17 October 2019
EMA/26554/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evenity

International non-proprietary name: romosozumab

Procedure No. EMEA/H/C/004465/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation or Term	Definition/Explanation
ABR	Amgen Europe B.V.
ADA	Antidrug antibody
ADCC	antibody dependent cell-mediated cytotoxicity
AFF	atypical femoral fracture
AHEG	Ad hoc expert group
AI	Auto injector
ALN	alendronate
AMD	ascending multiple-dose
ANCOVA	analysis of covariance
ARI	Amgen, Rhode Island
ATO	Amgen, Thousand Oaks
AUC	area under the concentration-time curve
BFR/BS	surface-based bone formation rates
BLE	Break loose and extrusion force
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BSAP	bone-specific alkaline phosphatase
BTM	bone turnover marker
CCI	Container closure integrity
CDC	complement dependent cytotoxicity
CEX	Cation exchange chromatography
CFU	colony-forming unit
CHO	Chinese Hamster Ovary
C_{max}	maximum serum concentration
CPP	critical process parameter
CQA	critical quality attribute
CSR	clinical study report
C_{trough}	trough concentration
DOE	design of experiments
DP	Drug product
DS	Drug substance
DXA	dual-energy X-ray absorptiometry

Abbreviation or Term	Definition/Explanation
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOS	end-of-study
ES/BS	surface based eroded surface
FA	final analysis
FBS	Fetal bovine serum
FEA	finite element analysis
FRAX	fracture risk assessment tool
HCP	host cell protein
HMW	High molecular weight
HR-pQCT	high resolution peripheral QCT
IPC	in-process control
iPTH	intact parathyroid hormone
IU	international units
LAL	limulus amoebocyte lysate
LIVCA	Limit of In Vitro Cell Age
LOCF	last observation carried forward
LRF	Log10 reduction factor
LRP	lipoprotein receptor-related protein
LRV	Log 10 Reduction Value
LS	least squares
MCB	Master cell bank
MDR	Medical Device Directive
MMA	Mixed mode anion chromatography
MMV	Mouse Minute Virus
MOP	men with osteoporosis
NNT	number needed to treat
NOAEL	no observed adverse effect level
OC	osteocalcin
OH	hydroxy
ONJ	osteonecrosis of the jaw
OVX	ovariectomized
P1NP	procollagen type 1 N-telopeptide
PA	primary analysis

Abbreviation or Term	Definition/Explanation
PD	Pharmacodynamics
PDGFR	platelet-derived growth factor
PFS	prefilled syringe
Ph Eur	European Pharmacopeia
PK	pharmacokinetics
PMO	postmenopausal women with osteoporosis
PO	orally
PrV	Pseudorabies virus
PTH	parathyroid hormone
PVDF	Polyvinylidene fluoride
QCT	quantitative computed tomography
QM, Q3M	each month, every third month
QW	each week
rCE-SDS	Reduced capillary electrophoresis sodium dodecyl sulphate
Reo-3	Reo virus 3
Rs.De	Resorption depth
RVLP	Retrovirus-like particles
SAP	statistical analysis plan
SC	subcutaneous
Scl-Ab	sclerostin antibody
sCTX	type I collagen C-telopeptide
SE-UHPLC	size exclusion ultra-high performance liquid chromatography
TPTD	Teriparatide
TEM	Transmission Electron Microscopy
TSE	Transmissible Spongiform Encephalopathy
UF/DF	ultrafiltration/diafiltration
WCB	Working cell bank
WCB	working cell bank
WFI	Water for injections
W.Th	wall thickness
xMuLV	Xenotropic murine leukemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant UCB Pharma S.A. submitted on 21 November 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Evenity, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0066/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0066/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance romosozumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice on 17 November 2011 (EMEA/H/SA/2197/1/2011/III), 15 March 2012 (EMEA/H/SA/2197/1/FU/1/2012/III), 27 June 2013 (EMEA/H/SA/2197/1/FU/2/2013/II) and 26 January 2017 (EMEA/H/SA/2197/1/FU/3/2016/II) for the development programme in question; the first three SA requests were submitted by Amgen targeting an indication of 'Treatment of osteoporosis in postmenopausal

women at increased risk of fracture', while the final SA request submitted by UCB targeted the indication in women and men, i.e. the indication assessed by the CHMP. The Scientific advice pertained to the following non-clinical and clinical aspects:

- Design and duration of the proposed non-clinical bone quality studies
- Adequacy of plans to characterise the carcinogenic potential
- Acceptability not to perform PK drug-drug-interaction studies
- Acceptability of the proposed pivotal Phase 3 study designs (Protocol 20070337 and Protocol 20110142) focusing on postmenopausal osteoporosis in women: population, endpoints, comparators, trial duration, timing of analyses, statistical analyses plans and adequacy of Phase 2 data to support Phase 3 design
- Sufficiency of the two Phase 3 studies (one placebo controlled, one alendronate controlled) to support benefit/risk assessment at the time of MAA
- Adequacy of the planned safety assessments and database
- Adequacy of plans to demonstrate bioequivalence study to support a 120mg/ml PFS product presentation, a 90 mg/mL PFS presentation and a 90mg/ml PFP product presentation
- Suitability of 90 mg/mL PFS and 90 mg/mL PFP presentations for administration by healthcare professionals or care givers, or for self-administration by patients following appropriate training
- Sufficiency of data to be generated in 3 clinical studies (20070337, 20110142, and 20060326) with long(er) term follow-up periods to satisfy the post licensing commitment for follow-up information for up to 5 years

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Andrea Laslop

The application was received by the EMA on	21 November 2017
The procedure started on	28 December 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	19 March 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	19 March 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 April 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	28 August 2018

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	6 September 2018
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	13 September 2019
The CHMP agreed on a list of outstanding issues to be addressed in writing to be sent to the applicant on	20 September 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 October 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	31 October 2018
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	08 November 2018
The CHMP agreed on a 2nd list of outstanding issues to be addressed in writing to be sent to the applicant on	15 November 2018
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	28 January 2019
Ad Hoc Expert group experts were convened to address questions raised by the CHMP on The CHMP considered the views of the Ad Hoc Expert group as presented in the minutes of this meeting.	07 February 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	15 February 2019
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	22 February 2019
The CHMP agreed on a 3rd List of outstanding issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	28 February 2019
The applicant submitted the responses to the 3rd CHMP List of Outstanding Issues on	26 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the 3nd List of Outstanding Issues to all CHMP members on	16 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	28 May 2019
The CHMP agreed on a 4rd List of outstanding issues to be addressed in writing to be sent to the applicant on	29 May 2019

The applicant submitted the responses to the 4rd CHMP List of Outstanding Issues on	5 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the 4th List of Outstanding Issues to all CHMP members on	12 June 2019
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the 4th List of Outstanding Issues to all CHMP members on	20 June 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Evenity on	27 June 2019

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula van Hennik Co-Rapporteur: Nithyanandan Nagercoil

The Applicant submitted written notice to the EMA, to request a re-examination of Evenity CHMP opinion of 27 June 2019 on	15 July 2019
The CHMP appointed Paula van Hennik as Rapporteur and Nithyanandan Nagercoil as Co-Rapporteur on	25 July 2019
The Applicant submitted the detailed grounds for the re-examination (Appendix 1 of Final Opinion) on	30 August 2019
The re-examination procedure started on	31 August 2019
The Rapporteur's re-examination assessment report was circulated to all CHMP members on	27 September 2019
The Co-Rapporteur's assessment report was circulated to all CHMP members on	27 September 2019
Ad hoc Expert group experts were convened to address questions raised by the CHMP on The CHMP considered the views of the Ad hoc Expert group as presented in the minutes of this meeting	3 October 2019
The Rapporteurs circulated the Joint Assessment Report on the detailed grounds for re-examination to all CHMP members on	11 October 2019
The detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP on	15 October 2019
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in	17 October 2019

its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation on	

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Romosozumab was intended for treatment of osteoporosis in postmenopausal women (PMO) and in adult men at increased risk of fractures. The approved indication is severe osteoporosis in postmenopausal women at high risk of fracture. Male osteoporosis ia not included in the approved indication (see section 3.5).

2.1.2. Epidemiology

Osteoporosis is defined as a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.

In Europe, 22 million women and 5.5 million men were estimated to have osteoporosis in 2010; and 3.5 million possibly osteoporosis related fractures were sustained. Most fractures occur at the spine, wrist and hip. The vast majority of osteoporotic fractures occur in postmenopausal women and the incidence increases markedly with age.

2.1.3. Aetiology and pathogenesis

Primary osteoporosis is often associated with oestrogen deficiency and/or age-related skeletal deterioration. Besides age and menopause, risk factors for osteoporosis include smoking, inactivity, previous fractures and white or Asian race.
Osteoporosis is characterised by an imbalance between bone resorption and bone formation.

2.1.4. Clinical presentation, diagnosis

Osteoporosis is characterised by low bone mineral density (BMD). Osteoporosis is defined by a T-score ≤ -2.50 in lumbar spine or total hip, according to WHO.

Osteoporosis per se is asymptomatic and does generally not become clinically apparent until a fracture occurs.

2.1.5. Management

In the EU, pharmacologic therapies for osteoporosis and the prevention of osteoporotic fractures consist of several types of antiresorptive therapies (including bisphosphonates, RANKL inhibitors and selective oestrogen receptor modulators), bone-forming agents (parathyroid hormone [PTH] analogues) and calcium and Vitamin D_3 preparations are also used.

2.1.6. About the product

Romosozumab (formerly known as AMG 785 and CDP7851) is a humanized IgG2 monoclonal antibody that binds and inhibits sclerostin. Romosozumab has a dual effect on bone turnover. 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 to expression of osteoclast mediators, thereby decreasing bone resorption.

The commercial product was proposed to be presented in a single-use plastic prefilled syringe (PFS) containing 1.17 mL of a 90 mg/mL romosozumab solution. Thus, 2 injections are required to achieve the 210 mg dose.

2.2. Quality aspects

2.2.1. Introduction

Romosozumab is a humanised IgG2 monoclonal antibody produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells.

The finished product is presented as a solution for subcutaneous injection in pre-filled pen (PFP) or pre-filled syringe (PFS). Each PFP or PFS contains 105 mg of romosozumab in 1.17 mL of solution (90 mg/mL).

Other ingredients are calcium acetate, glacial acetic acid, sodium hydroxide, sucrose, polysorbate 20 and water for injections. The finished product is a clear to opalescent, colourless to light yellow solution.

Evenity is presented as a pack of 2 PFP or 2 PFS, or a multipack containing 6 (3 packs of 2) PFP or PFS. Not all pack sizes may be marketed.

The PFS and PFP are for single use and are disposable. The PFS is made from cyclo-olefin polymer plastic with a stopper (chlorobutyl) and insert moulded stainless steel needle and elastomeric needle shield (synthetic rubber). The PFP is a handheld mechanical injection device pre-assembled with the PFS.

2.2.2. Active Substance

General Information

Romosozumab consists of 2 heavy chains of the lgG2 subclass and 2 light chains of the human kappa subclass. Romosozumab contains 36 total cysteine residues involved in both intrachain and interchain disulfide bonds. There are 6 intermolecular disulfides. Each heavy chain contains 449 amino acids with 4 intrachain disulfides. Each light chain contains 214 amino acids with 2 intrachain disulfides.

Manufacture, process controls and characterisation

Manufacturer(s)

Romosozumab active substance is manufactured at Immunex Rhode Island Corporation (referred to as Amgen Rhode Island or ARI) in accordance with current Good Manufacturing Practices (cGMP). ARI is a registered commercial active substance manufacturing facility.

Description of the manufacturing process and process controls

The manufacturing process begins with cell culture and harvest of CHO cells. The process includes steps for expanding the culture in shake flasks, a culture bag, and expansion bioreactors to inoculate the N production bioreactor to produce romosozumab. The purification of romosozumab is achieved through a series of chromatography, filtration, and viral inactivation steps.

The manufacturing process, divided into the different unit operations, is adequately described and justified with a sufficient level of detail included also covering target set limits and acceptable ranges for the critical process parameters (CPPs) as well as in-process controls (IPCs) for each process-step. Product pools may be held prior to further processing at the subsequent step in accordance with validated hold times. This is found acceptable.

The applicant also states that "Any reprocessing event will be preceded by an approved reprocessing protocol. No reprocessed material will be released for use without appropriate regulatory notification and approval as required." This is found acceptable.

Control of materials

All materials have been listed and specifications for non-compendial materials have been provided. No material of biological origin, except the CHO production cell line, was used in the manufacturing process. Foetal bovine serum (FBS) was used in development of the production cell line (pre-master cell bank (MCB)). Acceptable information has been provided for the FBS. TSE and virus safety is further discussed below.

The cell line development and cell banking has also been described in sufficient detail.

Characterisation of MCB, working cell bank (WCB) and cells at the limit of *in vitro* cell age (LIVCA) have been performed in compliance with ICH Q5A and ICH Q5D. Sterility, mycoplasma testing, isoenzyme analysis, and viral testing were performed (for test for adventitious agents, please refer to section "Adventitious agents safety" below). The specification acceptance criteria were met, showing that the cell banks are sterile and free of detectable mycoplasma and viruses, with the exception of expected A-type and C-type retrovirus like particles as expected for CHO cells. A protocol containing detailed acceptance criteria for creation of potential future WCB has also been provided. This protocol is found acceptable and no variation application is needed for new WCB conforming to these criteria.

In addition, acceptable data confirming genetic stability of the production cell lines have been provided.

Control of critical steps and intermediates

The control strategy for the romosozumab active substance process includes direct control of process inputs and evaluation of the performance of the process. A performance indicator is a measurement (output) which is used to evaluate in-process performance. Performance indicators allow direct assessment of product quality and/or process consistency. Performance indicators are evaluated against predetermined limits during process validation and a subset of performance indicators are designated as in-process controls (IPCs) for routine manufacture. IPCs that should be controlled within a defined range to ensure final product quality are designated as critical. Limits for IPCs are categorised as rejection, action, or control limits (Table 1). Rejection limits are established to assure no adverse impact to patient safety. A rejection limit, if exceeded or, in some cases, equalled, results in batch rejection. Action limits facilitate monitoring of process consistency. An excursion to an action limit requires an investigation which includes an assessment of impact to the product and processes, investigation of potential root cause, and as appropriate, corrective and/or

preventive actions to prevent recurrence. If an IPC action limit is exceeded, resolution of the investigation is a pre-requisite for lot disposition and can result in lot rejection if product impact is determined.

In addition to action and rejection limits, the process monitoring program establishes and assesses internal control limits which provide additional confirmation that the manufacturing process is operating in a state of statistical control and helps to identify potential process trends or shifts. Internal control limits are initially established to be the same as the action limits. Once sufficient manufacturing experience has been obtained, internal control limits are established using generally accepted statistical process control practices. For parameters not amenable to statistical treatment (e.g. microbial control limits), the limits are set to provide sufficient sensitivity for process monitoring. Control limits are reviewed periodically and can be revised over time to reflect the expected performance of the manufacturing process.

A summary of the critical process parameters for the active substance process has been provided and the rationale for their classification and acceptable ranges has been given.

Process validation

The commercial manufacturing process for romosozumab has been validated by demonstrating that the process met pre-defined acceptance criteria for performance when run within defined process parameters. Acceptable ranges for process parameters and acceptance criteria for performance indicators were defined based upon process characterisation and small-scale studies. The process verification and evaluation data is comprehensive and in support for a consistent performance of the manufacturing process. The verification and evaluation were performed on 3 consecutive process validation batches of active substance. Process verification and evaluation were performed at commercial scale but some aspects were run at reduced scale such as viral inactivation and viral clearance. The validation was run at set-points while the ranges of process parameters were challenged during the process characterisation and small-scale studies in manufacturing process development. This is found acceptable.

Manufacturing process development

The applicant has thoroughly described the studies on manufacturing process development, including process development and process characterisation of both the cell culture and the purification process, the integrated control strategy, given a description of the lot history as well as a demonstration of comparability of active substance.

Comparability

The comparability of active substance has been assessed throughout development. The commercial process has, in addition, been scaled-up and transferred from the clinical manufacturing site at ATO to the commercial site at ARI. A comprehensive comparability strategy was designed and executed in accordance with the guidance in ICH Q5E by lot release, characterisation and stress stability data. The results presented on the comparability assessment show that active substance manufactured at ATO and ARI are comparable.

Process characterisation (cell culture and purification)

The commercial manufacturing process was characterised in order to define a robust control strategy that consistently delivers the required quality of the active substance. The studies served as a basis for establishing controls for process parameters as well as for defining IPCs for routine manufacturing and establishment of acceptance criteria for the process validation. The process-parameters were evaluated in small-scale studies through design of experiments (DoE) and/or univariate experiments. The small scale models and DoE experiments are found justified and acceptable. The applicant’s definition of acceptable

ranges allows for variation of more than one process parameter at a time. No design space is claimed. The proposed manufacturing description with the identified acceptable ranges is generally acceptable, as is the applicant's definition of acceptable ranges. It was assured that any negative effects due to potential interactions between process parameters will be detected by the proposed control strategy. This is found acceptable.

As requested by the CHMP, the applicant has provided a sufficient justification regarding the chosen impact ratio limit for criticality (>0.2) for process parameters.

High mannose content in active substance pool

The applicant proposed not to add routine monitoring of high mannose as an IPC or in the active specification but instead commits to perform high mannose tests as a characterisation method in comparability studies to support process changes. The justification is based upon the conclusions from the product quality attribute risk assessment taking into account that high mannose is controlled consistently to levels shown to be safe and efficacious during commercial manufacturing. The high mannose content of romosozumab was sufficiently justified at a level that would not cause a significant change on the clearance when compared to the actual range seen in romosozumab active substance commercial manufacturing. In addition, the applicant presented data on clinical immunogenicity rates for two other monoclonal antibodies, which is found relevant for this issue. This is found acceptable.

Characterisation

Extensive biochemical characterisation of romosozumab was performed using state-of-the art methods. All elucidation of structure studies were conducted on romosozumab material manufactured, the commercial process. Primary structure, glycosylation, disulfide structure, charge variants, and size variants were characterised and a few complementary analytical methods. The results support the expected amino acid sequence of the protein. In addition, common product variants were identified. Protein oxidation and deamidation was investigated and relevant sites were identified. The expected glycosylation site, Asn299 was elucidated as the single N-glycosylation site. Furthermore, the typical IgG2 disulfide structure was observed and romosozumab was shown to exist primarily in its expected monomeric form. Overall, the analytical procedures and the results are found acceptable.

The biophysical evaluation confirmed that romosozumab is folded and contains well-defined secondary and tertiary structures that are consistent with other IgG2 antibodies. Two potency assays were applied to measure biological activity of romosozumab *in vitro*. A cell-based reporter gene bioassay demonstrated that romosozumab inhibits the action of sclerostin. Furthermore, an antigen binding assay was applied to monitor romosozumab's ability to bind to sclerostin.

Five product-related impurities were identified and evaluated. All impurities were demonstrated to be well-controlled by the manufacturing process, recommended storage conditions, and associated analytical monitoring. The process-related impurities HCP, DNA and residual protein A were demonstrated to be reduced to low or non-detectable levels in active substance, in small-scale studies as well as in commercial scale. were evaluated for clearance and all tested reagents were cleared below the assay limit of quantitation (LoQ) through the process. The estimated worst-case dose was demonstrated not to be critical. The methods used and results obtained for impurities are found acceptable.

Specification

The specification for the active substance is listed in Table 2 and includes control of identity, purity and impurities, potency and adventitious agents.

Relevant tests are included in the specification for the active substance although the number and extent of the proposed tests were originally considered sparse. The applicant proposed instead several in-process control tests at different steps during the purification process. The combination of tests as IPCs and in the specification is considered acceptable. This is considered acceptable. All these control parameters are included in the finished product specifications and this is considered as acceptable.

The justification given for omitting analyses from routine testing is found acceptable and justified. As requested by the CHMP, the applicant provided an acceptable justification that the polyclonal antibody used in the HCP assay can detect a sufficiently high percentage of HCPs present.

As requested by the CHMP, the active substance specification has been updated with references to in-house method numbers and Ph. Eur. references in order to have a clear link to the description and validation of analytical procedures used for release and stability testing.

Analytical procedures

The analytical methods used to test active substance are described in the dossier and system and sample suitability criteria are defined. The bioassay measuring the ability of romosozumab to inhibit sclerostin is acceptably described and validated, the relative potency is calculated in accordance with the 4-Parameter Logistic (4 PL) model described in Ph Eur 5.3. As requested, validation reports have been submitted to show that the in-house bioburden method is comparable to Ph Eur 2.6.12. The method descriptions are found acceptable. Comprehensive analytical validation summaries in line with ICH Q2 (R1) are provided for all non-compendial methods.

Batch analysis

Batch analysis data for romosozumab active substance has been presented for all lots used during clinical development and for active substance manufactured at commercial scale at the commercial manufacturing facility (ARI). All data complies with the active substance specifications in place at the time of manufacture. The information is sufficient and acceptable, demonstrating consistency in manufacturing.

Reference standard

The applicant employs a comprehensive and controlled process to manage romosozumab reference standards. The process includes production of early, interim reference standards during clinical development, production of a primary reference standard from commercial material, production of working reference standards as necessary through the lifecycle of the product, and a stability and shelf-life extension program to ensure all reference standards remain appropriate for use. The history of the romosozumab reference standards was provided. A comparison of release data from the current interim, the primary and the working romosozumab reference standards was provided, which demonstrates consistency and continuity between all three reference standards. A reference standard qualification protocol is included to demonstrate how future working reference standards will be qualified as fit-for-purpose.

Container closure

The romosozumab active substance container closure system is a 10 L polycarbonate carboy container sealed with a polypropylene screw cap closure containing a thermoplastic elastomer gasket. The container closure system is described in sufficient detail and no concerns are raised.

Stability

The proposed shelf-life for romosozumab active substance is 60 months when stored at the recommended storage condition of -30°C.

The on-going stability program for active substance at the recommended storage condition at -30°C includes 60 months stability data for 3 primary lots, 24 to 36 months stability data for 3 production lots and 36 to 48 months stability data for 2 supporting lots. In addition, data are presented on experimental (-20°C for 1 month), accelerated (+5°C for 6 months) and stressed (+25°C for 6 months and +40°C for 3 months) storage conditions.

The primary lots produced at ATO are representative of lots produced at the commercial manufacturing scale and site at ARI as demonstrated through analytical comparability analysis described in the section on manufacturing process development.

From the active substance specification, it is seen that the same limits are applied for active substance both at release and at stability (end-of-shelf-life specification) for all tests with one exception.

The proposed shelf-life for romosozumab active substance of 60 months at -30°C is found acceptable.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the EMA.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

The composition of Evenity solution for injection in pre-filled syringe and in pre-filled pen is presented. All excipients are of compendial quality and comply with the corresponding Ph. Eur. monographs. No formula overages are included.

Pharmaceutical development

An acceptable overview is provided on the development of the formulation, including satisfactory data supporting the proposed composition of the commercial finished product.

Pivotal clinical studies were performed with a 70 mg/ml formulation in glass syringes with a fill volume of 1 mL while the commercial 90 mg/mL formulation is for a fill volume of 1.17 mL in plastic a cyclic olefin polymer) syringes. The 90 mg/mL formulation was developed to reduce the number of injections required per dose from three to two. The final 90 mg/ml formulation was included in a bioequivalence and a clinical non-inferiority study.

Several analytical comparability studies were conducted to evaluate impact to finished product quality after changes to the active substance process, finished product primary container, concentration, fill volume and

changes in finished product manufacturing sites. The comparability between the 70 mg/mL and the 90 mg/mL finished product has been sufficiently demonstrated.

The primary container closure system consists of a plastic syringe barrel with an insert moulded stainless steel needle, an elastomeric needle shield and a fluoropolymer laminated chlorobutyl elastomeric plunger-stopper.

The information provided for the delivery devices is comprehensive, and confirms the suitability of the chosen devices. The pre-filled syringe and the pre-filled pen (auto-injector) forms two separate integral products, and are not considered as separate medical devices. However, design verification was performed as per ISO 11608-1, and compliance with Medical Device Directive Essential Requirements has been demonstrated as expected. It is also stated that the risk management principles in ISO 14971:2012 *"Medical Devices – Application of Risk Management to Medical Devices"* were used throughout the development.

Manufacture of the product and process controls

Manufacture

Evenity is manufactured and filled into the primary container closure system at Patheon, Monza, Italy and shipped to Amgen Europe BV, Breda, Netherlands for final assembly of the pre-filled syringe and the pre-filled pen.

The manufacturing process is summarised in a flow chart and detailed in a written narrative description. The manufacturing process includes the following process steps; active substance thawing and pooling, dilution with formulation buffer, sterile filtration, aseptic filling, plunger-stopper placement and final assembly of the PFS and the PFP. Up to three active substance lots can be pooled together and mixed to reach the target batch size. The product is manufactured aseptically and the solution is passed though both a pre-filter and a sterile filter (both 0.22 µm).

It is noted that the maximal times for buffer hold, active substance post thaw and filtered formulated finished product hold as listed in P.3.3 and validated in P.3.5 are significantly shorter than those in section P.2.3. For future extension of hold times it has been confirmed that the applicant will submit variation applications according to the existing EU classification guideline on variation applications.

Initially only limited information was included about the assembly of the pen/auto-injector.

This was accepted based on an acceptable validation scheme for the Breda site. The rationale for omission of a few specification tests has been acceptably justified.

No reprocessing has been described in the dossier.

Process controls

The IPCs are deemed suitable for controlling and monitoring the manufacturing process.

Two critical IPCs with action limits have been defined for bioburden, > 10 CFU/10 mL before the pre-filter and ≥ 1 CFU/10 mL before the sterile filter. It has been shown that the filters used during formulation and filling have excess filter capacity that exceeds the worst case microbial challenge. This justification is found acceptable together with a discussion comparing the probability of detecting a contamination with a 10 mL sample versus a 100 mL sample (with reference to the EBE position paper published, October 12, 2016).

Process validation

The process validation studies described in the dossier comprise finished product process validation, sterilisation process validation, filter validation and transport validation.

The process validation studies follow a traditional approach. Three consecutive commercial-scale batches were produced in September 2015. The bracketed approach for process validation with two batches at the minimum and one lot at the maximum batch size is found acceptable. All validation batches complied with the established in-process and release specifications, no critical deviations were observed.

The aseptic filling has been sufficiently validated with media fills, and data is presented supporting the proposed hold time from start of sterilisation filtration to completion of syringe filling. Acceptable results from filter validation are presented including results for microbial retention capacity, extractables profile and chemical compatibility.

Results from transport validation studies have been presented. Shipping containers used for transport are qualified to demonstrate that temperature is controlled for a pre-defined temperature range and duration. Finished product exposed to transport was analytically tested to confirm that quality attributes were maintained. The Company has a platform of qualified insulated shipping containers comprised of various sizes and durations. The applicant has confirmed that the shipping containers used during the simulation tests are representative of that used for actual shipping of the finished product.

No new impurities are added during finished product manufacture.

Product specification, analytical procedures, batch analysis

Specifications

The specifications for the finished product were presented and include control of identity, purity and impurities, potency and other general tests.

Quality attribute acceptance criteria were established using a statistical data set comprising release testing results from finished product lots manufactured at the clinical site using the commercial finished product process, as well as stability data at the recommended storage conditions. This approach to set specification limits only based on statistical considerations including tolerance intervals was not fully acceptable.

