output: t14-05-004-exposure-race-ethnic.rtf (Date Generated: 04JUN2018:11:20:21) Source Data: adam.adsl

Please note that the exposure from OP0002 study and pediatric osteogenesis imperfecta study has not yet been incorporated into the total exposure.

Part II Module SIV Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

SIV.1.1 Criterion

Table Part II–7: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
Hypocalcemia	
Reason for exclusion	Romosozumab may exacerbate hypocalcemia, since its mechanism of action suggests that administration of romosozumab may be associated with decreases in serum calcium as a result of increased bone formation and increased demands for calcium for matrix mineralization. Hypocalcemia should be corrected prior to initiating romosozumab. Patients should be adequately supplemented with calcium and vitamin D before and during treatment with romosozumab. Romosozumab is contraindicated in patients with hypocalcemia.
Is it considered to be included as missing information?	No
Rationale	Hypocalcemia is an important identified risk which has been characterized based on monitoring and evaluation in the clinical development program. Transient hypocalcemia has been observed in patients receiving romosozumab.
Hypersensitivity	
Reason for exclusion	All monoclonal antibodies could potentially be associated with hypersensitivity reactions, including anaphylactic events. Romosozumab is contraindicated in patients with known clinically significant hypersensitivity to romosozumab or to any component of the product formulation.
Is it considered to be included as missing information?	No
Rationale	Hypersensitivity was monitored in the development program and is recognized as an important identified risk. From the 12-month, placebo-controlled osteoporosis safety analysis set, there is evidence to suggest a causal relationship between romosozumab and hypersensitivity. Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria were observed in the romosozumab groups.

Table Part II–7: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
BMD T-score of ≤ -3.5 at the total hip, or femoral neck based on dual energy X-ray absorptiometry (DXA) scans^a	
Reason for exclusion	In placebo-controlled studies, it was considered unethical to enroll study participants with a T-score ≤ -3.5 when approved therapies were available because these study participants would remain untreated for 12 months if randomized to the placebo group. In study 20110142, study participants with a BMD T-score of ≤ -3.5 at the total hip or femoral neck were allowed as the comparator was alendronate and not placebo, therefore all study participants would receive active treatment throughout the study.
Is it considered to be included as missing information?	No
Rationale	The safety and efficacy of romosozumab is not expected to differ in study participants with lower BMD T-scores. In several animal models of osteopenia, the safety and efficacy of romosozumab or surrogate romosozumab antibodies did not differ from controls. In active controlled studies of the romosozumab program, patients were included without exclusion criteria based on low BMD, which did not appear to affect the safety and efficacy profile of the drug.
Any severe (SQ3) or more than 2 moderate (SQ2) vertebral fractures based on lateral spine x-rays^a	
Reason for exclusion	In placebo-controlled studies, it was considered unethical to enroll study participants with vertebral fractures when approved therapies were available because these study participants would remain untreated for 12 months if randomized to the placebo group. In study 20110142, study participants with vertebral fractures were allowed as the comparator was alendronate and not placebo, therefore all study participants would receive active treatment throughout the study.
Is it considered to be included as missing information?	No
Rationale	The safety and efficacy of romosozumab is not expected to differ in study participants with vertebral fractures. Improvements in fracture healing was observed in monkeys with stabilized fibular fractures administered romosozumab with corresponding increases in bone formation, bone mass, and bone strength at nonfractured bone.

Table Part II–7: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
History of hip fracture^a	
Reason for exclusion	In placebo-controlled studies, it was considered unethical to enroll study participants with history of hip fracture when approved therapies were available because these study participants would remain untreated for 12 months if randomized to the placebo group. In study 20110142, study participants with hip fracture were allowed as the comparator was alendronate and not placebo, therefore all study participants would receive active treatment throughout the study.
Is it considered to be included as missing information?	No
Rationale	The safety and efficacy of romosozumab is not expected to differ in study participants with hip fractures. Improvements in fracture healing was observed in monkeys with stabilized fibular fractures administered romosozumab with corresponding increases in bone formation, bone mass, and bone strength at nonfractured bone. In the Phase 2 hip fracture study 20080394, study participants were administered romosozumab at different doses over 12 weeks and observed for a total of 52 weeks to investigate the effect of romosozumab compared with placebo on time to functional healing of a fresh unilateral hip fracture. The adverse events (AEs) were comparable between placebo and the total romosozumab groups and no new safety risks were identified.
Use of agents affecting bone metabolism	
Reason for exclusion	In placebo-controlled studies, it was considered unethical to enroll study participants using agents affecting bone metabolism when approved therapies were available because these study participants would remain untreated for 12 months if randomized to the placebo group.
Is it considered to be included as missing information?	No
Rationale	Patients are expected to benefit from treatment with romosozumab even if they have previously been treated with agents affecting bone metabolism. In study 20080289, study participants showed significant increases in BMD at the spine and the hip after transitioning from bisphosphonate therapy. Adverse reactions observed in this study were generally consistent with those seen in women not transitioning from bisphosphonate therapy.

Table Part II–7: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
History of metabolic or bone disease (except osteoporosis)	
Reason for exclusion	Patients with other bone diseases such as sclerosteosis, Paget’s disease, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, Cushing’s disease, hyperprolactinemia, and malabsorption syndrome could confound the efficacy results.
Is it considered to be included as missing information?	No
Rationale	Romosozumab is indicated for the treatment of PMO, and not for the use in sclerosteosis, Paget’s disease of bone, or osteogenesis imperfecta. Osteoporosis in Cushing’s disease would be considered glucocorticoid induced osteoporosis and romosozumab is not indicated for the use in glucocorticoid induced osteoporosis. Nonclinical data indicate that romosozumab will increase bone mass in animals with glucocorticoid induced bone loss. Efficacy and safety of romosozumab in women with PMO who also suffer from hyperprolactinemia is not expected to be different from the general osteoporosis population. Patients with ankylosing spondylitis were excluded from the trial because due to their underlying disease it would be impossible to reliably assess BMD changes at the spine (secondary endpoint) – based on the available data, there is no indication that efficacy and safety at other skeletal sites would differ. In patients with malabsorption syndrome hypocalcemia is a possible manifestation of the disease and has to be corrected before romosozumab use, hypocalcemia of any cause is listed as a contraindication.
History of solid organ or bone marrow transplants	
Reason for exclusion	It was considered unethical to enroll osteoporosis patients after organ or bone marrow transplant in a placebo-controlled trial.
Is it considered to be included as missing information?	No
Rationale	Osteoporosis post-transplant is often due to glucocorticoid use. Romosozumab is not indicated for glucocorticoid induced osteoporosis. Romosozumab will increase bone mass in animals with glucocorticoid-induced bone loss. If the osteoporosis in these transplant patients is not considered due to glucocorticoid use, safety and efficacy of romosozumab is not expected to differ.

Table Part II–7: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
History of osteonecrosis of the jaw (ONJ)	
Reason for exclusion	It was considered potentially confounding for the interpretation of the safety data to enroll patients with a history of ONJ, as it may be difficult to differentiate between ongoing or new events in the trial. In study 20070337, ONJ was an exclusion criterion due to study participants receiving denosumab for which ONJ is a known ADR. In study 20110142, clinical study sites were instructed to follow the local prescribing instructions for alendronate.
Is it considered to be included as missing information?	No
Rationale	The efficacy of romosozumab is not expected to differ in study participants with a history of ONJ. Sclerostin antibody treatment caused greater alveolar crest height and bone mass with maintenance of local bone resorption in response to inflammation in an ovariectomized rat model of localized periodontitis. These data support that in rats with periodontal disease, a known risk factor for ONJ, administration of sclerostin antibody does not impair the local response to injury and thus would not predispose to retention of necrotic bone. In a similar study using the rat model of periodontitis, there was no evidence of ONJ-like lesions when assessed using radiography or histology in the areas of periodontitis following treatment with a sclerostin antibody.
Vitamin D insufficiency, defined as 25 (OH) vitamin D levels <20ng/mL	
Reason for exclusion	Uncorrected vitamin D levels can confound results.
Is it considered to be included as missing information?	No
Rationale	Vitamin D insufficiency is expected to be corrected through specific measures: Study participants in clinical trial were supplemented with calcium and vitamin D to provide a sufficient calcium pool for the expected and significant increase in bone mass which is needed for bone mineralization in the first several months after initiation of treatment with romosozumab. Patients should be adequately supplemented with calcium and vitamin D before and during treatment.

Table Part II–7: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
Current, uncontrolled hyperthyroidism or hypothyroidism, defined as thyroid-stimulating hormone outside of the normal range	
Reason for exclusion	Uncorrected hypothyroidism or hyperthyroidism can confound results.
Is it considered to be included as missing information?	No
Rationale	The safety and efficacy of romosozumab is not expected to differ in study participants with uncorrected hypothyroidism or hyperthyroidism. There were no effects on the thyroid gland in chronic toxicity studies in the rat and monkey. Nonclinical studies in hypothyroid and hyperthyroid mice demonstrate upregulation of sclerostin in bone in both conditions, suggesting sclerostin therapy may benefit thyroid hormone-associated bone disease (Tsourdi et al, 2015). In the 12-month, placebo-controlled osteoporosis safety analysis set, the study participant incidence of AEs in the high level group term of Thyroid gland disorders were balanced between placebo and romosozumab. Also, the AE of Thyroid function test abnormal was balanced.
Current, uncontrolled hyperparathyroidism or hypoparathyroidism, defined as PTH outside the normal range	
Reason for exclusion	Uncorrected hyperparathyroidism or hypoparathyroidism can confound results.
Is it considered to be included as missing information?	No
Rationale	Romosozumab is not indicated for the treatment of hyperparathyroidism or hypoparathyroidism. In the 12-month, placebo-controlled osteoporosis safety analysis set, the study participant incidence of AEs in the high level group term of Parathyroid gland disorders was balanced between placebo and romosozumab. Also, the AE of Blood parathyroid hormone increased was balanced.
Possible diagnosis of multiple myeloma or related lymphoproliferative disorder	
Reason for exclusion	Study participants diagnosed with multiple myeloma or related lymphoproliferative disorder can suffer fractures, in particular vertebral fractures, due to underlying malignancy and therefore confound the results.
Is it considered to be included as missing information?	No

Table Part II–7: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
Rationale	The findings of the lifetime study and the weight-of-evidence factors including the chronic toxicity studies in rats and monkeys collectively indicate that romosozumab administration would not pose a carcinogenic risk to humans. In the 12-month, placebo-controlled osteoporosis safety analysis set, the total study participant incidence of AEs in the system organ class of Neoplasms benign, malignant or unspecified was balanced between placebo and romosozumab. The AEs in the high level group terms of Plasma cell neoplasms, Lymphomas non-Hodgkin's unspecified histology; Leukaemias; Lymphomas NEC were generally similar.

AE=adverse event; ALN=alendronate; BMD=bone mineral density; DXA=dual energy x-ray absorptiometry; ONJ=osteonecrosis of the jaw; PMO=postmenopausal osteoporosis; PTH=parathyroid hormone;

^a Based on the placebo-controlled studies

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

[Table Part II–8](#) provides an example of overview of exposure in special population typically under-represented in clinical trial development programs.

Table Part II–8: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant or breastfeeding women	Pregnant and breastfeeding women are out of scope of the targeted indication. Pregnant and breastfeeding women were not included in the clinical development program; therefore excluded, no information exists on the safety and efficacy of romosozumab in this population. Across the romosozumab clinical trial program, there were no reported pregnancies after maternal romosozumab exposure and 1 reported pregnancy after paternal romosozumab exposure. The female partner had an elective termination for family planning reasons, and no AEs were reported. Romosozumab is not recommended for use in pregnancy. It is unknown whether romosozumab is present in human breast milk. The effects of romosozumab in breastfed infants have not been assessed. Studies with other IgG monoclonal antibodies have shown that concentrations in breast milk as well as oral bioavailability for the infant are generally very low.
Patients with relevant comorbidities^a Patients with hepatic impairment	No formal pharmacokinetic studies of romosozumab have been conducted in patients with hepatic impairment. Romosozumab is a monoclonal antibody and is not metabolized in the liver. Romosozumab is not expected to have direct impact on cytochrome P450 (CYP450) and other drug metabolizing enzymes or transporters. In addition, romosozumab is not expected to modulate cytokine levels which could exert an indirect impact on CYP450 activities. In the chronic toxicity studies in rats and cynomolgus monkeys, romosozumab administration was not associated with changes in liver function tests or hepatic histopathology.

Table Part II–8: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Patients with renal impairment	In a phase 1 study of romosozumab (study 20110227), healthy study participants (8 study participants) and study participants with stage 4 renal impairment (8 study participants) or stage 5 renal impairment requiring hemodialysis (8 study participants) were exposed to romosozumab (N=24). In the 12-month placebo-controlled osteoporosis safety set, 18 study participants with eGFR 15 to <30mL/min/1.73m² were enrolled (10 treated with romosozumab; 8 with placebo); all were part of study 20070337. No study participants with stage 5 renal impairment were enrolled in any study in this Safety Set. No AEs were reported in this subgroup of study participants with stage 4 renal impairment in either treatment arm. No deaths occurred during the first 12 months of treatment with romosozumab. One SAE (preferred term “death”, cause unknown) was reported 311 days after the first dose of study medication in period 2, during which the subject received 2 doses of denosumab 60mg. This death was not considered to be related to romosozumab. A population pharmacokinetic analysis indicated an increase in romosozumab exposure with increasing severity of renal impairment. However, based on both the renal impairment study and population PK analysis, this increase is not clinically meaningful and no dose adjustment is necessary in these patients. Patients with severe renal impairment (eGFR 15 to 29mL/min/1.73 m²) or receiving dialysis are at greater risk of developing hypocalcemia.
Patients with rheumatoid arthritis	In Study 20070337, rheumatoid arthritis was an exclusion criterion due to study participants in both treatment groups receiving denosumab in the second year (ie, in an uncontrolled fashion) to avoid potential interaction with TNF treatment. A phase 3 study (Study 20110142) did not exclude study participants with a past medical history of rheumatoid arthritis. Out of a total of 2040 study participants who received at least one dose of romosozumab, there were 27 (1.3%) study participants with a past medical history of rheumatoid arthritis.

Table Part II–8: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Population with relevant different ethnic origin	From the 12-month placebo-controlled osteoporosis safety analysis set (N=6199), white or Caucasian race included 3986 (64.3%) study participants and non-white race (black or African American, Hispanic or Latino, Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, other) included 2213 (35.7%) study participants in the total romosozumab population.
Subpopulations carrying relevant genetic polymorphisms	No genetic factors have been identified as markers that would correspond to a higher risk for AEs.
Pediatric patients	Pediatric patients were excluded from romosozumab clinical studies pertaining to the indication of severe osteoporosis in postmenopausal women at high risk of fracture; therefore, no information exists on the safety and efficacy of romosozumab in this population for the foresaid indication. The evaluation of romosozumab in pediatric patients with Osteogenesis Imperfecta is currently ongoing.
Elderly	Of the 6199 study participants treated with romosozumab in completed clinical studies, 3920 patients (63.2%) were >65 years old.

AE=adverse event; CYP450=cytochrome P450; eGFR= estimated glomerular filtration rate;

IgG=immunoglobulin G; PK=pharmacokinetics; SAE=serious adverse event

^a There were no limitations for inclusion in the clinical trial development program for the population of patients with cardiovascular impairment and for immunocompromised patients. There are no data available for patients with a disease severity different from inclusion criteria in clinical trials.

Part II Module SV Postauthorization experience

SV.1 Postauthorization exposure

SV.1.1 Method used to calculate exposure

A conservative view was adopted by assuming that all patients receive complete dosage regimens at the time of treatment. Patient exposure is estimated using the available UCB sales data from 01 Jan 2019 (international birth date on 08 Jan 2019) to 31 Aug 2025 for the cumulative time interval. Note that sales data are only available to UCB on a month-to-month basis.

The total amount of product sold during the cumulative reporting interval is derived from the UCB sales data reported.

The standard monthly dose (SMD) is assumed to be 210mg according to the summary of product characteristics (SmPC) (Aug 2024). For calculation purposes, a year is defined as 12 months. The patient exposure to romosozumab is calculated using the following formula:

$$\text{Patient-years} = \frac{(\text{total amount of product distributed})/\text{SMD}}{12 \text{ months in year}}$$

Patient exposure estimates for countries where marketing authorization is held by the UCB's license partner are obtained directly from this company, may be based on a different set of assumptions, and are reported in [Section SV.1.3](#).

SV.1.2 Exposure

For the cumulative time interval from 01 Jan 2019 to 30 Apr 2021, CCI of product was distributed contributing to approximately CCI patients-years. Data on exposure by region are presented for the cumulative time interval in [Table Part II–9](#).

Table Part II–9: Patient exposure by region for the cumulative time interval from 01 Jan 2019 to 31 Aug 2025

Region	Sub-Region	Country	Patient-years cumulatively
CCI			

Table Part II–9: Patient exposure by region for the cumulative time interval from 01 Jan 2019 to 31 Aug 2025

Region	Sub-Region	Country	Patient-years cumulatively
		CCI	
Total			CCI

SV.1.3 Postauthorization exposure from License Partner

The cumulative number of patient-years of exposure to romosozumab where UCB's license partner has marketing authorization is presented in [Table Part II–10](#).

**Table Part II–10: Patient exposure by region for the cumulative time interval
from 01 Jan 2019 to 31 Aug 2025**

Country	Patient-years for the cumulative interval
CCI	
Total	CCI

Other=emerging markets in Asia, Africa, the Middle East, and Latin America where UCB's license partner is the marketing authorization holder



Part II Module SVI Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Based on the characteristics and target population of this drug, no potential for drug abuse or misuse is anticipated.

Part II Module SVII Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Table Part II–11: Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Non important risk	Justification for non-inclusion
Injection site reactions (ISRs)	Although ISRs are causally associated with romosozumab administration, these ISRs are well characterized. They were reported as non-serious events, with most reported as mild to moderate in severity without leading to product discontinuation. Also, these events appeared to be local ISRs without systemic involvement and they resolved. As these ISRs are well characterized, appear to be generally tolerable and do not warrant additional clinical actions to minimize the risk, ISRs do not need to be included in the Risk Management Plan since this does not meet the definition of “important identified risk.”
Nasopharyngitis, headache, arthralgia, neck pain, muscle spasms, and sinusitis	Risks with minimal clinical impact on patients.

ISR=injection site reaction

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table Part II–12: Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks	
Hypersensitivity	
Risk benefit-impact	This risk was detected in the clinical trial setting. Data to evaluate safety concerns derive from clinical studies. All monoclonal antibodies could potentially be associated with hypersensitivity reactions, including anaphylactoid events. From the 12-month, placebo-controlled osteoporosis safety analysis set there is evidence to suggest a causal relationship between romosozumab and hypersensitivity, including angioedema: 1 Subject (<0.1%) on romosozumab versus 3 subjects (<0.1%) on placebo; erythema multiforme: 1 subject (<0.1%) on romosozumab versus 0 on placebo; rash: 54 subjects (1.4%) on romosozumab versus 34 subjects (0.9%) on placebo; dermatitis: 42 subjects (1.1%) on romosozumab versus 61 subjects (1.6%) on placebo and urticaria: 20 subjects (0.5%) versus 23 subjects (0.6%) on placebo. Risk of hypersensitivity has been considered in the overall benefit-risk assessment with benefit-risk balance remaining positive.

Table Part II–12: Risks considered important for inclusion in the list of safety concerns in the RMP

	Routine pharmacovigilance will be implemented to monitor this risk. Hypersensitivity is included in contraindications (SmPC Section 4.3) and warnings and precautions for use (SmPC Section 4.4).
Immunogenicity (development of antibodies to romosozumab)	
Risk benefit-impact	This risk was detected in the clinical trial setting. Data to evaluate safety concerns derive from clinical studies prevalence rates. Antibodies can result in a variety of effects, such as reduction or elimination of the activity of the test article, neutralizing the endogenous molecule, and/or hypersensitivity reactions. Antidrug antibodies and neutralizing antibodies had a limited impact on safety in clinical trials (SmPC Section 4.8). Risk of immunogenicity has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities will be implemented to monitor this risk.
Hypocalcemia	
Risk benefit-impact	This risk was detected in the clinical trial setting. Data to evaluate safety concerns derive from clinical studies prevalence rates. Romosozumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream. Patients treated with romosozumab should receive adequate calcium and vitamin D supplementation. Patients with severe renal impairment (estimated glomerular filtration rate 15 to 29mL/min/1.73m²) or receiving dialysis are at greater risk of developing hypocalcemia. Risk of hypocalcemia has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities will be implemented to monitor this risk. Romosozumab is contraindicated in patients with hypocalcemia. Information relating to hypocalcemia is described in contraindications (SmPC Section 4.3) and in special warnings and precautions for use (SmPC Section 4.4). Additional risk minimization measures are listed in EU-RMP Part V.
Serious cardiovascular events of myocardial infarction (MI) and stroke	
Risk benefit-impact	This risk was detected in the clinical trial setting. Data to evaluate safety concerns derive from clinical studies, and pharmacoepidemiological background prevalence rates. This risk has been detected based on an imbalance of MI and stroke events between romosozumab and alendronate in 1 of the 2 pivotal fracture studies, the alendronate-controlled study, 20110142. The imbalance resulted from small differences in terms of absolute subject numbers and absolute risk differences. No imbalance of CV events was observed in the larger placebo-controlled fracture study 20070337. In study 20110174, the differences in

Table Part II–12: Risks considered important for inclusion in the list of safety concerns in the RMP

	incidence of serious cardiac ischemic events and cerebrovascular events reported between the romosozumab group and placebo were less apparent; the absolute number of events was small. No evidence of any mechanistic association between sclerostin inhibition and atheroprogession or MACE-1 events was established based on the totality of nonclinical evidence. When subjects with a history of MI or stroke were excluded from the population, the absolute incidences in treatment arms, as well as the imbalances between control and romosozumab arms were significantly lower for MACE and all individual components (MI, stroke, and CV events leading to death) (refer to section characterization of the risk in Table Part II–16). These data show that applying a contraindication for patients with a history of MI or stroke minimizes the risk of these events. The CV incidences of MI and stroke in 20110142 are within the epidemiological background incidences for the osteoporosis population at increased risk of fracture. Risk of serious cardiovascular events of MI and stroke has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Independent adjudication for serious cardiovascular adverse events is carried out as part of routine pharmacovigilance activities in clinical studies as appropriate. A targeted follow-up questionnaire will be utilized in the postmarketing setting. Additional pharmacovigilance activities (see EU-RMP Part III) will be implemented to monitor this risk. Information relating to serious cardiovascular events of MI and stroke is described in contraindications (SmPC Section 4.3) and in special warnings and precautions for use (SmPC Section 4.4). Additional risk minimization measures are listed in EU-RMP Part V.
Important potential risks	
Osteonecrosis of the jaw (ONJ)	
Risk benefit-impact	This risk was detected in the clinical trial setting. Data to evaluate safety concerns derive from clinical studies and pharmacoepidemiological background prevalence rates. ONJ is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks in a patient without prior history of radiation therapy to the jaws or obvious metastatic disease to the jaws (Ruggiero et al, 2014). Although a triggering traumatic event is usually involved, ONJ can be asymptomatic (American Association of Oral and Maxillofacial Surgeons, 2007; Shoback 2007; Ruggiero et al, 2006; Woo et al, 2006). Risk of ONJ has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities will be implemented to monitor this risk. Independent adjudication for events of ONJ is carried out as part of

Table Part II–12: Risks considered important for inclusion in the list of safety concerns in the RMP

	routine pharmacovigilance activities in clinical studies as appropriate. Information relating to ONJ is described in the special warnings and precautions for use section (SmPC Section 4.4). Additional risk minimization measures are listed in EU-RMP Part V.
Atypical femoral fracture (AFF)	
Risk benefit-impact	This risk was detected in the clinical trial setting. Data to evaluate safety concerns derive from clinical studies and pharmacoepidemiological background prevalence rates. AFFs are defined as fractures located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare (Shane et al, 2014). In addition, as defined by the 2013 American Society for Bone and Mineral Research Task Force, at least 4 out of 5 major features must be present. These include: • Associated with no trauma or minimal trauma, as in a fall from a standing height or less • Fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex. • Non comminuted or minimally comminuted • Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”) Some case series have reported a possible association between AFF and long term bisphosphonate therapy (Meier et al, 2012; Whitaker et al, 2012; Dell et al, 2010; Odvina et al, 2009; Lenart et al, 2008; Odvina et al, 2005). Risk of AFF has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities will be implemented to monitor this risk. Independent adjudication for events of AFF is carried out as part of routine pharmacovigilance activities in clinical studies as appropriate. Information relating to AFF is described in the special warnings and precautions for use (SmPC Section 4.4).
Serious infections	
Risk benefit-impact	This risk was detected in the clinical trial setting. Data to evaluate safety concerns derive from clinical studies prevalence rates. This is considered a potential risk based on a numerical imbalance of overall infections SAEs in the 12-month Placebo-Controlled Osteoporosis Safety Analysis Set, also when adjusted for patient-years. No imbalance was observed for overall infections. No imbalance in overall or serious infections was observed in the alendronate-controlled study 20110142. A further review of MedDRA terms showed that the imbalances were not driven by specific type of infections,

Table Part II–12: Risks considered important for inclusion in the list of safety concerns in the RMP

	or causative micro-organisms. Some imbalances in abnormalities of counts of white blood cells, neutrophils and lymphocytes were observed in pivotal clinical studies, but no consistent relationship is present between these abnormalities and serious infections events. Slight changes in hematology parameters were observed in rats and cynomolgus monkeys receiving romosozumab, comprising a mild regenerative anemia with compensatory hematopoiesis, a mild decrease in platelet numbers and a mild increase in platelet volume. These were considered an expected but indirect effect of sclerostin inhibition, arising from a Wnt-signalling effect on hematopoiesis, and were not associated with adverse clinical consequences in the animals. In addition, there is no evidence that inhibition of sclerostin would lead to any effects on the immune system or the ability of the body to respond to infection. Risk of serious infections has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine and additional pharmacovigilance activities will be implemented to monitor this risk (see EU-RMP Part III).
Missing information: Osteoporosis rebound effects	
Risk benefit-impact	With the available evidence, it is unknown whether discontinuation of romosozumab therapy without transition to antiresorptive treatment could be associated with an increased risk of fractures as compared to the baseline.

AFF=atypical femoral fracture; AUC=area under the curve; CI=confidence interval; CV=cardiovascular; mAB=monoclonal antibody; MACE=major adverse cardiac events; MI=myocardial infarction; ONJ=osteonecrosis of the jaw; QM=once every month; QW=every week; RMP=risk management plan; SAE=serious adverse event; SC=subcutaneous(ly); SmPC=summary of product characteristics

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The important potential risk of serious infection is removed from the list of safety concerns based on the final results of EU PASS OP0006 study.

The study population comprised of all postmenopausal women who received romosozumab within the indicated population in Europe as per the SmPC or other osteoporosis medications of interest for the first time during the study period (reporting period: Jan 2020 through Jan 2025). The following databases were used in the final safety analysis: Integrated Primary Care Information (IPCI) from the Netherlands, Sistema d'Informació per al Desenvolupament de la Investigació a l'Atenció Primària (SIDIAP)/Information System for Research in Primary Care from Spain, National Diabetes Register (NDR) from Denmark, Clinical Practice Research Datalink (CPRD) Gold and CPRD Aurum from the UK, and German Pharmacoepidemiological Research Database (GePaRD) from Germany. The total number of romosozumab users across databases was 2505 (921 in GePaRD, 608 in NDR, 567 in SIDIAP, 310 in CPRD Aurum, and 99 in IPCI); there were no romosozumab users in the CPRD Gold database. After applying the inclusion and exclusion criteria, 75.3% of romosozumab users across databases were eligible for the study (n=1887). The number of eligible users of osteoporosis medications was 311,058 for

alendronate; 59,595 for oral bisphosphonate prescriptions; 23,320 for intravenous bisphosphonate; 70,640 for denosumab; and 12,014 for teriparatide.

A comparative safety analysis for matched users of romosozumab compared to alendronate users was performed for the primary outcome of serious infection leading to hospitalization and the secondary outcome of serious Covid-19 infection leading to hospitalization. Common and random effects meta-analyses were used to obtain an overall hazard ratio (HR) by pooling database-specific HRs. The pooled estimated risk of serious infections in romosozumab users was not significantly different from alendronate users, as shown by a common effects model (HR of 1.12 [95% CI: 0.84, 1.51]) and a random effects model (HR of 1.07 [95% CI: 0.73, 1.57]). The heterogeneity across databases was low with an I^2 of 26.4% (95% CI: 0.0%, 72.1%). The planned comparative safety analysis showed that, in the study population, there was no evidence of increased risk of serious infection or serious Covid-19 infection associated with romosozumab use as compared to alendronate.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Although the male osteoporosis population is not part of the target population, safety data in men are included in the tables below for completeness of the safety profile.

Important identified risks

Important identified risks with romosozumab treatment are characterized in the tables below.

Table Part II–13: Important identified risk: hypersensitivity

MedDRA terms	Standardized MedDRA query for hypersensitivity (narrow)
Potential mechanisms	Two types of allergic reactions, immunoglobulin E (IgE)- and non-IgE mediated, appear to be related to monoclonal antibody administration. The IgE mediated reactions can cause both wheal and flare reactions at the injection site, but may also be associated with urticaria and anaphylaxis. The mechanism of non-IgE reactions is unclear.
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derive from clinical studies. This risk was detected in the clinical trial setting.

Table Part II–13: Important identified risk: hypersensitivity

Characterization of the risk	<u>Frequency with 95% CI</u>																											
	In the pooled studies for 12-month, placebo-controlled osteoporosis safety analysis set (N=3858 for the romosozumab group and N=3770 for the placebo group), the study participants incidence of adverse events potentially related to hypersensitivity was 6.7% in romosozumab treated study participants and 6.9% in placebo treated study participants (RR [95% CI] = 0.97 [0.82, 1.15]).																											
	In the alendronate-controlled Study 20110142 (N=2040 for the romosozumab 210mg QM group and N=2014 for the alendronate 70mg QW group), the study participants incidence of adverse events potentially related to hypersensitivity was 6.0% in romosozumab-treated study participants and 5.9% in alendronate-treated study participants (RR [95% CI] = 1.02 [0.80, 1.30]), during the 12-month, double-blind period.																											
	<u>Severity:</u>																											
	<table><tr><th colspan="3">Pooled Studies for 12-month placebo-controlled osteoporosis</th></tr><tr><td></td><td>Placebo (N=3770) n (%)</td><td>Romosozumab 210mg QM (N=3858) n (%)</td></tr><tr><td colspan="3">Hypersensitivity</td></tr><tr><td>Mild</td><td>177 (4.7)</td><td>191 (5.0)</td></tr><tr><td>Moderate</td><td>86 (2.3)</td><td>70 (1.8)</td></tr><tr><td>Severe</td><td>3 (< 0.1)</td><td>6 (0.2)</td></tr><tr><td>Life-threatening</td><td>1 (< 0.1)</td><td>1 (< 0.1)</td></tr><tr><td>Fatal</td><td>0 (0.0)</td><td>1 (< 0.1)</td></tr><tr><td>Unknown</td><td>0 (0.0)</td><td>0 (0.0)</td></tr></table>	Pooled Studies for 12-month placebo-controlled osteoporosis				Placebo (N=3770) n (%)	Romosozumab 210mg QM (N=3858) n (%)	Hypersensitivity			Mild	177 (4.7)	191 (5.0)	Moderate	86 (2.3)	70 (1.8)	Severe	3 (< 0.1)	6 (0.2)	Life-threatening	1 (< 0.1)	1 (< 0.1)	Fatal	0 (0.0)	1 (< 0.1)	Unknown	0 (0.0)	0 (0.0)
	Pooled Studies for 12-month placebo-controlled osteoporosis																											
		Placebo (N=3770) n (%)	Romosozumab 210mg QM (N=3858) n (%)																									
	Hypersensitivity																											
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	Moderate	86 (2.3)	70 (1.8)																									
Severe	3 (< 0.1)	6 (0.2)																										
Life-threatening	1 (< 0.1)	1 (< 0.1)																										
Fatal	0 (0.0)	1 (< 0.1)																										
Unknown	0 (0.0)	0 (0.0)																										
N=Number of study participants who received ≥ 1 dose of investigational product; n=Number of study participants reporting ≥ 1 event; QM=once every month																												
12-month, placebo-controlled osteoporosis safety analysis set includes study participants who were randomized and received at least 1 dose of romosozumab 210mg QM or placebo in Studies 20070337, 20060326, 20101291 and 20110174.																												
Program: /userdata/stat/amg785/meta/eu_2017osteo/analysis/css/adhoc/program/t-ah-rmp-risk-adjcv-db-337-174.sas; Output: trmp-08-500-001-ah-rmp-risk-adjcv-db-337-174.rtf (Date Generated: 29 Jun 2017:19:04:54) Source Data: adam.adadjcv																												

Table Part II–13: Important identified risk: hypersensitivity

	Study 20110142		
		Alendronate 70mg QW (N=2014) n (%)	Romosozumab 210mg QM (N=2040) n (%)
	Hypersensitivity		
	Mild	89 (4.4)	91 (4.5)
	Moderate	35 (1.7)	33 (1.6)
	Severe	1 (< 0.1)	1 (< 0.1)
	Life-threatening	0 (0.0)	0 (0.0)
	Fatal	0 (0.0)	1 (< 0.1)
	Unknown	0 (0.0)	0 (0.0)
N=Number of study participants who received ≥ 1 dose of investigational product; n=Number of study participants reporting ≥ 1 event; QM=once every month; QW=every week The case of fatal outcome in the pooled, placebo-controlled studies was a PPD year-old PPD who developed unspecified cardiovascular disease and was hospitalized on Day 345, approximately 9 days after receiving PPD twelfth dose of romosozumab. PPD died 20 days later due to circulatory collapse; antibodies remained negative. This fatal event was considered unrelated to romosozumab by the Investigator. In Study 20110142, the fatal event occurred in a PPD-year-old PPD with a medical history of PPD and PPD, who died due to circulatory collapse in Day 11. PPD had received one dose of romosozumab. This fatal event was considered unrelated to romosozumab by the Investigator. <u>Long-term outcomes</u> No long-term outcome is expected after resolution of hypersensitivity reactions. <u>Impact on quality of life</u> For severe or life threatening hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalized for treatment. Generally, patients recover when their hypersensitivity reaction is treated.			
Risk factors and risk groups	Known hypersensitivity to romosozumab and any of its excipients.		
Preventability	No data are available on potential measures to prevent hypersensitivity reactions to romosozumab. The appropriate contraindication information on hypersensitivity to romosozumab and any of its excipients is included in the labeling information.		
Impact on the risk-benefit balance of the product	Risk of hypersensitivity has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities are implemented to monitor this risk. Hypersensitivity is included in Contraindications (SmPC Section 4.3) and Special Warnings and Precautions for use (SmPC Section 4.4). Further information is also provided in the Patient Information Leaflet.		