During the procedure, additional justification with respect to the clinical relevance and qualification of the shelf-life life limits for the purity parameters was asked for. The limits were further supported by the clinical use of higher doses than the proposed commercial dose (210 mg). This justification to maintain the active substance and finished product release and stability specifications for the purity assays can be accepted. This is found acceptable.

The initially proposed specification did not include certain tests. Such tests were included during the procedure.

Analytical procedures and reference standards

A comprehensive validation report for the rCE-SDS is provided. All other methods, except for the polysorbate 20 method, are either identical to those used for analysis of active substance or compendial methods and the validation reports are deemed acceptable.

The specification for finished product was updated during the procedure with acceptance criteria for pH, osmolality and polysorbate 20 and a footnote "Complies if tested, controlled by real-time release testing (RTRT)". This is acceptable.

Batch analysis

The batch analysis data presented for the three process verification batches complies with the limits in the proposed finished product specification. It is noted that results for potency, osmolality, pH and polysorbate 20 content are included although these tests initially not were included in the proposed finished product specification.

In conclusion, the batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process proposed for Evenity in pre-filled syringes and pre-filled pens.

Reference standard

The same reference standard(s) are used for both romosozumab active substance and finished product testing.

Container closure

The primary container closure consists of a 1 mL syringe with an insert moulded stainless steel needle covered with an elastomeric needle shield and a chlorobutyl elastomeric plunger stopper laminated with a FluroTec film on the product contact surface.

Drawings for all parts of the PFS are provided and dimensions of the syringe barrel and the plunger-stopper are listed in this section of the dossier. Compliance to the requirements in Ph Eur monographs 3.2.2.1 (Plastic containers…), 3.1.3 (Polyolefins) and 3.2.9 (Rubber closures…) is demonstrated in section P.2.4 of the dossier. This information is found acceptable.

Regarding the plastic syringe barrel, no detailed information about the composition of the plastic was included in the initial application. It was stated that it is durable, transparent, heat resistant and practically insoluble in most solvents. Additional information, in line with the requirements in Ph Eur 3.2.2 (Plastic container for pharmaceutical use) and the Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03, EMEA/CVMP/205/04 was provided as response to a CHMP request. This is found acceptable.

Results from studies of elemental impurities in accordance with ICH Q3D were presented. No issue was identified.

Stability of the product

The proposed shelf life for the finished product is 3 years when stored at 2 – 8°C, with an optional short-term storage at room temperature (up to 25°C) for up to 30 days in the original container. If not used within this period, the product should be discarded. The PFP and PFS should be kept in the outer carton in order to protect from light.

The stability studies were performed per ICH Q5C for Biotechnological/Biological Products and ICH Q1A for New Active substances and Products.

The testing and reporting for the nine finished product batches included in the stability studies are still ongoing and an overview of the data obtained thus far is presented in the dossier. The study is on-going for up to 48 months.

The three primary stability lots were manufactured at the clinical scale manufacturing site (ATO) and the three process verification batches were manufactured at the commercial scale manufacturing site (Patheon, Italia), both using active substance from Process 2. The ATO process is considered representative of commercial production and the product has been shown to be comparable to commercial production. The three supporting stability lots were manufactured using active substance at clinical scale at the ATO manufacturing site. For the three process verification batches manufactured at the commercial manufacturing site, up to 30 months data are available.

At long term storage all test parameters remained within the specification limits and no significant changes were observed for any of the parameters tested for up to 48 months storage at 2-8ºC. During accelerated and stressed storage the primary degradation pathways for romosozumab were shown.

Results from studies evaluating moisture permeability for the plastic syringe are presented in section P.2.4 of the dossier. These results indicate that the water loss in both long term and accelerated conditions will be far less than the significant change of 5% described in ICH Q1A (R2). The lack of control of protein concentration during the stability studies is considered as acceptably justified.

While it is noted that functionality test for the PFS were characterised during design verification, no test has been included in the release specification. However, since the applicant has demonstrated on three lots (with repeated testing) that PFS functionality is unaltered during the 36 months shelf life, the lack of a release test is found acceptable.

For the purity parameters that show change over time, detailed information about the statistical analysis of the long-term stability data have been presented in line with ICH Q1E Guideline.

. However, the statistical evaluation of the stability data shown that all purity parameters have predicted expiry results well beyond the 36 month proposed expiry also when the proposed short term storage at room temperature are included.

The proposed shelf life and storage conditions are considered acceptable.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the EMA.

Post approval change management protocol(s)

The applicant has provided a Post-Approval Change Management Protocol (PACMP) for extension of the in-process pool hold times during the manufacturing of active substance in support of classification of future applications for extensions of in-process hold times as Type IB variations. The PACMP is found acceptable.

Adventitious agents

No material of biological origin (except the CHO production cell line) is used during manufacture. A TSE certificate has been provided for the FBS used during development of the MCB. The risk of TSE transmission is deemed negligible. The information provided is acceptable.

The viral testing of the MCB, WCB and limit of *in vitro* cell age (LIVCA) has been performed in compliance with ICH Q5A. No viral contamination was detected with the exception of the expected A-type and C-type retrovirus-like particles. Sufficient detailed information has been provided for the test methods used.

Unprocessed bulk is tested for adventitious agents using in vitro tests. Four different cell lines are used, MRC-5, Vero cells, CHO-K1 and 324K cells. The detection limit of the 324K *in vitro* method have been demonstrated to be sufficiently sensitive in detecting minute virus of mice (MMV) to ensure a safety margin for the finished product (in combination with the reduction factor demonstrated for MMV in the process).

Both dedicated viral reduction steps in the manufacturing process (viral inactivation by low pH and virus filtration) and three chromatography steps (Protein A chromatography, cation exchange chromatography and mixed-mode anion exchange chromatography) have been validated for virus removal or inactivation. The results from virus studies demonstrate that substantial clearance is achieved for viruses having a wide range of physicochemical properties in the romosozumab process.

Acceptable information has been provided for the virus clearance studies and the data shows effective reduction of a wide range of model viruses. The virus clearance studies have been performed in compliance with ICH Q5A and CPMP/BWP/268/95. Data supporting the relevance of the down-scaled process steps as models for the commercial process has been presented in sufficient detail. The results provided also support the claimed viral clearance throughout the resin lifetime for each of the chromatography steps. Information regarding the validation of virus removal in the nanofiltration step has been provided demonstrating robust removal of small non-enveloped viruses such as MMV. Furthermore, information on the quantitative polymerase chain reaction (qPCR) method used to calculate clearance data for murine xenotropic leukemia virus-related virus (xMuLV) and pseudorabies virus (PRV) at the Protein A chromatography step has been provided.

In addition, acceptable safety margin has been demonstrated for retrovirus-like particles for the Evenity process.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

The manufacturing process of active substance is adequately described, validated and controlled with a sufficient level of details included also covering target set limits and acceptable ranges for the critical process parameters as well as in-process controls for each process-step.

The MCB and WCB are properly tested and qualified. Romosozumab was thoroughly characterised to provide a comprehensive understanding of its structural and functional properties. The characterisation included biochemical, biophysical, biological and forced degradation studies.

The proposed shelf-life for romosozumab active substance of 60 months at -30 °C is found acceptable.

Finished product

An acceptable overview is provided on the development of the formulation, including satisfactory data supporting the composition of the commercial finished product. The manufacturing process, limited to active substance thawing, formulation, sterile filtration and aseptic filling, has been acceptably described and validated.

The information provided for the delivery devices, the pre-filled syringe and pre-filled pen, is comprehensive, and confirms the suitability of the chosen devices. Design verification was performed and compliance with essential requirements has been demonstrated.

The justification of specification for the purity parameters are supported by the clinical use of higher doses compared to the commercial dose (210 mg). The proposed shelf-life limits for the purity parameters are considered to be clinically qualified.

Data presented support the proposed shelf-life for the finished product of 3 years when stored at 2 – 8 °C and with an optional short-term storage at room temperature of not more than 30 days.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Evenity is approvable from a quality point of view.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The applicant is recommended to provide the final validation report for the commercial automated pen assembly

2.3. Non-clinical aspects

2.3.1. Pharmacology

Romosozumab is a humanized monoclonal immunoglobulin (IgG2) that binds and inhibits sclerostin, a negative regulator of canonical Wnt signalling in cells of the osteoblast lineage and bone formation, which has been developed for the treatment of osteoporosis in postmenopausal women and men at increased risk for fractures. A number of binding and cellular *in vitro* studies as well as *in vivo* studies have been conducted to characterize the pharmacological activity of romosozumab.

Primary pharmacodynamics

In vitro studies

In vitro binding studies showed that romosozumab binds with high affinity to both human and rodent and non-rodent sclerostin.

The affinity for rat and cynomolgus monkey sclerostin (KD of 3 pM and 23 pM, respectively) was slightly higher and lower, respectively, than for human sclerostin (KD of 11 pM).

Investigation of the effects of romosozumab on binding of sclerostin to LRPs showed that romosozumab blocked the binding of human sclerostin to the closely related key Wnt signalling co-receptors LRP5 and LRP6, but not the binding of human sclerostin to LRP4, thought to play a facilitator role in sclerostin's inhibitory effect on Wnt signalling. This is considered mechanistically sufficient to block sclerostin's inhibitory activity and allow for the increases in bone formation and bone mineral density observed with administration of romosozumab *in vivo*.

In a study of mineralization in a mouse osteoblast cell line (MC3T3-E1-BF), romosozumab concentrations from 10 µg/ml was shown to inhibit the inhibitory effect on mineralization induced by 1 µg/ml human, cynomolgus, rat, and mouse sclerostin. Sclerostin is thought to inhibit the differentiation of osteoblasts to a mineralization phenotype. The statistically significant results obtained in this cell-based model of bone formation indicate that romosozumab is likely to have bone building activity *in vivo*.

In vivo studies

Romosozumab in female bone depleted rats and monkeys

Weekly subcutaneous injection of romosozumab at 3, 10, or 50 mg/kg to skeletally mature, bone depleted ovariectomized (OVX) rats and at 3 and 30 mg/kg to aged bone depleted OVX cynomolgus monkeys for 12 months resulted in a rapid and dose-dependent net positive bone balance with formation exceeding resorption and increases in cortical and cancellous (trabecular) bone mass and enhanced bone geometry from a dose level of 3 mg/kg.

Bone mass levels equalled or exceeded pre-OVX levels within the first 3 months of the dosing phase. By the end of the dosing phase at Week 52, bone mass generally exceeded both OVX and sham vehicle controls with e.g. increases in total bone mineral density (BMD) compared to OVX vehicle controls in rats and monkeys in femur, in lumbar spine and in proximal tibia metaphysis.

By the end of the dosing phase at Week 52, bone mass generally exceeded both OVX and sham vehicle controls with e.g. increases in total bone mineral density (BMD) compared to OVX vehicle controls in rats and monkeys of up to 53% and 29%, respectively, in femur, 61% and 29%, respectively, in lumbar spine and ~~30~~ 40% and 28%, respectively, in proximal tibia metaphysis.

At all time points and doses, romosozumab significantly increased total slice area at the proximal tibia metaphysis and tibial diaphyseal cortical thickness compared to OVX controls.

The dose-dependent gains in bone mass in romosozumab treated rats and monkeys were associated with proportionally greater bone strength at the lumbar spine, femoral neck, and femur diaphysis consistent with proximal tibia and vertebral increased bone volume, mineralized volume and trabecular thickness, indicating that bone quality was maintained or improved.

Aorta mineralization in the romosozumab treated cynomolgus monkeys was investigated by radiological methods. No evidence of mineralization of aorta was observed at the end of a 52-week treatment or at recovery 26 weeks after end of a 26-week treatment.

Some reversal of the romosozumab-related changes in bone mass, geometry and biomechanical strength parameters was observed after a 26-week recovery following a 26-week treatment period at 30 mg/kg.

The highest mean serum concentrations of romosozumab obtained in rats at the 3, 10 and 50 mg/kg dose levels were 1.6-fold, 8.6-fold and 42.3-fold, respectively, the steady-state C_{max} of approximately 28.1 µg/mL obtained in patients at the recommended dose of 210 mg. In monkeys the mean romosozumab $AUC_{0\text{-}tau}$ x 4 (to represent exposure for 1 month) was 688 and 11 800 µg·day/mL at 3 and 30 mg/kg, respectively, equivalent to 16512 and 283200 µg·h/mL which is 1.4-fold and 23.2-fold-fold the $AUC_{0\text{-}tau}$ of 12216 µg·hr/mL obtained in patients. Thus, the exposure levels in the OVX rats and monkeys treated for 12 months covered the clinical exposure and up 36-fold and 23-fold multiples of the clinical exposure, respectively.

In a second study in aged bone-depleted OVX cynomolgus monkeys, weekly subcutaneous injection of romosozumab at 3 mg/kg for 26 weeks resulted in rapid increases in cortical and cancellous (trabecular) bone mass. Increases in bone mass over time were related to an early increase in bone formation.

Cortical BMD at the distal radial metaphysis and diaphysis showed a minimal decrease with treatment. Despite the decrease in radial BMD, increased cortical activation frequency during the second half of the study, covariate analysis of BMC and biomechanical parameters obtained at the end of the study demonstrated that radial bone strength was maintained by romosozumab.

Romosozumab in male monkeys with fibular or ulnar osteotomy

Bi-weekly subcutaneous administration of romosozumab at 30 mg/kg for 10 weeks following bilateral fibular osteotomy in male adolescent cynomolgus monkeys significantly increased BMD at the lumbar spine, femur, distal radius and proximal tibia (up to 23% of osteotomy controls [lumbar spine]) primarily by effects on trabecular bone, attributed to increases in trabecular thickness (up to 1.5-fold of osteotomy controls [lumbar spine]). For cortical bone, treatment with romosozumab induced significantly increased bone geometry (e.g. increased cortical thickness) only at the distal radius. Increases in BMD at the lumbar spine were translated to increased bone strength (up to 70% of osteotomy controls). Increases in bone mass and trabecular/cortical thickness were associated with increased biochemical bone turnover markers (both formation [osteocalcin and procollagen type 1 N telopeptide] and resorption [C-telopeptide]) and bone formation rates observed by histomorphometry.

Romosozumab treatment significantly increased fracture callus bone mineral content relative to osteotomy controls associated with a lower incidence of delayed/non-union, reduced gap width between bone ends, more abundant bone within the osteotomy gap and less chondral tissue and fibrovascular/ granulation tissue in the callus. The increased callus bone mass was associated with a significant increase in torsional stiffness (48%) and non-significant increases in maximum torque (32%) and AUC (38%) compared to osteotomy controls.

The mean trough serum romosozumab concentrations ranged from 36 to 60 µg/mL which is approximately 1.1 to 1.8-fold the steady-state C_{max} of approximately 33 µg/mL obtained in patients.

In another study, bi-weekly subcutaneous administration of romosozumab at 30 mg/kg during 10 and 28 weeks following bilateral fibular osteotomy and ulnar osteotomy, respectively, in male adolescent cynomolgus monkeys resulted in increased modelling based bone formation, increased final wall thickness (W.Th) at remodelling sites, decreased eroded surface (ES/BS) in vertebral cancellous bone, and increased periosteal and endocortical bone formation in the vertebral cortex. These effects are proposed to contribute to the early increase in spine BMD observed with the romosozumab treatment. Following the self-regulation of bone formation with continued treatment, a decrease in remodelling space secondary to reduced ES/BS and a positive bone balance secondary to decreased final resorption depth (Rs.De) and increased W.Th contribute to the progressive increase in spine BMD.

Surrogate antibody r13C7 in bone depleted rats

Weekly subcutaneous injection of r13C7 at 25 mg/kg to skeletally mature, bone depleted OVX rats for 26 weeks resulted in continuously increased bone mass and bone strength of vertebrate (up to 80%) and non-vertebrate bones (up to 40%) compared to OVX controls up to end of dosing, with bone formation increases that peaked early and returned toward control levels over time. Bone resorption as reflected in serum biomarkers, histomorphometric parameters at trabecular and cortical sites of vertebrate and non-vertebrate bones, and reduced *ex vivo* osteoclastogenesis was decreased compared to OVX controls.

Treatment with r13C7 significantly increased expression of genes coding for Wnt inhibitors (*sost*, *dkk1*, *mepe*, and *dmp1)* through 26 weeks at the vertebra, and at some time points at the tibia, indicating that romosozumab induced bone formation is self-regulated.

In another study, retreatment of OVX rats with twice weekly subcutaneous injections of 5 mg/kg r137C for 6 weeks following an initial 6-week treatment phase and a treatment-free 12-week withdrawal period resulted in increased bone formation (e.g. trabecular and cortical bone formation rates [BFR/BS]) and BMD and decreased bone resorption (e.g. trabecular ES/BS) at the lumbar spine and femur-tibia to the levels observed during the initial treatment phase.

In a third study, retreatment of OVX rats with twice weekly subcutaneous injections of 5 mg/kg r137C for 6 weeks following an initial 12-week treatment phase with r137C and a 12-week treatment phase with twice weekly subcutaneous injections of 10 mg/kg osteoprotegerin (OPG-Fc, a RANKL inhibitor) did not further increase the BMD at the lumbar spine and femur after the initial treatment period with r137C and the maintenance of BMD with OPG-Fc which indicate self-regulation of r13c7-induced increase in bone formation.

In a fourth study, pre- and co-treatment with alendronate (subcutaneous injections of 28 µg/kg twice weekly for 6 weeks) did not have any significant effect on the increased bone formation, bone mass, and bone strength induced by once weekly subcutaneous injections of 25 mg/kg r137C for 6 weeks.

Secondary pharmacodynamics

In addition to its effects in animal models of osteoporosis, sclerostin antibodies (Scl-Ab) have also been tested in other animal bone loss models. Repeated administration of Scl-Ab (r13c7 25 mg/kg, SC or 10 mg/kg, IP) up to 6 weeks was effective in increasing bone formation and preventing the disease-associated decrease in bone mass and strength in models of androgen ablation (osteopenia), inflammation, and skeletal disuse/unloading.

In a rodent fracture repair model, Scl-Ab (r13c7, 25 mg/kg, SC) administered for 9 weeks was shown to increase bone mass in the fracture callus, resulting in improvements in functional strength.

As expression of sclerostin has been reported in chondrocytes, the effects of both systemic Scl-Ab (r13c7, 25 mg/kg, SC) as well as local (intraarticular) administration of smaller FAB fragment of Scl-Ab (385 µg in 50µL, IA) were tested in the rat medial meniscal tear (MMT) model of osteoarthritis (OA). The results from these two studies did not indicate a significant effect of Scl-Ab on the progression of induced osteoarthritis following 3 weeks of treatment. However, a trend to increased severity of MMT-induced osteoarthritis was observed after systemic administration of Scl-Ab as evident by decrease in the percent area of any cartilage matrix (54% inhibition, p=0.07) which in turn is a sign of greater degeneration.

Whereas the precise role of sclerostin in the development and progression of OA is still unclear, the overall results from nonclinical studies and clinical safety data, where adverse advents of osteoarthritis were balanced between romosozumab and control groups, indicate that osteoarthritis would be of low potential risk in connection with romosozumab treatment.

Theoretical concerns regarding the effects of sclerostin antibodies

The applicant has provided a comprehensive theoretical discussion on the possible secondary pharmacological effects of sclerostin antibodies and its subsequent activation of Wnt signalling, with possible safety concerns that could be identified, are summarised and discussed below.

Vascular calcification

Sclerostin is an inhibitor of mineralization in bone, related to its effects on osteoblast differentiation. Because sclerostin is constitutively expressed in the aorta and in vascular calcified foci, there is a theoretical concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification (VC). The potential association of sclerostin with VC has been suggested in by a number of published studies in animals

and in man. Sclerostin mRNA and protein levels are upregulated in calcified aortas in transgenic animals (Enpp1 knockout mice) in vivo as well as in calcifying murine vascular smooth muscle cells (VSMCs) in vitro. Sclerostin expression has also been shown to increase in calcified human aorta valves and in most, but not all, cross-sectional observational studies, circulating sclerostin levels positively associates with cardiovascular calcification. In addition, recent data indicate that sclerostin overexpression may protect the aorta from atherosclerosis and inflammation in animals (Krishna et al. 2013, 2017). Thus, these findings together with the constitutive expression of SOST protein in calcifying vascular tissues support a potential role of sclerostin in limiting calcification not only in bone but also in the vasculature.

Even though there were no effects of romosozumab on cardiovascular function in the repeat dose toxicity studies in intact animals, romosozumab treatment increased the rate of serious cardiovascular adverse events in clinical trials. The applicant did not provide data on the effect of prolonged romosozumab treatment on vascular calcification in normal and diseased vasculature such as in the atherosclerosis mouse model. As such, it is not clear, if a sclerostin specific antibody would possibly amplify the atherosclerotic effects. The applicant was initially asked to further address this safety issue. This should include providing clarifying information on the suggested protective role of sclerostin in vascular calcification and a discussion about the effect of a sclerostin antibody on promoting atherosclerosis and its possible cardiovascular safety consequences using study data (e.g. mechanistic studies in vitro and/or in vivo) or published literature. The applicant has provided a comprehensive response in order to clarify the suggested protective role of sclerostin in vascular calcification in diseased tissue and the effect of sclerostin inhibition on promotion of atherosclerosis. The Applicant´s responses included the submission of five new non-clinical studies including in vivo studies in an atherosclerosis disease model (high fat diet-fed ApoE -/- mice). Romosozumab, or its ratized antibody form had no apparent effects on vascular calcification in healthy normal animals as discussed in the previous round of the MAA submission. The data provided from the in vivo study in a disease model (study 124609) using high fat diet-fed ovariectomized ApoE knock-out mice (study 124609) showed that sclerostin inhibition by the anti-sclerostin antibody r13C7 had no effect on aortic total plaque volume or mineralized plaque volume or no change in inflammatory cytokines and chemokines such MCP-1, IL-6, TNFα, (although these were affected by the ApoE -/- genotype per se) or in genes associated with matrix degradation and calcification, such as Mmp-9, Spp1 or TNfrsf11b.

Sclerostin expression studies by immunohistochemistry in advanced human atherosclerotic plaque suggests that sclerostin was not expressed in most of the advanced human atherosclerotic plaques (77%) and showed no apparent association with patient medical history of artery disease or with cardiovascular outcome during the 3-year follow up period. In those cases where sclerostin was detected, this was restricted to deeper parts of the plaque/vessel wall (T. median and adjacent T. intima) and was of decreased intensity compared to control aorta. Sclerostin expression was never seen in the superficial region of the plaques next to the vessel lumen. The only association between absence of sclerostin expression and plaque features was dystrophic calcification occurring in necrotic acellular areas of human carotid artery atherosclerotic plaques. This is more likely a consequence of the advanced nature of the plaque, reflecting passive calcification, rather than a direct functional association with calcification

Additionally, there was no obvious relationship between plaque OPN level or the presence of the pro-inflammatory cytokines MCP-1, IL-6 and TNFα. Thus, these data indicate that sclerostin is not likely to affect advanced plaque biology to a large extent. Further contribution for the absence of a mechanistic link between sclerostin and atherosclerosis is derived from genome-wide association studies (GWAS). Human genetic data showed that a natural genetic modulation of SOST expression in aorta and tibial artery by a common SNP (allele C of the SNP rs2741856) in human populations had a significant effect on bone physiology but no detectable effect on risk of myocardial infarction or stroke. Evidence for increased thrombogenesis (as a

component of plaque rupture and erosion) was examined by studying dysregulation of prostanoid metabolism and platelet activation. In these studies, romosozumab did not induce platelet activation in human whole blood at up to 300µg/mL which is a concentration approximately 10-fold greater than the clinical Cmax. Vasospasm (as functional alteration in coronary circulation with vasoconstriction and acute changes in blood pressure (flow) as mediator) was studied on isolated healthy human coronary arteries. Romosozumab (or human recombinant sclerostin) did not induce vasoconstriction at concentrations up to 300µg/mL which is a concentration approximately 10-fold greater than clinical Cmax at 210 mg QM.

During the procedure, EMA and CHMP had been made aware of, as a third party intervention, an article by Jonas Bovijn et al (Lifelong genetically lowered sclerostin and risk of cardiovascular disease), pre-published online on BioRxiv (doi: https://doi.org/10.1101/531004) as a manuscript in preprint and not yet peer-reviewed.

The scope of the article was to investigate the potential cardiovascular risk of sclerostin suppression by gene analysis and to compare the results from a meta-analysis of the published data from the romosozumab Phase III studies.

The authors identified two SNPs (single nucleotide polymorphisms) in a region indicated to affect express ion of the SOST gene, encoding for sclerostin, in human bone. Mutations in or close to this this region has been associated with Van Buchem disease, characterised by decreased levels of sclerostin. Thus, subjects with point mutations identified by the SNPs are presumed by the authors to have low sclerostin levels. The authors estimated the effects on risk of e.g. osteoporosis, fracture and coronary heart disease (CHD), by combining data from up to 478,967 participants of European ancestry from three prospective cohorts and up to 1,030,836 participants from nine genome-wide association study (GWAS) consortia.

In summary, subjects identified by the SNP displayed higher risk of myocardial infarction and/or coronary revascularisation (69,649 cases; OR 1.18; 95% CI, 1.06-1.32; P=0.003) and type 2 diabetes (OR 1.15; 95% CI, 1.05-1.27; P=0.003), higher systolic blood pressure (1.3mmHg; 95% CI 0.8-1.9; P=5.9×10-6) and waist-to-hip-ratio adjusted for BMI (0.05 SDs; 95% CI, 0.02 to 0.08; P=8·5×10-4) but with lower risk of fracture (OR 0.59; 95% CI, 0.54-0.66; P= 1.4×10-24), and osteoporosis (OR 0.43; 95% CI, 0.36-0.52; P=2·4×10-18).

The CHMP identified some weaknesses with the study. The SNPs of choice are downstream of the target gene (>30kb). While the DNA region containing the SNPs is likely of importance to the target gene expression, the exact relation between the two chosen SNPs and the target gene expression is not as well established. The association between the chosen SNPs and BMD was weaker in some populations, and it is considered that the possibility of genetic pleiotropy has not been fully accounted for.

In the view of the CHMP, the data presented in the article suggest a potential mechanism for sclerostin in the development of cardiovascular disease. The results may be indicative of an increased CV risk with low levels of sclerostin; however, the data are not considered conclusive.

Cancer

Because romosozumab is a bone-forming agent and an activator of canonical Wnt signalling, questions regarding carcinogenic risk have been raised. These concerns arise from the association of mutations in the canonical Wnt pathways with human cancers through activating mutations or epigenetic changes in the intracellular signalling components or experimental overexpression of Wnt ligands where hyperplasia is followed by neoplasia.

Chronic hormonal perturbation is a risk for tumorigenesis in rats that may or may not always translate to humans. Hormonal signals are major players in regulating sclerostin expression in osteocytes (Suen et al. 2015) with androgens and estrogens inhibiting Sost expression (Delgado-Calle et al. 2016). The applicant was requested to elaborate if a reversal effect of an increase in androgens or estrogens occurs after anti-sclerostin treatment and to which degree this could present a risk for carcinogenicity (i.e. oestrogen dependent cancers) in humans. An evaluation of all the nonclinical data did not provide any evidence that chronic treatment with romosozumab is associated with any effects in male or female reproductive organs or sex hormone levels. In addition, there was no evidence of an increased incidence in neoplasia in the reproductive organs in the lifetime rat pharmacology study. Thus, romosozumab treatment is unlikely to pose an increased risk of sex hormone-related carcinogenicity in humans.