Table Part II–13: Important identified risk: hypersensitivity

Public health impact	Identified as an unfavorable effect, but no significant public health impact is expected.
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CI=confidence interval; IgE=immunoglobulin E; MedDRA=Medical Dictionary for Regulatory Activities; N=number; PMO=postmenopausal osteoporosis; QM=once every month; QW=every week; RR=relative risk; SmPC=summary of product characteristics

Table Part II–14: Important identified risk: immunogenicity (development of antibodies to romosozumab)

MedDRA terms	Preferred terms: Antibody test positive, Drug effect decreased, Drug effect delayed, Drug ineffective, Drug specific antibody present, Human antichimeric antibody positive, Inhibiting antibodies, Inhibiting antibodies positive, Neutralising antibodies, Neutralising antibodies positive, No therapeutic response, Non-neutralising antibodies positive, Therapeutic product ineffective, Therapeutic reaction time decreased, Therapeutic response decreased, Therapeutic response delayed, Treatment failure
Potential mechanisms	Development of ADA is primarily through humoral response due to the activation of an adaptive response to foreign antigens.
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derive from clinical studies prevalence rates. This risk was detected in the clinical trial setting.
Characterization of the risk	<u>Frequency with 95% CI</u> In the pooled studies for 12-month, placebo-controlled osteoporosis safety analysis set (N=3858 for the romosozumab group and N=3770 for the placebo group), 17.9% (691 of 3858) of subjects in the romosozumab group were positive at any time for binding ADA, and 0.2% (6 of 3858) were positive at any time for neutralizing ADA. Of subjects with a postbaseline result and a negative or no result at baseline, 17.2% (665 of 3858) developed binding ADA, and 0.2% (6 of 3858) developed neutralizing ADA. In the alendronate-controlled Study 20110142, among subjects who received romosozumab, the overall incidence of anti-romosozumab antibodies at any study visit in the double-blind period and through month 18 was 15.6% for binding antibodies and 0.6% for neutralizing antibodies. <u>Severity</u> No impact to the efficacy and a limited impact on the safety of romosozumab was observed by the presence of anti-romosozumab antibodies. <u>Reversibility</u> Reversibility of immunogenicity has not been specifically studied. However, most ADA-positive subjects become ADA-negative by end of study. <u>Long-term outcomes</u> No long-term outcome effect of immunogenicity is expected. <u>Impact on quality of life</u>

Table Part II–14: Important identified risk: immunogenicity (development of antibodies to romosozumab)

	No clinical sequelae have been associated with development of anti-romosozumab antibodies.
Risk groups or risk factors	No risk groups or risk factors have been identified during the clinical studies.
Preventability	No preventative measures are known.
Impact on the risk-benefit balance of the product	Risk of immunogenicity has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities are implemented to monitor this risk.
Public health impact	An impact on public health is not anticipated.

ADA=antidrug antibodies; CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; N=number

Table Part II–15: Important identified risk: hypocalcemia

MedDRA terms	Preferred terms: Adjusted calcium decreased, Blood calcium decreased, Calcium deficiency, Calcium ionised decreased, Chvostek's sign, Hypocalcaemia, Hypocalcaemic seizure, Trousseau's sign
Potential mechanisms	Romosozumab blocks sclerostin and increases bone formation due to the activation of bone lining cells, increased bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells. Additionally, romosozumab results in changes in expression of osteoclast mediators, thereby decreasing bone resorption. This mechanism of action of romosozumab suggests that administration of romosozumab may be associated with decreases in serum calcium as a result of increased bone formation and decreased bone resorption.
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derive from clinical studies prevalence rates. This risk was detected in the clinical trial setting.

Table Part II–15: Important identified risk: hypocalcemia

Characterization of the risk	<u>Frequency with 95% CI</u> In the pooled studies for 12-month, placebo-controlled osteoporosis safety analysis set (N=3858 for the romosozumab group and N=3770 for the placebo group), the study participant incidence of hypocalcemia adverse events was < 0.1% in romosozumab-treated study participants and 0.0% in placebo treated study participants. The study participant incidence of serum albumin calcium below the lower limit of normal was 0.4% in romosozumab and 0.1% in placebo. In the alendronate-controlled Study 20110142 (N=2040 for the romosozumab 210mg QM group and N=2014 for the alendronate 70mg QW group), the study participant incidence of hypocalcemia adverse events was < 0.1% in romosozumab treated study participants and < 0.1% in alendronate treated study participants (RR [95% CI] = 0.99 [0.06, 15.77]), during the 12-month double-blind period. No serious adverse events of hypocalcemia were reported in romosozumab-treated study participants. <u>Severity</u> In the 12-month, placebo-controlled osteoporosis safety analysis set and in Study 20110142, during the 12-month, double-blind period, no romosozumab subject had a decrease in albumin adjusted serum calcium $\geq$ grade 3. In the 12-month, placebo-controlled osteoporosis set, a non-serious grade 2 (moderate) event of hypocalcemia was reported in a romosozumab subject where the calcium supplementation was withheld in clinical setting of reported serious adverse events of congestive heart failure, and chronic obstructive pulmonary disease. In Study 20110142 during the double-blind period, a grade 1 adverse event of hypocalcemia was reported in a romosozumab subject within the setting of a serious adverse event of hyponatremia. In the 12-month, placebo-controlled osteoporosis set, the subject incidence of the worst decrease grade of postbaseline calcium corrected by albumin grade 1 was 0.2% in romosozumab and < 0.1% in placebo; grade 2 was 0.2% in romosozumab and < 0.1% in placebo. <u>Reversibility</u> Generally, patients recover when their hypocalcemia is treated. <u>Long-term outcomes</u> No long-term outcome is expected after resolution of hypocalcemia. <u>Impact on quality of life</u> If severe symptomatic hypocalcemia occurs, patients may be hospitalized for treatment.
Risk groups or risk factors	Risk factors include severe renal impairment (creatinine clearance < 30mL/min) and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, dialysis, and some medications (Finkelstein, 2001).

Table Part II–15: Important identified risk: hypocalcemia

Preventability	Pre-existing hypocalcemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy, and supplementation with calcium and vitamin D is important during therapy in all patients receiving romosozumab. Clinical monitoring of calcium levels is recommended during treatment.
Impact on the risk-benefit balance of the product	Risk of hypocalcemia has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities are implemented to monitor this risk. Romosozumab is contraindicated in patients with hypocalcemia. Hypocalcemia is included in the Contraindications (SmPC Section 4.3) and Special Warnings and Precautions for Use (SmPC Section 4.4). Further information is also provided in the Patient Information Leaflet. Additional risk minimization measures are listed in EU-RMP Part V.
Public health impact	Identified as an unfavorable effect, but no significant public health impact is expected.

CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; N=number; PMO=postmenopausal osteoporosis; QM=once every month; QW=every week; RR=relative risk; SmPC=summary of product characteristics

Table Part II–16: Important identified risk: serious cardiovascular events of myocardial infarction and stroke

MedDRA terms	Narrow myocardial infarction Standardized MedDRA query (SMQ) and Marketing Authorization Holder MedDRA query for stroke
Potential mechanisms	Sclerostin is constitutively expressed in the aorta and is upregulated in areas of vascular and valvular calcification in diseases associated with abnormal mineral homeostasis. Patients with lifelong absence of sclerostin (ie, sclerosteosis or van Buchem disease), or those heterozygous for the SOST mutations do not show increases in early onset vascular calcification or cardiovascular disease. These patients can serve as a model of what may be expected in study participants treated with a sclerostin inhibitor such as romosozumab. There is no evidence in the literature or according to leaders in the field of early onset vascular calcification of increased cardiovascular risk for individuals with SOST mutations (Beighton, 2011a; Beighton, 2011b). In addition, nonclinical studies have found no evidence of a plausible mechanistic link between sclerostin inhibition and atheroprotection in an atherosclerotic mouse model or of an association between the absence of sclerostin expression in human atherosclerotic plaques and a prior history of arterial disease or subsequent MACE. A genome wide association study also showed no association between genes linked to MI and stroke and mutations leading to reduced or lack of sclerostin in humans. One study assessing sclerostin inhibition and cardiovascular risk was recently published (Bovijn, 2020). The author concluded that inhibition of sclerostin may elevate cardiovascular risk, warranting a rigorous evaluation of the cardiovascular safety of romosozumab and other sclerostin inhibitors. Review

Table Part II–16: Important identified risk: serious cardiovascular events of myocardial infarction and stroke

	by UCB concluded that with consideration given to the multiple limitations and flaws identified with this publication, this study does not provide strong evidence to support a hypothesis that sclerostin inhibition leads to an increased risk of adverse CV events.
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derive from clinical studies, and pharmacoepidemiological background prevalence rates. This is considered a risk based on clinical trial data from an alendronate-controlled study of more than 4000 patients. The imbalance was not observed in the larger placebo-controlled study, Study 20070337. Evaluations that have been performed to date could not determine the cause of the imbalance in the incidence of positively-adjudicated cardiovascular serious adverse events in Study 20110142.
Characterization of the risk	<u>Frequency with 95% CI</u> During Studies 20070337, 20110174 and 20110142, serious adverse events, deemed by the Investigator to be of potential cardiovascular origin or etiology were submitted to an independent committee for adjudication (Duke Clinical Research Institute [DCRI]). In addition, serious adverse events with terms mapping to a predefined preferred term list potentially indicative of cardiovascular etiology and all deaths were also adjudicated. <i>Serious cardiovascular adverse events</i> In the pooled, placebo-controlled studies 20070337 in women and 20110174 in men (N=3744 for the romosozumab 210mg QM group and N=3657 for the placebo group), the study participant incidence of the DCRI-positively adjudicated serious cardiovascular adverse events was 1.4% in romosozumab treated study participants and 1.3% in placebo treated study participants (RR [95% CI] = 1.10 [0.75, 1.62]) during the 12-month, double-blind period. In the alendronate-controlled Study 20110142 in women (N=2040 for the romosozumab 210mg QM group and N=2014 for the alendronate 70mg QW group), the study participant incidence of the DCRI-positively adjudicated serious cardiovascular adverse events was 2.5% in romosozumab treated study participants and 1.9% in alendronate treated study participants (RR [95% CI] = 1.30 [0.86, 1.97]), during the 12-month double-blind period. A subsequent independent post-hoc cardiovascular adjudication of all adverse events for the 3 studies was carried out by the Thrombolysis in Myocardial Infarction (TIMI) Study Group. TIMI evaluation showed no difference in the interpretation of DCRI based conclusions. In the pooled, placebo-controlled Studies 20070337 in women and 20110174 in men, the subject incidence of the TIMI-positively adjudicated serious cardiovascular adverse events was 1.4% in romosozumab-treated study participants and 1.2% in placebo-treated study participants (RR [95% CI] = 1.20 [0.81, 1.80]) during the 12-month, double-blind period. In the alendronate-controlled Study 20110142 in women, the subject incidence of TIMI-positively-adjudicated serious cardiovascular adverse events was 2.4% in romosozumab-treated study participants and 1.7% in alendronate-treated

Table Part II–16: Important identified risk: serious cardiovascular events of myocardial infarction and stroke

study participants (RR [95% CI] = 1.38 [0.90, 2.12]), during the 12-month double-blind period. <i>Myocardial infarction and stroke</i> For the placebo-controlled Study 20070337 in women, 12-month double-blind period, the subject incidence of DCRI-positively adjudicated MI events was 0.3% in romosozumab-treated study participants and 0.2% in placebo-treated study participants; the hazard ratio was 1.12 (95% CI: 0.43, 2.91). The study participant incidence of DCRI-positively adjudicated stroke events was 0.2% in romosozumab-treated study participants, 0.3% in placebo-treated study participants; the hazard ratio was 0.80 (95% CI: 0.32, 2.02). For the placebo-controlled Study 20110174 in men, 12-month double-blind period, the subject incidence of DCRI-positively adjudicated MI events was 0.6% in romosozumab-treated study participants and 0% in placebo-treated study participants; the hazard ratio could not be calculated. The subject incidence of DCRI-positively adjudicated stroke events was 1.8% in romosozumab-treated study participants, 1.2% in placebo-treated study participants; the hazard ratio was 1.54 (95% CI: 0.16, 14.83). For the alendronate-controlled Study 20110142 in women, 12-month double-blind period, the subject incidence of DCRI-positively adjudicated MI events was 0.8% in romosozumab-treated study participants and 0.2% in alendronate-treated study participants; the hazard ratio was 3.21 (95% CI: 1.18, 8.77). The subject incidence of DCRI positively adjudicated stroke events was 0.6% in romosozumab treated study participants, 0.3% in alendronate-treated study participants; the hazard ratio was 1.86 (95% CI: 0.74, 4.67). <i>Incidence of MACE-1 and individual components by history of MI or stroke through 12 months (pooled data of the 3 pivotal studies: 20110142, 20070337, and 20110174) (DCRI adjudicated)</i> <table> <tr> <th>3 pivotal studies</th><th>Control (placebo or ALN) Total</th><th>Romo 210mg QM Total</th><th>Control (placebo or ALN) ≥75 yrs</th><th>Romo 210mg QM ≥75 yrs</th></tr> <tr> <td colspan="5">MACE-1</td></tr> <tr> <td>History MI/stroke (Yes)</td><td>7/303 (2.3)</td><td>11/295 (3.7)</td><td>2/159 (1.3)</td><td>9/156 (5.8)</td></tr> <tr> <td>History MI/stroke (No)</td><td>46/5368 (0.9)</td><td>66/5489 (1.2)</td><td>32/2033 (1.6)</td><td>43/2101 (2.0)</td></tr> <tr> <td colspan="5">MI</td></tr> <tr> <td>History MI/stroke (Yes)</td><td>1/303 (0.3)</td><td>4/295 (1.4)</td><td>0/159 (0.0)</td><td>3/156 (1.9)</td></tr> <tr> <td>History MI/stroke (No)</td><td>12/5368 (0.2)</td><td>22/5489 (0.4)</td><td>8/2033 (0.4)</td><td>12/2101 (0.6)</td></tr> <tr> <td colspan="5">Stroke</td></tr> <tr> <td>History MI/stroke (Yes)</td><td>4/303 (1.3)</td><td>4/295 (1.4)</td><td>2/159 (1.3)</td><td>3/156 (1.9)</td></tr> </table>					3 pivotal studies	Control (placebo or ALN) Total	Romo 210mg QM Total	Control (placebo or ALN) ≥75 yrs	Romo 210mg QM ≥75 yrs	MACE-1					History MI/stroke (Yes)	7/303 (2.3)	11/295 (3.7)	2/159 (1.3)	9/156 (5.8)	History MI/stroke (No)	46/5368 (0.9)	66/5489 (1.2)	32/2033 (1.6)	43/2101 (2.0)	MI					History MI/stroke (Yes)	1/303 (0.3)	4/295 (1.4)	0/159 (0.0)	3/156 (1.9)	History MI/stroke (No)	12/5368 (0.2)	22/5489 (0.4)	8/2033 (0.4)	12/2101 (0.6)	Stroke					History MI/stroke (Yes)	4/303 (1.3)	4/295 (1.4)	2/159 (1.3)	3/156 (1.9)
3 pivotal studies	Control (placebo or ALN) Total	Romo 210mg QM Total	Control (placebo or ALN) ≥75 yrs	Romo 210mg QM ≥75 yrs																																													
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Stroke																																																	
History MI/stroke (Yes)	4/303 (1.3)	4/295 (1.4)	2/159 (1.3)	3/156 (1.9)																																													