In the lifetime rat pharmacology study (study 107895) two osteosarcomas were observed at 50 mg/kg in male rats (incidence was 3.7% vs. historical average incidence of 0.38%; range 0-3.33%). In the literature there are reports of overexpression of Wnt signalling components in osteosarcoma and silencing of sclerostin expression in an osteosarcoma cell lines using si-RNA resulted in enhanced Wnt signalling, increased proliferation and invasion in vitro.

Aberrantly high canonical Wnt signalling has been implicated in the development and /or maintenance of many cancers including colorectal, prostate, lung, breast and bone cancers, but elevated WNT signalling may not correlate with reduced patient survival in all types of cancer. As WNT signalling appears to promote tumour initiation, growth, and generation of metastases in a cancer-type-specific manner, the mechanistic link between sclerostin inhibition and the risk of cancer as well as the osteosarcomas observed in the rat carcinogenicity study has been discussed by the applicant with regard to the long-term clinical safety of romosozumab treatment (see toxicology section).

Hyperostosis

Hyperostosis (increased bone mass resulting in altered bone size and/or shape) with adverse neurological consequences is a feature of patients with loss-of-function mutation in sclerostin (i.e. sclerosteosis and van Buchem disease). Theoretical considerations for potential bone overgrowth or hyperostosis occurring with romosozumab treatment have, thus, been raised. Preclinical toxicity data in rat and monkeys suggest dose-dependent increases in bone mass following chronic treatment with romosozumab (≥ 3 mg/kg, SC) but hyperostosis was only evident in the rat, consistent with the pharmacologic activity of the antibody. The severity of the hyperostosis appeared to be increased in female rats as compared to males in the "1-month Subcutaneous Injection Toxicity Study of AMG 785 in the Sprague Dawley Rat With a 10–week Recovery Period" (Study 105908). The Applicant is asked to interpret this gender difference and discuss the possible cause for this finding (see details in the toxicology part).

There were no obvious adverse neurological consequences due to nerve compression observed in rats and monkeys based on assessment of clinical scores, food consumption, ophthalmologic examinations, electrocardiogram, blood pressure measurements and macroscopic or microscopic examination of the brain, spinal cord, sciatic nerve, and optic nerve. In addition, the current clinical trial data indicate that romosozumab at the clinical dose of 210 QM for 1 year was not associated with hyperostosis.

Sacropenia

In some recent non-clinical studies, a reduced muscle weight has been reported in Sost knock-out mice. Sarcopenia is, however, not a feature of patients with loss-of-function mutation in sclerostin (i.e. sclerosteosis and van Buchem disease). Moreover, inhibition of sclerostin with Scl-Ab did not appear to affect skeletal muscle mass in rats and no gross observations were recorded for muscle mass in rats exposed for up

to 98 weeks at 50 mg/kg romosozumab. In addition, the available clinical data including HRpQCT Imaging do not give strong support that clinically significant sarcopenia would be a potential risk with romosozumab treatment.

Osteonecrosis of the jaw (ONJ)

ONJ is a condition characterized by necrotic exposed bone in the maxillofacial region and there is a strong association of ONJ with suppression of bone turnover. In patients with sclerosteosis, who have a lifelong absence of sclerostin due to loss-of-function mutations, there appears to be no reported cases with ONJ. Moreover, dental disease and inflammation in rats with lifetime romosozumab exposure was not associated with ONJ-like findings. Osteonecrosis of the jaw is, however, a known AEs associated with longer term exposure of antiresorptive drugs. In the current clinical safety evaluation, four cases of ONJ have occurred in romosozumab clinical programme (one during romosozumab treatment and three when romosozumab was followed by denosumab or alendronate treatment). This information should be included in the SmPC document (see Clinical section).

Atypical femoral fracture (AFF)

Based on the mode of action of romosozumab and because inhibition of bone resorption is a component of the dual effect of romosozumab, there is a potential concern for increased risk of promoting atypical femoral fractures (AFFs). In an animal model of fracture healing after fibular osteotomy, romosozumab (30 mg/kg 2QM) did not affect the degree of cortical porosity within the fibular cortex near the site of osteotomy after 10 weeks. However, in the clinical safety evaluation, there was one subject in the romosozumab group, and no placebo subject had a positively adjudicated case of AFF in the 12-month placebo-controlled population. Based on the mechanism of action of romosozumab it is therefore reasonable to conclude that romosozumab treatment has contributed to the AFF events that occurred in the clinical programme and that this risk should be considered as an identified risk for romosozumab and appropriate information should be included in the SmPC document (see Clinical section).

Exacerbation of TNF-α-driven inflammatory diseases

Expression of sclerostin in synoviocytes from patients with RA and hTNF-α transgenic (hTNFtg) mice suggest a role of sclerostin as a negative regulator of TNF-α production in the synovium. Some non-clinical studies, but not all, indicate that administration of a Scl-Ab to hTNFtg mice exacerbated joint destruction, which in turn has raised concerns that administration of romosozumab may exacerbate disease in patient with TNF-α driven comorbidities. However, the overall current clinical trial data set do not indicate that TNF-mediated inflammatory adverse events would be a potential risk with romosozumab treatment. In the ongoing clinical trials subjects having potential TNF-α-comorbidities will be monitored for effects of romosozumab on disease exacerbation.

Haematopoiesis

Because romosozumab-mediated effects on bone formation occur through regulation of the osteoblast lineage, effects on haematopoiesis are a theoretical concern. As a consequence of the intended pharmacological activity of romosozumab, to increase canonical Wnt signalling in stromal cells and the osteoblast lineage, reversible hematologic changes including significant decreases in mean red cell numbers were seen in rats and to a smaller extent in cynomolgus monkeys administered romosozumab subcutaneously up to 100 mg/kg for 26 weeks. The available clinical trial data indicate that romosozumab at 210 mg QM for 1 year has no apparent effect on haematopoiesis.

Glucose metabolism

Studies in rodents indicate a potential role of bone in regulation of glucose metabolism mediated through serum OCN, which romosozumab increases through its effect on bone formation. In repeat-dose toxicity studies in rats administered romosozumab at doses up to 300 mg/kg QW, a significant and dose-dependent increases in fasting blood glucose was observed in males (about 24% at 300 mg/kg, SC) and in females (19 % at 100 mg/kg, SC). In contrast to rats, in repeat-dose studies in cynomolgus monkeys administered doses of up to 300 mg/kg IV QW and SC with exposures up to 200-fold greater than the clinical exposure at 210 mg QM, respectively, showed no significant changes or patterns in fasting glucose. The clinical trials indicate that romosozumab treatment had no significant effects on fasting glucose. Thus, preclinical data in cynomolgus monkeys and clinical data indicate that romosozumab should not have major effects glucose metabolism.

Safety pharmacology

Safety pharmacology endpoints were evaluated in a single dose neurobehavioral study in rat and in a single dose combined cardiovascular/respiratory study in cynomolgus monkey. In addition, the effect of romosozumab on cardiovascular function (ECG and blood pressure) in monkeys was assessed in the 1-month repeat dose toxicity study at doses up to 300 mg/kg SC and IV and in the 6-month repeat dose toxicology study at dose up to 100 mg/kg SC. The applicant did not submit any in vitro safety studies such as hERG channel testing. This is acceptable considering the nature of the drug product (a monoclonal antibody).

No adverse neurobehavioral or respiratory effects were observed in rat or cynomolgus monkey safety pharmacology studies administered romosozumab with exposure margins at NOAEL (300 mg/kg) exceeding 200-fold to the clinical exposure (Cmax) at the 210 mg dose.

In the single dose cardiovascular safety pharmacology study in cynomolgus monkey, a significant romosozumab-related increase in heart rate and blood pressure was observed at multiple occasions at the high dose (300 mg/kg, IV) with drug plasma concentration > 200-fold greater than the clinical exposure at the recommended 210 mg dose. The effect of on heart rate and blood pressure after a high single IV dose in monkeys is of uncertain etiology but it may be the result of a direct effect on the cardiovascular system by romosozumab. Nevertheless, the exposure margin at NOAEL (100 mg/kg; IV) in monkeys after single intravenous dosing was estimated to be ~ 60-fold to clinical C_{max} (33 µg/mL).

In addition, safety pharmacology evaluations were also incorporated within the 4-week and 6-month repeat-dose toxicity studies in monkeys. The results of these studies indicate that romosozumab had no effect on cardiovascular (blood pressure, heart rate, ECGs, QT/QTc) functions after subcutaneous dosing with exposure margins exceeding 200-fold to the clinical exposure.

Pharmacodynamic drug interactions

No dedicated pharmacodynamic drug interaction studies were conducted with romosozumab. This is acceptable for an antibody product.

2.3.2. Pharmacokinetics

The pharmacokinetic (PK) properties of romosozumab (also referred to as AMG 785) were evaluated in rats and monkeys after intravenously or subcutaneous administration of one or two doses. Rodent versions of romosozumab were used in rat pharmacology and PK/PD studies, including rat 137c (r13c7) and mouse 13c7

(m13c7). The toxicokinetic (TK) properties after multiple subcutaneous dosing were evaluated in the toxicology studies performed in rats, rabbits, and monkeys.

Methods

Romosozumab
Specific analytical methods were developed to quantify romosozumab in rat, rabbit, and monkey sera using ELISA-based methods for each species. The applicant provided validation reports for the analytical methods used, demonstrating suitability of the methods for the purpose of analysis.

The principle of the method is, in brief, that microplate wells are coated with mouse α-hu-AMG 785, monoclonal antibody that is used as a capture reagent. The captured AMG 785 is detected with a horseradish peroxidase (HRP) labeled mouse α-hu-AMG 785 monoclonal antibody. In GLP-safety studies, serum romosozumab concentrations in rat and cynomolgus monkey were determined with a lower limit of quantification of 50-875 ng/mL.

None of the method validations applied in pivotal toxicity studies were formally performed under GLP. It is acknowledged that some of the studies are performed according to GLP principles, e.g. QA audit of different steps of the study. The classification of the studies as non-GLP is not considered to have any impact on the results from the studies.

Some unclarities were noted regarding the bioanalysis method used before the final bioanalytical method was set. Regarding the study in rat with the rodent version (m13C7) no description of the assay method was found although referred to in the report as "The bioanalytical memo report". In the exploratory studies in Cynomolgus monkeys both studies (105779 and 105876) were stated to be analysed with immobilized biotinylated recombinant human sclerostin as a capturing reagent. The study report for study 105779 however describes the method where the mouse anti human-AMG785 antibody is used. None of these issues are considered to influence the nonclinical evaluation of the product, and no action is thus needed.

Neutralizing antibodies
Specific analytical methods were developed to quantify neutralizing anti-romosozumab antibodies in rat and monkey sera. Two assays were developed, a binding antibody assay to detect antibodies capable of binding to romosozumab, and a neutralizing antibody assay to determine the neutralizing activity against romosozumab. Binding anti-romosozumab antibodies (ADA, Anti-drug antibody) were detected using a validated electrochemiluminescent (ECL) bridging immunoassay. The assay sensitivity is 3.9 ng/mL in rat and 1.95 ng/mL in cynomolgus monkey. If positive for binding antibodies, the neutralizing activity of these samples was assessed in a validated ECL-based competitive target binding assay. The sensitivity in this assay is 0.75 µg/mL in both rat and monkey.

The presence of romosozumab in serum may interfere with the assay sensitivity for ADA detection (>10 µg/mL) and neutralizing antibody detection (>0.06 µg/mL) therefore, exposures must be interpreted with caution.

Single dose pharmacokinetics

Single dose pharmacokinetics of m13c7 and r13c7 and romosozumab was evaluated in rats. Single does romosozumab PK was evaluated in monkeys.

Rat
A non-linear increase of exposure of m13C7 was observed over the dose range 0.1 to 10 mg/kg (IV). With the 100 increase in dose, AUC_{inf} increased from 23 to 18000 µg*h/mL, a 779-fold increase. Half-life values

increased with dose (6 h at 0.1 mg/kg and 28 h at 10 mg/kg), and clearance decreased (4.4 mL/h/kg at 0.1 mg/kg and 0.56 mL/h/kg at 10 mg/kg). With subcutaneous administration, similar AUC_{inf} values were observed at the same dose IV (481(sc) vs 472 (IV) µg*h/mL at 1 mg/kg), the median T_{max} was 24 h.

A greater than dose-proportional increase was also seen in the range 5 to 35 mg/kg in rats administered AMG785 SC. Similar values were measured using the different formulations with different concentrations (10 and 70 mg/mL). For the 5 mg/kg, SC, group, the mean CL/F value was 2.42 mL/h/kg. The exposure based on AUC was 2-fold greater after 35 mg/kg IV (45100 µg*h/mL) compared with the same dose SC (22700-25800 µg*h/mL). After SC administration, T_{max} was observed at 48 h.

The other rodent analogue of the antibody, r13C7, was investigated in ovariectomised aged female rats. The animals were administered 100 mg/kg SC with an observed C_{max} of 403 µg/mL at the T_{max} 96 h. The exposure expressed as AUC_{0-672} was 112000 µg*h/mL.

Monkey

Female cynomolgus monkeys were administered romosozumab SC (3, 30, 30 mg/kg) twice with one month between the doses. After the first dose, a non-linear increase of the exposure was observed. A 10-fold increase in dose resulted in a 12-fold increase in C_{max} (18 µg/mL at 3 mg/kg, 210 µg/mL at 30 mg/kg) and 21-fold increase in AUC_{inf} (2570 µg*h/mL at 3 mg/kg and 54300 µg*h/mL at 30 mg/kg). Half-lives increased with dose (41 h at 3 mg/kg and 71 h at 30 mg/kg), CL/F values decreased with dose (1.2 mL/h/kg at 3 mg/kg and 0.6 at 30 mg/kg). The median T_{max} was 45 hours.

Summary

The PK was non-linear over the dose ranges investigated, with a greater than dose proportional increase in exposure in both rats and monkeys and with m13C7 and romosozumab. Absorption following SC administration was approximately 100% at 1 mg/kg but decreased to about 50% when the rats were administered 35 mg/kg. The T_{max} after SC administration ranged between 24 and 96 hours across the studies and species. The half-life ranged between 6-28 h in rats (m13C7) and 40-71 h in monkeys (romosozumab) with longer times with increased dose.

Distribution

No dedicated studies on tissue distribution were performed and this is considered acceptable. The estimated volume of distribution at steady state (Vss) in rats, 37-59 mL/kg, was in the same range as reported estimates of plasma volumes in rats.

The fetal-to-maternal serum concentration ratio in rat following administration of romosozumab 10 mg/kg was 89% and following 300 mg/kg 41%. The results indicate that romosozumab crosses the placenta.

Metabolism

No dedicated metabolism studies were performed, and this is considered acceptable and in agreement with ICH S6(R1). The metabolic pathways of biotechnology-derived pharmaceuticals are generally understood and include degradation to small peptides and individual amino acids.

Excretion

No excretion of intact romosozumab in urine is expected due to its molecular size. Therefore, no specific studies to measure romosozumab excretion in urine were conducted. The absence of studies is considered acceptable.

Pharmacokinetic drug interactions

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology derived substances do not metabolize via CYP450 enzymes. Therefore, the absence of PK interaction studies is agreed.

Other pharmacokinetic studies

A study was conducted to determine and compare the pharmacokinetics of romosozumab when administered as two different formulations via a single SC injection to cynomolgus monkeys. The exposure of the two different manufacturing processes as assessed by Cmax and AUC was comparable.

2.3.3. Toxicology

The toxicological profile of romosozumab has been evaluated in an extensive set of non-clinical studies. The program includes repeat-dose studies up to 26 weeks with 14 weeks recovery in rats and monkeys; reproductive toxicity studies in rats, a carcinogenicity study in rats, a carcinogenicity study in rats with an "irrelevant" human IgG_2 mAb, local tolerance studies, tissue-cross reactivity study and several mechanistic studies.

The subcutaneous (SC) route of administration was utilized in all toxicology studies to match the intended clinical administration route, with intravenous dosing included in some repeat-dose studies to obtain higher systemic exposures.

The Sprague Dawley rat and cynomolgus monkey were selected as the main rodent and non-rodent toxicology species as romosozumab binds to human, rat, and cynomolgus monkey sclerostin with similar affinity and is pharmacologically active in these species.

Immunogenicity was evaluated as part of the general toxicology program. Romosozumab was immunogenic in the rat, rabbit and monkey. To ensure robust assessment of the toxicity of romosozumab in longer term studies, rats and monkeys positive for ADAs with high signal/noise and reduced serum romosozumab concentration and/or presence of neutralizing antibodies were removed from study and data analyses. Therefore, in studies of longer duration than 1 month, the initial numbers of animals allocated on study were greater than that being evaluated.

Single-dose toxicity

A formal single-dose toxicity study was not conducted. No acute toxicity was observed following a single intravenous dose (300 mg/kg) in cynomolgus monkeys or rats in safety pharmacology studies or after the first dose in repeat-dose toxicology studies in the rat and cynomolgus monkey at dose levels up to 300 mg/kg IV and SC.

Repeat-dose toxicity

Romosozumab has been evaluated in repeat-dose toxicity studies in rats (up to 26 weeks with 14 weeks recovery) and in monkeys (up to 26 weeks with 14 weeks recovery).

A 4-week repeat-dose study was also conducted in the rabbit to evaluate the suitability of the rabbit as a second species for developmental toxicity studies. Romosozumab was highly immunogenic in the rabbit resulting in immune complex disease in some animals and thus was considered unsuitable for assessment of potential developmental toxicity of romosozumab.

In view of the MoA of romosozumab, pivotal toxicology studies included assessment of one or more of the following endpoints: bone formation and resorption biomarkers; cancellous and cortical bone densitometry, cancellous and/or cortical bone biomechanical strength, and bone histomorphometric indices. As these data are not considered to add critical value from a toxicological perspective, only high-level results of these investigations are presented.

Romosozumab treatment was generally well tolerated with minimal inflammatory infiltrates at injection sites in repeat-dose studies in rat and monkey. Romosozumab-related effects observed in the rat and monkey administered doses up to 300 mg/kg/week for 14 days or 1 month and up to 100 mg/kg/week for 6 months were either a direct or indirect consequence of the pharmacological effects on bone.

Primary effects on bone
At all dose levels up to 100 mg/kg/week (the maximum dose level in both species) in the 26-week studies, the combined histomorphometric, densitometric, biomechanical, and/or bone biomarker data in the rat and monkey collectively support that romosozumab increased bone formation on cancellous, endocortical, and periosteal surfaces with maximal effects on bone formation biomarkers at 4 weeks that progressively declined with continued treatment. In rat, thickening of calvarium and long bones, and firm bone marrow was evident macroscopically. Dose-dependent increases in cortical and cancellous bone mass were observed in the rat and monkey. Some partial reversal of the bone mass effect was apparent at the end of recovery in both species, notably at the lower doses.

Biomechanical and ash testing of bones in the monkey demonstrated that normal bone quality and mineralization was maintained with romosozumab treatment. There were no notable effects on bone resorption parameters during dosing, and minimal increases were observed during the recovery period in the rat.

Secondary effects
As a consequence of the increased bone formation, the bone marrow space was reduced leading to impaired erythropoiesis.

In rats, this was reflected as decreases in erythrocyte parameters (red blood cell count, haemoglobin and haematocrit; up to 16%) and an increase in red cell distribution (up to 20%). These decreases in erythrocyte parameters were generally associated with dose-related decreases in platelet number (up to 19%). A regenerative red cell and platelet response was indicated by significant increases in reticulocytes (up to 101%) and platelet volume (up to 10%). These effects on hematology parameters were seen at all dose levels (i.e. ≥ 10 mg/kg/week) and showed evidence of reversibility during recovery. As a compensatory mechanism, increased spleen weights and increased extramedullary hematopoiesis in spleen and liver was observed.

In monkeys administered romosozumab for 26 weeks, hematologic changes included slight decreases in mean red cell number (up to 12%) observed at all dose levels. The clinical trial data indicate that romosozumab at 210 mg QM for 1 year does not have effects on hematopoiesis as there were no major changes in hematology parameters.

Additional alterations in clinical pathology parameters observed in the 26-week monkey study include reversible transient reductions in serum calcium and phosphorus (up to 16% in males at 100 mg/kg/week) at Weeks 4 and 12. As the decreases corresponded temporally to maximal increases in bone formation markers, the reductions are considered consequences of the high demand for calcium and phosphorus to support normal bone mineralization. Transient hypocalcaemia has been observed in patients receiving romosozumab (SmPC section 4.8), and contraindication in uncorrected hypocalcemia is included in section 4.3, and

recommendations regarding monitoring and vitamin supplementation is included in section 4.4. In addition, hypocalcemia is proposed as an important identified risk in the RMP.

In rats, reversible increases in serum phosphorus and urea occurred at 100 mg/kg/week in males and transient dose-dependent increases in glucose in females at equal to or greater than 10 mg/kg/week. No effect on glucose levels was observed in monkey at exposures up to 200-fold greater than the clinical AUC exposure.

Genotoxicity

Romosozumab is a recombinant protein made up entirely of naturally occurring amino acids and contains no inorganic linkers, synthetic organic linkers or other non-protein portions. Therefore, romosozumab would not react directly with DNA or other chromosomal material and no genotoxicity studies have been conducted. This is agreed.

Carcinogenicity

Carcinogenicity assessment is based on a discussion of sclerostin biology, results of pharmacological and toxicological studies with romosozumab, together with results of a 2-year study of romosozumab in rats and another, pharmacologically inactive but immunogenic foreign IgG2 antibody as additional control.

In the romosozumab 2-year study, treatment was generally well-tolerated at dose levels of 3, 10 and 50 mg/kg/week for 98 weeks. There were no romosozumab-related effects on mortality or cause of death. Pharmacologically-mediated increased skeletal radiopacity, increased bone mass and geometry at the femur metaphysis and diaphysis by pQCT, and microscopic changes of hyperostosis of bones, and secondary extramedullary hematopoiesis in spleen and liver, and mononuclear cell infiltrate at the injection sites were observed. Two tumors reached statistical significance, renal lipoma in females at 50 mg/kg/week and adrenal cortical adenoma in males at 10 mg/kg/week. Both tumors are considered incidental and not related to romosozumab administration. Although not statistically significant, two osteosarcomas were noted in males at the highest dose tested, 50 mg/kg/week (incidence 3.7%), but not in any of the other study groups. Bone neoplasms and osteosarcomas are rare in Sprague-Dawley rats with a background incidence of 0.38%, ranging from 0 to 3.33%, based on historical control data from the Test Facility. Thus, the incidence of osteosarcomas in males at 50 mg/kg/week is slightly outside of the historical control range. There were no metastases noted indicating a late onset and solitary nature and there were no observed proliferative precursor osteoblastic changes or benign bone tumors. The predicted $AUC_{0\text{-}168h}$ exposure in the three treatment groups have been calculated using the Week 25 steady state $AUC_{0\text{-}168h}$ values from the 6-month repeat dose rat study based on exposures in ADA-negative animals and are 1840, 12900 and 62000 µg·h/mL at 3, 10 and 50 mg/kg/week, respectively. The corresponding AUC exposure margins are around 0.6, 4 and 19 versus the clinical therapeutic exposure.

An additional lifetime study in rats was conducted with an irrelevant antibody (AMG 589, a human IgG_2 monoclonal antibody to human calcitonin gene related peptide) that is pharmacologically inactive and immunogenic in the Sprague Dawley rat to determine possible effects related to lifetime exposure to a foreign antibody. The weekly subcutaneous administration of AMG 589 was well-tolerated at 50 mg/kg/week for up to 98 weeks. There was no neoplastic change attributed to AMG 589. Non-neoplastic changes consisted of increased incidence of minimal mononuclear cell infiltration at the injection site and was graded minimal in most affected animals.

Reproductive and developmental toxicity

A full reproductive and developmental toxicity package has been performed in rats, including preliminary and definitive embryo-fetal development (EFD) studies, a combined fertility and EFD study, and a pre-and post-natal development study. Romosozumab treatment was generally well tolerated across studies.

Male and female fertility
In the combined fertility and EFD study, there were no romosozumab-related effects on mating, fertility, or male reproductive assessments (sperm parameters or organ weights), and there were no effects on estrous cycling or any ovarian or uterine parameters. The NOAEL for male and female fertility is therefore 300 mg/kg/week. Mean maternal romosozumab exposure ($AUC_{0\text{-}168h}$) at 300 mg/kg on GD 13 was 179.8 mg·h/mL and represents around 59-fold margin over clinical AUC exposure.

Embryo-fetal development
The effect of romosozumab on embryo-fetal development was evaluated in one DRF study and in 2 pivotal EFD studies. In the combined fertility and EFD study, no romosozumab-related external or visceral malformations or variations and no skeletal malformations were observed. At 300 mg/kg/week, 3 fetuses (2.0%) from 3 litters (13.6%) had reduced ventral processes on the 6th cervical vertebra (synonymous with "the arch(es) in the 6th cervical vertebrae having the appearance of the arch(es) in the 7th cervical vertebra"), which was attributed to romosozumab. At 300 mg/kg/week, maternal romosozumab exposure ($AUC_{0\text{-}168h}$) on GD 13 was 179.8 mg·h/mL and represents ~59-fold margin over clinical AUC exposure. The mean fetal romosozumab serum concentrations on GD 20 was 114 μg/mL.

In the DRF EFD study, there were no romosozumab-related effects on maternal, embryo, or fetal parameters, including external, visceral or skeletal fetal malformations or variations. Exposures ($AUC_{0\text{-}144}$ GD 13) achieved in dams at 300 mg/kg/week was 103 mg·hr/mL representing around 30-fold margin over clinical AUC exposure, which is a conservative estimate of the margin because it is based on $AUC_{0\text{-}144}$ rather than $AUC_{0\text{-}168}$. The mean fetal romosozumab serum concentrations at 300 mg/kg/week on GD 19 was 65.8 μg/mL.

In the pivotal embryo-fetal development study, there were no romosozumab-related effects on maternal or litter parameters or fetal soft tissue malformations or variations. Like in the combined fertility and EFD study, the skeletal variation of reduced ventral processes of 6th cervical vertebrae was observed at ≥100 mg/kg/week. At 100 mg/kg/week, this variation was observed in 4 fetuses (2.2%) of 4 litters (16.7%), and at 300 mg/kg/week, it was observed in 5 fetuses (3.0%) of 4 litters (18.2%). As the incidences were dose-related and exceeded testing facility historical control range, the alteration is considered related to romosozumab administration.

External fetal malformations were observed in 1 of 22 litters at 300 mg/kg/week. Seven of 16 fetuses from this litter had external malformations of extra digits on the fore- and/or hindpaws; 6 of 7 fetuses also had external malformations of fused digits. In addition to these external malformations, 3 of 7 fetuses had associated skeletal malformations including extra digits, extra distal phalanges, fused phalanges, absence of ossified metacarpals, and/or bent tibia in fore - and/or hind-limbs, as well as skeletal variations that included incompletely ossified phalanges, misaligned metacarpals, large ulnae, misaligned metatarsals and large tibias, irregularly shaped metacarpals, broad ribs, irregularly shaped ilia. At GD 21, the dam of this litter (#10979) was ADA-positive with serum romosozumab concentration lower than the group mean at 300 mg/kg (83.9 μg/mL versus a mean of 121 μg/mL). Although the gross external and skeletal malformations occurred in only one litter, the litter and fetal incidences exceeded the historical range of the testing facility at the time of the conduct of this study.