Table Part II–16: Important identified risk: serious cardiovascular events of myocardial infarction and stroke

History MI/stroke (No)	14/5368 (0.3)	20/5489 (0.4)	13/2033 (0.6)	13/2101 (0.6)
CV death				
History MI/stroke (Yes)	2/303 (0.7)	5/295 (1.7)	0/159 (0.0)	5/156 (3.2)
History MI/stroke (No)	26/5368 (0.5)	31/5489 (0.6)	17/2033 (0.8)	24/2101 (1.1)
ALN=alendronate; CV=cardiovascular; DCRI=Duke Clinical Research Institute; MACE=major adverse cardiac event; MI=myocardial infarction				
Severity				
DCRI-positively adjudicated events of MI				
Pooled studies for 12-month, placebo-controlled osteoporosis				
	Placebo N=3657 n (%)	Romosozumab 210mg QM N=3744 n (%)		
Myocardial infarction				
Mild	-	-		
Moderate	2 (<0.1)	1 (<0.1)		
Severe	4 (0.1)	6 (0.2)		
Life-threatening	1 (<0.1)	2 (<0.1)		
Fatal	1 (<0.1)	1 (<0.1)		
N=Number of study participants in the safety analysis set; n=Number of study participants reporting ≥ 1 event; QM=once every month 12-month, placebo-controlled safety analysis set includes study participants who were randomized and received at least 1 dose of romosozumab 210mg QM or placebo in Studies 20070337 and 20110174				
Program: /userdata/stat/amg785/safety/RMP/analysis/2018_crmp/tables/program/t-rmp-risk-adjcv-mi-str-db-337-174.sas; Output: t14-05-007-rmp-risk-adjcv-mi-db-337-174.rtf (Date Generated: 20 Jun 2018:13:23:35) Source Data: timi.adadjcv				
Study 20110142, 12-month double-blinded period				
	Alendronate 70mg QW N=2014 n (%)	Romosozumab 210mg QM N=2040 n (%)		
Myocardial infarction				
Mild	-	-		
Moderate	0 (0.0)	2 (<0.1)		
Severe	1 (<0.1)	8 (0.4)		
Life threatening	4 (0.2)	4 (0.2)		
Fatal	0 (0.0)	3 (0.1)		

Table Part II–16: Important identified risk: serious cardiovascular events of myocardial infarction and stroke

N=Number of study participants in the safety analysis set; n=Number of study participants reporting ≥ 1 event; QM=once every month; QW=every week <i>Program: /userdata/stat/amg785/safety/RMP/analysis/2018_crmp/tables/program/t-rmp-risk-adjcv-mi-str-db-142.sas; Output: t14-05-009-rmp-risk-adjcv-mi-db-142.rtf (Date Generated: 20 Jun 2018:12:22:39) Source Data: timi.adadjcv</i> <i>DCRI-positively adjudicated events of stroke</i>		
Pooled studies for 12-month, placebo-controlled osteoporosis		
	Placebo (N = 3657) n (%)	Romosozumab 210mg QM (N = 3744) n (%)
Stroke		
Mild	0 (0.0)	1 (<0.1)
Moderate	2 (<0.1)	3 (<0.1)
Severe	4 (0.1)	3 (<0.1)
Life-threatening	2 (<0.1)	3 (<0.1)
Fatal	3 (<0.1)	2 (<0.1)
N=Number of study participants in the safety analysis set; n=Number of study participants reporting ≥ 1 event 12-month, placebo-controlled osteoporosis safety analysis set includes study participants who were randomized and received at least 1 dose of romosozumab 210mg QM or placebo in Studies 20070337 and 20110174 <i>Program: /userdata/stat/amg785/safety/RMP/analysis/2018_crmp/tables/program/t-rmp-risk-adjcv-mi-str-db-337-174.sas; Output: t14-05-008-rmp-risk-adjcv-str-db-337-174.rtf (Date Generated: 20 Jun 2018:13:23:35) Source Data: timi.adadjcv</i>		
Study 20110142, 12-month, double-blind period		
	Alendronate 70mg QW (N = 2014) n (%)	Romosozumab 210mg QM (N = 2040) n (%)
Stroke		
Mild	-	-
Moderate	3 (0.1)	2 (<0.1)
Severe	3 (0.1)	4 (0.2)
Life-threatening	1 (<0.1)	5 (0.2)
Fatal	0 (0.0)	2 (<0.1)
Unknown	0 (0.0)	1 (<0.1)
N=Number of study participants in the safety analysis set; n=Number of study participants reporting ≥ 1 event <i>Program: /userdata/stat/amg785/safety/RMP/analysis/2018_crmp/tables/program/t-rmp-risk-adjcv-mi-str-db-142.sas; Output: t14-05-010-rmp-risk-adjcv-str-db-142.rtf (Date Generated: 20 Jun 2018:12:22:39). Source Data: timi.adadjcv</i>		

Table Part II–16: Important identified risk: serious cardiovascular events of myocardial infarction and stroke

	<u>Long-term outcomes</u> Myocardial infarction may result in a complication of heart failure. Stroke may result in a long-term or permanent functional disability depending upon the severity of the incident and how quickly medical care is given. Patients who experienced MI or stroke are at higher risk of developing further cardiac events or strokes and are at increased risk for mortality. <u>Impact on quality of life</u> Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalized for treatment and disability or death may occur.
Risk groups or risk factors	The romozosumab osteoporosis development program was conducted in an older subject population who are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Hak et al, 2000; Schulz et al, 2004). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including anthracyclines, antipsychotic agents, NSAIDs and COX2 inhibitors (Smith et al, 2004; Murphy and Dargie, 2007). Patients with a history of MI or stroke have highest absolute risk of MACE events.
Preventability	Those at risk of cardiovascular events should follow established medical guidelines and practices.
Impact on the risk-benefit balance of the product	Risk of serious cardiovascular events of MI and stroke has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. When study participants with a history of MI or stroke were excluded from the population, the absolute incidences in treatment arms, as well as the imbalances between control and romozosumab arms were significantly lower for MACE and all individual components (MI, stroke, and CV events leading to death) (refer to section characterization of the risk in Table Part II–16). These data showed that applying a contraindication for patients with a history of MI or stroke minimizes the risk of these events. Independent adjudication for serious cardiovascular adverse events is carried out as part of routine pharmacovigilance activities in clinical studies as appropriate. A targeted follow-up questionnaire is utilized in the postmarketing setting. Additional pharmacovigilance activities (see EU-RMP Part III) are implemented to monitor this risk. Information relating to serious cardiovascular events of MI and stroke is described in the Contraindications (SmPC Section 4.3), in the Special Warnings and Precautions for Use (SmPC Section 4.4) and in the Undesirable effects sections (SmPC Section 4.8). Additional risk minimization measures are listed in EU-RMP Part V.
Public health impact	Identified as an unfavorable effect, but the impact on public health cannot currently be estimated due to the low number of reported events.

Table Part II–16: Important identified risk: serious cardiovascular events of myocardial infarction and stroke

AHA=American Heart Association; CHD=coronary heart disease; CI=confidence interval;
COX=cyclooxygenase; CV=cardiovascular; DCRI=Duke Clinical Research Institute; MACE=major adverse cardiac events; MedDRA=Medical Dictionary for Regulatory Activities; MI=myocardial infarction; N=number; NSAIDs=nonsteroidal anti-inflammatory drugs; PMO=postmenopausal osteoporosis; QM=once every month; QW=every week; RR=relative risk; SmPC=summary of product characteristics; SMQ=standardized MedDRA query; TIMI=Thrombolysis in Myocardial Infarction study group.

Important potential risks

Important potential risks with romosozumab treatment are characterized in the tables below.

Table Part II–17: Important potential risk: osteonecrosis of the jaw

MedDRA terms	Preferred terms: Exposed bone in jaw, Osteonecrosis, Osteonecrosis of jaw, Primary sequestrum, Secondary sequestrum, Sequestrectomy, Tertiary sequestrum, abscess jaw, Abscess oral, Alveolar osteitis, Bone debridement, Bone disorder, Bone erosion, Bone fistula, Bone infarction, Chronic recurrent multifocal osteomyelitis, Dental fistula, Dental necrosis, Gingival abscess, Gingival erosion, Gingival ulceration, Jaw disorder, Jaw lesion excision, Jaw operation, Loose tooth, Maxillofacial operation, Necrosis, Noninfective gingivitis, Oral cavity fistula, Oral surgery, Oroantral fistula, Ostectomy, Osteitis, Osteomyelitis, Osteomyelitis acute, Osteomyelitis chronic, Osteomyelitis drainage, Pain in jaw, Periodontal destruction, Periodontal inflammation, Periodontal operation, Periodontitis
Potential mechanisms	The etiology of osteonecrosis of the jaw (ONJ) is currently unknown; however, romosozumab decreases bone resorption and as such its use could theoretically lead to an inability to repair bone defects, such as after invasive dental procedures or dental fracture, which by itself or by additional unknown mechanisms may be a risk factor for ONJ. However, in an ONJ rat model, utilizing ligature-induced experimental periodontitis, sclerostin inhibition enhanced structural bone parameters but did not induce ONJ-like lesions.
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derive from clinical studies and pharmacoepidemiological background prevalence rates. This risk was detected in the clinical trial setting.

Table Part II–17: Important potential risk: osteonecrosis of the jaw

Characterization of the risk	<u>Frequency with 95% CI</u> In the pooled studies for 12-month, placebo-controlled osteoporosis safety analysis set (N=3858 for the romosozumab group and N=3770 for the placebo group), the subject incidence of adjudicated positive ONJ adverse events was < 0.1% (1 of the 3858 study participants) in romosozumab-treated study participants and 0.0% in placebo-treated study participants. In the alendronate-controlled Study 20110142, during the 12-month double-blind period, there were no adjudicated positive ONJ adverse events. The positively adjudicated ONJ adverse event and impaired healing, which was described as a delay of gum healing after dental treatment in a romosozumab subject approximately 13 months after initial dose, was reported from the pooled 12-month, placebo-controlled osteoporosis safety analysis set as serious; it is unresolved. In Study 20110142, 1 positively adjudicated adverse event of ONJ was reported as nonserious and 1 positively adjudicated adverse event ONJ was reported as serious. <u>Severity</u> The 1 case of positively adjudicated ONJ in pooled 12-month, placebo-controlled osteoporosis safety analysis set was reported as grade 1 (mild) in severity. In the alendronate-controlled Study 20110142, there was 1 case of positively adjudicated ONJ in the alendronate/alendronate group, reported as grade 2. There was 1 case of positively adjudicated ONJ in the romosozumab/alendronate group, reported as grade 3. <u>Reversibility</u> It is possible to recover from ONJ with the appropriate treatment. <u>Long-term outcomes</u> No long-term effect is expected after resolution of ONJ. <u>Impact on quality of life</u> Surgical treatment may be required; bone resection is not usually necessary.
Risk groups or risk factors	Risk factors include bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, 2006; Ruggiero et al, 2006).
Preventability	Preventive measures include preventive dentistry prior to treatment with romosozumab, good oral hygiene, and routine dental checks while receiving romosozumab. Patients who are suspected of having or who develop ONJ while on romosozumab should receive care by a dentist or an oral surgeon. Discontinuation of romosozumab therapy should be considered based on individual benefit-risk assessment.

Table Part II–17: Important potential risk: osteonecrosis of the jaw

Impact on the risk-benefit balance of the product	Risk of ONJ has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities are implemented to monitor this risk. Independent adjudication for events of ONJ is carried out as part of routine pharmacovigilance activities in clinical studies as appropriate. Information relating to ONJ is described in the Special Warnings and Precautions for use (SmPC Section 4.4). Further information is also provided in the Patient Information Leaflet. Additional risk minimization measures are listed in EU-RMP Part V.
Public health impact	Identified as an unfavorable effect, but no significant public health impact is expected.

CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; N=number; ONJ=osteonecrosis of the jaw; SmPC=summary of product characteristics

Table Part II–18: Important potential risk: atypical femoral fracture

MedDRA terms	Preferred terms: Atypical femur fracture, Atypical fracture, Femur fracture
Potential mechanisms	Prolonged suppression of bone turnover may be associated with increased risk of AFF, but the pathogenesis remains unclear. The causes of AFF are likely multi-factorial. Based on nonclinical studies of bisphosphonates, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF (Shane et al, 2010).
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derive from clinical studies and pharmacoepidemiological background prevalence rates. This risk was detected in the clinical trial setting.

Table Part II–18: Important potential risk: atypical femoral fracture

Characterization of the risk	<u>Frequency with 95% CI</u> In the pooled studies for 12-month, placebo-controlled osteoporosis safety analysis set (N=3858 for the romosozumab group and N=3770 for the placebo group), the subject incidence of adjudicated positive AFF adverse events was <0.1% in romosozumab-treated study participants and 0.0% in placebo-treated study participants. In the alendronate-controlled Study 20110142, during the 12-month double-blind period, there were no adjudicated positive AFF adverse events. The adjudicated positive AFF adverse event reported in a romosozumab subject in the pooled 12-month, placebo-controlled osteoporosis safety analysis set was serious and resolved. <u>Severity</u> The adjudicated positive AFF adverse event was reported as a right femur shaft fracture grade 3 (severe). During the open-label treatment period, the 3 events in the romosozumab/alendronate group were reported as grade 3. <u>Reversibility</u> It is possible to recover from AFF with the appropriate treatment. <u>Long-term outcomes</u> As with other hip fractures, AFF can cause short-term or long-term disability. <u>Impact on quality of life</u> Surgery is generally required.
Risk groups or risk factors	Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al, 2012; Giusti et al, 2011). AFFs have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, and hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, 2010).
Preventability	No data are currently available on potential measures to prevent AFF.
Impact on the risk-benefit balance of the product	Risk of AFF has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine pharmacovigilance activities are implemented to monitor this risk. Independent adjudication for events of AFF is carried out as part of routine pharmacovigilance activities in clinical studies as appropriate. Information relating to AFF is described in the Special Warnings and Precautions for use (SmPC Section 4.4). Further information is also provided in the Patient Information Leaflet.
Public health impact	Identified as an unfavorable effect, but no significant public health impact is expected.

AFF=atypical femoral fracture; CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; N=number; SmPC=summary of product characteristics

Table Part II–19: Important potential risk: cardiac arrhythmias

MedDRA terms	MedDRA narrow SMQ: Cardiac Arrhythmia																											
Potential mechanisms	The potential mechanism is unknown. Nonclinical studies have found no evidence of a plausible association between sclerostin antibody and an increase risk of cardiac arrhythmias. There is no evidence in the literature of an association between sclerostin antibody and cardiac arrhythmia.																											
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derived from clinical studies and postmarketing cases. This risk was detected in the postmarketing setting (review of case reports within Eudravigilance and signal detection based on disproportionality) There is insufficient evidence to date to establish a causal relationship between the occurrence of cardiac arrhythmia and the use of romosozumab. However, while cofounding factors were reported in most of the cases which precluded an assessment of a causal relationship, some events were reported with a close temporal relationship. Furthermore; while an imbalance of MACE was observed within the pivotal Phase III study (Study 20110142), the precise etiology has yet to be elucidated and may be related to cardiac arrhythmia. Thus, the risk of cardiac arrhythmia will be considered as an important potential risk.																											
Characterization of the risk	<u>Frequency with 95% CI</u> In the pooled studies for 12-month, placebo-controlled osteoporosis safety analysis set (N=3858 for the romosozumab group and N=3770 for the placebo group), the incidence of adverse events potentially related to cardiac arrhythmias was 1.7% in romosozumab treated study participants and 1.8% in placebo treated study participants (RR [95% CI] = 0.98 [0.70, 1.37]). In the alendronate-controlled Study 20110142 (N=2040 for the romosozumab 210mg QM group and N=2014 for the alendronate 70mg QW group), the incidence of adverse events potentially related to cardiac arrhythmias was 2.2% in romosozumab-treated study participants and 2.2% in alendronate-treated study participants (RR [95% CI] = 1.01 [0.67, 1.52]), during the 12-month, double-blind period. Severity <table><tr><th colspan="3">Pooled studies for 12-month placebo-controlled osteoporosis</th></tr><tr><th></th><th>Placebo (N = 3770) n (%)</th><th>Romosozumab 210mg QM (N = 3858) n (%)</th></tr><tr><td colspan="3">Seriousness</td></tr><tr><td>All AEs</td><td>66 (1.8)</td><td>66 (1.7)</td></tr><tr><td>SAEs</td><td>11 (0.3)</td><td>9 (0.2)</td></tr><tr><td colspan="3">Severity</td></tr><tr><td>Mild</td><td>36 (1.0)</td><td>35 (0.9)</td></tr><tr><td>Moderate</td><td>30 (0.8)</td><td>29 (0.8)</td></tr><tr><td>Severe</td><td>3 (<0.1)</td><td>5 (0.1)</td></tr></table>	Pooled studies for 12-month placebo-controlled osteoporosis				Placebo (N = 3770) n (%)	Romosozumab 210mg QM (N = 3858) n (%)	Seriousness			All AEs	66 (1.8)	66 (1.7)	SAEs	11 (0.3)	9 (0.2)	Severity			Mild	36 (1.0)	35 (0.9)	Moderate	30 (0.8)	29 (0.8)	Severe	3 (<0.1)	5 (0.1)
Pooled studies for 12-month placebo-controlled osteoporosis																												
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Moderate	30 (0.8)	29 (0.8)																										
Severe	3 (<0.1)	5 (0.1)																										

Table Part II–19: Important potential risk: cardiac arrhythmias

	Life-threatening	0 (0.0)	3 (<0.1)
	Fatal	0 (0.0)	0 (0.0)

N = Number of study participants who received ≥ 1 dose of investigational product.

n = Number of study participants reporting ≥ 1 event.

12-month placebo-controlled osteoporosis safety analysis set includes study participants who were randomized and received at least 1 dose of romosozumab 210 mg QM or placebo in Studies 20070337, 20060326, 20101291 and 20110174.

Cardiac Arrhythmias includes only treatment-emergent adverse events as a result of a narrow search/scope in SMQ.

Program: /userdata/stat/amg785/safety/RMP/analysis/2021_eu/tables/t-rmp-risk-freq-ca-osteo4.sas

Output: t-08-501-001-rmp-risk-freq-ca-osteo4.rtf (Date Generated: 26MAY21:19:01:14)

Source: css.adsl, css.adae, eoicss.cardiac_arrhythmias

In the pooled studies for 12-month, placebo-controlled osteoporosis safety analysis, of the 66 cardiac arrhythmias reported in the romosozumab group, most were reported as mild to moderate in severity, 5 were severe and 3 were life-threatening.

In the alendronate-controlled Study 201101426, of the 45 cardiac arrhythmias in the romosozumab group, most were reported as mild to moderate in severity, 4 were severe, 1 was life-threatening and 1 was fatal.

Reversibility

In the pooled studies for 12-month, placebo-controlled osteoporosis safety analysis set, 8 of the 9 serious cardiac arrhythmias in the romosozumab group resolved, and no fatal cardiac arrhythmia was reported.

In the alendronate-controlled Study 201101426 of the 9 serious cardiac arrhythmias in the romosozumab group resolved, and 1 fatal event was reported. The fatal event of ventricular tachycardia occurred in a PPD-year-old PPD patient who developed a MI and subsequent ventricular tachycardia approximately 3 weeks after initiation of romosozumab. The event of ventricular tachycardia was reported as not related by the investigator. The event of ventricular tachycardia appears to have developed as a complication of the concurrent MI in this subject. Multiple cardiovascular risk factors are reported for the event of MI such as history of PPD.

Postmarketing data

A total of 52 postmarketing cases with 54 events of cardiac arrhythmias were reported up to 07 Jan 2021 (DLP of the cumulative review). The post-marketing reporting rate for arrhythmias was 0.47 per 1000 patient-years. The majority (42 of 52) of the cases were reported from Japan with a reporting rate of 0.43 per 1000 patient-years. Of note, the vast majority of exposure was in Japan. Median age at event in those 52 cases was 80 years. The events with the PT of Arrhythmia (20 of 54) and Atrial fibrillation (17 of 54) were the most frequently reported. Assessment of the individual cases found that most either had insufficient information on which to base a meaningful medical causality assessment or were confounded. One case was assessed as having an alternative etiology. While 2 cases reported a ‘positive dechallenge’, given the episodic nature of most cardiac arrhythmias and the PK of romosozumab, this does not

Table Part II–19: Important potential risk: cardiac arrhythmias

	provide meaningful evidence for causality attribution. No cases were considered possibly related to romosozumab. <u>Long-term outcomes</u> The clinical spectrum of cardiac arrhythmia varies widely from asymptomatic ECG abnormalities to SCD. Death is a potential outcome of cardiac arrhythmias. Atrial fibrillation (most common sustained arrhythmia) is strongly associated with an approximately 3 to 5-fold increased risk of stroke, consequently resulting to higher morbidity and mortality (Benjamin et al, 1998) <u>Impact on quality of life</u> Cardiac arrhythmias vary greatly in severity. For severe disease, patients may be hospitalized for treatment, and disability or death may occur.
Risk groups or risk factors	An analysis of real-world data in the USA, as per the first interim report of the FDA postmarketing requirement, revealed that a greater proportion of women with PMO exposed to romosozumab compared to other osteoporosis medications were older and had important comorbidities (eg, COPD, diabetes, hyperlipidemia, hypertension, and smoking habits) and pre-existing arrhythmia. These constitute strong predisposing risk factors for the risk of cardiac arrhythmia among romosozumab users
Preventability	No preventive measures are known.
Impact on the risk-benefit balance of the product	Risk of cardiac arrhythmias has been considered in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine and additional pharmacovigilance activities are implemented to monitor this risk (see EU-RMP Part III).
Public health impact	No significant public health impact is expected.

CI=confidence interval; COPD= chronic obstructive pulmonary disease; DLP= data lock point; ECG=electrocardiogram; FDA= Food and Drug Administration; MedDRA=Medical Dictionary for Regulatory Activities; MACE=major adverse cardiac events; MI=myocardial infarction; PMO=postmenopausal osteoporosis; QM=once every month; QW=every week; PK=pharmacokinetics; PT= Preferred Term; RR=relative risk; SCD=sudden cardiac death; SMQ=standardized MedDRA query; TEAE= treatment-emergent adverse event

SVII.3.2 Presentation of the missing information

Osteoporosis rebound effects

Evidence source:

Studies 20110142, 20070337 and 20110174:

These pivotal Phase 3 studies had an exposure of ~5800 study participants to romosozumab 210mg QM. A total of 761 study participants discontinued romosozumab treatment during the 12-month treatment period of the studies. Of these 761 study participants, 279 study participants had follow-up assessments while the remaining 482 study participants had either withdrawn consent, died or were lost to follow-up. Of the 279 study participants, a total of 125 study participants were identified as having discontinued romosozumab treatment during the 12-month treatment period who either experienced one or multiple fractures or had a percentage change in BMD leading to a BMD lower than their initial baseline for any anatomical site.

Of these 125 study participants:

- Eighty-nine study participants had a percentage change in BMD at any anatomical site fall below their initial baseline within 12 months after discontinuation (mean % change in BMD below baseline was -2.1%; range of -0.14 to -9.9%)
- Three study participants experienced a fracture within 12 months after discontinuation (2 study participants in 20110142 and 1 subject in 20070337). In all cases the fracture was a single morphometric vertebral fracture; there were no cases of multiple vertebral fractures. Bone turnover markers were not available in these study participants. Of these 3 study participants (n=2 for which BMD assessment was available), only one subject had a BMD fall below her initial baseline within the 12 months after discontinuation (interestingly this subject only received 1 dose of romosozumab). For this one subject, the largest percent change below baseline was -4% at the femoral neck.

Study 20060326:

In this supportive Phase 2 study, 52 study participants received romosozumab 210mg QM for 24 months, with a total of 6 study participants identified as having discontinued treatment during the 24-month treatment period. Of these 6 study participants:

- Three study participants had a BMD at any anatomical site fall below their initial baseline within 12 months after discontinuation (mean % change in BMD below baseline was -1.8%, range of -0.14 to -4.8%).
- None of the 6 study participants experienced a fracture within 12 months after discontinuation.

Additionally, 20 study participants received romosozumab 210mg QM for 24 months followed by placebo treatment for 12 months. Of these 20 study participants:

- Ten study participants had a BMD at any anatomical site fall below their initial baseline upon the completion of the 24-month romosozumab treatment period followed by the 12-month placebo treatment period (mean % change in BMD below baseline was -2.5%, range of -0.14 to -9.1%).
- One subject experienced a tibia/fibula fracture attributed to a fall. This subject also had a BMD fall below her initial baseline after the 36-month treatment period (for this subject the largest percent change was -0.2% below baseline at the total hip). In this subject, during the placebo treatment period, sCTX increased by 86%.

Collectively across the exposed population in the studies described, few study participants (4 [<1%]) experienced a fracture within the 12-month observation period following the discontinuation of romosozumab and no cases of multiple vertebral fractures were observed. Of these 4 study participants, 2 had a BMD fall below their initial baseline.

Nonclinical data:

Weekly subcutaneous injection of romosozumab at 30mg/kg to aged bone-depleted ovariectomized cynomolgus monkeys for 26 weeks followed by a 26-week treatment-free period resulted in either partial or full reversal of the romosozumab treatment-related changes in parameters assessing bone mass, bone structure and biomechanical strength. No evidence of a rebound effect was observed.

Anticipated risk/consequences of the missing information:

Increased risk of fractures as compared to the baseline following discontinuation of romosozumab therapy without transition to antiresorptive treatment.

Part II Module SVIII Summary of the safety concerns

Table Part II–20: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity Immunogenicity (development of antibodies to romosozumab) Hypocalcemia Serious cardiovascular events of myocardial infarction and stroke
Important potential risks	Osteonecrosis of the jaw Atypical femoral fracture Cardiac arrhythmias
Missing information	Osteoporosis rebound effects

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for safety concerns: targeted follow-up questionnaires are utilized in the postmarketing setting for the important identified risk of serious cardiovascular (CV) events of MI and stroke and for the important potential risk of cardiac arrhythmias. The specific follow-up questionnaires are enclosed in EU-RMP [Part VII Annex 4](#).
- Other forms of routine pharmacovigilance activities for osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and serious cardiovascular events of MI and stroke: ongoing adjudication of potential serious adverse events reported in clinical studies as appropriate. Adjudications Manuals for ONJ, AFF, and serious cardiovascular events of MI and stroke are described in [Module 5.3.5.3](#) of the Integrated Summary of Safety.

III.2 Additional pharmacovigilance activities

Additional pharmacovigilance activities are conducted in form of post-approval safety studies:

1. Adherence to the risk minimization measures (RMM) (OP0005)
2. Characterization of CV events (with an additional focus on cardiac arrhythmias) in real world conditions to augment the data from the interventional trials (OP0004)

As further described below, a total of 2 specific PASS (observational database studies using a multi-database approach) are conducted to address the key areas of RMM adherence and important risks.

Table Part III–1: Overview of the ongoing romosozumab EU PASS studies

Objective	PASS	Description	Study type
RMM effectiveness	PASS #1 (OP0005)	Adherence to RMM PASS	Observation multi-database
CV events including cardiac arrhythmias	PASS #2 (OP0004)	CV risk PASS	Observation multi-database

CV=cardiovascular; PASS=post authorization safety study; RMM=risk minimization measures

III.2.1 European non-interventional PASS for romosozumab by the **CCI**

Additional pharmacovigilance activities are conducted in the form of 2 observational database studies using similar data structure and multi-database approach. For further clarity, the RMM adherence related PASS is separated from the CV risk PASS.

Separate studies are conducted due to differences concerning the matching strategy in the comparative assessment and outcome validation. These run in parallel and will therefore not

incur any delay in the reporting of such data. A summary of the key information for the 2 studies is presented below.

European non-interventional PASS related to adherence to the risk minimization measures for romosozumab by the CCI (OP0005)

– Study short name and title:

European Non-interventional Post-Authorization Safety Study related to adherence to the risk minimization measures for romosozumab by the CCI

– Rationale and study objectives:

Serious cardiovascular events of MI and stroke are considered as important identified risk for romosozumab. Based on the totality of the evidence, the Applicant proposed RMM to ensure favorable benefit-risk balance of romosozumab use. Accordingly, a prospective non-interventional PASS was initiated to describe adherence to the RMM in real-world conditions. The objective of the study is to evaluate adherence to the RMM in the product information based on analysis of the utilization patterns and estimation of compliance with contraindications and target indication amongst incident romosozumab users in real-world conditions.

– Study design:

Prospective non-interventional study with a multi-national multi-database approach (population-based cohort study in users of romosozumab or other osteoporosis medication) through the CCI.

Adherence to the RMM in the product information is planned to be studied by estimating the compliance with contraindications and target indication amongst incident romosozumab users and analyzing the utilization patterns.

Planned outcome measures are listed below.

- *Incidence and prevalence of romosozumab use*

Furthermore, subgroup analysis will be performed with respect to prevalence in the below groups:

- Prevalence of patients with history of stroke or MI within romosozumab users (compliance with contraindication)
- Prevalence of compliance with restriction of indication within romosozumab users
- *Treatment compliance and persistence in romosozumab users.*

Baseline characteristic of the above patient groups (all users, contraindication group, restriction of indication group) will be also presented to provide insight in the key patient characteristics eg, demography, osteoporosis related history and cardiovascular risk factors. Based on selected baseline characteristic (country, age, medical history), stratified estimates of the considered drug utilization measures will be presented as well.

– Study population:

New users of romosozumab will be identified. In order to establish a comprehensive understanding of romosozumab user in the real-world practice no exclusion criteria will be considered.

– Milestones:

The RMM adherence PASS Protocol provides further details on the study. The PASS protocol was approved by EMA on 17 Sep 2020 (EMA/H/C/004465/MEA/001) and registered in the EU PASS register (EUPAS35956). The latest approved version of protocol is submitted with this updated version of the RMP. Data collection started on 01 Oct 2020 and will be finalized after the final comparative analysis of the CV PASS is completed. Interim descriptive reports were generated and submitted every six months during the first two years of the study and thereafter annual descriptive reports are generated and submitted to the regulatory authorities. These reports will be followed with the final study report which is estimated to be available by Dec 2026 after marketing authorization.

For further details on the PASS protocol amendments, please see EU RMP [Part VII](#).

European non-interventional PASS related to serious cardiovascular events of MI and stroke and all-cause mortality for romosozumab by the CCI [REDACTED] (OP0004)

– Study short name and title:

European non-interventional post-authorization safety study related to serious cardiovascular events of MI and stroke and all-cause mortality for romosozumab by the CCI [REDACTED].

– Rationale and study objectives:

Serious cardiovascular events of MI and stroke are considered as important identified risk for romosozumab. Cardiac arrhythmias are considered as important potential risk for romosozumab.

The objective of the non-interventional PASS is to characterize the serious cardiovascular events (MI, stroke, all-cause, cardiovascular death and cardiac arrhythmias) in romosozumab users and in comparable patients receiving alternative osteoporosis medications. Events in scope were identified with previously validated algorithms by the CCI [REDACTED] members.

– Study design:

Prospective non-interventional study with a multi-national multi-database approach (population-based cohort study in users of romosozumab or other osteoporosis medication) through the CCI [REDACTED].

The study will report cardiovascular event (stroke, MI, death including cardiovascular death and cardiac arrhythmias) incidence in romosozumab users and in comparable patients receiving other osteoporosis therapies. Descriptive cardiovascular event incidence information will be generated by predefined strata to supplement signal detection (ie, by age, post-fracture, no cardiovascular history, cardiovascular risk factors, etc). Furthermore,

exploration of the predictive risk factors of cardiovascular events in patients receiving romosozumab will be implemented.

A propensity-matched cohort study will be undertaken for the proposed comparative safety analyses to investigate the risk of cardiovascular events including cardiac arrhythmias in new users of romosozumab compared to new users of other osteoporotic medications.