Pre- and post-natal development

There were no romosozumab-related effects on maternal parameters. For the F_1 generation during the pre-weaning period, there were no romosozumab-related effects on clinical signs, macroscopic observations including external malformations of the digits, pup viability, or pup body weights. On lactation day 21, there were no effects on femur length and no romosozumab-related microscopic changes in the femur. No skeletal abnormalities in the C6 cervical vertebrae in F_1 generation pups were observed indicating that the reduced ventral process finding in fetuses represent a developmental delay. pQCT revealed slight changes in femoral bone mass or cortical geometry. At lactation day 21, total and cortical/subcortical femoral metaphyseal vBMC and vBMD (males and females) and trabecular vBMC and vBMD (females) were minimally decreased at ≥ 60 mg/kg/week.

For the F_1 generation pups that continued on study after lactation day 21, there were no romosozumab-related effects on survival, growth, sexual maturation, behavioral endpoints (learning and memory or activity), mating and fertility, male reproductive organ weights or ovarian and uterine parameters, or macroscopic observations. In conclusion, romosozumab had no adverse effects on pre-and post-natal development endpoints in the rat.

Local tolerance

Studies were performed to evaluate the local tolerance of romosozumab at different concentrations and the two formulations used in the nonclinical and clinical program, Process 1 (sodium acetate formulation) and Process 2 (calcium acetate formulation). The results show that the local response to romosozumab is concentration-dependent and that both formulations elicit similar responses at a fixed concentration. The sodium or calcium acetate formulations of romosozumab were used in repeat-dose toxicity studies in which romosozumab was well-tolerated locally and was associated with minimal inflammatory infiltrates.

Immunogenicity

Immunogenicity was evaluated as part of the general toxicology program. Romosozumab was immunogenic in the rat, rabbit and monkey. ADAs had minimal impact on studies up to 1-month duration as 3 to 4 weeks of dosing is generally required for an immune response. To ensure robust assessment of the toxicity of romosozumab in longer term studies, rats and monkeys positive for binding ADAs with high S/N and reduced serum romosozumab concentration and/or presence of neutralizing antibodies were removed from study and data analyses. There were no adverse consequences of ADAs in rats and monkeys. In the rabbit, adverse consequences of the immune response to romosozumab (immune complex disease) occurred in a few animals. It should be noted that immunogenicity to a human protein in non-clinical species is of no predictive value for the clinical situation.

Immunotoxicity

Immunotoxicity endpoints, specifically immunophenotypic analyses of circulating B-cells, were evaluated as part of a 52-week bone quality study in cynomolgus monkeys. This analysis was conducted because reduction in bone marrow B cells has been reported in sclerostin-knockout mice (*Sost*$^{-/-}$ mice; Cain et al, 2012). No romosozumab-related effects were observed on circulating B-cell numbers.

Tissue cross-reactivity

A TCR study was performed with romosozumab using normal tissues from humans, cynomolgus monkeys, rabbits, and rats. *In vitro* binding of romosozumab was observed in osteocytes in cryosections of human, cynomolgus monkey, and rabbit bone samples. Specific binding was not observed in rat bone. Romosozumab

binding was observed in stromal fibres of the aorta or pulmonary artery in a heart section from one monkey where these tissues elements were present.

Mechanistic studies

Transcriptional changes following Scl-ab (r13C7) administration in OVX rats
Two mechanistic studies were conducted in aged OVX rats to gain insight into the acute and chronic transcriptional changes that occur in the osteoblast lineage (i.e. osteoblasts, lining cells, and osteocytes) in response to Scl-Ab (r13C7, a rat version of romosozumab).

During the first week following a single dose of Scl-Ab, an upregulation of a small number of canonical Wnt target genes with known roles in osteoblastogenesis accompanied by upregulation of numerous bone matrix genes were observed. In general, a similar pattern was observed in all 3 cell populations. Among canonical Wnt target genes, *Wisp1* and *Twist1* were the most responsive followed by *Bglap*, *Gja1* and *Mmp2*. The responsive extracellular matrix genes include those encoding specific structural components of osteoid matrix, including collagens and non-collagenous matrix proteins (eg, *Omd*, *Bgn, Dcn, Sparc*), and genes involved in matrix synthesis (eg, *Lepre, Lox, BMP1*) and matrix mineralization (eg, *Alpl)*.

Pathway analyses also indicated that Scl-Ab regulated a limited number of genes related to cell cycle arrest and B cell development. Decreased cell cycle activity was flagged largely due to significantly increased expression of two p53 target genes and cell cycle inhibitors, *Cdkn1a* (*p21*) and *Cgref1*, coupled with a decreased expression of *Cdc25b* in all cell types*.* Cxc*l12* and *Cd24* were identified in the B cell development biological pathways and were significantly downregulated.

Following administration of Scl-Ab for 26 weeks, histomorphometrical analysis of vertebrae revealed a rapid and marked increase in vertebral bone formation rate/bone surface (BFR/BS) and osteoblast numbers (Ob.N) with maximal bone formation rate/bone surface on Day 29, followed by a progressive decline with continued dosing through Day 183. During the recovery, bone formation rate/bone surface was initially suppressed and then returned to vehicle levels. Trabecular bone mass progressively increased through Day 183 and declined during recovery. Osteoclastic surface/bone surface (Oc.S/BS) was decreased during dosing and increased in the recovery period with corresponding changes in expression of major regulators of osteoclastogenesis. Reduction in osteoprogenitors preceded the reduction in osteoblasts and bone formation and correlated with significant transcriptional changes in the osteocyte. Transcriptional changes included induction of signalling pathways known to regulate Wnt signalling and suppress mitogenesis and cell cycle progression. The temporal correspondence of these changes suggests that this coordinated response of downstream regulatory pathways modulates the transcriptional output of canonical Wnt signalling and contributes to self-regulation of bone formation with long-term Scl-Ab treatment. The most significant signalling changes in cancellous osteocytes occurred in pathways that would limit cell cycle progression. The temporal relationship between these transcriptional changes and changes in bone formation rate/bone surface suggests that suppression of mitogenesis and cell cycle progression may contribute to the self-regulation of bone formation observed with long-term Scl-Ab treatment. Evidence of p53 signalling was present in femur cortical osteocytes at times of maximal bone formation and was not associated with a reduction in bone formation. These differences between cancellous and cortical suggest that p53 signalling functions to reduce bone formation in cancellous bone and operates to coordinate proliferation and growth in cortical bone.

Comparison of effects of romosozumab and hPTH in bone
Another study was conducted in adolescent rats to compare the effects of romosozumab and hPTH (1-34) at the level of the osteoblast lineage in vertebrae using stereological methods. Romosozumab generally affected greater increases in cancellous and cortical bone mass than PTH, correlating with bone formation

rate at 4 weeks in the spine and mid-femur without corresponding increases in bone resorption indices. The increases in vertebral bone formation rate at 4 weeks attenuated with continued treatment to a greater extent with romosozumab than with PTH. At 4 weeks, both romosozumab and PTH affected equivalent increases in total osteoblast numbers. Osteoblast density remained similar across groups while mineral apposition rate was significantly higher with romosozumab at week 4, reflecting an increase in individual osteoblast vigour relative to vehicle and PTH. After 26 weeks romosozumab maintained bone formation rate with fewer osteoblasts and lower osteoblast density by increasing the osteoblast footprint (bone surface area occupied by an Ob) and increasing mineral apposition rate, compared with PTH. This reduction in osteoblast density at the formative site was associated with a coordinated reduction in osteoprogenitors that was more pronounced than the effects with PTH. These time-dependent reductions in subpopulations of the osteoblast lineage may be integral to the greater attenuation or self-regulation of bone formation observed at the vertebra with romosozumab. The observation that hPTH requires more osteoblasts at the formative site with correlative increased numbers of progenitors compared with romosozumab indicates potentially greater stimulus for progenitor pool proliferation with PTH, an effect that could increase carcinogenic risk in bone in the rat.

Effect of Scl-Ab on osteoprogenitor proliferation in OVX rats
Following a single Scl-Ab (r13C7) administration at 50 mg/kg, the total number of BrdU-labeled osteoblasts was significantly increased at Day 9 by approximately 270%. Following 4 weekly Scl-Ab administrations at 50 mg/kg, the total number of BrdU-labeled osteoblasts was increased by about 70% compared with concurrent vehicle controls. Although the total number of BrdU-labeled osteoblasts remained increased at Day 29 with Scl-Ab treatment, it was significantly reduced compared with the number of BrdU-labeled osteoblasts at Day 9. The data suggest that the increased osteoprogenitor proliferation attenuates with continued treatment. The decrease in proliferation at day 29 (versus Day 9) occurs coincident with decreases in osteoprogenitor numbers, even though bone formation remains significantly increased and is temporally associated with the onset of transcriptional changes in the osteocyte consistent with suppression of mitogenesis and cell cycle progression. These coordinated effects on osteoprogenitor proliferation and number, coupled with the timing of signalling changes in the osteocyte, suggest that the transcriptional changes in the osteocyte reflect the transcriptional profile in the osteoprogenitors, or the osteocyte directly communicates with or influences the proliferation status of osteoprogenitor populations.

RMP safety specification

The applicant did not identify any non-clinical safety findings to be considered as potential or identified risks in the RMP. This is agreed.

2.3.4. Ecotoxicity/environmental risk assessment

Monoclonal antibodies such as romosozumab are most likely catabolized to individual amino acids and/or small peptides by endogenous proteases and high molecular weight prevents intact urinary excretion and as such, excretion of active drug is not expected. It is not expected to have an adverse effect on the environment. The Applicant has adequately justified the absence of studies to assess the environmental risk of romosozumab.

2.3.5. Discussion on non-clinical aspects

Pharmacology

In vitro pharmacodynamics studies demonstrated that romosozumab binds to sclerostin with high affinity, inhibits binding of sclerostin to the extracellular domains of LRP5 and LRP6 and prevents the inhibitory effect of sclerostin on matrix mineralization in a cell-based assay. This is in line with results presented in the public literature, i.e. in osteoblastic cell cultures treated with sclerostin, Scl-Ab has been shown to restore Wnt signalling (Veverka et al. 2009) and matrix mineralization (Li et al. 2009). The Wnt signalling pathway plays a significant role in skeletal development, adult skeletal homeostasis, and bone remodelling. Inhibition of Wnt/beta-catenin via interaction with LRP4/5/6 in the skeleton seems to be the main mechanism of action, somehow confirmed by the lack of extraskeletal complications in sclerosteosis or van Buchem disease. In addition, Thouverey and Caverzasio 2015 showed that sclerostin can prevent osteoblast differentiation without antagonizing LRP5/6 and can activate platelet-derived growth factor (PDGFR) signalling resulting in the inhibition of osteoblast differentiation in vitro. PDGFR signalling critically regulates post infarction repair (Zymek et al. 2006), which would be reduced or inhibited by romosozumab treatment. The clinical experience with other PDGFR inhibitors, especially Imatinib (having only weak activity against other TKs) showing only rarely cardiotoxic effects, together with the artificial nature of the study published by Thouverey and Caverzasio 2015 (i.e. a minor and transitory increase in p-PDGFR, the "activation of PDGFR signalling required for the inhibitory action of sclerostin on osteoblast differentiation" was only shown in the mesenchymal cell line and not in other cell types closer to osteoblasts, artificially high levels of sclerostin [in excess of 1000-fold higher than circulating sclerostin levels in the human] were used and tested only at a single concentration [10 µg/mL]) do however not indicate any safety concerns in this regards.

In vivo pharmacodynamic effect of romosozumab was demonstrated in rat and cynomolgus monkey models of postmenopausal bone loss and in male cynomolgus monkeys with fibular and ulnar osteotomy at exposure levels similar to the clinical exposure and up 36-fold and 19-fold multiples of the clinical exposure in rats and monkeys, respectively. Romosozumab (or rodent-specific surrogates) displayed dose-dependent increase in bone formation and restoration of bone mass and bone strength as well as improved healing of bones. As romosozumab binds to human, cynomolgus monkey, and rat sclerostin with a similar strong affinity and was shown to be pharmacologically active in rats and cynomolgus monkeys *in vivo*, the rationale for inhibition of sclerostin in the treatment of osteoporosis and the use of rats and cynomolgus monkeys to assess primary- and safety pharmacology studies to support the clinical program is justified.

The initial bone formation response to antibody neutralization of sclerostin occurs via stimulation of osteoblasts and activation of quiescent bone lining cells to produce matrix as evaluated in animal models of osteoporosis (Ominsky et al. 2015). However, sustained treatment with Scl-Ab in OVX rats is associated with a blunting in the levels of serum bone formation markers P1NP and osteocalcin (Stolina et al. 2014). This early reduction of the bone formation response likely reflects changes in the pathways that effect self-regulation following treatment with Scl-Ab. In the studies of romosozumab in rat and cynomolgus monkeys provided, increases in bone mass over time were related to an early increase in bone formation. Furthermore, treatment of rats with the surrogate antibody r13C7 resulted in significantly increased expression of genes coding for Wnt inhibitors (*sost, dkk1, mepe, and dmp1*), also indicating that romosozumab induced bone formation is self-regulated. The effects observed in nonclinical studies were consistent with the overall temporal pattern of serum biomarker responses and increases in BMD observed in humans.

Overall, the *in vivo* safety pharmacology studies performed in normal intact rats and monkeys indicate no adverse cardiovascular effects (ECG, QT/QTc, heart rate and blood pressure) or any other findings concerning the safety parameters after subcutaneous dosing of romosozumab up to 300 mg/kg, with estimated exposure margins of > 210 -fold to the clinical exposure (C_{max}: 28.1 µg/mL at the 210 mg dose).

Based on the expression pattern of sclerostin and its known role as an inhibitor of canonical Wnt signalling, the applicant has provided a comprehensive theoretical discussion on the possible secondary pharmacological effects of sclerostin antibodies and its subsequent activation of Wnt signalling, with possible safety concerns that could be identified. Potential concerns regarding the secondary pharmacology of romosozumab on vascular calcification and cardiovascular safety have been suggested. The applicant was during the procedure asked to further discuss this issue. In response to this question, the applicant has presented a thorough review, including new non-clinical in vivo and in vitro mechanistic data, to clarify the suggested protective role of sclerostin in vascular calcification and provided a detailed discussion on the effect of sclerostin inhibition on promoting atherosclerosis and its possible consequences for cardiovascular safety. A weight of evidence assessment of all available non-clinical data indicates no obvious mechanistic association between sclerostin inhibition and vascular calcification or promotion of atherosclerosis, in normal and/or diseased tissue. Further non-clinical testing is, thus, not likely to contribute to the overall benefit / risk assessment in humans. Therefore, this issue will not be pursued from a non-clinical point of view.

Toxicology

The toxicological profile of romosozumab has been evaluated in an extensive set of non-clinical studies in relevant species and in agreement with applicable guidelines.

Romosozumab treatment was generally well tolerated with minimal inflammatory infiltrates at injection sites in repeat-dose studies in rat and monkey. Romosozumab-related effects observed in the rat and monkey administered doses up to 300 mg/kg/week for 14 days or 1 month and up to 100 mg/kg/week for 6 months were either a direct or indirect consequence of the pharmacological effects on bone.

The available data in the rat and monkey collectively support that romosozumab increased bone formation. As a consequence of the increased bone formation, the bone marrow space was reduced leading to impaired erythropoiesis. The increased bone formation did not cause any adverse clinical consequences, such neurological or locomotor effects in rats or monkeys. Furthermore, no mineralization in tissues outside bone was observed.

In the 1-month rat study, the severity of the hyperostosis was increased in females as compared to males. Likewise, in the 6-month rat study, vertebral cancellous bone formation rates were increased at 10 mg/kg/dose in females but not males, suggesting that the anabolic response on cancellous bone surfaces had attenuated in males. In male rats given 100 mg/kg/dose, dynamic indices of bone formation (reflecting the surface extent of cancellous bone formation) were, in general, decreased compared with controls. The Applicant speculates that the greater hyperostosis observed in the females could be related to the smaller bone area and higher trabecular bone density in this gender at baseline, meaning that any increase in the thickness of the trabecular bone would be more evident in females than males by histopathology. Most importantly, the apparent sex differences in bone mineral density observed in these two rat studies did not appear to impact the intended pharmacology of romosozumab.

A clarification has been provided on the human $AUC_{0\text{-}tao}$ of 12888 µg·h/mL used for the exposure margin calculations. This value represents the clinical exposure as estimated from population PK analysis completed prior to availability of Phase 3 clinical data. In the final population PK analysis including the Phase 3 clinical data, the human $AUC_{0\text{-}tau}$ presented in Report 119384A is 509 µg·day/mL which is equivalent to 12216

µg·h/mL (509 µg·day/mL x 24 h). As this value is within approximately 5% of the human $AUC_{0\text{-}tau}$ value used to calculate the exposure margins, it is agreed that there is no impact on the conclusions previously made.

In the romosozumab rat carcinogenicity study, two osteosarcomas (OSAs) were observed in the male 50 mg/kg/week group (high dose), but not in the other romosozumab-treated groups or in the vehicle control groups. OSAs are rare in Sprague-Dawley rats with a background incidence of 0.38%, ranging from 0 to 3.33%, based on historical control data from the Test Facility. Thus, the incidence of osteosarcomas in males at 50 mg/kg/week of 3.7% (2/54 males) is slightly higher than the historical control range. However, the incidence was not statistically significantly different from the vehicle control incidence. A further discussion on the osteosarcomas has been provided by the Applicant.

In male 4041, one OSA was detected radiographically in the left proximal tibia at Day 572 following early euthanasia (cause of death, pituitary adenoma). This OSA was not observed macroscopically and would likely not have been detected in a standard carcinogenicity study. In male 4069, one OSA was detected radiographically and macroscopically on the frontal bone/skull at Day 587 and was the cause of death due to local extension. There were no metastases in either case and no other bone tumours were identified in the study. With exception of focal osteoblast hyperplasia observed in a single male at 10 mg/kg on Day 534, no pre-neoplastic lesions were observed in the carcinogenicity study, or in a 6-month rat study with dose levels up to 100 mg/kg/week. Focal osteoblast hyperplasia was also observed in one control animal in the rat carcinogenicity study with an irrelevant mAb.

The day of observation of the spontaneous OSAs in the historical control dataset ranged from Day 447 to Day 710, i.e. an onset occurring late in the conduct of the study. The OSAs in the romosozumab-treated males were also observed at a late stage of the study, i.e. on Days 572 and 587, respectively.

It should be noted that the carcinogenicity study included whole-body autoradiography, whereas the historical incidence of OSAs in SD rats at the laboratory at the time this study was conducted was derived from carcinogenicity studies where detection of OSA was restricted to the routine microscopic evaluation of sternum and/or single long bone sections in addition to any skeletal macroscopic abnormalities. Historical data from studies where whole-body radiography was conducted are not available. It is therefore reasonable to assume that the inclusion of whole body radiographs and the expanded bone evaluations would enhance the sensitivity for detection of potentially malignant bone lesions.

The Applicant also briefly presented carcinogenicity data from other bone-forming agents including parathyroid hormone, hPTH (1-84), and its analogue, teriparatide hPTH (1-34) in male SD and/or F344 rats showing a high incidence of OSA (16.4 to 51.7%). These OSAs were often metastatic and were associated with proliferative osteoblastic changes such as osteoblast hyperplasia, focal stromal proliferation and benign bone tumour formation. The earliest time of OSA observation was reported to be around 12/13 months. Taken together, based on the low incidence, the lack of pre-neoplastic lesions, the late onset, and the lack of accompanied metastasis and other bone tumors, the conclusion is that the OSAs are likely incidental in nature. Consequently, these data do not indicate a potential risk to humans regarding bone malignancies.

A complete reproductive and developmental toxicity package in rats has been performed although romosozumab was intended for treatment of osteoporosis in post-menopausal women and in adult men only.-

In the evaluation of male and female fertility, there were no romosozumab-related effects on fertility parameters. In addition, there were no gross or microscopic changes in reproductive organs observed in repeat-dose studies in rats and monkeys for up to 26-weeks of duration.

The effect of romosozumab on embryo-fetal development was evaluated in one DRF study and in 2 pivotal EFD studies. Across EFD studies, a slight increase in the incidence of reduced ventral processes on the 6th cervical vertebrae was observed at 300 mg/kg/week in the combined fertility and EFD studyThe ventral processes develop into the carotid tubercles on the 6th cervical vertebra, an anatomic structure which does not occur in human (Walker 2002). This skeletal variation is considered a developmental delay because development of the ventral processes of the cervical vertebrae proceeds in an anterior-to-posterior direction and the ventral processes on the 7th cervical vertebrae have not started to develop at the time of fetal examination (GD 21). The absence of skeletal abnormalities in the C6 cervical vertebrae in F1 generation pups in the pre- and post-natal development study further supports a developmental delay.

Across the four rat reproductive and developmental studies, external/skeletal digit malformations were observed in 1 of 75 litters (7 of 1021 fetuses or 0.7% incidence) at a dose of 300 mg/kg/week. While it is agreed that the incidence is low, both syndactyly and polydactyly are rare malformations in Sprague Dawley rats. As sclerostin has been suggested a role in digit formation, the Applicant was asked to further discuss the relevance of the digit malformations observed in rats for the human situation.

The Applicant has provided a discussion on the human relevance of the observed external/skeletal digit malformations and argues that the digit malformations are likely unrelated to romosozumab due to the low incidence, and presence in an ADA-positive dam with systemic exposure lower than in other dams at the same dos level. While it is agreed that the incidence of the digit malformations is low, both syndactyly and polydactyly are rare malformations in Sprague Dawley rats. In literature, incidences of syndactyly of 0.01% (0-0.32%; 29 studies), and 0.07% (0-0.73%; 17 studies) are reported (Nakatsuka et al, 1997). The same is true for polydactyly, where incidences of 0.02% (0-0.30%; 29 studies) are reported (Nakatsuka et al, 1997). Also in Ema et al, 2014, low spontaneous incidences of syndactyly are presented; 0.04% (0-0.30%; 7 studies), and 0.08% (0-0.30%; 4 studies).

Sclerostin has been suggested a role in digit formation as shown in humans with loss-of-function mutations in the SOST gene (sclerosteosis) and sclerostin knock-out mice (Sost -/-). Incidence of syndactyly in human subjects with sclerosteosis occurs at a rate of approximately 75% (Beighton et al 1984) and at 4% in Sost -/- mice (Collette et al 2013). As sclerostin has been suggested a role in digit formation, the observed malformations are considered potentially related to romosozumab treatment.

Digit formation occurs late during organogenesis in rats (approximately GD 13 to 17) and humans (approximately GD 37 to 60). In rats, maternal IgG crosses the yolk sac by FcRn-mediated transport mechanisms and significant pre-natal exposure has been reported to occur during the period of organogenesis (DeSesso et al 2012). Although, fetal exposure was not determined at the time of organogenesis in the performed EFD studies, significant fetal romosozumab exposure was reported at GD20 and would be expected to be present at the key period for digit formation. From this perspective, a local direct effect of romosozumab in the rat embryo is considered plausible. On the other hand, in humans, FcRn-mediated placental IgG transfer is low in the period of organogenesis and begins to increase in early second trimester, reaching highest levels late in the third trimester (Pentsuk and Van der Laan, 2009). Thus, the human is unlikely to be at risk from a direct effect of an IgG antibody such as romosozumab on organogenesis. In conclusion, the external/skeletal digit malformations observed in 1 of 75 litters (7 of 1021 fetuses) at a dose of 300 mg/kg/week are considered potentially related to romosozumab treatment as these malformations are rare in SD rats and as sclerostin has been suggested a role in digit formation. However, due to differences in timing of placental IgG transfer between rats and humans, a potential risk to the developing human fetus following maternal exposure to romosozumab is considered low.

2.3.6. Conclusion on non-clinical aspects

There were no objections to approval of Evenity from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

See tables below:
Table 3: Summary of Romosozumab Clinical Pharmacology Studies, and
Table 7. Summary of Studies contributing to the submitted efficacy data in the romosozumab programme

2.4.2. Pharmacokinetics

A total of 19 clinical studies were conducted as part of the romosozumab clinical pharmacology program. Seven studies were designed primarily as clinical pharmacology studies, including studies evaluating healthy subject PK and initial tolerability, patient PK and tolerability, PK in renal impairment, and patient PK and PK/PD studies. An additional 12 clinical studies (ie, biopharmaceutic, efficacy, and safety studies) provided supportive data, including immunogenicity, PK, and PD data for romosozumab including 5 biopharmaceutics studies. A general outline of the studies providing PK information is presented below.

Table 1: Summary of Romosozumab Clinical Pharmacology Studies

Study[a]	Healthy Subjects	Patients[a]	Initial PK/ Tolerability	Intrinsic Factor PK	Population PK	PD	PK Sampling
Healthy Subject Pharmacokinetics and Initial Tolerability							
20060220	●		●		●	●	Intensive
20090378	●		●		●	●	Intensive
Patient Pharmacokinetics and Initial Tolerability							
20060221		●	●		●	●	Intensive
Intrinsic Factor Pharmacokinetics							
20110227	●[b]			●	●	●	Intensive
Patient Pharmacokinetics and Pharmacokinetics/Pharmacodynamics							
20060223		●			●	●	Intensive
20090153		●				●	Intensive
20110253		●			●	●	Sparse
Other Studies Contributing Pharmacokinetic and Pharmacodynamic Data							
Biopharmaceutics Studies[c]							
20101180	●				●	●	Intensive
20120277	●				●	●	Intensive
20090418	●					●	Intensive
20120274	●						Intensive
20150197	●					●	Intensive
Efficacy and Safety Studies in Osteoporosis							
20070337		●			●	●	Sparse
20110174		●			●	●	Sparse
20060326		●			●	●	Sparse
20101291		●			●	●	Sparse
20110142		●			●[d]	●	Sparse
20080289		●				●	None
20120156		●				●	None

BMD = bone mineral density; PD = pharmacodynamics; PK = pharmacokinetics.
[a] Subjects with low bone mass, low BMD, and/or osteoporosis, as defined by BMD T-scores.
[b] Included healthy subjects and subjects with stage 4 renal impairment and end stage renal disease requiring hemodialysis.
[c] Described in Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods of this marketing application.
[d] Study 20110142 data were subjected to an external validation analysis that is described in Report 119384A – Addendum 2.
Note: Population PK analyses were conducted with data from 8 phase 1 studies, the 2 phase 2 efficacy and safety studies (20060326 and 20101291), and 2 phase 3 studies (20110174 and 20070337). Pharmacokinetic/PD analyses were conducted with data from Studies 20060326, 20101291, and 20070337.

Romosozumab analysis

A validated enzyme-linked immunosorbent assay was used to quantify serum romosozumab concentrations. The results of the submitted pre-study validation of the analytical method are satisfactory. Polyclonal rabbit anti- romosozumab antibodies influence the analysis. The extent of this influence by human antibodies is unknown. This means that an effect of antibodies on romosozumab exposure is difficult to separate from interference. It may also be easier to detect antibodies in patients with low exposure.