The study population will be selected from members of the CCI [REDACTED].

– Study population:

Adult women newly exposed to romosozumab in line with the target population (postmenopausal women with severe osteoporosis at high risk of fracture without a history of MI or stroke) or other osteoporosis medications (oral bisphosphonates [alendronate, risedronate, ibandronate], zoledronate, denosumab, teriparatide).

Exploration of additional data sources and analysis:

To enhance the completeness of identification of romosozumab users and the monitoring of CV events, the feasibility of conducting the PASS in European populations fully covered through nationwide healthcare databases with consistent reimbursement rules, access to health care, and medical coding systems will also be explored. In addition to the SNIIRAM database that covers 98% of the French population already included in the study, the Applicant will also evaluate the option of including Nordic countries, with healthcare databases covering about the same percentage of the population (~98%) and will implement if feasible.

If feasible, these populations will be analyzed separately within the PASS and will facilitate the implementation of the planned subgroup analyses providing a more complete population-based monitoring of the CV risk.

Additionally, the Applicant will also evaluate the opportunity to integrate existing European high-quality, population-based registries of CV events into the current PASS. This will enable a more accurate control of bias in the comparison between patients prescribed romosozumab and patients treated with currently available therapies for osteoporosis and thus minimize channeling bias. Furthermore, the quality of the assessment of CV outcomes will be enhanced by the registry validation procedures. Cardiovascular registries in Sweden and in other European countries are currently being evaluated. Implementation of this will be dependent on the willingness of the relevant registries to participate.

In designing the above described enhancements of the PASS, it is aimed to cover large enough study population to provide a sufficient sample size to estimate the study parameters with adequate power and thus precision.

– Milestones:

The PASS protocol was approved by EMA on 17 Sep 2020 (EMA/H/C/004465/MEA/002) and registered in the EU PASS register (EUPAS35881). The latest approved version of protocol is submitted with this updated version of the RMP. Interim descriptive reports are generated and submitted every six months during the first two years of the study to the Agency and thereafter annual descriptive reports are generated and submitted to the regulatory authorities. As soon as the pre-defined study size for the comparative assessment

is reached (with follow-up time for at least 12 months) the interim comparative report will be shared alongside of the annual descriptive reports (year 5 [2025] after marketing authorization). These reports will be followed with the final study report which is estimated to be available by Dec 2026 after marketing authorization when all patients fulfil their maximum follow-up period of 24 months.

Milestones for activities which are to be evaluated for feasibility will be determined once the evaluation is complete.

For further details on the PASS protocol amendments, please see EU RMP [Part VII](#).

III.3 Summary Table of additional Pharmacovigilance activities

The summary of ongoing and planned additional pharmacovigilance activities is provided in [Table Part III–2](#).

Table Part III–2: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
European non-interventional PASS related to the adherence to the risk minimization measures by the CCI (OP0005) Ongoing	To study the adherence to the risk minimization measures in the product information by estimating the compliance with contraindications and target indication amongst incident romosozumab users, and analyzing the utilization patterns.	Serious cardiovascular events of myocardial infarction and stroke	• Final PASS protocol • Interim descriptive reports • Annual descriptive reports until study completion - Final study report	• Final PASS protocol approved by EMA on 17 Sep 2020. • Interim descriptive reports are generated and submitted every 6 months during the first 2 years of the study. • Annual descriptive reports are generated and submitted starting in year 3 (2023) after marketing authorization. • Final study report is estimated to be available by Dec 2026.
European noninterventional PASS related to serious	The main objective is to evaluate potential differences in terms of serious	Serious cardiovascular events of myocardial	• Final PASS protocol	• Final PASS protocol approved by EMA on 17 Sep 2020.

Table Part III–2: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
cardiovascular adverse events of myocardial infarction and stroke, and all-cause mortality for romosozumab by the CCI (OP0004) Ongoing	cardiovascular adverse events including cardiac arrhythmias between romosozumab and currently available therapies used in comparable patients in real-world conditions.	infarction and stroke Cardiac arrhythmias	• Interim descriptive reports • Annual descriptive reports • Interim comparative report • Final study report	• Interim descriptive reports are generated and submitted every 6 months during the first 2 years of the study. • Annual descriptive reports are generated and submitted starting in year 3 (2023) after marketing authorization. • Interim comparative report is estimated in year 5 (2025) after marketing authorization. • Final study report is estimated to be available by Dec 2026.

EMA= European Medicines Agency; PASS=post-authorization safety study.

PART IV PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed postauthorization efficacy studies that are conditions of the marketing authorization or that are specific obligations for romosozumab.

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 Routine Risk Minimization Measures

Description of routine risk minimization measures by safety concern is presented in [Table Part V-1](#).

Table Part V-1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Hypersensitivity	Routine risk communication: SmPC Section 4.3 (Contraindications), Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects). Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for management after a clinically significant allergic reaction are included in SmPC Section 4.4. Other routine risk minimization measure: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2). Further information is also provided in the Patient Information Leaflet.
Immunogenicity (development of antibodies to romosozumab)	Routine risk communication: SmPC Section 4.8 (Undesirable effects) Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measure: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2).

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Hypocalcemia	Routine risk communication: SmPC Section 4.2 (Posology and method of administration), Section 4.3 (Contraindications), Section 4.4 (Special warnings and precautions for use), Section 4.8 (Undesirable effects). Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for prevention and monitoring of signs and symptoms of hypocalcemia are included in SmPC Section 4.4 and SmPC Section 4.2. No dose adjustment is required in patients with renal impairment (SmPC Section 4.2). Recommendation for monitoring of calcium levels in patients with severe renal impairment or receiving dialysis is included in SmPC Section 4.4. Other routine risk minimization measure: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2). Further information is also provided in the Patient Information Leaflet.
Serious cardiovascular events of myocardial infarction and stroke	Routine risk communication: SmPC Section 4.3 (Contraindications: history of myocardial infarction or stroke), Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for evaluation of the individual benefit-risk balance and discontinuation of treatment in patients who experience myocardial infarction and stroke are included in SmPC Section 4.4. Other routine risk minimization measure: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2). Further information is also provided in the Patient Information Leaflet.
Important potential risks	
Osteonecrosis of the jaw	Routine risk communication: SmPC Section 4.4 (Special warnings and precautions for use) Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for prevention, monitoring of signs and symptoms, and management of patients with osteonecrosis of the jaw are included in SmPC Section 4.4. Other routine risk minimization measure: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2). Further information is also provided in the Patient Information Leaflet.

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Atypical femoral fracture	Routine risk communication: SmPC Section 4.4 (Special warnings and precautions for use) Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for monitoring of signs and symptoms and management of patients with atypical femoral fracture are included in SmPC Section 4.4. Other routine risk minimization measure: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2). Further information is also provided in the Patient Information Leaflet.
Cardiac arrhythmias	Routine risk communication: None. Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other routine risk minimization measure: Recommendations for evaluation of the individual benefit-risk balance is included in SmPC Section 4.4 (Special warnings and precautions for use).
Missing information	
Osteoporosis rebound effects	Routine risk communication: None. Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation to transition to antiresorptive therapy following completion of romosozumab therapy is included in SmPC Section 4.2. Other routine risk minimization measure: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2).

SmPC=summary of product characteristics

V.2 Additional risk minimization measures

Additional risk minimization measures include educational materials for prescribers, patients and caregivers, to reinforce the key safety information in the SmPC and the Patient Information Leaflet (PIL) with the aim to further minimize the risks

V.2.1 Educational material

I Prescriber Guide

Objectives

To enhance awareness and educate prescribers about the important identified risks of serious cardiovascular events of MI and stroke and of hypocalcemia and important potential risk of ONJ, and the appropriate prevention, early diagnosis and adequate management of these events.

Rationale for the additional risk minimization activity

Romosozumab represents a new class of anti-osteoporotic treatment with a dual mode of action, for which initial treatment is recommended to be followed by an antiresorptive treatment. This educational tool is proposed to support a proper individual benefit-risk discussion, increase awareness and reinforce the importance of prevention, early recognition and appropriate management of these events.

Target audience and planned distribution path

The primary audience is healthcare professionals who are expected to prescribe romosozumab.

In addition to paper versions of the educational materials, they will also be made available through a dedicated website targeted to healthcare professionals. Healthcare professionals will be able to review and download the educational materials and order additional paper versions of the materials. The distribution path will be agreed at national level.

More details of educational material are provided in EU-RMP [Part VII Annex 6](#).

Plans to evaluate the effectiveness of the interventions and criteria for success

Adherence to the risk minimization measures in the product information is studied by analyzing the utilization patterns, estimating the compliance with contraindications and target indication amongst incident romosozumab users (behavioral process indicator of effectiveness).

Safety outcomes indicators will be measured in the other PASS (CV events) and routine pharmacovigilance will serve to measure the safety outcome indicators.

II Patient Alert Card

Objectives

To ensure that key information regarding romosozumab, the important identified risks of serious cardiovascular events of MI and stroke and of hypocalcemia and important potential risk of ONJ, as well as the prevention, early diagnosis and appropriate management of these events, is carried by the patient and/or caregiver at all times in a concise format. This can also be shown to non-osteoporosis healthcare professionals also treating the patient at any time, including in conditions of emergency.

Rationale for the additional risk minimization activity

Information on these risks is presented to further raise awareness and promote prevention, early diagnosis and adequate management of these events.

Target audience and planned distribution path

Patients (and/or their caregivers) who have been prescribed romosozumab are intended to keep this card with them at all times, so the information reaches the relevant healthcare professional as appropriate.

In addition to paper versions of the educational materials, healthcare professionals will be able to download a printed version of the Patient Alert Card (PAC) through a dedicated website targeted to healthcare professionals. The distribution path will be agreed at national level.

The distribution and use of the PAC will be further leveraged through connection with the Patient Support Program (PSP). This program will be implemented in all EU countries where

romosozumab will be marketed and is intended to support patients with their treatment. The PAC will be both included in the Patient Welcome Kit that will be provided to each patient by the physician at initial prescription and added to the PSP website with the possibility of downloading additional copies of the PAC.

Further, a nurse support telephone system will be implemented as part of the PSP in some countries (currently planned in UK, Ireland, Germany and Spain). The nurse will have a conversation with patient/caregivers.

- As to whether the PAC has been received, remind and encourage the patient to carry it at all times, and will respond to any further questions.
- Will collect information on the use and understanding of the PAC – this will provide evidence of effectiveness.

More details of educational material are provided in EU-RMP [Part VII Annex 6](#).

Plans to evaluate the effectiveness of the interventions and criteria for success

Adherence to the risk minimization measures in the product information is studied by analyzing the utilization patterns, estimating the compliance with contraindications and target indication amongst incident romosozumab users (behavioral process indicator of effectiveness).

Safety outcomes indicators will be measured in the other PASS (CV events) and routine pharmacovigilance will serve to measure the safety outcome indicators.

III Risk minimization impact of the educational materials with regard to the cardiovascular risk

Specifically for the risk of serious cardiovascular events of MI and stroke, the Prescriber Guide, in conjunction with the PAC, are expected to minimize the risk by:

- Enabling a rapid re-assessment of benefit-risk before maintaining romosozumab in case of a change in cardiovascular risk.
- Promoting early diagnosis and adequate management of cardiovascular events and hence reduce the severity of cardiovascular events if they would occur.

Preventing or reducing the probability of MI and stroke through facilitating appropriate selection of patients by means of a careful individual benefit-risk assessment before prescription.

V.2.2 Information letter on the cardiovascular risk

In order to increase awareness also in cardiologists and neurologists, who may be consulted, an information letter has been sent with key information on romosozumab, the cardiovascular risk, and a link to the abovementioned HCP website.

V.3 Summary of risk minimization measures

[Table Part V–2](#) provides a summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Hypersensitivity	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2 -Posology and method of administration). SmPC Section 4.3 (Contraindications), Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects). Further information is also provided in the PIL. Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: None
Immunogenicity (development of antibodies to romosozumab)	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2 - Posology and method of administration). SmPC Section 4.8 (Undesirable effects) Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: None

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hypocalcemia	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2 - Posology and method of administration). SmPC Section 4.2 (Posology and method of administration), Section 4.3 (Contraindications), Section 4.4 (Special warnings and precautions for use), Section 4.8 (Undesirable effects). All patients should receive vitamin D and calcium supplementation. No dose adjustment is required in patients with renal impairment (see SmPC Section 4.4 [for recommendations relating to monitoring of calcium] and SmPC Section 4.2). Further information is also provided in the PIL. Additional risk minimization measures: - Prescriber Guide - Patient Alert Card	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: None

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious cardiovascular events of myocardial infarction and stroke	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2 -Posology and method of administration). SmPC Section 4.3 (Contraindications), Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) Further information is also provided in the PIL. Additional risk minimization measures: - Prescriber Guide - Patient Alert Card - Information letter	Routine PhV activities beyond adverse reactions reporting and signal detection: ongoing adjudication of potential serious adverse events reported in clinical studies as appropriate. Targeted follow-up questionnaires are utilized in the postmarketing setting. Additional PhV activities: - European non-interventional PASS (OP0005) related to the adherence to the risk minimization measures by the CCI (effectiveness on behavior). - European non-interventional PASS (OP0004) related to serious cardiovascular events of myocardial infarction and stroke and all-cause mortality for romosozumab by the CCI.
Important potential risks		
Osteonecrosis of the jaw	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2 -Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). Further information is also provided in the PIL. Additional risk minimization measures: - Prescriber Guide - Patient Alert Card	Routine PhV activities beyond adverse reactions reporting and signal detection: ongoing adjudication of potential serious adverse events reported in clinical studies as appropriate. Additional PhV activities: None

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Atypical femoral fracture	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2 -Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). Further information is also provided in the PIL. Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: ongoing adjudication of potential serious adverse events reported in clinical studies as appropriate. Additional PhV activities: None
Cardiac arrhythmias	Routine risk minimization measures: Recommendations for evaluation of the individual benefit-risk balance is included in SmPC Section 4.4- (Special warnings and precautions for use). Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: A targeted follow-up questionnaire will be utilized in the postmarketing setting. Additional PhV activities: European non-interventional PASS (OP0004) related to serious cardiovascular events of myocardial infarction and stroke and all-cause mortality for romosozumab by the CCI

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Missing information		
Osteoporosis rebound effects	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis (SmPC Section 4.2 -Posology and method of administration). Recommendation to transition to antiresorptive treatment following completion of romosozumab treatment in SmPC Section 4.2 (Posology). Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detections: None. Additional PhV activities: None.

HCP=healthcare professional; PASS=post-authorization safety study; PhV=pharmacovigilance; PIL=Patient Information Leaflet; SmPC=summary of product characteristics.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR EVENITY (ROMOSUZUMAB)

This is a summary of the risk management plan (RMP) for EVENITY. The RMP details important risks of EVENITY, how these risks can be minimized, and how more information will be obtained about EVENITY's risks and uncertainties (missing information).

EVENITY's SmPC and its patient information leaflet (PIL) give essential information to healthcare professionals and patients on how EVENITY should be used.

This summary of the RMP for EVENITY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of EVENITY's RMP.

I The medicine and what it is used for

EVENITY is authorized for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture (see SmPC for the full indication). It contains romosozumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of EVENITY's benefits can be found in EVENITY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: <https://www.ema.europa.eu/en/medicines/human/EPAR/evenity>.

II Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of EVENITY, together with measures to minimize such risks and the proposed studies for learning more about EVENITY's risks, are outlined below.

Measures to minimize the risks identified for medicinal products include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of EVENITY, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that

immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of EVENITY is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of EVENITY are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of EVENITY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hypersensitivity Immunogenicity (development of antibodies to romosozumab) Hypocalcemia Serious cardiovascular events of myocardial infarction and stroke
Important potential risks	Osteonecrosis of the jaw Atypical femoral fracture Cardiac arrhythmias
Missing information	Osteoporosis rebound effects

II.B Summary of important risks

Summary of important risks

Important identified risk: hypersensitivity	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies. This risk was detected in the clinical trial setting.
Risk factors and risk groups	Known hypersensitivity to romosozumab and any of its excipients.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration).