Anti-romosozumab antibody assays
During the clinical studies, the assessment of antibodies against romosozumab followed a standard multi-tier hierarchical approach to identify binding antibodies (ADAs) with screening and confirmation by drug inhibition, using a validated electrochemiluminescent bridging immunoassay (sensitivity 5ng/mL, lower limit of reliable detection (LLRD) 20ng/mL and a drug tolerance level (DTL) of 12.5µg/mL at LLRD). If confirmed positive, serum samples were tested for neutralizing anti-romosozumab antibodies (NAbs) using a validated competitive binding assay (sensitivity 0.125µg/mL, LLRD 0.75µg/mL and a drug tolerance of 62.5ng/mL at LLRD).

The screening assay was set up to allow for 5% false positive results, which is appropriate for ADA screening in favour not to miss true positives. Although some of the measured Cmax levels are well above (30-60 µg/ml) the DTL of 12.5 µg/ml at the LLRD (20 ng/ml), at higher ADA concentrations (~500 ng/ml) the assay is still sensitive enough to detect ADAs in the presence of up to 100 µg/ml of romosozumab in the sample. This is regarded acceptable for studies in which patients were treated with the fixed dose of 210 mg, reaching mean Cmax levels below the DTL.

Overall, the validation of the immunogenicity assays was appropriately conducted. Some issues required clarification.

The applicant has satisfactorily clarified that the method performance characteristics for both assays were established from serum samples from both a healthy population and a romosozumab patient specific population. Further, the applicant has described their efforts to develop a more drug tolerant neutralizing antibody method by introducing an acid-treatment and neutralization procedure to remove drug from antidrug antibody (ADA). However, no improvement could be observed and a 4-month treatment-free period was introduced to allow for drug washout to ensure a reliable assessment of NAb's. This strategy is agreed upon.

Anti-denosumab (AMG 162) antibody assays
For some clinical studies, denosumab was used as an antiresorptive treatment following administration of romosozumab. Samples collected from those subjects were also tested for anti-denosumab antibodies.

The overall approach for detection of binding antibodies against denosumab is regarded acceptable and in accordance with current guidelines and recommendations for immunogenicity assessment. A cell-based bioassay was performed to determine the neutralizing capacity of ADAs based on the principle of TRAP mRNA expression by RAW 264.7 cells after addition of recombinant RANKL. This bioassay strategy for determination of anti-AMG 162 neutralizing antibodies followed recent guidance and was thoroughly validated according to current recommendations.

Mode of PK analysis
Individual serum romosozumab concentration-time data collected with intensive sampling were analyzed by noncompartmental PK analysis methods. Additionally, population PK (PPK) and PK/PD analyses in healthy subjects and postmenopausal women with low BMD or osteoporosis were performed using non-linear mixed effects modelling.

Absorption
The bioavailability of romosozumab was estimated to be 50 to 70% after SC administration of 1 and 5 mg/kg. Generally, Cmax was observed within the first week after administration.

Bioequivalence has been demonstrated between phase III (Process 2 ATO) and commercial substance (Process 2 ARI) in a pre-filled syringe (PFS). Bioequivalence has also been shown between process 2 ARI substance administered as PFS and autoinjector (AI/Pen) as well as the 70 and 90 mg/ml solutions of process 2 ATO substance. The other formulations used during the development give rise to reasonably similar exposure.

Elimination, Dose and time-dependencies
The mode of elimination is likely target binding mediated plus FC-receptor mediated IgG degradation. Romosozumab exhibited nonlinear PK across the SC and IV dose ranges of 0.1 to 10 mg/kg and 1 to 5 mg/kg, respectively (eg, 550-fold increase in mean AUCinf for the 100-fold increase in SC dose from 0.1 to 10 mg/kg). The extent of nonlinearity was most pronounced between 1 and 3 mg/kg s.c.

The serum romosozumab concentrations declined with a mean half-life of approximately 11 to 18 days during the beta (plateau) phase and 6 to 7 days during the gamma (terminal) phase. The different half-lives reflect the nonlinearity. The mean effective t1/2 was 12.8 days. This estimate is likely a reasonable estimation valid for the clinical situation where a 210 mg dose is administered once a month.

No time-dependency in the pharmacokinetics was detected. The exposure at multiple dose conditions is approximately doubled the exposure after a single-dose. Possibly, the accumulation is less pronounced in patients, but data are conflicting. Trough concentrations are slowly increasing over at least one year. (Romosozumab is intended for a 1-year treatment.)

Target population
Comparing results of studies in healthy volunteers and patients using a non-compartmental approach, there are no clear indications that the pharmacokinetics differ between populations. Possibly the accumulation is different, but data are conflicting. No difference in PK between healthy volunteers and patients was detected in the population PK analysis.

Effects of ADAs on romosozumab exposure
A total of 8.8% of subjects in the phase 1 studies and 18.6% of subjects in the phase 2 and 3 studies in women with PMO developed binding ADAs after at least 1 dose of romosozumab.

Neutralizing antibodies were detected in 2.4% (20 of 832) and 0.9%, respectively.

Presence of binding ADAs appeared to decrease romosozumab exposure (trough concentrations) up to 22% at months 3, 6, and 9. The exposures became comparable (less than 10% difference in mean values) at month 12 between ADA positive and ADA negative subjects.

Based on a small data set (low number of patients with neutralising antibodies) at month 3, 6, 9, and 12, the exposure was 33, 46, 58 and 60% lower in patients with neutralising antibodies. At present, as the effect of ADAs on the analysis of romosozumab is not known but interference is indicated from data with rabbit anti-romosozumab. It cannot be concluded that the reduced concentrations are true and not just caused by analytical interference. Regardless, sparse data indicate that the efficacy appears unchanged (Study 20101291). Furthermore, patients with ADA will not be identified during treatment.

Special populations
Ethnicity, age and gender

No clinically significant ethnic differences in romosozumab exposure have been observed. There are no studies in children. Many of the studies where pharmacokinetics has been followed have included elderly patients. There is no conventional study comparing young and elderly patients. The mean (SD) age in FRAME (20070337), ARCH (20110142) and BRIDGE (20110174) was 70.9(7.0), 74.3(7.5) and 72.1(7.3) years, respectively. The age range was 55 to 90 yrs.

A significant effect of gender on CL and central volume was detected in the population PK analysis, where females were found to have a lower exposure than males. However, the difference in exposure between genders was less than 0.8-fold and not considered clinically relevant. Furthermore, the difference in exposure between genders is also counteracted by the effect of bodyweight on exposure, as men have a higher mean bodyweight than women.

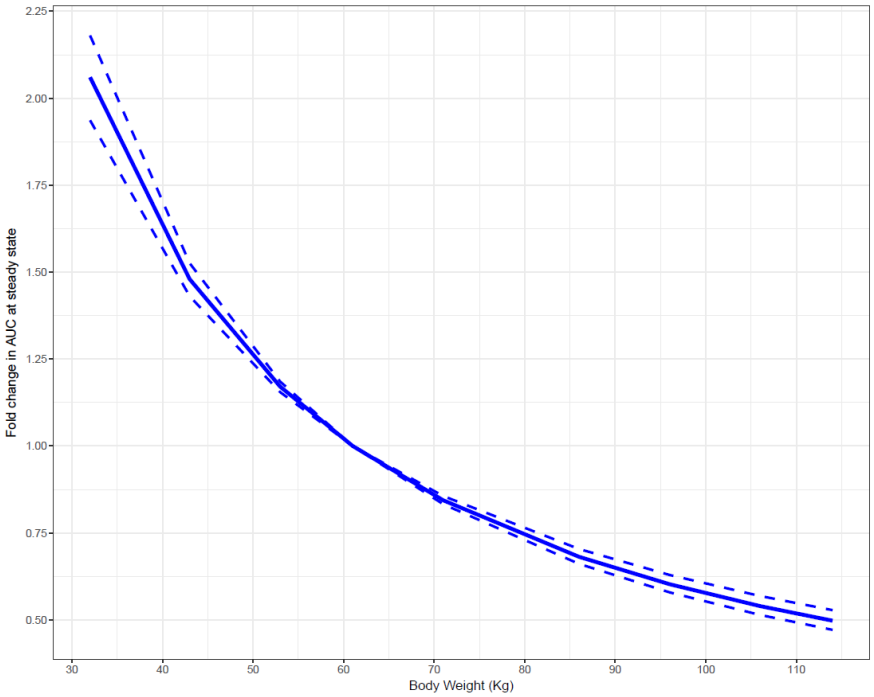
Renal impairment
Impaired renal function has been implicated with disturbances of the Wnt pathway with an elevated level of serum sclerostin reported in CKD subjects. A study was conducted in healthy subjects, subjects with stage 4 CKD (eGFR 15 to 29 mL/min/1.73 m2 or ESRD receiving hemodialysis. The mean exposure (AUC) of romosozumab for subjects with stage 4 CKD was 44% higher than for subjects with normal renal function. Mean romosozumab exposure was similar between subjects with ESRD receiving hemodialysis and healthy subjects. The results from the population PK analysis are in line with the results from the dedicated renal impairment study. The clinical relevance of the increase in exposure in patients with stage 4 RI is unknown. Hypocalcemia was reported in >30% of the subjects with renal impairment. This is further discussed in the Clinical Efficacy and Safety AR.

At present, no other populations with significantly altered sclerostin levels as compared to the phase III population has been identified.

Hepatic impairment
There is no study investigating the effect of impaired hepatic function on the pharmacokinetics of romosozumab. However, no effect is expected unless the sclerostin concentrations are altered.

Body weight
According to the population PK analysis, body weight was found to be the most influential factor of romosozumab PK. Weight-based doses were used in early phase 1 studies. A fixed dose of 70 mg, 140 mg, and/or 210 mg QM was used in all phase 2 and phase 3 studies. The mean exposure was similar when applying weight based (3mg/kg) and when having flat dosing (only one dose level, 210 mg). However, the variability was higher when not applying bodyweight-based dosing. When applying flat dosing, the exposure is doubled in patients weighing 32 kg and halved in patients weighing 114 kg (see Figure 1). Based on clinical efficacy and safety data in patients with low and high bodyweight, the difference in exposure appears to lack clinical relevance.

Figure 1: Fold change in AUC at steady state by body weight (32-114kg): median (solid line) and 95% confidence intervals (dotted lines), based on population PK analysis



Drug interactions

No interaction studies have been performed. Pre-treatment with alendronate did not affect romosozumab exposure. No interactions due to drug induced alterations in sclerostin have been identified.

Exposure relevant for safety evaluation

Data is conflicting regarding the exposure at the therapeutic doses. Using the popPK model, the applicant has simulated that the Cmax would be 33 ug/ml and AUC 633 ug*day/ml. There is a slight accumulation of romosozumab after monthly multiple dosing and the popPK analysis revealed that the exposure is higher in subjects with lower body weight and in patients with stage 4 renal impairment. The PPK-analysis also showed a lower clearance (12% for "manufacturing process 2").

Relationship between plasma concentration and effect

A concentration-response model has been developed to describe the relationship between romosozumab concentration, BTMs (P1NP and sCTX), and BMD gains at the lumbar spine. However, the model predictions indicate clear model misspecification and hence conclusions regarding the concentration-bone turnover markers relationship from the model should not be made. In present state, the model is not advised to be used in future applications.

2.4.3. Pharmacodynamics

Romosozumab is a humanized monoclonal antibody that binds and inhibits sclerostin as primary target. The pharmacodynamics principles have been sufficiently described by the applicant and the choice of PD markers is endorsed as they are considered clinically relevant, commonly used markers. PD evaluations of the effect of romosozumab on bone metabolism markers and bone mineral density (BMD) were investigated in seven phase

I studies in healthy men and healthy postmenopausal women (Study 20060220, Study 20090378), in subjects with stage 4 renal impairment or ESRD requiring haemodialysis (Study 20110227), and in men and postmenopausal women with low BMD or osteoporosis (Study 20060221, Study 20060223, Study 20090153, Study 20110253). Two phase II and five phase III studies provided supportive clinical pharmacology data.

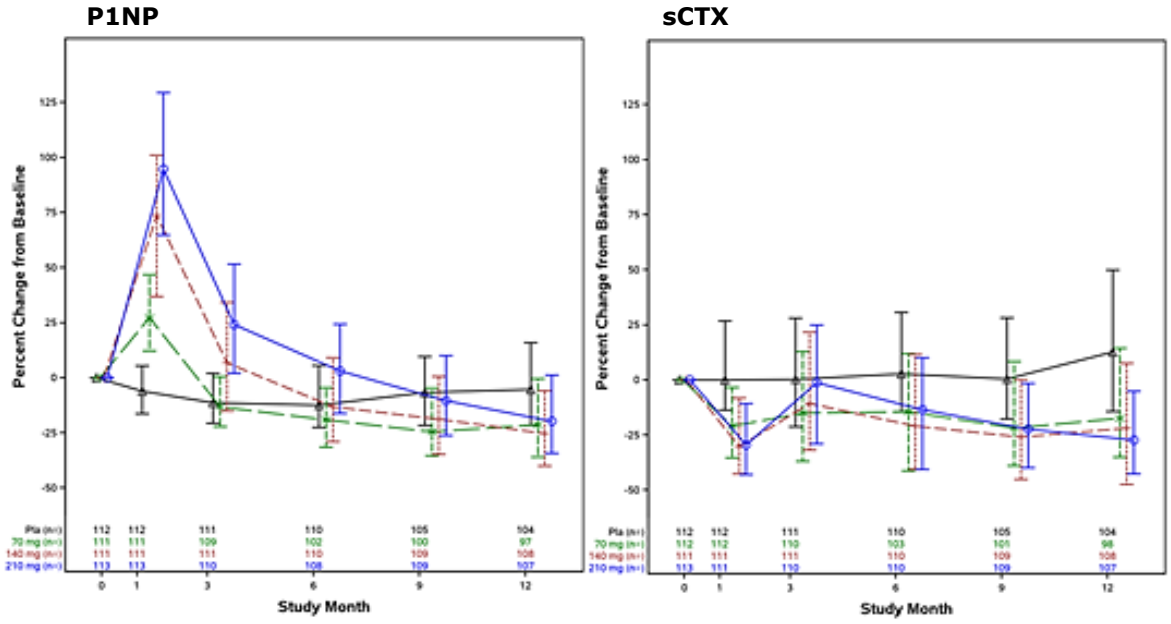
In the first in human study (20060220), romosozumab induced a dose-dependent increase in BMD compared to placebo. Clear differences from placebo in P1NP, BSAP and sCTX concentrations could be seen for doses ≥1mg/kg SC. Doses of ≥3mg/kg romosozumab SC showed a clear difference from placebo in osteocalcin concentrations. Due to a serious adverse event (nonspecific hepatitis) in the 10mg/kg dose group, the dose was decreased to 5mg/kg. As effects were more pronounced in the dose groups over ≥1mg/kg and antibodies were only detected in the higher groups of 5 and 10mg/kg in this study, doses from 1 to 3mg/kg were selected for the following studies.

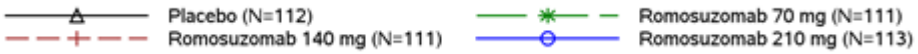
Bone turnover markers (BTMs)

Following a single dose SC dose of romosozumab at 0.1 to 10 mg/kg, increases in the bone formation marker P1NP (procollagen type 1 N-telopeptide) levels were observed for doses from 3 mg/kg. The bone resorption marker sCTX (type I collagen C-telopeptide) levels decreased following administration of doses greater than 1 mg/kg. For both markers, the change from baseline reached maximum 1-2 weeks after exposure and return to baseline after 8-12 weeks.

In phase 2 dose-finding study 20060326, five romosozumab dosing regimens (70 mg QM, 140 mg Q3M, 140 mg QM, 210 mg Q3M, 210 mg QM), placebo, alendronate and teriparatide were evaluated regarding BTM. In study 20101291, three romosozumab doses (70 mg QM, 140 mg QM and 210 mg QM) were compared to placebo.
The combined results on P1NP and sCTX from the two studies (QM romosozumab dosing regimens and placebo) are shown in Figure 2. The results were used in determining the dosing regimen for the pivotal studies, as discussed below.

Figure 2: P1NP and sCTX Percent Change from Baseline by Visit Median and Inter-quartile Ranges (Dose-ranging Efficacy Analysis Set Study 20060326 and 20101291)





In the two pivotal phase 3 studies in women, the romosozumab effect on BTM was evaluated in substudies. In 20070337, 64 subjects in the romosozumab/denosumab group and 65 subjects in the placebo/denosumab group were included and in 20110142, 157 subjects from the romosozumab treatment arm and 141 subjects from the alendronate arm were included. The results from the two studies were similar. The results from study 20070337 are presented in Figure 3 and Figure 4.

Figure 3: P1NP Percent Change from Baseline by Visit Median and Inter-quartile Ranges (BTM and Biomarker Substudy Efficacy Analysis Set) (20070337 24-Month Primary Analysis Period)

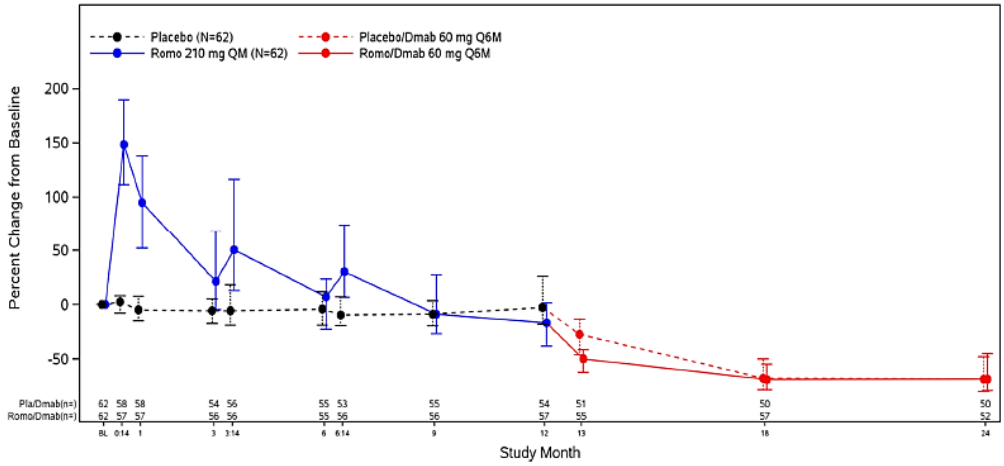
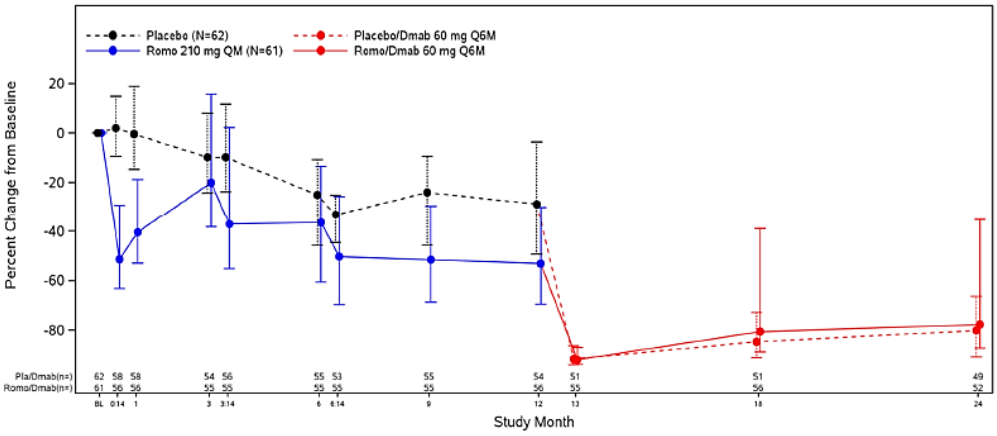


Figure 4: sCTX Percent Change from Baseline by Visit Median and Inter-quartile Ranges (BTM and Biomarker Substudy Efficacy Analysis Set) (20070337 24-Month Primary Analysis Period)



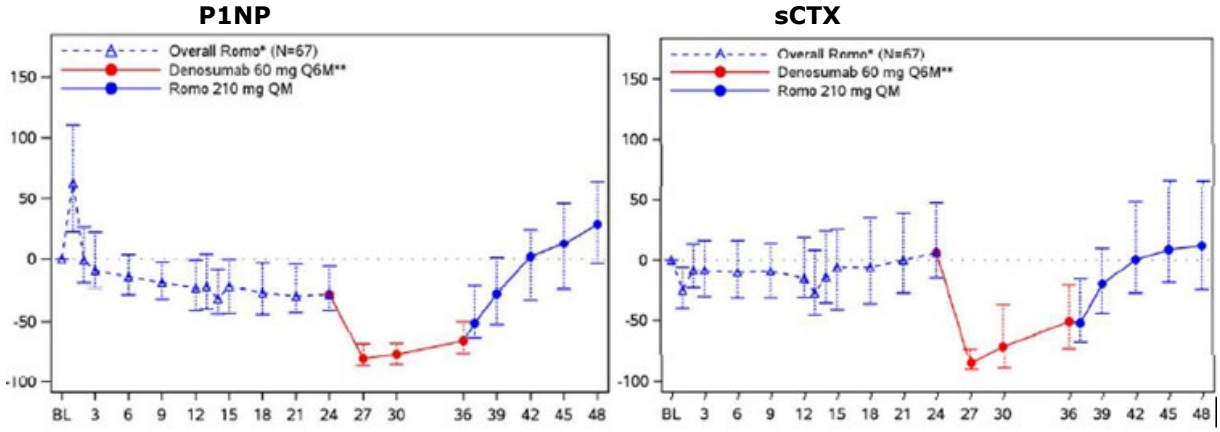
It is noted that the range of values was large (e.g. serum C-telopeptide (sCTX) ranged from 43 to 4597 ng/L at baseline in the romosozumab group in 20070337).

The bone formation marker P1NP showed a rapid increase in the romosozumab group that peaked at time point of first assessment (day 14 in 20070337**;** 1 month in 20110142) and returned to baseline by month 9 in 20070337 and by month 6 in 20110142.
In both studies, serum concentrations of bone specific alkaline phosphatase (BSAP) and osteocalcin followed a similar pattern to P1NP, peaking at month 1 and declining thereafter, with levels near baseline at month 12.

Samples for the bone resorption marker sCTX were collected in the fasted state and at approximately the same time of day throughout each study as recommended. sCTX decreased in the romosozumab group early in treatment (minimum at day 14) and remained below the baseline level at month 12 in the 20070337 substudy. In 20110142, sCTX showed a similar decrease at month 1 (time point of first assessment) and remained reduced but above the levels in the alendronate group through month 12.
Romosozumab effects on BTM in men with osteoporosis (study 20110174) were comparable to those in study 20070337. In both studies, the median percent change from baseline in P1NP was significantly greater in the romosozumab group than in the placebo group at month 1 ($p<0.001$) and month 3 ($p<0.001$).
In 20070337, in contrary to the other studies, CTX appears to decrease over the first 12 months also in the placebo group. According to the Applicant, this was due to an assay shift due to a change in reagent. Re-testing of all samples in this study showed greater stability in the placebo group. The same pattern on BTM was seen in supportive study 20120156. Study 20080289 evaluated romosozumab effect in subjects with prior exposure to bisphosphonates. P1NP rose rapidly with a peak at 14 days after first dose and trended back towards baseline over the 12-month treatment period. sCTX declined rapidly and returned to baseline by month 3, with levels remaining near baseline for the remaining treatment period.

Study 20060326 included a 12 months off-treatment phase with denosumab or placebo (month 24-36) followed by 12-month retreatment (month 36-48) with romosozumab (Figure 5).

Figure 5: P1NP and CTX Percent Change from Baseline by Visit: Medians and Quartiles (Full Analysis Set for Subjects Enrolled in the Retreatment Phase) (20060326 Interim Analysis [Month 48])



Follow-up treatment with denosumab after romosozumab discontinuation resulted in a sustained decrease of both P1NP and sCTX. Retreatment with romosozumab resulted in a slower but more sustained increase in P1NP compared to the initial romosozumab treatment period. As opposed to the initial treatment period, there was a slow increase in sCTX towards baseline during retreatment, with sCTX above baseline from month 42.

In study 20110227, the effect of romosozumab in subjects with renal impairment (eGFR 15-29 ml/min/1.73m2) or haemodialysis compared to healthy subjects was studied. The number of patients in each group is very limited (N=8) and the standard deviations was very broad. It is considered that data not fully support dosing recommendations in this population.

Sclerostin concentrations

After a single dose of romosozumab 3 mg/kg, total sclerostin levels increased around 10,000% from baseline with a maximum at the first measurement (d 5-8 in 20060223) and slowly returned to baseline.
Also in the pivotal studies 20070337 and 20110142, sclerostin levels were markedly elevated at the first measurement after the first romosozumab administration (20070337 14,700% at day 14; 20110142 8,800% at 1 month). The sclerostin levels remained elevated during romosozumab treatment (20070337 14,000% and 20110142 11,000% at month 12).

It is assumed that the elevated levels of sclerostin are driven by romosozumab-bound sclerostin as antibody-ligand complexes may have a slower clearance than the unbound ligand. According to the Applicant, an assay to measure free sclerostin levels in the presence of sclerostin-romosozumab complex is not available, due to the complexities encountered when developing such an assay.

Immunogenicity (pharmacodynamic and clinical aspects)

Development of ADA

In phase 1-studies, about 7.9% (66 of 832) of the subjects developed binding antibodies after at least 1 dose of romosozumab. All positive subjects showed a persistent binding response with a positive result at the last time point tested. Neutralizing antibodies were detected in 2.1% (18 of 832) of all romosozumab dosed subjects.
Incidence of anti-drug antibodies (ADA) antibodies in studies the phase 2 and 3 studies in postmenopausal women (20070337, 20060326, 20101291, 20120156, 20080289 and 20110142) is presented in Table 4.

Table 2: Anti-Romosozumab Antibodies (all romosozumab doses in phase 2 and 3 studies in postmenopausal women)

Total number of romosozumab treated subjects	6,525
Subjects with result at baseline	6,035
Positive ADA at baseline	30 (0.5%)
Subjects with result post baseline	6,243
Binding ADA:	
Developing	1,147 (18.4%)
Transient	510 (8.2%)
Neutralising ADA:	
Developing	51 (0.8%)
Transient	12 (0.2%)

The incidence of binding and neutralizing antibodies in subjects dosed with romosozumab 210 mg QM was 17.8% (1,053 of 5,913) and 0.6% (36 of 5,913), respectively. This was similar to the incidences in the overall studies.

In study 20060326, no new subject developed positive neutralizing anti-romosozumab antibodies during the retreatment phase having been previously antibody negative.

Effect of ADA on efficacy

The change in BMD from baseline was selected as the efficacy marker to evaluate the effect of binding and neutralizing antibodies on efficacy.

The results from phase 3 studies in are given below (20070337 Table 5; 20110142 Table 6).

Table 3: Bone Mineral Density Percent Change from Baseline by Anti-romosozumab Antibody Status Through Month 15 (Romosozumab Arm in Primary Analysis Set for BMD) (20070337 24-Month Primary Analysis Period)

	Antiromosozumab Antibody Status at Month 15		
Percent Change From Baseline	All Negative Mean (SD)	Any Binding Positive Mean (SD)	Any Neutralizing Positive Mean (SD)
Lumbar spine			
N	2534	636	25
Month 12	13.1 (6.0)	13.1 (5.9)	11.6 (5.0)
Month 24	16.7 (7.0)	16.7 (7.2)	15.1 (7.7)
Total hip			
N	2588	650	25
Month 12	6.0 (4.2)	6.1 (4.2)	7.4 (4.6)
Month 24	8.5 (4.8)	8.8 (5.1)	9.0 (7.6)
Femoral neck			
N	2588	650	25
Month 12	5.5 (4.6)	5.7 (4.7)	7.3 (6.4)
Month 24	7.5 (5.1)	7.7 (5.6)	9.3 (8.9)

Table 4: Bone Mineral Density Percent Change from Baseline by Anti-romosozumab Antibody Status Through Month 18 (Romosozumab Arm in Primary Analysis Set for BMD: Descriptive Statistics, Observed Data) (20110142 Primary Analysis Period)

	Antiromos0zumab Antibody Status Through Month 18		
Percent change from baseline	Antibody Negative (N = 1450)	Binding Antibody Positive (N = 289)	Neutralizing Antibody Positive (N = 11)
Lumbar Spine			
Month 12			
n	1421	283	11
Mean (SD)	13.7 (7.2)	13.8 (7.1)	13.8 (8.5)
Month 24			
n	1299	263	11
Mean (SD)	15.4 (8.4)	14.8 (8.7)	14.0 (7.6)
Total Hip			
Month 12			
n	1463	299	12
Mean (SD)	6.2 (5.3)	6.3 (5.0)	6.3 (4.5)
Month 24			
n	1338	276	11
Mean (SD)	7.2 (5.8)	7.5 (5.7)	6.9 (4.8)
Femoral Neck			
Month 12			
n	1463	299	12
Mean (SD)	5.3 (5.5)	5.3 (5.4)	7.9 (6.4)
Month 24			
n	1338	276	11
Mean (SD)	6.3 (6.1)	6.6 (5.4)	7.5 (4.2)

In studies 20070337 and 20110142, there were no consistent difference in mean percent changes in BMD between subjects with neutralising antibodies compared to subjects with no antibodies. In study 20060326, only 9 subjects developed neutralising ADA (4 in the 140 mg Q3M treatment group, 5 in the 210 Q3M group and 1 in the 210 mg QM group), making any comparisons unreliable.

As opposed to the effect of neutralising antibodies on group level, there was one report of an abating effect of such antibodies on individual level. One subject from phase 1 study 20060220 with positive neutralizing

antibodies was inadvertently enrolled and dosed in a subsequent study (20060221). A rapid decline in romosozumab serum concentrations was observed in this subject after the first dose in study 20060221 and serum concentrations were not measurable after day 6, despite continued dosing. Consistent with these pharmacokinetic data, there were no notable changes in pharmacodynamic markers.

In the study on male subjects with osteoporosis (20110174), no subject developed neutralising ADA up to month 12; however, one subject developed neutralising antibodies during the follow-up period.

Secondary pharmacodynamics

Secondary pharmacology has not been specifically investigated in clinical studies and a discussion on this issue has not been identified in the dossier. Possible secondary pharmacodynamic effects of romosozumab might be mediated via decreased calcium levels. A decrease in calcium levels, followed by increased levels of iPTH could be seen, but only in patients with renal impairment signs of hypocalcaemia could be observed.

Romosozumab is neither expected to affect pharmacodynamic properties of concomitantly administered drugs nor are concomitant drugs expected to affect pharmacodynamic properties of romosozumab; no studies on pharmacodynamic interactions with other medicinal products or substances have been conducted which is acceptable as monoclonal antibodies like romosozumab are large molecules which do not undergo renal or hepatic metabolism. Monoclonal antibodies IgG are eliminated by catabolism and, in case of romosozumab, by degradation of the romosozumab-sclerostin complex. They are therefore not subject to significant drug interactions. There is no evidence to suggest that sclerostin affects the level or activity of inflammatory proteins or cytokines that affect CYP-enzyme expression.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Romosozumab shows an expected nonlinearity in the pharmacokinetics. Elimination is target mediated and Fc-receptor mediated. Clearance is dependent on bodyweight. The exposure is increased in patients with low weight and reduced in patients with high body weight. Presence of ADAs may give rise to increased clearance of romosozumab. However, ADAs appear to interfere with the analysis of romosozumab and ADAs may also be detected more often in patients having reduced romosozumab levels. Thus, the actual effect on PK is unknown. Limited clinical data available does not indicate loss of efficacy of neutralising ADAs and routine ADA analysis is unlikely.

The applicant has submitted satisfactory results from pre-study validations of the romosozumab bioanalytical methods and appropriate assay within-study validation data has been provided.

A higher mean romosozumab exposure has been found in stage 4 renal impairment. Hypocalcaemia was reported in >30% of the subjects with renal impairment. Safety in patients with renal impairment is further discussed in the clinical part of the assessment.

The population PK modelling results indicate that the model describe romosozumab serum concentrations well. The model is descriptive of data, although mechanistic interpretations should be made with caution. The PK covariate analysis is considered adequate. The popPK analysis identified several significant covariates which have been discussed in the appropriate sections.

Pharmacodynamics

Romosozumab induced a rapid, dose-dependent increase in the bone formation marker P1NP in clinical phase 2 and 3 studies, in both men and women. In dose-finding studies 20060326 and 20101291, the dosing regimen romosozumab 210 mg SC QM, which was used in the pivotal studies and is the proposed posology for the commercial product, exerted the largest effect on P1NP. This supports the proposed dosing regimen. In spite of continued dosing, the increase in P1NP was transient and returned to baseline after 6-9 months. The transient effect of romosozumab on P1NP may represent a regulatory mechanism to prevent excessive bone formation. This, together with BMD data discussed in section 3.3.5, supports discontinuing romosozumab after a limited time. The decrease in the bone resorption marker sCTX was also transient and returned towards baseline by 3 months but remained below baseline through 12 months. This supports the proposed duration of treatment of 12 months.
The effect on sCTX was less dose-dependent compared to bone formation markers, indicating that the selected dose of 210 mg QM may promote the most potent bone forming effect, without an increased antiresorptive effect compared to lower doses.

Study 20060326 included a 12 months off-treatment phase with denosumab or placebo (month 24-36) followed by 12-month retreatment (month 36-48) with romosozumab. During denosumab treatment, both P1NP and sCTX decreased markedly and remained >50% below baseline values at month 36. As there was no wash-out period after denosumab/placebo, the BTMs were still considerably lower at the beginning of romosozumab retreatment in denosumab treated subjects. This could be an explanation to the somewhat divergent effect on BTM with romosozumab retreatment after denosumab compared to untreated subjects. This may in part explain the limited effect on BMD with romosozumab retreatment after denosumab (see section 3.3.5).

20080289 included subjects with prior exposure to bisphosphonates. The general effect on BTM indicates that previous treatment with bisphosphonates does not impair the effect of romosozumab treatment, which is further supported by BMD data (see section 3.3.5). The reason for the differences in effect duration compared to studies in bisphosphonate naïve subjects is not fully understood.

The Applicant proposes that the marked elevation in sclerostin levels (11,000-14,000%) during romosozumab treatment represent romosozumab-bound sclerostin, as the concentration profile of sclerostin was similar to that of romosozumab. It is agreed that in some cases, antibody-ligand complexes in may have a slower clearance than the unbound ligand. According to the Applicant, an assay to measure free sclerostin levels in the presence of sclerostin-romosozumab complex is not available, due to the complexities encountered when developing such an assay.

The incidence of binding and neutralizing antibodies in subjects dosed with romosozumab 210 mg QM was 17.8% and 0.6%, respectively, in the phase 2 and 3 clinical studies in women. In the study on male subjects (20110174), no subject developed neutralising ADA up to month 12.
No consistent effect on BMD of neutralising ADA was seen on group level. However, there was one report of an abating effect of such antibodies on individual level.

Taking into account the relatively low number of neutralising antibodies across the studies (0.8% of all romosozumab treated subjects in the 6 phase 2 and 3 studies) and the inconsistency in effect of ADA on mean percent change in BMD at different locations, the problem with developing anti-romosozumab antibodies in efficacy is considered limited.

Secondary pharmacology has not specifically been investigated in clinical studies, but romosozumab can cause a range of secondary effects including hypocalcaemia. Romosozumab is not expected to affect the

pharmacodynamics properties of other medicinal products or substances under concomitant treatment nor are co-medications expected to alter pharmacodynamics properties of romosozumab, as degradation is mediated via catabolism and a specific AMG 785-sclerostin complex and not via renal or hepatic metabolism and sclerostin is not known to affect cytokine or CYP enzyme expression.

Concentration-response

A concentration-response model was developed to describe the relationship between romosozumab concentration, BTMs (P1NP and sCTX), and BMD gains at the lumbar spine. However, the visual predictive checks clearly indicate model misspecification. The final model is not considered adequate to make conclusions on the relation between plasma concentration and the time course of bone turnover markers. Subsequently, in present state, the model should not be used in future applications of romosozumab. However, it is not perceived that further model development would change the dosing recommendation in the present application.

2.4.5. Conclusions on clinical pharmacology

The pharmacodynamic data on bone turnover markers support the proposed romosozumab dosing regimen 210 mg QM.
During romosozumab treatment the serum sclerostin levels increase up to 14,000%. This may be an effect of a slower elimination of antibody-bound ligand. This cannot be further investigated, as it has not been possible to develop an assay to measure free sclerostin levels in the presence of sclerostin-romosozumab complex. However, there are no signs of lack-of-efficacy indicative of increased levels of free sclerostin during the study. In the seven efficacy/safety phase 2 and 3 studies, the number of neutralising antibodies was low (<1%). The effect of such antibodies in bone mineral density was inconsistent. On individual level, there was one report of an abating effect of such antibodies.
Overall the available pharmacokinetic and pharmacodynamic data were found to be adequate for this application.

2.5. Clinical efficacy

Table 5. Summary of Studies contributing to the submitted efficacy data in the romosozumab programme

Study Identifier/Title/	Phase	Population/Subject Number/Centres	Length of Study and Dose	Status
Pivotal studies				
20070337 (FRAME) *A Multicenter, International, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Efficacy and Safety of Romosozumab Treatment in*	3	Postmenopausal women with osteoporosis N = 7,180 (3,589 romosozumab; 3,591 placebo) 222 centres (Europe, Central/Latin	36 months Primary analysis: 24 months (12 months romosozumab or placebo + 12 months of open	Complete

Postmenopausal Women With Osteoporosis		America, Asia/Pacific, North America, and Australia/New Zealand)	label denosumab treatment). 210 mg SC QM	
20110142 (ARCH) *A Multicenter, International, Randomized, Double-blind, Alendronate-controlled Study to Determine the Efficacy and Safety of Romosozumab in the Treatment of Postmenopausal Women With Osteoporosis*	3	Postmenopausal women with osteoporosis and high fracture risk N=4,093 (2,046 romosozumab; 2,047 alendronate) 270 centres (Europe, the Middle East, Central/Latin America, North America, Asia/Pacific, Australia/New Zealand, and South Africa)	Event driven At least >330 subjects confirmed clinical fracture and 24 months (12 months romosozumab or alendronate + 12 months of open label alendronate treatment) Median follow up 33months 210 mg SC QM	Complete
20110174 (BRIDGE) *A Multicentre, Randomized, Double-blind, Placebo-controlled Study to Compare the Efficacy and Safety of Romosozumab With Placebo in Men With Osteoporosis*	3	Men with osteoporosis N=245 (163 romosozumab; 82 placebo) 31 centres (Europe, Latin America, Japan, and North America)	15 months Primary analysis: 12 months (romosozumab or placebo) 210 mg SC QM	Complete
Dose-ranging studies/Supportive studies				
20060326	2a	Postmenopausal women with low BMD N=419 (51 to 54 in each of 5 romosozumab arms; 52 placebo; 55 teriparatide; 51 alendronate) 29 centres (Europe, North America, Argentina)	72 months Primary analysis: 12 months *Treatment details are given below the table.	Complete by the time of this report

20101291	2b	Postmenopausal Japanese women with osteoporosis N=252 (63 in each of the 3 romosozumab groups; 63 placebo)	15 months Primary analysis: 12 months 70 mg, 140 mg, or 210 mg QM	Complete
20120156	3	Postmenopausal women with osteoporosis N = 294 (118 in 70 mg/mL, 123 in 90 mg/mL romosozumab groups; 53 placebo)	9 months Primary analysis: 6 months Romosozumab 90 mg/mL (2 SC injections) vs 70 mg/mL (3 SC injections)	Complete
20080289 (STRUCTURE)	3b	Postmenopausal women with osteoporosis N = 436 (218 romosozumab; 218 teriparatide)	12 months Transition from oral bisphosphonate therapy to romosozumab or teriparatide	Complete

* Study 20060326**:**
Months 1-24: romosozumab 70 mg, 140 mg, or 210 mg SC QM, or 140 mg or 210 mg SC Q3M (24 months) **or** placebo (24 months), **or** teriparatide 20 µg SC QD (12 months) or alendronate 70 mg PO QW (12 months) followed by romosozumab 140 mg SC QM (12 months)
Months 24-36: placebo or denosumab 60 mg SC Q6M
Months 36-48: Romosozumab retreatment (all subjects independent of previous treatment)

Months 48-72: Zoledronic acid 5 mg intravenously or no intervention for an additional 24 months.

2.5.1. Dose response studies

Dose-response study 20060326

Study 20060326 was a randomized, placebo-controlled, parallel group study in postmenopausal women with low BMD. The subjects were treated as described in legend to the table above, and
Table.
The TPTD treatment arm was finalised after 12 months and the ALN treatment arm was crossed over to 140 mg romosozumab QM after 12 months and finalised before the retreatment phase.

The primary analysis was performed at month 12. The primary endpoint was percent change from baseline in bone mineral density (BMD) at the lumbar spine for the individual romosozumab groups and pooled placebo group. Results though 48 months are submitted.

For all subjects enrolled, the mean age was 66.8 years, 86.4% of subjects were white, and the mean baseline lumbar spine and total hip BMD T-scores were -2.29 and -1.53, respectively.

Table 6: DXA Lumbar Spine BMD Percent Change from Baseline to Month 12 (Primary Efficacy Subset) (20060326 12-Month Primary Analysis)

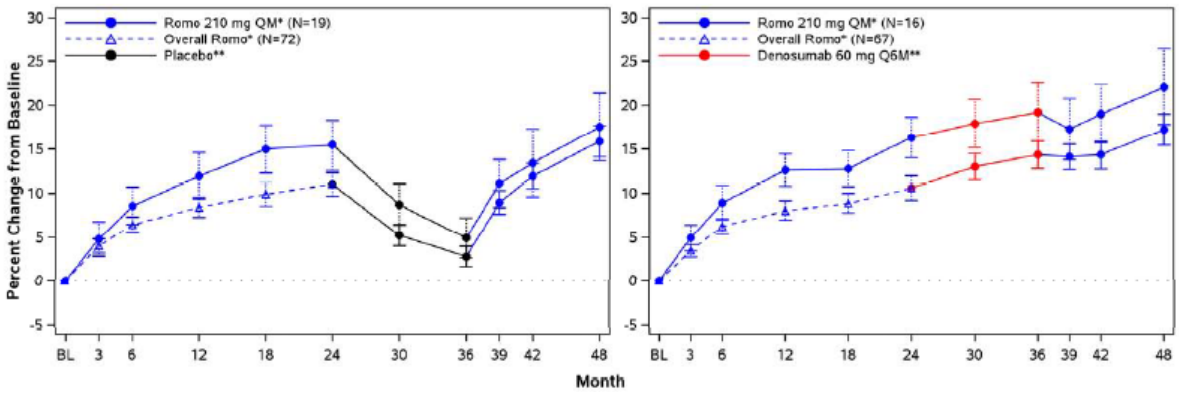
	Placebo	ALN PO	TPTD SC	Romosozumab SC				
	Total (N = 50)	70 mg QW (N = 51)	20 µg QD (N = 49)	70 mg QM (N = 49)	140 mg Q3M (N = 52)	140 mg QM (N = 48)	210 mg Q3M (N = 53)	210 mg QM (N = 50)
Month 12								
n	47	47	46	44	49	46	51	49
LS Mean	-0.1	4.1	7.1	5.4	5.4	9.1	5.5	11.3
95% CI	(-1.2, 0.9)	(3.0, 5.1)	(6.1, 8.2)	(4.3, 6.4)	(4.4, 6.5)	(8.0, 10.2)	(4.4, 6.6)	(10.3, 12.4)
Difference from Placebo [a]								
p-value				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Difference from ALN								
p-value				0.0853	0.0853	<0.0001	0.0853	<0.0001
Difference from TPTD								
p-value				0.0276	0.0276	0.0276	0.0276	<0.0001

ALN = alendronate; BMD = bone mineral density; CI = confidence interval; DXA = dual-energy X-ray absorptiometry; LS = least squares; N = Number of subjects randomized and have baseline and at least one postbaseline BMD measurements on or prior to month 12; PO = orally; QD = every day; QM = every month; Q3M = every 3 months; QW = every week; SC = subcutaneously; TPTD = teriparatide
Linear mixed effects model with the percent change from baseline to months 3, 6, and 12 in DXA BMD as dependent variable, and baseline BMD value, machine type, geographic region, interaction of baseline BMD and machine type, visit, treatment (categorical) and interaction of treatment and visit as independent variables. Data after month 12 are excluded from the models.
[a] p-value is adjusted by the Hochberg procedure for comparison to placebo.

The primary endpoint was met as all romosozumab treatment arms increased lumbar spine BMD compared to placebo (Table 8). The effect was dose-dependent and larger when romosozumab was given QM than Q3M. Up to month 24, fracture event rate was comparable between romosozumab (all doses) and placebo (14/255; 5.5% vs 2/50; 4.0%). The highest number of fractures (6/50; 8.6%) was seen in the romosozumab 70 mg group. The limited absolute number of events, especially in the placebo group, precludes firm conclusions.

In a limited number of subjects treated with 210 mg romosozumab QM after a 12 month off-treatment period with placebo (N=19) or denosumab (N=16), lumbar spine BMD was determined during a retreatment phase with romosozumab (Figure 6).

Figure 6: DXA Lumbar Spine BMD Percent Change from Baseline by Visit (Observed Data) Means and 95% CIs (Full Analysis Set for Subjects Enrolled in the Retreatment Phase and Initially Randomized to Romosozumab) (20060326 Interim Analysis [Month 48])



The effect on lumbar spine BMD of the initial romosozumab treatment was sustained when followed by an antiresorptive agent but returned to baseline if treatment was discontinued. Romosozumab retreatment after an antiresorptive agent resulted only in limited additional increase in lumbar spine BMD and none in total hip and femoral neck. In patients who had discontinued treatment for a year, in contrast, the response to re-treatment was similar to the initial response.

The effect on bone turnover markers in this study is discussed in the Pharmacodynamics section.

Dose-response study 20101291

Study 20101291 was a double-blind, placebo-controlled study in postmenopausal Japanese women with a BMD T-score ≤ -2.50 but not ≤ -4.00 at the lumbar spine or ≤ -3.50 at the total hip or femoral neck. Mean age was 67.7 years and the mean baseline lumbar spine, total hip and femoral neck BMD T-scores were -2.70, -1.94 and -2.29, respectively.

Table 7: Lumbar Spine BMD Percent Change from Baseline at Month 12

		Romosozumab		
	Placebo (N = 59)	70 mg SC (N = 55)	140 mg SC (N = 62)	210 mg SC (N = 59)
LS Mean	0.9	8.4	13.3	16.9
95% CI	(0.1, 1.8)	(7.6, 9.3)	(12.1, 14.5)	(15.5, 18.4)
p-value[a]		< 0.0001	< 0.0001	< 0.0001
p-value[b]			< 0.0001	< 0.0001
p-value[c]				0.0001

The primary endpoint was met as all romosozumab treatment arms increased lumbar spine BMD compared to placebo (Table 9). The effect was dose-dependent.

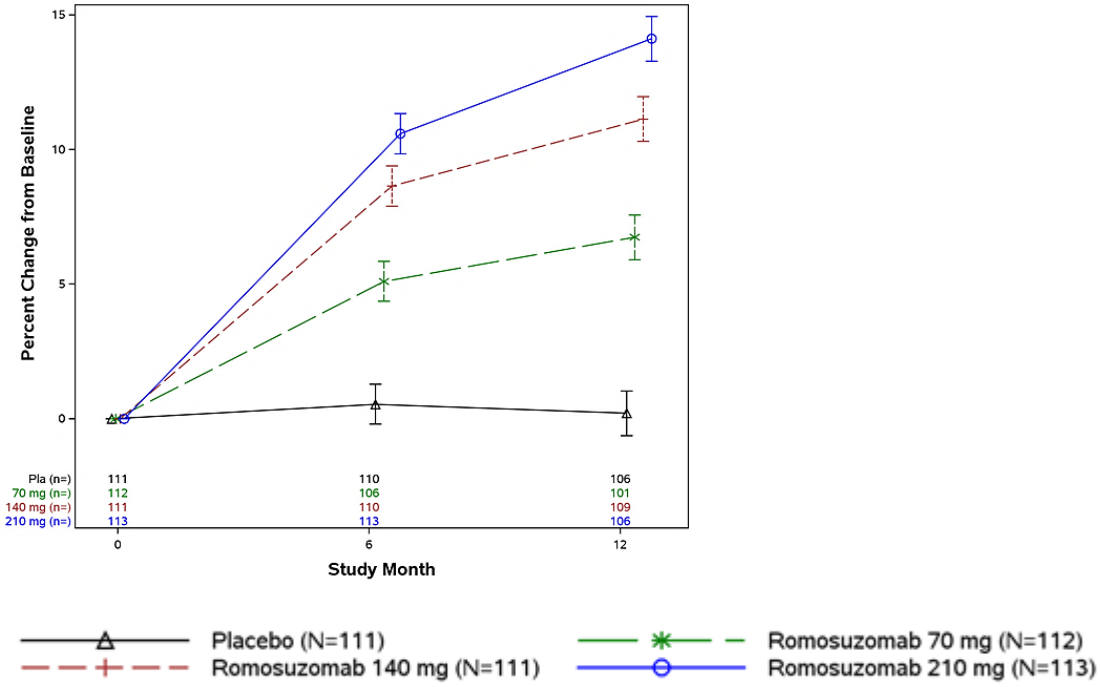
At twelve months, there was a statistically significant increase in BMD with 210 mg compared to 70 mg romosozumab at total hip (4.7 vs 2.1%; p<0.0001) and femoral neck (3.8 vs 1.9%; p=0.0036) and compared to 140 mg romosozumab at total hip (4.7 vs 3.2%; p= 0.0018).

Of the 6 reported treatment-emergent clinical fractures up to month 12, 1 occurred in the placebo group (N=63) and 5 occurred in one of the romosozumab groups (N=189). 1 additional fracture was reported in the placebo group month 12-15. The number of events is too low to enable a comparison between the treatments.

Impact of the results from both studies on dosing recommendations

The combined results from studies 20060326 and 20101291 on lumbar spine BMD are shown in Figure 7.

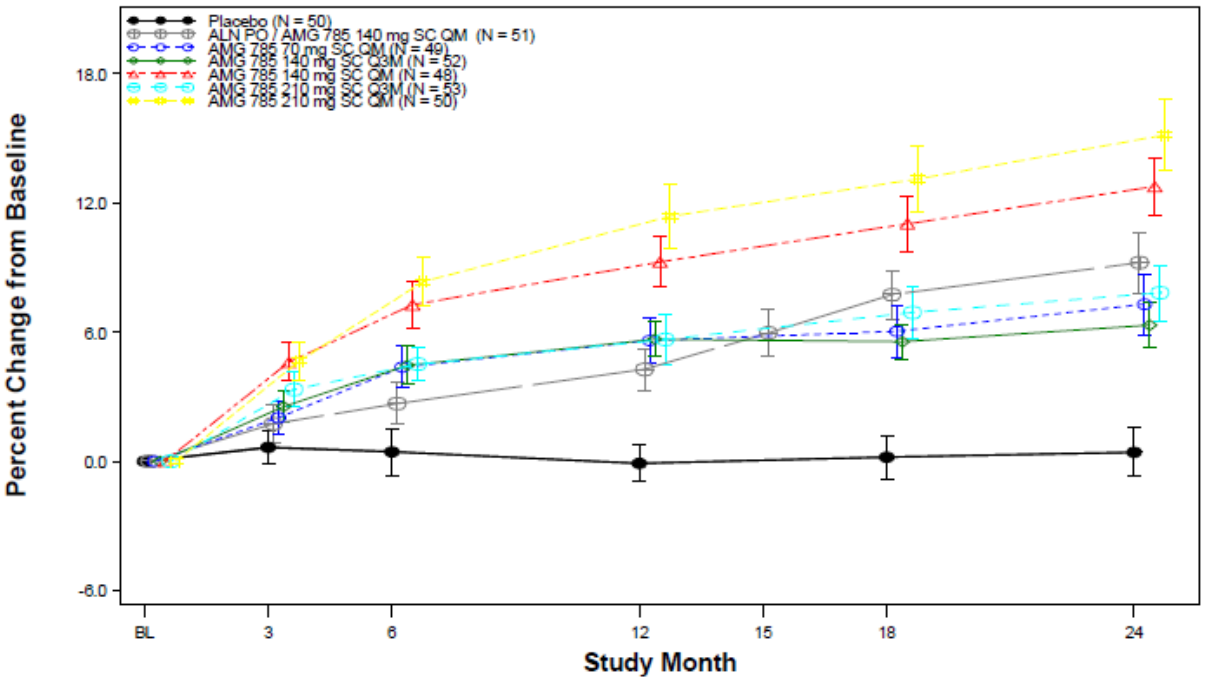
Figure 7: Lumbar Spine BMD Percent Change from Baseline by Visit Least Squares Means and CIs From Repeated Measures Model (Dose-ranging Efficacy Analysis Set)



Romosozumab 210 mg QM was associated with greater increases in lumbar spine BMD than 70 mg QM and 140 mg QM. The results on total hip and femoral neck BMD were similar to the results on lumbar spine. Efficacy was significantly lower when romosozumab was given in 3-month intervals for both of the Q3M doses tested. The same dose-response pattern was seen on bone turnover markers as discussed in the Pharmacodynamics section.

The treatment duration in 20060326 was 24 months (Figure 8).

Figure 8: Lumbar Spine BMD Mean (95% CI) Percent Change From Baseline by Visit (Primary Efficacy Subset) (20060326 Month 24 Interim Analysis)



Lumbar spine BMD continued to increase during the entire treatment period; however, the increase was largest during the first 6 months of treatment. The effect on bone turnover markers was partly sustained through 12 months as discussed in the Pharmacodynamics section. Based on these results, the treatment duration for the subsequent phase 2 and phase 3 studies was decided to 12 months.

In silico modelling studies

A dose-response model, to describe the relationship between dose and BMD gains at both lumbar spine and total hip (119384B) was provided to support the generated data.