Summary of important risks

	SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use) and SmPC Section 4.8 (Undesirable effects). Further information is also provided in the PIL. Additional risk minimization measures: None
Important identified risk: immunogenicity (development of antibodies to romosozumab)	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies prevalence rates. This risk was detected in the clinical trial setting.
Risk factors and risk groups	No risk groups or risk factors have been identified during the clinical studies.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.8 (Undesirable effects) Additional risk minimization measures: None
Important identified risk: hypocalcemia	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies prevalence rates. This risk was detected in the clinical trial setting.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance < 30mL/min), dialysis, and some medications.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.2 (Posology and method of administration), SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.8 (Undesirable effects). Recommendations for prevention and monitoring of signs and symptoms of hypocalcemia are included in SmPC Section 4.4 and SmPC Section 4.2. No dose adjustment is required in patients with renal impairment (SmPC Section 4.2). Recommendation for monitoring of calcium levels in patients with severe renal impairment or receiving dialysis is included in SmPC Section 4.4. Further information is also provided in the PIL.

Summary of important risks

	Additional risk minimization measures: Prescriber Guide and Patient Alert Card
Important identified risk: serious cardiovascular events of myocardial infarction and stroke	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies, and pharmacoepidemiological background prevalence rates. This risk has been detected based on an imbalance of myocardial infarction and stroke events between romosozumab and alendronate in 1 of the 2 pivotal fracture studies, the alendronate-controlled study, 20110142 in women. The imbalance resulted from small differences in terms of absolute subject numbers and absolute risk differences. No imbalance of cardiovascular events was observed in the larger placebo-controlled fracture study 20070337 in women. In study 20110174 in men, the differences in incidence of serious cardiac ischemic events and cerebrovascular events reported between the romosozumab group and placebo were less apparent; the absolute number of events was small. No evidence of any mechanistic association between sclerostin inhibition and atheroprogession or M-1 events was established based on the totality of nonclinical evidence including 2 recent studies evidence.
Risk factors and risk groups	The romosozumab osteoporosis development program was conducted in an older subject population who are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population. Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including anthracyclines, antipsychotic agents, nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors. Patients with a history of myocardial infarction or stroke have highest absolute risk of major adverse cardiac events.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.8 (Undesirable effects) Further information is also provided in the PIL. Additional risk minimization measures: Prescriber Guide, Patient Alert Card and information letter
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - European non-interventional post-authorization safety study related to the adherence to the risk minimization measures (effectiveness on behavior) by the CCI (OP0005). - European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke and all-cause mortality for romosozumab by the CCI (OP0004).

Summary of important risks

	See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies and pharmacoepidemiological background prevalence rates. This risk was detected in the clinical trial setting.
Risk factors and risk groups	Risk factors include bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use) Further information is also provided in the PIL. Additional risk minimization measures: Prescriber Guide and Patient Alert Card
Important potential risk: atypical femoral fracture	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies and pharmacoepidemiological background prevalence rates. This risk was detected in the clinical trial setting.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, and hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use) Further information is also provided in the PIL. Additional risk minimization measures: None
Important potential risk: cardiac arrhythmias	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derived from clinical studies and postmarketing cases.

Summary of important risks

	This risk was detected in the postmarketing setting (review of case reports within Eudravigilance and signal detection based on disproportionality) There is insufficient evidence to date to establish a causal relationship between the occurrence of cardiac arrhythmia and the use of romosozumab. However, while cofounding factors were reported in most of the cases which precluded an assessment of a causal relationship, some events were reported with a close temporal relationship. Furthermore, while an imbalance of MACE was observed within the pivotal Phase III study (Study 20110142), the precise etiology has yet to be elucidated and may be related to cardiac arrhythmia. Thus, the risk of cardiac arrhythmia will be considered as an important potential risk.
Risk factors and risk groups	An analysis of real-world data in the USA, as per the first interim report of the FDA postmarketing requirement, revealed that a greater proportion of women with PMO exposed to romosozumab compared to other osteoporosis medications were older had important comorbidities (eg, COPD, diabetes, hyperlipidemia, hypertension, and smoking habits) and pre-existing arrhythmia. These constitute strong predisposing risk factors for the risk of cardiac arrhythmia among romosozumab users.
Risk minimization measures	Routine risk minimization measures: Recommendations for evaluation of the individual benefit-risk balance is included in SmPC Section 4.4- (Special warnings and precautions for use). Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke and all-cause mortality for romosozumab by the CCI (OP0004). See Section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Osteoporosis rebound effects	
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). Recommendation of follow-on therapy in SmPC Section 4.2 (Posology). Additional risk minimization measures: None

HCP=healthcare professional; PASS=post-authorization safety study; PhV=pharmacovigilance; PIL=Patient Information Leaflet; SmPC=summary of product characteristics.

II.C Postauthorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are a condition of the marketing authorization or which are a specific obligation.

II.C.2 Other studies in post-authorization development plan

Additional pharmacovigilance activities include the followings:

- 1. European non-interventional post-authorization safety study related to adherence to the risk minimization measures for romosozumab by the CCI (OP0005)**

Study short name and title:

European non-interventional post-authorization safety study related to adherence to the risk minimization measures for romosozumab by the CCI .

Purpose of the study:

Adherence to the risk minimization measures in the product information is studied by estimating the compliance with contraindications and target indication amongst incident romosozumab users and analyzing the utilization patterns.

- 2. European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke, and all-cause mortality for romosozumab by the CCI (OP0004)**

Study short name and title:

European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke and all-cause mortality for romosozumab by the CCI .

Purpose of the study:

Serious cardiovascular events of myocardial infarction and stroke are considered an important identified risk and cardiac arrhythmias are considered an important potential risk for romosozumab.

The objective of the non-interventional post-authorization safety study is to characterize the serious cardiovascular events (myocardial infarction, stroke, all-cause, cardiovascular death and cardiac arrhythmias) in romosozumab users and in comparable patients receiving alternative osteoporosis medications. Events in scope were identified with previously validated algorithms by the CCI members.

PART VII ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

For the important identified risk of serious cardiovascular events of MI and stroke, targeted follow-up questionnaires are utilized in the postmarketing setting.

For the important potential risk of cardiac arrhythmias, a targeted follow-up questionnaire is utilized in the postmarketing setting.

The follow-up questionnaires are included below.

Reporter Information (Please indicate dates as DD-MON-YYYY)

Date of this report _____	The person completing this report is
Reporter's name: _____	☐ The Patient
Phone (include country code): _____	☐ A close contact of the Patient
Email: _____	☐ A family member of the Patient
Address: _____	☐ The Patient's physician
City _____	☐ Other health care professional (specify): _____
State/Province _____	
Postal Code: _____ Country _____	☐ Other (specify): _____

Section A. Patient Information (Please indicate dates as DD-MON-YYYY)

Initials _____ / Identifier _____	Age at the time of the event _____ years
Gender ☐ Female ☐ Male	Weight _____ lb _____ kg
<u>Medical History and/or Risk Factors</u>	<u>Medical History and/or Risk Factors (continued)</u>
☐ Hypertension -> ☐ controlled ☐ uncontrolled ☐ unknown	☐ Other prior cardiovascular event (specify): _____
☐ Diabetes -> ☐ controlled ☐ uncontrolled ☐ unknown	_____ Date: _____
☐ Prior stroke -> ☐ ischemic ☐ hemorrhagic ☐ unknown	☐ Hypercholesterolemia
Date of prior stroke _____	☐ Hyperlipoproteinemia ☐ LDL high ☐ HDL low
☐ Prior transient ischemic attack (TIA) Date _____	☐ Overweight ☐ Obese BMI: _____
☐ Prior MI (specify type) _____ Date _____	☐ Physically inactive
☐ Prior PCI ☐ Prior CABG	☐ Stress (describe): _____
☐ Heart failure ☐ Cardiac valve disease	☐ Alcohol use
☐ Coronary artery disease (CAD) ☐ Carotid artery disease	☐ Tobacco use
☐ Congenital heart disease ☐ Patent foramen ovale (PFO)	☐ Illicit drug use (specify): _____
☐ Aortic disease ☐ Peripheral artery disease	☐ Aminoglycoside antibiotics
☐ Prior thromboembolism	☐ Prior fracture(s) of (specify type): _____
☐ Family history of ischemic heart disease, MI, stroke, TIA, etc.	_____ and _____ (date)
(specify) _____	☐ Other relevant history (specify): _____
relationship to patient _____	
Cardiac arrhythmias:	
☐ Atrial fibrillation ☐ Ventricular tachycardia	☐ Bradyarrhythmia (specify the etiology, if known) _____
☐ Atrial flutter ☐ Ventricular fibrillation	☐ Premature Ventricular Complexes (PVC)
☐ Paroxysmal supraventricular tachycardia (PSVT)	☐ Torsades de Pointes
☐ Bundle branch block ☐ Wolff-Parkinson-White syndrome	☐ Sick sinus syndrome
☐ Sinus tachycardia ☐ Prolonged QT interval	
☐ Other (specify) _____	

Section C. Romosozumab Exposure Information (prior to MI event)

Indication ☐ Postmenopausal osteoporosis ☐ Male osteoporosis ☐ Other (specify): _____ ☐ Don't know	Total number of doses received PRIOR to the event _____ First dose (Month 1) administered on _____ Last dose PRIOR to event onset was on _____ (Month # _____)
Dose, Route, Frequency ☐ 210 mg, SC, once every month (up to 12 doses) ☐ Other (specify) _____ ☐ Don't know	Action taken SPECIFICALLY for the reported event ☐ None, Romosozumab dosing continued, administered on _____ (dates) ☐ Romosozumab dose(s) skipped Number of doses missed _____ Dosing resumed on _____ (date) ☐ Romosozumab was discontinued on _____ (date) and the final dose was administered on _____ (date) ☐ Not applicable. Romosozumab held or stopped PRIOR to onset of the event due to _____
Expiration Date _____	Lot / Batch # _____ (check ☐ if not known)

Section D. Past and Current medications

List medications that the patient was taking at the time that the event occurred. Please also include recently administered medications that may be relevant to the reported event such as cardiovascular medications or medications with cardiovascular side effects, including NSAIDs.

Drug	Daily Dose, frequency and route of administration	Therapy Dates start/stop (dd/mm/yyyy)	Total #of doses received	Indication

Section E. Event Information (Please indicate dates as DD-MON-YYYY)

Diagnosis _____	Date Event Started _____																
Signs and Symptoms (check all that apply, include start date if different than above) <table><tr><td>☐ Sudden chest pain</td><td>☐ Nausea</td><td>☐ Palpitations</td><td>☐ Anxiety or feeling of impending doom</td></tr><tr><td>☐ Back, neck, or jaw pain</td><td>☐ Vomiting</td><td>☐ Light-headedness</td><td>☐ Headache</td></tr><tr><td>☐ Shortness of Breath</td><td>☐ Indigestion</td><td>☐ Dizziness</td><td>☐ Change in level of consciousness</td></tr><tr><td>☐ Weakness or fatigue</td><td>☐ Sweating</td><td>☐ Syncope</td><td>☐ Other symptoms (specify) _____</td></tr></table>		☐ Sudden chest pain	☐ Nausea	☐ Palpitations	☐ Anxiety or feeling of impending doom	☐ Back, neck, or jaw pain	☐ Vomiting	☐ Light-headedness	☐ Headache	☐ Shortness of Breath	☐ Indigestion	☐ Dizziness	☐ Change in level of consciousness	☐ Weakness or fatigue	☐ Sweating	☐ Syncope	☐ Other symptoms (specify) _____
☐ Sudden chest pain	☐ Nausea	☐ Palpitations	☐ Anxiety or feeling of impending doom														
☐ Back, neck, or jaw pain	☐ Vomiting	☐ Light-headedness	☐ Headache														
☐ Shortness of Breath	☐ Indigestion	☐ Dizziness	☐ Change in level of consciousness														
☐ Weakness or fatigue	☐ Sweating	☐ Syncope	☐ Other symptoms (specify) _____														
Event Outcome ☐ Event is still ongoing ☐ Event resolved _____ (date) ☐ Outcome of event is unknown ☐ Event was fatal _____ (date) Autopsy performed: ☐ Yes ☐ No ☐ Unknown Autopsy results: _____																	

Section F. Myocardial Infarction (MI) Classification

☐ Spontaneous - MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in coronary artery

- ☐ Secondary - MI related to condition other than CAD e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH)
- ☐ Sudden Cardiac Death - Sudden unexpected cardiac death, including cardiac arrest, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block
- ☐ MI related to percutaneous coronary intervention (PCI) ☐ MI related to coronary artery bypass graft (CABG)
- ☐ MI related to stent thrombosis ☐ Type unknown

Section G. Evaluations, Diagnostic, & Laboratory Measures ☐ Check here if copy of the report(s) are included

Date	Type	Results / Findings			Date	Type	Results / Findings		
	Electrocardiogram					Chest x-ray			
	Echocardiography					Other consult report			
	Coronary angiography					Hospital record			
	Cardiac stress test					Other (specify)			
Date	Test performed	Results	Ref. range	Units	Date	Test performed	Results	Ref. Range	Units
	troponin _____ (specify type)					troponin _____ (specify type)			
	LD-1 / LD-2					WBC			
	Myoglobin					RBC			
	Creatine kinase (CK)					Hemoglobin			
	CK-MB					Hematocrit			
	CRP					Platelet count			
	hs-CRP					Mean platelet volume			
	BNP					Potassium			
	NT-proBNP					Sodium			
	PT					Calcium			
	PTT					Bicarbonate			
	INR					Phosphorus			
	AST					Magnesium			
	Alkaline phosphatase					Chloride			
	Direct/total bilirubin					Fasting glucose			
	Total cholesterol					Random glucose			
	LDL					Toxicology screen			
	HDL								
	VLDL								
	Triglycerides								

Section H. Medical Management

Initial treatment location		Required hospital admission ☐ Yes ☐ No	Admitted to intensive care unit (ICU) ☐ Yes ☐ No
☐ On-site (ambulance, rescue)		Admission date _____	ICU admission date _____
☐ Physician's office or clinic		Discharge date _____	ICU discharge date _____
☐ Emergency room		If dates unk, overall length of hospital stay	If dates unk, overall length of ICU stay
☐ Other (specify) _____		☐ less than 24 hours	☐ less than 24 hours
☐ Unknown		☐ _____ days	☐ _____ days
Treatment for the acute event			
☐ beta-adrenergic receptor blocker (specify) _____	Antiplatelet therapy	Anticoagulant therapy	
☐ nitroglycerin	☐ aspirin	☐ bivalirudin	
☐ oxygen	☐ clopidogrel	☐ heparin (unspecified)	
☐ cardiopulmonary resuscitation (CPR)	☐ abciximab	☐ heparin low molecular weight (LMWH)	
☐ external defibrillator	☐ prasugrel	☐ heparin unfractionated (UFH)	
☐ implantable cardioverter-defibrillator (ICD)	☐ eptifibatide	☐ fondaparinux	
☐ percutaneous coronary intervention (PCI)	☐ ticagrelor (P2Y ₁₂ inhibitor)		
☐ other (specify) _____	☐ tirofiban (glycoprotein IIb/IIIa inhibitor)		
Please list any prophylactic medications prescribed to patient after the acute event (for example, lipid lowering medications, anticoagulant therapy, etc.): _____			
Date of Report _____		Reporter's Name _____	
Patient's Initials _____ / Identifier _____			

Reporter Information (Please indicate dates as DD-MON-YYYY)

Date of this report _____	The person completing this report is
Reporter's name: _____	☐ The Patient
Phone (include country code): _____	☐ A close contact of the Patient
Email: _____	☐ A family member of the Patient
Address: _____	☐ The Patient's physician
City _____	☐ Other health care professional (specify): _____
State/Province _____	
Postal Code: _____ Country _____	☐ Other (specify): _____

Section A. Patient Information (Please indicate dates as DD-MON-YYYY)

Initials _____ / Identifier _____	Age at the time of the event _____ years
Gender ☐ Female ☐ Male	Weight _____ lb _____ kg

Section B. Romosozumab Exposure Information

Indication ☐ Postmenopausal osteoporosis ☐ Male osteoporosis ☐ Other (specify): _____ ☐ Don't know	Total number of doses received PRIOR to the event _____ First dose (Month 1) administered on _____ Last dose PRIOR to event onset was on _____ (Month # _____)
Dose, Route, Frequency ☐ 210 mg, SC, once every month (up to 12 doses) ☐ Other (specify) _____ ☐ Don't know Expiration Date _____ Lot / Batch # _____	Action taken SPECIFICALLY for the reported event ☐ Romosozumab dosing continued, administered on _____ (dates) ☐ Romosozumab dose(s) skipped Number of doses missed ____ Dosing resumed on _____ (date) ☐ Romosozumab was discontinued on _____ (date) and the final dose was administered on _____ (date) ☐ Romosozumab held or stopped PRIOR to onset of the event (check ☐ if not known)

Section C. Past and Current medications

List all medications that the patient was taking at the time that the event occurred. Please also include recently administered medications that may be relevant to the reported event.

Drug	Daily Dose, frequency and route of administration	Therapy Dates start/stop (dd/mm/yyyy)	Total #of doses received	Indication

Section D. Event Information (Please indicate dates as DD-MON-YYYY)

Diagnosis:
Date Event Started:
Additional Signs and Symptoms reported ☐ Fluttering ☐ Bradycardia ☐ Diaphoresis ☐ Weakness ☐ Jugular Venous distension ☐ Neck discomfort ☐ Angina ☐ Nausea ☐ Anxiety ☐ Unexplained recurrent palpitations ☐ Irregular heart beats ☐ Syncope ☐ Shortness of breath ☐ Hypotension ☐ Tachycardia ☐ Dizziness ☐ Loss of consciousness ☐ Rapid pulse ☐ Other symptoms:
Event Outcome ☐ Event is still ongoing ☐ Event resolved _____ (date) ☐ Outcome of event is unknown ☐ Event was fatal _____ (date) Autopsy performed: ☐ Yes ☐ No ☐ Unknown Autopsy results _____
Treatment/Intervention following the event ?

Section E. Patient's Medical History

☐ Genetic (congenital heart disease) ☐ Coronary artery disease ☐ Previous Heart Surgery : _____
☐ Patient experienced Arrhythmias prior start of Evenity - If yes, type of Arrhythmias : _____
☐ Congestive Heart Failure
☐ Other heart problems

☐ Obesity ☐ Hypertension ☐ Diabetes ☐ Hyperthyroidism ☐ Hypothyroidism ☐ Stress ☐ Asthma/COPD
☐ Digoxin Toxicity ☐ Rheumatoid arthritis ☐ Systemic lupus erythematosus ☐ Electrolyte imbalance
☐ Travel to high altitude ☐ Tobacco use ☐ Alcohol use ☐ Illicit drug use
☐ Herbal supplement ☐ OTC cough and cold medication ☐ Hyperlipidemia ☐ Covid-19 infection
☐ Other relevant medical history:

Section F. Laboratory Measures ☐ Check here if copy of the report(s) are included

	Results / Units	Reference/ Units	Date (DD-MON-YYY)
Blood Pressure			
Blood Gases			
PH			
PCO ₂			
PO ₂			
HCO ₃ ⁻			
Thyroid Function Test			
T3			
T4			
TSH			
Cardiac Biomarkers/Enzymes			
Myoglobin			
Troponin			
Creatine Kinase			
Complete Serum Chemistry & Electrolytes			
K ⁺			
Na ⁺			
Ca ⁺⁺			

Measured total calcium			
Measured total Albumin			
Corrected Calcium Level			
Phosphorus			
Mg ⁺⁺			
Cl ⁻			
Fasting glucose			
Random glucose			
Complete Blood Count			
WBC			
Hgb			
Hct			
RBC			
Iron			
Cholesterol panel			
HDL			
LDL			
Triglycerides			
Total Cholesterol			

Section G. Additional Relevant Findings (indicate & attached reports if available)

Additional Diagnosis	Relevant Findings	Date (DD-MON-YYY)
Electrocardiogram (EKG)		
Echocardiography (ECHO)		
Magnetic resonance imaging (MRI)		
Intra-cardiac electrophysiology study (EPS)		
Cardiac computerized tomography (CT)		
Chest x-ray		
Rhythm strip		
Exercise stress test		
Holter monitor test		
Hospital admission/discharge summary		
Any other relevant test performed		

REPORTER

Name:

Address:

City:

State/ Province:

Country:

Postal Code:

Email:

Phone: (include country code

SIGNATURE_____**Title**_____**Date**_____

Reporter Information (Please indicate dates as DD-MON-YYYY)

Date of this report _____	The person completing this report is
Reporter's name: _____	☐ The Patient
Phone (include country code): _____	☐ A close contact of the Patient
Email: _____	☐ A family member of the Patient
Address: _____	☐ The Patient's physician
City _____	☐ Other health care professional (specify): _____
State/Province _____	☐ Other (specify): _____
Postal Code: _____ Country _____	

Section A. Patient Information (Please indicate dates as DD-MON-YYYY)

Initials _____ / Identifier _____	Age at the time of the event _____ years	
Gender ☐ Female ☐ Male	Weight _____ lb _____ kg	
<u>Medical History and/or Risk Factors</u>		
☐ Hypertension -> ☐ controlled ☐ uncontrolled ☐ unknown	<u>Medical History and/or Risk Factors (continued)</u>	
☐ Diabetes -> ☐ controlled ☐ uncontrolled ☐ unknown	☐ Prior thromboembolism	
☐ Prior stroke -> ☐ ischemic ☐ hemorrhagic ☐ unknown	☐ Other prior cardiovascular event (specify): _____	
Date of prior stroke _____	☐ Severe headaches ☐ Migraine headaches	
☐ Prior transient ischemic attack (TIA) Date _____	☐ Physically inactive	
☐ Prior MI (specify type) _____ Date _____	☐ Overweight ☐ Obese BMI _____	
☐ Prior PCI ☐ Prior CABG	☐ Alcohol use ☐ Tobacco use	
☐ Heart failure	☐ Illicit drug use (specify): _____	
☐ Cardiac valve disease	☐ Birth control use (specify): _____	
☐ Coronary artery disease (CAD)	☐ Estrogen use (specify): _____	
☐ Carotid artery disease	☐ Prior carotid angioplasty or stenting	
☐ Congenital heart disease	☐ Prior endarterectomy	
☐ Patent foramen ovale (PFO)	☐ Hypercoagulable disorder (specify): _____	
☐ Aortic disease	☐ Lupus (i.e. anti-phospholipid syndrome)	
☐ Peripheral artery disease	☐ Vasculitis	
☐ Family history of ischemic heart disease, MI, stroke, TIA, etc. (specify) _____	☐ Prior fracture(s) of _____ (specify type) and _____ (date)	
relationship to patient _____	☐ Other relevant history (specify): _____	
☐ Hypercholesterolemia		
☐ Hyperlipoproteinemia ☐ LDL high ☐ HDL low		
<u>History of cardiac arrhythmias</u>		
☐ Atrial fibrillation	☐ Ventricular tachycardia	☐ Paroxysmal supraventricular tachycardia (PSVT)
☐ Atrial flutter	☐ Ventricular fibrillation	☐ Sinus tachycardia
☐ Bundle branch block	☐ Torsades de Pointes	☐ Premature Ventricular Complexes (PVC)
☐ Prolonged QT interval	☐ Sick sinus syndrome	☐ Wolff-Parkinson-White syndrome
☐ Bradyarrhythmia (specify the etiology if known) _____		
☐ Other (specify) _____		

Section C. Romosozumab Exposure Information (prior to stroke event)

Indication ☐ Postmenopausal osteoporosis ☐ Male osteoporosis ☐ Other (specify): _____ ☐ Don't know	Total number of doses received PRIOR to the event _____ First dose (Month 1) administered on _____ Last dose PRIOR to event onset was on _____ (Month # _____)
Dose, Route, Frequency ☐ 210 mg, SC, once every month (up to 12 doses) ☐ Other (specify) _____ ☐ Don't know	Action taken SPECIFICALLY for the reported event ☐ None, Romosozumab dosing continued, administered on _____ (dates) ☐ Romosozumab dose(s) skipped Number of doses missed _____ Dosing resumed on _____ (date) ☐ Romosozumab was discontinued on _____ (date) and the final dose was administered on _____ (date) ☐ Not applicable. Romosozumab held or stopped PRIOR to onset of the event due to _____
Expiration Date _____	Lot / Batch # _____ (check ☐ if not known)

Section D. Past and Current medications

List medications that the patient was taking at the time that the event occurred. Please also include recently administered medications that may be relevant to the reported event such as cardiovascular medications or medications with cardiovascular side effects, including NSAIDs.

Drug	Daily Dose, frequency and route of administration	Therapy Dates start/stop (dd/mm/yyyy)	Total #of doses received	Indication

Section E. Event Information (Please indicate dates as DD-MON-YYYY)

Diagnosis _____	Date Event Started _____
Signs and Symptoms (check all that apply, include start date if different than above)	
☐ Paralysis or weakness of an arm/leg/one side of face	☐ Personality changes
☐ Inability to speak/slurred speech	☐ Depression
☐ Muscle weakness	☐ Decreased sensation
☐ Loss of balance or coordination	☐ Difficulty in swallowing
☐ Uncontrolled eye movements	☐ Drooling
☐ Abnormal eye movements (specify)	☐ Nausea
☐ Unilateral drooping eyelid (ptosis)	☐ Vomiting
☐ Memory loss	☐ Drowsiness
	☐ Difficulty in reading/writing
	☐ Other (specify)
Event Outcome	
☐ Event is still ongoing	☐ Event resolved _____ (date)
☐ Event was fatal _____ (date)	☐ Unknown
Autopsy performed: ☐ Yes ☐ No	
Autopsy results: _____	

Section G. Evaluations, Diagnostic, & Laboratory Measures (Please indicate dates as DD-MON-YYYY)

☐ Check here if copy of the report(s) are included

Date	Type	Results / Findings			Date	Type	Results / Findings		
	Electrocardiogram (EKG)					Computerized tomography (CT)			
	Electroencephalogram (EEG)					Magnetic resonance imaging (MRI)			
	Doppler ultrasound					Magnetic resonance angiography (MRA)			
	Carotid ultrasound/duplex					Hospital record			
	Lumbar puncture					Other (specify)			
Date	Test performed	Results	Ref. range	Units	Date	Test performed	Results	Ref. range	Units
	WBC					Total cholesterol			
	RBC					LDL			
	Hemoglobin					HDL			
	Hematocrit					VLDL			
	Platelet count					Triglycerides			
	PT					Anti-cardiolipin antibodies			
	PTT					IgG			
	INR					IgM			
	Potassium					IgA			
	Sodium					Lupus			
	Calcium					Anticoagulant			
	Bicarbonate					dRWT/MRWT			
	Phosphorus					StacLOT-LA test			
	Magnesium								
	Chloride					ESR			
	Fasting glucose					Lp(a)			
	Random glucose					D-dimer			

Section F. Stroke Classification

- ☐ Ischemic - An acute neurological vascular event with focal neurologic signs lasting more than 24 hours, without evidence of primary intracranial hemorrhage
- ☐ Hemorrhagic - An acute neurological vascular event with focal neurologic signs lasting more than 24 hours or sudden severe headache and meningeal signs, and evidence of intracranial hemorrhage by neuroimaging or autopsy
- ☐ Uncertain type

Section H. Medical Management (Please indicate dates as DD-MON-YYYY)

Initial treatment location		Required hospital admission ☐ Yes ☐ No		Admitted to intensive care unit (ICU) ☐ Yes ☐ No	
☐ On-site (ambulance, rescue) ☐ Physician's office or clinic ☐ Emergency room ☐ Other (specify) _____ ☐ Unknown		Admission date _____ Discharge date _____ If dates unk, overall length of hospital stay ☐ less than 24 hours ☐ _____ days		ICU admission date _____ ICU discharge date _____ If dates unk, overall length of ICU stay ☐ less than 24 hours ☐ _____ days	
Treatment for the acute event		Treatment of comorbidities, as applicable		Please indicate any prophylactic medications prescribed to patient after the acute event	
☐ aspirin ☐ alteplase ☐ streptokinase ☐ Pro-Urokinase (pro-UK) ☐ urokinase ☐ tissue plasminogen activator (tPA) ☐ endovascular therapy (specify) _____ ☐ supplemental oxygen ☐ mechanical ventilation ☐ other (specify): _____		☐ acetaminophen ☐ dextrose ☐ insulin ☐ thiamine ☐ other (specify) _____		☐ lipid lowering therapy _____ ☐ anticoagulation therapy _____ ☐ aspirin ☐ other (specify) _____	
Please indicate any follow-up procedures that may be scheduled: _____					
Date of Report _____			Reporter's Name _____		
Patient's Initials _____ / Identifier _____					

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Prior to the launch of romosozumab in each Member State the Marketing Authorization Holder (MAH) will agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the relevant National Competent Authority.

The educational program is aimed at further minimizing the risks of serious cardiovascular events of MI and stroke, hypocalcemia, and of ONJ by reinforcing the key safety information available in the SmPC and the PIL.

The MAH shall ensure that all physicians who are expected to prescribe romosozumab are provided with/have access to the following educational materials:

- Prescriber Guide
- Patient Alert Card

Draft key messages of the additional risk minimization measures

Healthcare professional educational material:

- Prescriber Guide:
 - A concise introduction to romosozumab and the purpose of the Prescriber Guide.
 - Relevant information to support healthcare professionals in the appropriate recognition, monitoring and management of the important identified risks of serious cardiovascular (CV) events of MI and stroke and of hypocalcemia and important potential risk of ONJ.
 - A reminder list of risk minimization actions to perform prior to prescription of romosozumab.
 - The healthcare professional should educate the patient and/or caregiver on these risks and ensure the patient is provided with a Patient Alert Card.
 - Reminding need for and how to report suspected adverse reactions.

Specifically for the risk of serious CV events of MI and stroke, the key elements of the Prescriber Guide and their expected impact on risk minimization are:

- Preventing or reducing the probability of MI and stroke through facilitating appropriate selection of patients by means of a careful individual benefit-risk assessment before prescription. The guide provides a checklist, which reminds the prescriber to verify the contraindication and perform a careful assessment of the cardiovascular risk profile before prescribing romosozumab.
- Enhance awareness on the CV risk. The guide includes a reminder to educate patients and/or caregivers on the CV risk and the use of the Patient Alert Card.
- Early awareness of the risk of a CV event to trigger appropriate interventions. The guide instructs a prompt medical evaluation for patients who develop symptoms suggestive of MI or stroke, which will enable a rapid re-assessment of the benefit-risk, leading to the appropriate actions regarding romosozumab treatment.

- Reminding the need to report side effects by patients, caregivers or any other HCP, will indirectly contribute to risk minimization by enabling more rapid identification of safety signals.

Healthcare professional and patient/caregiver educational material:

- Patient Alert Card:
 - A concise introduction to romosozumab treatment and the purpose of the Patient Alert Card
 - Signs and/or symptoms of the safety concerns serious cardiovascular events of MI and stroke, hypocalcemia, and ONJ and when to seek attention from a healthcare professional
 - The importance of carrying the Patient Alert Card at all times and showing it to all healthcare professionals
 - Contact details of the prescriber
 - Important information for other healthcare professionals relevant to the patient taking romosozumab, including for the important identified risks of serious cardiovascular events of MI and stroke and of hypocalcemia and important potential risk of ONJ

Specifically for the risk of serious CV events of MI and stroke, the key elements of the Patient Alert Card and how they will act as a risk minimization measure are:

- By providing information via the alert card to the patient :
 - Enable a careful individual benefit-risk assessment before prescribing romosozumab by emphasizing contraindication and warnings and precautions with respect to the CV risk, providing a reminder to the patient/caregiver to share information on history of MI or stroke and other CV conditions/risk factors to the osteoporosis specialist. This will contribute to preventing or reducing the probability of MI and stroke through facilitating appropriate selection of patients.
 - Prompt rapid medical intervention by including a list of symptoms of MI and stroke for which the patient should seek immediate medical attention. This will promote early diagnosis and adequate management of potential CV events and hence would be expected to reduce the severity of CV events, if they would occur.
- By informing other healthcare providers (beyond the osteoporosis specialist) through the patient presenting the alert card:
 - Drive early awareness of the risk of a CV event to trigger appropriate interventions. Information regarding the patient's romosozumab treatment and the associated risk of MI and stroke will reach non-osteoporosis healthcare professionals also treating the patient, including in conditions of emergency. This raises awareness that a CV event may be the cause of the patient's symptoms and so trigger the appropriate interventions.
 - The card also includes the administration dates of romosozumab and contact details of the prescribing physician to be contacted for advice if needed.

- Remind physicians to share any changes in CV conditions/risks with the OP specialist, which will enable a rapid re-assessment of the benefit-risk, leading to appropriate actions regarding romosozumab treatment.
- Reminding the need to report side effects by patients, caregivers, or any other HCP, will indirectly contribute to risk minimization by enabling more rapid identification of safety signals.

Healthcare professional information letter on the cardiovascular risk:

In order to increase awareness in cardiologists and neurologists, who may be consulted, an information letter on the cardiovascular has been sent. The key elements of this letter are:

- A concise introduction to romosozumab treatment
- Background information on the safety concern of myocardial infarction and stroke
- A reminder list of risk minimization measures
- The link to the dedicated website targeted to healthcare professionals