In study 119384B (dose-BMD modelling) The applicant developed a model to explain the gain in BMD depending on dose and covariates (race [Japanese vs. non-Japanese], age, age post menopause, body weight, baseline P1NP and baseline sCTX, baseline BMD at lumbar spine or total hip, and prior alendronate or denosumab treatment) including a total of 776 women (postmenopausal women with low BMD, Japanese women with postmenopausal osteoporosis, women with postmenopausal osteoporosis) from two phase 2 studies (20060326 and 20101291) and a sub study of study 20070337. The results indicate a dosing regimen of 210 mg SC QM provided the greatest and fastest BMD gain compared to the other dosing regimens evaluated (mean placebo corrected BMD gains at 12 months at lumbar spine of 11.4% [95%CI: 10.5 to 12.2] and total hip of 6.0% [95%CI: 5.1 to 6.7]). For a given dose similar BMD response at lumbar spine and total hip have been suggested for a monthly and quarterly (3-fold higher) dosing. Romosozumab maximal response (E_{max}) was 31.7% (95%CI: 26.2 to 41.4%) at lumbar spine and 17.0% (95%CI: 14.1 to 22.9%) at total hip. The half-lives associated with the rate of onset are approximately 5.4 months at lumbar spine and 8.25 months at total hip. The final model included the effects of baseline BMD, sCTX, body weight, and study on maximal response and prior treatment (alendronate or denosumab) on rate of onset:

BMD values greater than or less than 0.76 g/cm2 were associated with lower or higher maximal response (0.1 g/cm2 increase or decrease associated with an approximately 5 or 6% decrease or increase). Baseline sCTX values greater than or less than 0.48 ng/mL were associated with higher or lower maximal response. Increasing body weight was associated with reduced maximal response at lumbar spine. Study 20070337 had a 20% higher maximal response (1.2x [95%CI: 0.967 to 1.44]) at total hip whereas maximal response at lumbar spine was the same. Japanese subjects had a higher maximal response at lumbar spine (1.2x (95%CI: 1.1 to 1.39) and a lower maximal response at total hip (0.752x (95%CI: 0.581 to 0.917).

Prior treatment (alendronate or denosumab) slowed the rate of onset for romosozumab treatment effect: alendronate at both lumbar spine (half-lives: 19.4 months) and total hip (40.4 months). Denosumab treatment showed an effect at lumbar spine (half-life of 6.2 months) and was not estimated for total hip.

The applicant included data from 393 postmenopausal women with low BMD, 241 Japanese women with postmenopausal osteoporosis and 142 women with postmenopausal osteoporosis. The index dataset however, contained only data without postmenopausal osteoporosis. The included study population in the final dataset corresponds with the intended target population in women. Although the intended target patients with postmenopausal osteoporosis are underrepresented and more data for these patients would have been preferable, the population is acceptable for the model in women. As the intended indication should also include men it would have been favourable to included data for men as well, especially as the PPK analysis suggests a higher exposure for men.

Japanese patients showed a differing response in both lumbar spine and total hip and even opposing effects were presented. These changes are small and probably not clinically relevant.

2.5.2. Main studies

The pivotal studies consist of two studies in postmenopausal women with osteoporosis and one bridging study in osteoporotic men:

20070337 (FRAME) was a phase 3, global, randomized, double-blind, placebo-controlled study with romosozumab 210 mg SC QM for a duration of 12 months in postmenopausal women with osteoporosis.

20110142 (ARCH) was a phase 3, global, randomized, double-blind, alendronate-controlled study with romosozumab 210 mg SC QM for a duration of 12 months in postmenopausal women with osteoporosis.

20110174 (BRIDGE) was a phase 3, randomized, double-blind, placebo-controlled study with romosozumab 210 mg SC QM for a duration of 12 months in men with osteoporosis.

The two pivotal studies in postmenopausal women are presented together.

Studies 20070337 and 20110142 in postmenopausal osteoporosis

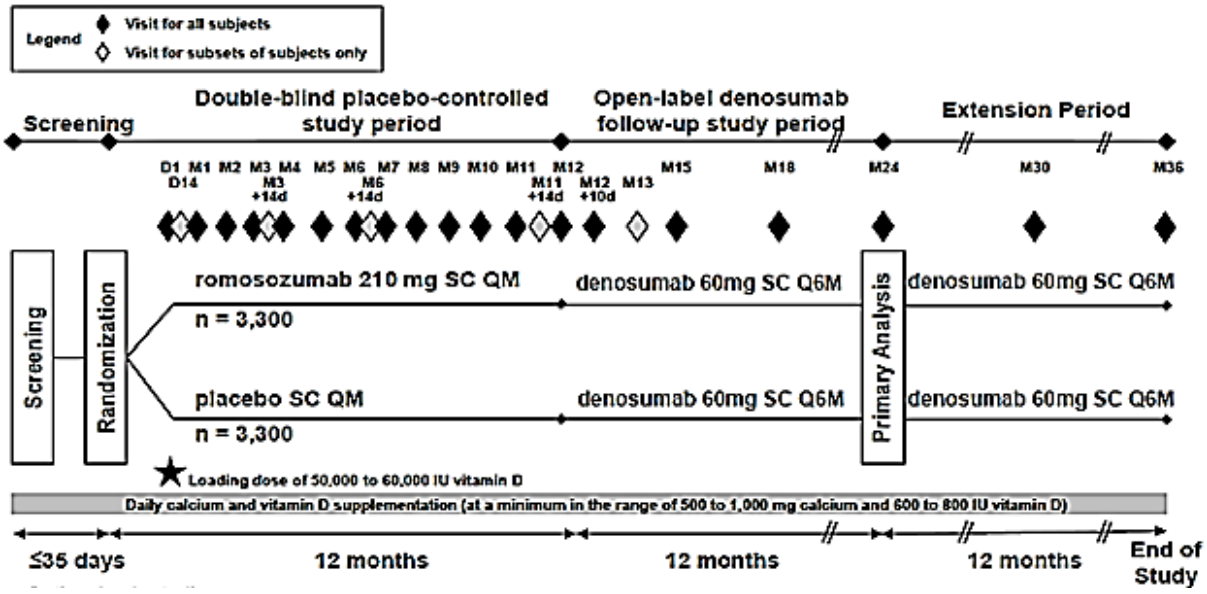
The following discusses the 2 main studies 20110142 (also known as ARCH study), also identified as study 142 in the subsequent text, as well study 20070337 (also known as FRAME study) also identified as study 337 in the subsequent text.

Methods

Study design

The study design for 20070337 is summarised in Figure 9.

Figure 9: Study 20070337 Design and Treatment Schema

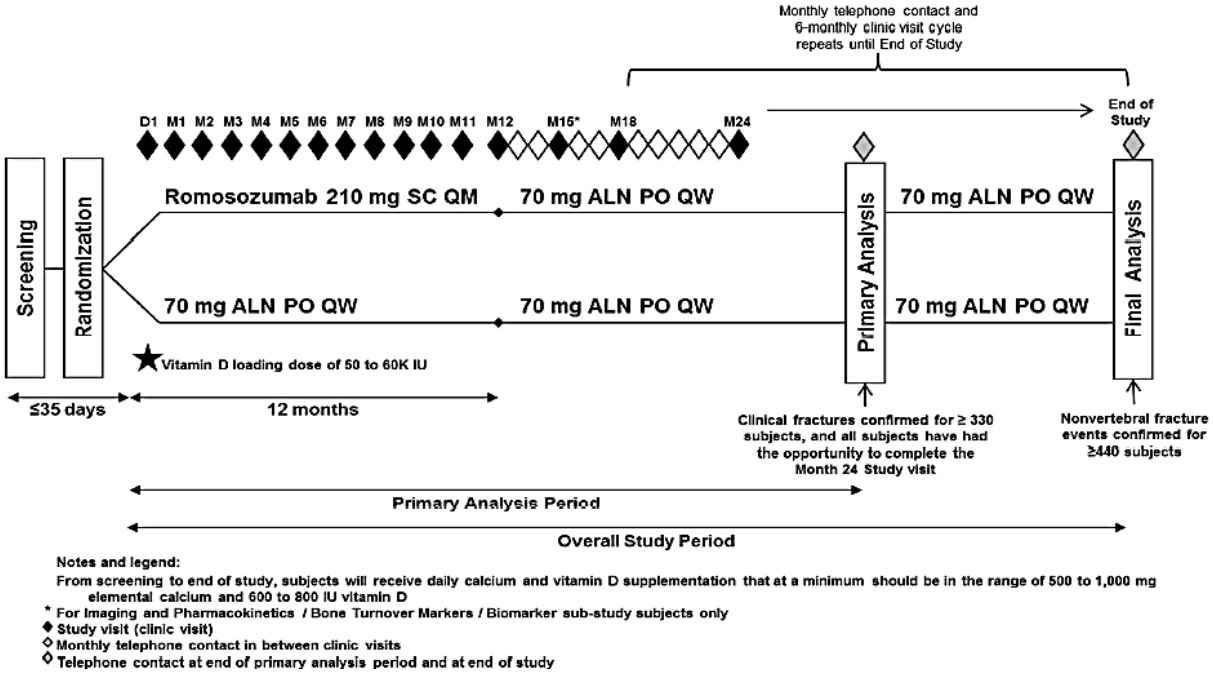


Substudies included the following: Bone turnover marker (BTM) and Biomarker sub-study, Forearm and Total Body DXA and HR-pQCT sub-study (Imaging sub-study I), Lumbar Spine and Proximal Femur DXA sub-study (Imaging sub-study II), Bone Biopsy sub-study, Calcium sub-study, Audiology sub-study, Osteoarthritis sub-study, Serum iPTH and Urinary Calcium sub-study.

In Amendment 4 (18 September 2013), the Applicant extended the trial duration to 36 months by including a 12-month open-label denosumab extension period.

The study design of 20110142 is summarised in Figure 10.

Figure 10: Study 20110142 Design and Treatment Schema



The study also included an imaging, PK, and BTM/biomarker substudy.

Study 20110142 was event-driven. The primary analysis was performed when clinical fracture events (non-vertebral fracture or clinical vertebral fracture) were confirmed for at least 330 subjects and all subjects completed the month 24 study visit. The study continued in an event-driven manner until at least 440 subjects experienced a non-vertebral fracture or if the superiority of romosozumab was proven for non-vertebral fractures at the primary analysis.

Study participants

Study 20070337 was conducted at 222 centres in Europe, Central/Latin America, Asia, North America, and Australia/New Zealand.

Study 20110142 was conducted at 270 centres in North America, Europe, Central and South America, and Asia/Pacific.

Main eligibility criteria are given below.

Inclusion criteria for 20070337

1. Ambulatory postmenopausal women, age ≥ 55 to ≤ 90 years at randomization.
2. BMD T-score ≤ -2.50 at the total hip or femoral neck.
3. At least 2 vertebrae in the L1 through L4 region and at least one hip are evaluable by DXA, as assessed by the principal investigator, e.g., based on lateral spine x-rays

Inclusion criteria for 20110142

1. Ambulatory postmenopausal women, age ≥ 55 to ≤ 90 years at randomization.

2. Subject meets at least one of the following BMD and fracture criteria

- BMD T-score ≤ -2.50 at the total hip or femoral neck AND EITHER at least one moderate (SQ2) or severe (SQ3) vertebral fracture OR at least 2 mild (SQ1) vertebral fractures

or

- BMD T-score ≤ -2.00 at the total hip or femoral neck AND EITHER at least 2 moderate (SQ2) or severe (SQ3) vertebral fractures OR a fracture of the proximal femur that occurred within 3 to 24 months prior to randomization

Exclusion criteria for 20070337

1. BMD T-score ≤ -3.50 at the total hip or femoral neck
2. History of hip fracture
3. Any severe (SQ3) or more than 2 moderate (SQ2) vertebral fractures.
4. History of osteonecrosis of the jaw
5. Contraindicated or intolerant to denosumab therapy (albumin-adjusted serum calcium status will be confirmed at the Month 11 study visit)

Exclusion Criteria for 20110142

1. Exclusion criteria related to contraindications or possible signs of intolerance to alendronate (ALN)

Main other Exclusion criteria for both studies

1. Use of other anti-osteoporotic agents with different, specified time points.
2. History of metabolic or bone disease (except osteoporosis) that may interfere with the interpretation of the results, such as sclerosteosis, Paget's disease, rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, Cushing's disease, hyperprolactinemia, and malabsorption syndrome and history of solid organ or bone marrow transplants
3. Vitamin D insufficiency
4. Current hyper- or hypocalcaemia, uncontrolled hyper- or hypothyroidism or uncontrolled hyper- or hypoparathyroidism
5. Current or possible diagnosis of multiple myeloma or related lymphoproliferative disorder
6. Malignancy within the last 5 years, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ.
7. Subject has any condition or illness (acute, chronic, or history), which in the opinion of the Investigator might interfere with the evaluation of the safety of the study product or may otherwise compromise the safety of the subject
8. Subjects with reported history of hearing loss associated with cranial nerve VIII compression due to excessive bone growth (e.g., as seen in conditions such as Paget's disease, sclerosteosis and osteopetrosis)

The difference in the eligibility criteria regarding BMD T-score limits and fracture history between the two studies allowed inclusion of subjects with a more severe osteoporosis in 20110142.

Treatments

The romosozumab dose 210 mg each month was based on the results from the phase 2 dose-ranging studies 20060326 and 20101291. Protocol required supplementation with calcium/vitamin D as concomitant medication.

To maintain the blind in study 20110142, subjects randomized to romosozumab received placebo for oral alendronate QW and subjects randomized to alendronate received placebo for romosozumab SC QM. After the double-blind period, subjects entered an alendronate follow-on study period in which they received oral alendronate 70 mg QW in an open-label fashion while remaining blinded to their initial treatment assignment.

It is noted, that a non-commercial process 2 ATO (70 mg/mL glass PFS presentation) was used in the main clinical studies. In contrast, process 2 ARI will be used for commercial manufacturing / PFS and prefilled AI/pen with 90 mg/mL romosozumab. This to be commercialised product has been tested in two clinical phase I studies (PK equivalence study 20150197 and equivalence study of auto-injector vs. prefilled syringe 20090418) and in the phase 3 study 20120156.

Outcomes/endpoints

The co-primary endpoint in 20070337 was the subject incidence of new vertebral fracture at month 12 and month 24.
The primary endpoints in 20110142 were the subject incidence of new vertebral fracture through 24 months and the subject incidence of clinical fracture through the primary analysis.

The secondary fracture endpoints in both studies were the subject incidence of different fractures at different time points as summarized in Table 10. Definitions of fracture endpoints are given under the table.

Table 8: Categorization of Fracture Endpoints as Primary, Secondary, or Exploratory in the Pivotal Fracture Studies (20070337 and 20110142)

	Study 20070337		Study 20110142		
Fracture Endpoint	Month 12	Month 24	Month 12	Month 24	Primary Analysis
New vertebral[a]	Co-primary[1]	Co-primary[1]	Secondary	Primary[1]	NA
Clinical	Secondary[2]	Secondary[4]	Secondary	Secondary	Primary[1]
Non-vertebral	Secondary[3]	Secondary[3]	Secondary	Secondary	Secondary[8,b]
Major non-vertebral	Secondary[5]	Secondary[5]	Exploratory	NA	Secondary
New/worsening vertebral	Secondary[6]	Secondary[6]	Exploratory	Secondary	NA
Hip	Secondary[7]	Secondary[7]	Secondary	Secondary	Secondary
Multiple new/worsening vertebral	Secondary	Secondary	Exploratory	Secondary	NA
Clinical vertebral	Exploratory	Exploratory	Secondary	Secondary	NA
Major osteoporotic	Secondary	Secondary	Secondary	NA	Exploratory
All osteoporotic	NA	NA	Secondary	NA	Secondary

a. The number in superscript denotes the testing sequence.

b. In Study 20110142, the testing sequence includes the 2 primary endpoints, 6 BMD endpoints, and then the endpoint for non-vertebral fracture through the primary analysis.

New vertebral fractures occurred when there was ≥ 1 grade increase from the previous grade of 0 in any vertebra from T4 to L4 on the Genant Semiquantitative Scoring Method.

Clinical fractures included symptomatic vertebral and non-vertebral fractures (excluding skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges). Clinical vertebral fractures were included regardless of trauma severity or pathologic fractures; non-vertebral fractures associated with high trauma severity or pathologic fractures were excluded.

Non-vertebral fracture was defined as a fracture present on a copy of radiographs or other diagnostic images, excluding skull, facial, mandible, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, metacarpus, finger phalanges, and toe phalanges. In addition, fractures associated with high trauma severity or pathologic fractures were excluded.

Major non-vertebral fracture was a subset of non-vertebral fractures including pelvis, distal femur (i.e., femur excluding hip), proximal tibia (i.e., tibia excluding ankle), ribs, proximal humerus (i.e., humerus excluding elbow), forearm, and hip.

Hip fracture was a subset of non-vertebral fractures including femur neck, femur intertrochanter, and femur subtrochanter.

Major osteoporotic fractures included hip, forearm, or humerus fractures that were not associated with a pathologic fracture regardless of trauma severity, and clinical vertebral fractures.

Secondary bone mineral density (BMD) endpoints are summarised in Table 11.

Table 9: Non-fracture endpoints in the study 20070337 and 20110142

Endpoint	Study 20070337	Study 20110142
Percent change from baseline in BMD at the lumbar spine	Secondary	Secondary
Percent change from baseline in BMD at the total hip	Secondary	Secondary
Percent change from baseline in BMD at the femoral neck	Secondary	Secondary
Percent change from baseline in BMD at the distal 1/3 radius	Substudy	-
BTMs (various including one or more of the following markers; P1NP, sCTX, OC, BSAP)	Substudy	Substudy
QCT determinations of BMD (at lumbar spine or hip) and/or BMC	Substudy	Substudy
Determinations of bone strength by FEA	Substudy	Substudy

Exploratory endpoints assessing health-related quality of life, pain experience, and activity restrictions during the study and after non-vertebral or clinical vertebral fractures were included in both studies.

Overall, from the romosozumab-licensure perspective, the focus chosen in study 20110142 to primarily investigate fracture protection advantages of a romosozumab-ALN treatment sequence over an ALN-alone treatment after a treatment period of 24 months is not considered optimal. Aside this non-optimality in definition of trial objective and primary endpoints, there is a high level of complexity coming from terminology and statistical analysis strategy, which aggravates reading and interpretation of the fracture data analyses. From a planning perspective, many conditions were set up to define when different analyses for different fracture endpoints were planned to be carried out, in varying analyses sets. Corresponding explanations are hard to follow, as throughout protocol, SAP and CSR the term 'primary analysis' is used in a non-consistent manner, as it sometimes refers to the actual analysis of primary endpoints, but sometimes also just to the point in time when primary endpoints are evaluated (mentioned for the analyses of actual secondary endpoints). As, from an assessment perspective, implications from these findings primarily concern the discussion of study results on secondary fracture endpoints (e.g. non-vertebral fractures), the efforts required to clarify all methodological/terminology issues in this regard are not considered worthwhile.

Sample size

The initially planned total sample size in study 20070337 was 5,600 subjects. The sample size was driven by the non-vertebral fracture endpoint and when study objectives were extended through month 24 (protocol amendment 1, 01 August 2012) the sample size was increased to 6,000 subjects (3,000 per arm).

Due to monitoring of fracture rate during the study by the sponsor, it was observed that the pooled non-vertebral fracture rate was 12.5% (relative) lower than expected under the original protocol assumptions of the incidence of non-vertebral fracture in the placebo group. Based on monitored pooled fracture rates, the final sample size was once again increased to a total of 6,600 subjects in Protocol Amendment 4 (18 September 2013), using assumptions of 2.1% (vs 2.4%) for new vertebral fracture rate and 3.5% (vs 4.0%) for non-vertebral fracture rate in the placebo group during the 12-month double-blind study period. However, there remained an open question concerning trial integrity based on the too limited information regarding the implemented monitoring of fracture data throughout the trial. The fact that sample size changes introduced by amendment 4 where triggered by monitoring of pooled/blinded fracture incidence data is of concern, as the mentioned monitoring was formally introduced by the very same amendment 4.

From the descriptions provided in the dossier it did not became clear what kind of monitoring of efficacy (fracture data) was done, when and how it was implemented, and which measures were foreseen to protect trial integrity as regards trial conduct (e.g. keeping the blind) and data analysis (no inflation of type-1-error by unplanned interim looks). With the answer provided, the Applicant describes interim trial analyses of blinded non-vertebral fracture occurrence data based on e-CRFs during trial conduct, seemingly without basis of an analysis plan for that particular purpose. Prior to Amendment 4, there is no study document which addresses the potential need for a sample size reassessment based on ongoing monitoring of pooled/blinded fracture data. In this context, the potential for unblinding is the most important aspect of concern related to the question of trial integrity. Concerning the measures taken to keep the trial blinded, the Company's reply is acknowledged. However, other related aspects related pertain to unbiasedness of estimates and adequate (non-inflated) type-1-error control, in particular in relation to results presented for the final (primary) efficacy analyses. Given the lack of planning documentation, of how to carry out the blinded review of (pooled) non-vertebral fracture occurrence data prior to writing Amendment 4, there still remained an uncertainty in this regard. The Company was therefore asked to confirm that all decisions taken for subsequent trial conduct following these (formally unplanned pre-amendment 4) analyses had had no relevant impact on the interpretation of the efficacy results. With their answer the Applicant confirmed that no unblinding occurred as a result of the sample size increase described in 20070337 Protocol Amendment 4 Section 10.2.5 or the

monitoring of pooled fracture rate following the implementation of this protocol amendment (refer to 20070337 Protocol Amendment 4 Section 10.2.4). The only data used was the blinded recruitment pattern and the blinded pooled information about accumulated fracture numbers. In addition, the Applicant clarified that no interim analysis (regardless whether formal or informal) was conducted and that, at no time, any odds ratio, risk ratio, or treatment-specific incidence was calculated based on the randomization code. Also, no statistical tests were executed and thus there was no need to adjust the alpha-level for confirmatory testing.

To provide further evidence that the decision to increase the sample size did not introduce a bias, additional post-hoc analyses were performed on subsets of subjects enrolled before and after Protocol Amendment 4. For non-vertebral fractures the Applicant concluded that the subset of patients enrolled before issuing of Protocol Amendment 4 [Subset 1] is mirroring the trending treatment differences seen in the full study result. With their reasonably extended answer, the Applicant confirmed that all decisions taken for subsequent conduct of study 20070337 following formally unplanned pre-amendment 4 analyses have no relevant impact on the interpretation of the efficacy results. Given the answer provided, concerns regarding damaged trial integrity are sufficiently alleviated.

In study 20110142 the sample size was estimated to approximately 4,000 subjects (2,000 per treatment arm). For new vertebral fractures the one-year incidence was expected to be 5.5%. Treatment with romosozumab/alendronate was expected to decrease the incidence of new vertebral fractures by 80%, representing a risk reduction of 50% compared to alendronate treatment alone.

The one-year incidence rate of non-vertebral fractures was expected to be 5.5%. Based on the alendronate treatment assumption, 25% risk reduction, the one-year non-vertebral incidence rate was expected to be approximately 4% when treated with alendronate.

Further, treatment with romosozumab/alendronate compared with alendronate alone was expected to reduce the risk of clinical fractures (non-vertebral fractures and clinical vertebral fractures) by approximately 30%. Under this assumption, subjects would need to be followed until the 330th subject had a confirmed clinical fracture to achieve a 90% power to detect the treatment effect using a 2-sided log-rank test at an overall significance level of 0.05.

Power calculations were also performed for the DXA BMD endpoints; using a two-sample t-test the power for each DXA BMD endpoint was >99%.

Randomisation

In study 20070337 eligible subjects were randomised in a 1:1 ratio to receive either romosozumab or matched placebo in a blinded fashion for the duration of the 12-month double-blind placebo-controlled study period. Randomisation was stratified by age (< 75 years, ≥ 75 years) and prevalent vertebral fracture (yes, no) as determined by site staff at randomisation based on local reading of the spine X-ray.

In study 20110142 eligible subjects were randomised 1:1 to receive either romosozumab or alendronate based on a randomisation schedule prepared by the Amgen Central Randomization Group before the start of the study. Randomisation was stratified by age (< 75 years, ≥ 75 years).

Blinding (masking)

Both studies were to be performed in a double-blind manner.

In study 20070337, each study centre received blinded study boxes that contained either 3 single-use, prefilled syringes (PFS) of romosozumab 70 mg/mL or 3 single-use PFSs of matched placebo. Blinded boxes of investigational product were assigned to specific subjects by box numbers obtained from the IVRS. After the 12-month double-blind placebo-controlled study period, subjects entered the 12-month open-label denosumab follow-up while still remaining blinded to their initial treatment assignment (romosozumab or placebo).

Besides treatment with either romosozumab or alendronate in study 20110142, subjects also received matched placebo for either alendronate or romosozumab. After the initial 12-month study period subjects received alendronate but were to remain blinded to their initial treatment assignment (romosozumab or alendronate); initial treatment assignments were not to be revealed until the study had ended.

In both studies, the assessment of vertebral and non-vertebral fractures and readings of DXA scans was performed centrally using a central imaging vendor. For assessment of incident vertebral fracture, readers were blinded to treatment assignment but not sequence. The imaging vendor charter for study 20070337 had been submitted. For study 20110142, no separate charter had been found. Upon request, the Applicant clarified that the same central imaging vendor as used for study 20070337 was used also for study 20110142. With their response, the imaging vendor charter for study 20110142 was submitted.

Also, and applying to both the studies, to maintain the blind on-study data including e.g. serum calcium, albumin-adjusted calcium, phosphorus, alkaline phosphatase, romosozumab levels, sclerostin and anti-romosozumab antibodies was not to be reported to any study-related personnel.

Statistical methods

In study 20070337, the primary analysis was, according to what had been planned, performed when all subjects had had the opportunity to complete the month 24 study visit.

In study 20110142, the primary analysis period was to end and the primary analysis performed when clinical fracture events (non-vertebral fracture or clinical vertebral fracture) had been confirmed for at least 330 subjects and all subjects had had the opportunity to complete their Month 24 study visit.

All the fracture-related efficacy endpoints were based on the results from the central imaging vendor analysis.

The analysis plan for study 20070337 and study 20110142 respectively shared a number of features. Changes made to each of the study SAP have been accounted for. The final SAP for study 20070337 was dated January 19, 2016. In study 20010142, changes to the SAP were made before the primary analysis data snapshot date of 27 February 2017. The date for database lock and unblinding had not been found for any of the studies. The Applicant provided the requested dates showing that (initial) unblinding in each study was conducted after approval of the (final) SAP. For each study respectively, the Applicant further stated that the primary analysis snapshot reflected a complete and accurate copy of the clinical study database at the date of snapshot. At the time of the primary analysis, neither the study 20070337 nor study 20110142 databases were locked. The Applicant's review of data changes that occurred in the database after the primary analysis identified minor changes in data for both studies without, however, implying any meaningful changes to the primary and key safety results previously reported in the Primary Analysis Clinical Study Reports for either study.

For study 20070337, the primary analysis data cut-off date was 14 December 2015 and the date for primary analysis snapshot and approval to unblind Amgen staff was 12 February 2016. The date for final approval of

the SAP was 19 January 2016. For study 20110142, the data cut-off date for the primary analysis was 27 February 2017 and the date for primary analysis snapshot and approval to unblind independent statistics team that performed the analysis was 18 April 2016. The date for final approval of the SAP was 7 April 2017.

The analyses planned and performed are overall acceptable. The approach to missing data and missing data imputation seemed however to deserve some consideration and clarifications and additional analyses were requested.

The Primary Efficacy Analysis Set for Vertebral Fracture included all randomised subjects who had a baseline and at least one post-baseline evaluation of vertebral fracture at or before the time point under consideration. Subjects with missing baseline Genant semi-quantitative scores were included in the primary efficacy subset if their first post-baseline spinal radiograph showed no fracture on the same vertebra, as they were assumed to have had no fracture of that vertebra at baseline. This analysis set was used as the primary analysis set for new, new or worsening, and multiple new or worsening vertebral fractures endpoints.

The Full Analysis Set included all randomised subjects and was used as the primary analysis set for e.g. non-vertebral fracture, clinical fracture, major non-vertebral fracture, major osteoporotic fracture and hip fracture efficacy endpoints.

Subject incidence of new vertebral fracture was analysed using logistic regression and any missing post-baseline vertebral fracture status due to missing x-ray assessment was imputed using the status from the last non-missing post-baseline visit. This was justified by that a vertebral fracture can only get worse or at best remains at the same severity over time i.e., once a vertebral fracture is identified, the subsequent spinal radiographs will always show fracture. While agreed in case a subject was found to have a vertebral fracture, the approach of carrying forward an early assessment if later assessments were missing in case a fracture was not found is however not that evident. To be included in the primary analysis set a subject was required to have both a baseline and at least one post-baseline assessment. In support of primary analyses, analyses based on the FAS for time-to-first new vertebral fracture using a stratified Cox proportional hazards model were performed. It seemed however as if LOCF was used also in this analysis. This needed to be clarified and if event status (fracture/no fracture), if missing, was carried forward to the end of the analysis period, an analysis of time to first new vertebral fracture through month 12 and month 24 (20070337) and through month 24 (20110142) respectively were to be repeated based on FAS without last observation carried forward and using appropriate censoring rules in case of a subject's early withdrawal from study and/or in case of missing assessments. In response to the above request, the Applicant acknowledged that the term last observation carried forward (LOCF) in the context of the Cox regression analysis for new vertebral fractures was misleading and confirmed that established definitions for censoring and first occurrence of event were applied in time-to-event analyses; no concern is raised, and no additional sensitivity analyses are needed.

For both studies, further supportive analyses, among them an analysis based on the PP set, were planned and have been performed, none of which however offered conservative or alternative methods for missing data imputation. Since stratification differed >5% in study 20070337, an analysis was performed using "verified strata". This analysis is endorsed as for completeness; the impact on the outcomes was small. In study 20110142, the only stratification factor was age and the difference in verified and randomised stratum concerned only 0.1% of the whole study population why the estimates from the analysis based on verified stratification were more or less identical to the result seen in the primary analysis. The primary analysis was further repeated based on the PP analysis set implying that the same approach for missing data imputation as was used in the primary analysis (i.e. LOCF) was used also here.

Time-to-event methods were used for the analyses of other fracture endpoints and were based on the full analysis set that included all randomised subjects which is endorsed. However, not many details regarding censoring rules had been found; in summary, subjects with no event of interest were to be censored for analysis of that event at the end of the analysis period of interest. This is appropriate in subjects who completed each analysis period without having a fracture. How censoring was applied in the time-to-event analyses in case of a subject's early withdrawal from study and missed visits was unclear. Upon request, the Applicant clarified that the censoring date for each study subject depended from her individual study duration and hence, that for patients dropping out earlier, their actual study end date was taken into account in the analysis. This is agreed to be the appropriate handling of censoring.

Also, for the analysis of subject incidence of clinical fracture (a primary endpoint in study 20110142, a secondary endpoint in study 20070337) based on Cox proportional hazards model, it had been stated that missing values for clinical vertebral fractures were imputed by carrying forward the last non-missing post-baseline value prior to the missing value. Given this and the lack of details regarding censoring, the Applicant was requested to clarify how and when LOCF was used in time-to-event analyses whereby the Applicant clarified that subject incidence of clinical fracture was analysed using a Cox proportional hazards model without using LOCF.

For the BMD endpoints, primary analyses were performed using ANCOVA (LOCF) with additional analyses performed using MMRM. Since MMRM analyses addresses the treatment effect if all patients would have been fully adherent, sensitivity analyses not relying on missing at random were requested. In response, the Applicant has provided sensitivity analyses using a control-based pattern multiple imputation approach for missing data instead of last observation carried forward. These sensitivity analyses are supported. Although estimated treatment differences are smaller compared with the pre-planned initially presented analyses, they confirm superior efficacy of the romosozumab arm versus the control arm in each of the studies (placebo in study 20070337 and alendronate in study 20110142). These analyses were based on all randomised subjects (i.e. the Full analysis Set) applying a method to handle missing data that is considered reasonable conservative.
In both studies methods for multiplicity adjustment were applied to maintain the overall 2-sided familywise error rate at 0.05 for the primary and secondary endpoints. Both studies a fixed-sequence testing procedure was used accounting also for multiplicity using the Hochberg procedure. Regarding the use of Hochberg within steps with two tests, in case only one of the analyses had been successful, the strategy had been less optimal since there had been no alpha to pass on to secondary endpoints.

In study 20070337, the sequential Testing Procedure included the following steps:

Step 1: Subject incidence of new vertebral fracture through month 12 and through month 24 (co-primary endpoints; nominal p-value for each endpoint < 0.05)

Step 2: Subject incidence of clinical fracture through month 12

Step 3: Subject incidence of non-vertebral fracture through month 12 and through month 24, using Hochberg procedure at 0.05 level within the step

Step 4: Subject incidence of clinical fracture through month 24

Step 5: Subject incidence of major non-vertebral fracture through month 12 and through month 24, using Hochberg procedure at 0.05 level within the step

Step 6: Subject incidence of new or worsening vertebral fracture through month 12 and through month 24, using Hochberg procedure at 0.05 level within the step

Step 7: Subject incidence of hip fracture through month 12 and through month 24, using Hochberg procedure at 0.05 level within the step

No further adjustment for multiplicity was planned implying nominal p-values for analyses of other secondary, exploratory endpoints and sub study endpoints.

In study 20110142, the primary endpoints were tested at the 0.05 level (2-sided), accounting for multiplicity using the Hochberg procedure. If both primary endpoints were significant at the 0.05 level, each of the following secondary DXA BMD endpoints were to be tested hierarchically at 0.05 according to the following sequence: percent change from baseline in BMD at lumbar spine at Month 24, percent change from baseline in BMD at total hip at Month 24, percent change from baseline in BMD at femoral neck at Month 24, percent change from baseline in BMD at lumbar spine at Month 12, percent change from baseline in BMD at total hip at Month 12, and percent change from baseline in BMD at femoral neck at Month 12. If all preceding endpoints had been significant, the non-vertebral fracture endpoint was to be tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test ($\alpha = 0.025$). The Lan-DeMets alpha spending function that approximates a Pocock boundary will be used to determine the significance level at the time of the primary analysis.

In both studies, additional supportive analyses were planned and have been performed in order to demonstrate the robustness of the results from the primary analysis.

Results

Participant flow

In 20070337, a total of 16,716 subjects were screened for the study and 7,180 were randomized to the romosozumab 210 mg and placebo groups.
In 20110142, a total of 16,916 subjects were screened for participation in the study and 4,093 subjects were randomized to the romosozumab 210 mg QM and alendronate 70 mg QW treatment groups.

A total of 32 subjects in 20110142 and 139 subjects in 20070337 discontinued the study due to "other reasons". The reasons for subjects discontinuing the study within this category varied, with the majority related to personal reasons, moving or logistical issues, or ineligible for the extension period of the study. Only 4 events in romosozumab subjects have been due to an AE. These AEs are however already listed in the AE profiles of the respective studies.

Table 10: Subject Disposition and Investigational Product Completion in the 12 Month Double-blind Study Period of the Pivotal Fracture Studies (Randomized Subjects)

	20070337		20110142	
	Placebo (N = 3591) n (%)	Romosozumab 210 mg QM (N = 3589) n (%)	Alendronate 70 mg QW (N = 2047) n (%)	Romosozumab 210 mg QM (N = 2046) n (%)
Completed double-blind period	3205 (89.3)	3185 (88.7)	1823 (89.1)	1831 (89.5)
Double-blind period investigational product accounting				
Never received double-blind investigational product	9 (0.3)	14 (0.4)	7 (0.3)	8 (0.4)
Completed double-blind investigational product	3135 (87.3)	3103 (86.5)	1738 (84.9)	1750 (85.5)
Discontinued double-blind SC investigational product	447 (12.4)	472 (13.2)	288 (14.1)	278 (13.6)
Consent withdrawn	252 (7.0)	259 (7.2)	148 (7.2)	127 (6.2)
Adverse event	92 (2.6)	100 (2.8)	65 (3.2)	68 (3.3)
Death	18 (0.5)	20 (0.6)	20 (1.0)	22 (1.1)
Other	35 (1.0)	36 (1.0)	26 (1.3)	22 (1.1)
Lost to follow-up	24 (0.7)	28 (0.8)	14 (0.7)	17 (0.8)
Noncompliance	15 (0.4)	16 (0.4)	10 (0.5)	15 (0.7)
Administrative decision	1 (<0.1)	0 (0.0)	1 (<0.1)	2 (<0.1)
Ineligibility determined	4 (0.1)	4 (0.1)	2 (<0.1)	2 (<0.1)
Protocol deviation	4 (0.1)	3 (<0.1)	1 (<0.1)	2 (<0.1)
Requirement for alternative therapy	2 (<0.1)	6 (0.2)	0 (0.0)	1 (<0.1)
Missing	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Discontinued double-blind oral investigational product	0 (-)	0 (-)	269 (13.1)	242 (11.8)
Consent withdrawn	0 (-)	0 (-)	139 (6.8)	110 (5.4)
Adverse event	0 (-)	0 (-)	58 (2.8)	62 (3.0)
Death	0 (-)	0 (-)	20 (1.0)	19 (0.9)
Other	0 (-)	0 (-)	22 (1.1)	18 (0.9)
Lost to follow-up	0 (-)	0 (-)	13 (0.6)	16 (0.8)
Noncompliance	0 (-)	0 (-)	11 (0.5)	10 (0.5)
Administrative decision	0 (-)	0 (-)	2 (<0.1)	3 (0.1)
Ineligibility determined	0 (-)	0 (-)	1 (<0.1)	2 (<0.1)
Protocol deviation	0 (-)	0 (-)	3 (0.1)	2 (<0.1)

Recruitment

42% of the randomised subjects in 20070337 and 52% of the subjects in 20110142 were included in Europe, predominantly in the Eastern and Central parts. In both studies, Columbia and Poland included the highest number of subjects.

Baseline data

Table 11: Baseline Demographics in Pivotal Fracture Studies (Full Analysis Set)

	20070337		20110142	
	Placebo (N = 3591)	Romosozumab 210 mg QM (N = 3589)	Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM (N = 2046)
Ethnicity - n (%)				
Hispanic or Latino	1416 (39.4)	1427 (39.8)	662 (32.3)	631 (30.8)
Not Hispanic or Latino	2175 (60.6)	2162 (60.2)	1385 (67.7)	1415 (69.2)
Race - n (%)				
White	2052 (57.1)	2063 (57.5)	1415 (69.1)	1447 (70.7)
Asian	441 (12.3)	425 (11.8)	149 (7.3)	137 (6.7)
Black or African American	74 (2.1)	77 (2.1)	23 (1.1)	19 (0.9)
American Indian or Alaska Native	63 (1.8)	64 (1.8)	7 (0.3)	5 (0.2)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	0 (0.0)	2 (<0.1)	0 (0.0)
Multiple	59 (1.6)	60 (1.7)	4 (0.2)	2 (<0.1)
Other	901 (25.1)	900 (25.1)	446 (21.8)	436 (21.3)
Missing	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Age (years)				
n	3591	3589	2047	2046
Mean	70.8	70.9	74.2	74.4
SD	6.9	7.0	7.5	7.5
Median	70.0	70.0	75.0	75.0
Min, Max	55, 90	55, 90	55, 90	55, 90
Geriatric group - n (%)[a]				
< 65 years	757 (21.1)	768 (21.4)	240 (11.7)	239 (11.7)
≥ 65 years	2834 (78.9)	2821 (78.6)	1807 (88.3)	1807 (88.3)
< 75 years	2470 (68.8)	2470 (68.8)	976 (47.7)	973 (47.6)
≥ 75 years	1121 (31.2)	1119 (31.2)	1071 (52.3)	1073 (52.4)
Geographic region - n (%)				
Asia Pacific and South Africa	419 (11.7)	410 (11.4)	216 (10.6)	213 (10.4)
Central and Eastern Europe and Middle East	1050 (29.2)	1043 (29.1)	798 (39.0)	835 (40.8)
Central/Latin America	1534 (42.7)	1550 (43.2)	727 (35.5)	674 (32.9)
North America	91 (2.5)	104 (2.9)	42 (2.1)	55 (2.7)
Western Europe and Australia/New Zealand	497 (13.8)	482 (13.4)	264 (12.9)	269 (13.1)

In both studies, the treatment arms were well balanced regarding age, ethnicity, race and BMI. Subjects in 20110142 were approximately 4 years older than in 20070337 and more subjects were ≥75 years old.

Baseline disease characteristics are summarised in Table 14.

Table 12: Key Baseline Disease Characteristics in Pivotal Fracture Studies (Full Analysis Set)

	20070337		20110142	
	Placebo (N = 3591)	Romosozumab 210 mg QM (N = 3589)	Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM (N = 2046)
Prior osteoporotic fracture at or after age 45 - n (%)				
Yes	1258 (35.0)	1270 (35.4)	2029 (99.1)	2022 (98.8)
No	2333 (65.0)	2319 (64.6)	18 (0.9)	24 (1.2)
Prevalent vertebral fracture - n (%)				
Yes	645 (18.0)	672 (18.7)	1964 (95.9)	1969 (96.2)
No	2839 (79.1)	2795 (77.9)	80 (3.9)	69 (3.4)
Not readable	107 (3.0)	122 (3.4)	2 (<0.1)	8 (0.4)
Missing	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Severe vertebral fracture - n (%)				
Presence	4 (0.1)	1 (<0.1)	1321 (64.5)	1369 (66.9)
Lumbar spine BMD T-score				
n	3481	3498	1946	1950
Mean	-2.71	-2.72	-2.99	-2.94
SD	1.04	1.04	1.24	1.25
Median	-2.78	-2.82	-3.06	-3.04
Min, Max	-5.8, 2.0	-5.5, 1.8	-6.4, 4.3	-6.4, 2.6
Total hip BMD T-score				
n	3590	3589	2046	2046
Mean	-2.46	-2.48	-2.81	-2.78
SD	0.47	0.47	0.67	0.68
Median	-2.52	-2.53	-2.75	-2.76
Min, Max	-3.5, 0.1	-3.5, 0.1	-5.5, -0.6	-5.6, -0.4
Femoral neck BMD T-score				
n	3590	3589	2046	2046
Mean	-2.74	-2.76	-2.90	-2.89
SD	0.29	0.28	0.50	0.49
Median	-2.72	-2.73	-2.85	-2.83
Min, Max	-3.5, -0.8	-3.6, -1.6	-5.4, -0.6	-4.9, -0.8

The baseline disease characteristics are generally well balanced between the treatment arms in both pivotal studies.

Consistent with the differences in inclusion and exclusion criteria, the percentages of subjects with a history of osteoporosis-related fractures and prevalent vertebral fractures were higher in 20110142, whereas the BMD T-score in all locations were higher in 20070337.

The 10-year probability of a major osteoporotic and hip fracture, according to the FRAX, was also similar between treatment groups, whereas generally lower in Central/Latin America, reflecting a population with a lower fracture risk. The CHMP guideline on the evaluation of medicinal products in the treatment of primary osteoporosis (CPMP/EWP/552/95 Rev. 2) puts an emphasis on the study of patients at high risk of fracture preferably expressing the 10-year probability of fracture in line with the recommendations of the WHO; for spine fracture probability of 15% to 20%, for hip fracture of 5% to 7.5%, for major non-vertebral fracture of 10% to 15% are given as inclusion criteria. In study 20070337 the mean 10-year probabilities of major osteoporotic fractures and of hip fractures calculated with femoral neck BMD were 13.4% (range: 2.7% to 69.7%) and 5.9% (range: 0.3% to 57.9%), respectively for the overall population. When looking on the FRAX data of the Central/Latin America population (which accounts for over 43%), a generally lower mean 10-year probability of major osteoporotic fractures and of hip fractures can be observed, 8,7% for major non-vertebral fractures and 3,9% for hip fractures, respectively. This was driven by a substantially lower incidence of previous

fractures, and a moderately lower incidence of parental hip fracture, current smoking status, secondary osteoporosis, and alcohol use. According to the Applicant, a number of reports in the scientific literature have indicated that lower non-vertebral fracture risk and FRAX scores in women from the Central/Latin American region is not unusual when considering similar ages and T-scores of the population in other countries.

Table 13: 10-year Probability of Fracture and Related Clinical Risk Factors by Geographic Region

	Western Europe and Australia/ New Zealand (N = 979)	Central and Eastern Europe (N = 2093)	Asia Pacific (N = 829)	North America (N = 195)	Central/ Latin America (N = 3084)	All (N = 7180)
10-year probability of hip fracture calculated with BMD - %						
n	972	2092	828	195	3076	7163
Mean	9.169	6.188	8.302	6.627	3.932	5.880
SD	7.371	4.810	6.714	5.951	3.169	5.330
Median	7.075	5.025	6.710	5.310	3.040	4.320
Q1, Q3	4.630, 11.205	3.530, 7.210	4.320, 10.025	3.160, 7.930	2.220, 4.420	2.790, 6.960
Min, Max	0.87, 56.11	0.73, 48.12	1.46, 57.89	1.04, 44.22	0.27, 38.53	0.27, 57.89
10-year probability of hip fracture calculated without BMD - %						
n	972	2092	828	195	3076	7163
Mean	6.862	4.678	5.938	5.067	2.830	4.337
SD	7.328	4.628	6.068	5.843	3.055	4.990
Median	4.440	3.275	3.815	3.190	1.930	2.680
Q1, Q3	2.275, 8.740	1.730, 6.000	2.035, 7.815	1.340, 6.500	1.180, 3.215	1.460, 5.280
Min, Max	0.14, 69.04	0.32, 42.56	0.48, 54.37	0.17, 36.79	0.20, 35.16	0.14, 69.04

Numbers analysed

Table 14: Analysis Sets for the 12- and 24-Month Analysis Periods

		Subjects in treatment arm			
		20070337 (FRAME)		**20110142 (ARCH)**	
Analysis set	Composition	Placebo	Romosozumab	Alendronate	Romosozumab
Primary analysis set for vertebral fractures	All randomized subjects with a baseline and ≥ 1 post baseline evaluation of vertebral fracture at or before the time point under consideration	12 months 3,322 24 months 3,327	12 months 3,321 24 months 3,325	24 months 1,834	24 months1,825

Primary efficacy analysis set for BMD	All randomized subjects with a baseline and ≥ 1 post baseline evaluation at or before the time point under consideration in the study period	12 months 3,148 24 months 2,877	12 months 3,151 24 months 2,861	Primary analysis 1,757	Primary analysis 1,750
Full analysis set	All randomized subjects	3,591	3,589	2,047	2,046
Per protocol set	Subjects compliant with the protocol and who met minimum investigational product exposure requirements as described in SAP	3,556*	3,565*	1,994*	2,010*
Safety analysis set	All randomized subjects who received ≥ 1 dose of investigational product in the 12-month double-blind period.	3,576	3,581	2,014	2,040

*Given number of subjects in Per protocol set reflects complete exclusion, i.e. exclusion of the subject throughout the12-month double-blind period. The size of Per protocol set varies at different time points due to partial exclusion (exclusion of the subject data after the first event leading to exclusion).

In the Primary analysis set for BMD in 20070337, approximately 88% of the FAS were included at 12 Months and approximately 80% at Month 24. In 20110142, approximately 86% of the FAS were included in the Primary analysis set for BMD.

The reasons for the relatively high discrepancy between the FAS and the Primary analysis sets (at least in the BMD analysis set) was not explicitly described but, based on the definition of each set, due to missing assessments, either at baseline and/or post-baseline. Although a rather high proportion of randomised subjects were excluded in e.g. the analyses of BMD endpoints, the exclusion rates were of the same size comparing randomised treatment groups irrespective of study. The applicant was requested to clarify how many subjects had missing assessments at each assessment time-point. In response to the above together with a request regarding clarification of the use of last-observation-carried-forward (LOCF) approach used in the fracture analyses, the Applicant clarified (for both studies) that LOCF imputation was only used at the vertebra level and not for completely missing x-rays. A summary of evaluable x-rays by nominal visit and treatment group was provided showing very similar patterns comparing the treatment groups. In study 20070337, the percentages of only partially available x-ray results per visit were all below 10%, in study 20110142 the percentages of only partially available x-ray results per visit were 11.6% for Month 12 and

below 7% for Month 24. Irrespective of study, they were comparable between both treatment groups at all time-points.

Outcomes and estimation

Study 20070337 met its co-primary endpoints as romosozumab reduced the subject incidence of new vertebral fractures compared with placebo during the 12-month double-blind period and through month 24 after both groups transitioned to denosumab.

Study 20110142 met both of its two primary endpoints as romosozumab/alendronate reduced subject incidence of new radiological vertebral fractures through month 24 and clinical fractures trough primary analysis period compared to alendronate only.

New radiological vertebral fractures

Table 15: Subject Incidence of New Vertebral Fracture in studies 20070337 and 20110142 Through Month 12 and Through Month 24 With Inference Based on Odds Ratio (Primary Efficacy Analysis Set for Vertebral Fractures, LOCF Imputation)

			Risk Comparison Estimates									
			Absolute Risk Reduction (%)[a]			Risk Ratio[a]			Odds Ratio[b]			
	Control n/N1 (%)	Treatment n/N1 (%)	Pt Est	SE	(95% CI)	Pt Est	SE[c]	(95% CI)	Pt Est	SE[c]	(95% CI)	p-value
New Vertebral Fracture Through Month 12												
Study 20070337	59/3322 (1.8)	16/3321 (0.5)	1.30	0.26	(0.79, 1.80)	0.27	0.28	(0.16, 0.47)	0.27	0.28	(0.15, 0.47)	<0.001
Study 20110142	85/1703 (5.0)	55/1696 (3.2)	1.84	0.68	(0.51, 3.17)	0.64	0.17	(0.46, 0.89)	0.63	0.18	(0.44, 0.89)	0.008
New Vertebral Fracture Through Month 24												
Study 20070337	84/3327 (2.5)	21/3325 (0.6)	1.89	0.30	(1.30, 2.49)	0.25	0.24	(0.16, 0.40)	0.24	0.25	(0.15, 0.39)	<0.001
Study 20110142	147/1834 (8.0)	74/1825 (4.1)	4.03	0.78	(2.50, 5.57)	0.50	0.14	(0.38, 0.66)	0.48	0.15	(0.36, 0.64)	<0.001

A consistent treatment effect was found across nearly all subgroup analyses for the new vertebral fracture endpoints in both studies.

The chosen primary endpoint in study 20070337, the subject incidence of new vertebral fracture after romosozumab treatment compared with placebo, is aligned with CHMP guidance (CPMP/EWP/552/95 Rev. 2) and represents in principle the established measure of efficacy for the treatment of postmenopausal osteoporosis. The first component of the co-primary endpoint is considered suitable to analyse the efficacy of romosozumab in the time window of intended treatment duration, i.e. 0 - 12 months (induction of fracture-protective effect). However, the second component of the co-primary endpoint, the vertebral fracture incidence during the (first) 24-months study period is not considered adequate to directly assess the maintenance of fracture protection after romosozumab cessation. This is because fracture events observed during the first year of treatment are counted again in this data analysis, and any relevant treatment effect already identified in the first year might suffice to reveal a significant result also for the co-primary 24-months analysis, even if there was no fracture protective effect after month 12.
In order to better support the persistence of the fracture-protective efficacy after cessation of romosozumab, the Applicant was asked to provide additional statistical evaluation of fracture data collected after treatment switch to denosumab (i.e. defining the 12-month time point as baseline for the analyses of effect maintenance). This additional analysis was to be carried out for the endpoints as defined in the sequential testing hierarchy. An additional statement was to be provided to indicate at which step hierarchical testing

would have stopped, if the testing of fracture incidence between months 12 and 24 would have been taken to replace all statistical tests based on 0-24-month data. The Applicant provided the additional analyses as requested.

Table 16: Subject Incidence Rates of Fracture Endpoints of 20070337 at Different Time Intervals

Fracture category	Incidence (n/N1 [%])		Relative risk reduction	Nominal
Timepoint [a]	Placebo [b]	Romosozumab [c]	% (95% CI)	p-value
New vertebral [d]				
Month 0-12	59/3322 (1.8)	16/3321 (0.5)	73% (53, 84)	<0.001
Month 0-24	84/3327 (2.5)	21/3325 (0.6)	75% (60, 84)	<0.001
Month 12-24	**27/2980 (0.9)**	**5/2953 (0.2)**	**81% (52, 93)**	**<0.001**
Clinical [e]				
Month 0-12	90/3591 (2.5)	58/3589 (1.6)	36% (11, 54)	0.008
Month 0-24	147/3591 (4.1)	99/3589 (2.8)	33% (13, 48)	0.002
Month 12-24	**62/3205 (1.9)**	**42/3185 (1.3)**	**32% (-1, 54)**	**0.052**
Nonvertebral [e]				
Month 0-12	75/3591 (2.1)	56/3589 (1.6)	25% (-5, 47)	0.096
Month 0-24	129/3591 (3.6)	96/3589 (2.7)	25% (3, 43)	0.029
Month 12-24	**55/3205 (1.7)**	**41/3185 (1.3)**	**25% (-12, 50)**	**0.16**
Major nonvertebral [e]				
Month 0-12	55/3591 (1.5)	37/3589 (1.0)	33% (-2, 56)	0.060
Month 0-24	101/3591 (2.8)	67/3589 (1.9)	33% (9, 51)	0.009
Month 12-24	**46/3205 (1.4)**	**31/3185 (1.0)**	**32% (-7, 57)**	**0.092**
New or worsening vertebral [d]				
Month 0-12	59/3322 (1.8)	17/3321 (0.5)	71% (51, 83)	<0.001
Month 0-24	84/3327 (2.5)	22/3325 (0.7)	74% (58, 84)	<0.001
Month 12-24	**29/2980 (1.0)**	**5/2953 (0.2)**	**83% (55, 93)**	**<0.001**
Hip [e]				
Month 0-12	13/3591 (0.4)	7/3589 (0.2)	46% (-35, 78)	0.18
Month 0-24	22/3591 (0.6)	11/3589 (0.3)	50% (-4, 76)	0.059
Month 12-24	**9/3205 (0.3)**	**4/3185 (0.1)**	**55% (-47, 86)**	**0.18**
Major osteoporotic [e]				
Month 0-12	63/3591 (1.8)	38/3589 (1.1)	40% (10, 60)	0.012
Month 0-24	110/3591 (3.1)	68/3589 (1.9)	38% (16, 54)	0.002
Month 12-24	**49/3205 (1.5)**	**30/3185 (0.9)**	**39% (3, 61)**	**0.034**
Multiple new/worsening vertebral [d]				
Month 0-12	9/3322 (0.3)	1/3321 (<0.1)	89% (13, 99)	0.011
Month 0-24	17/3327 (0.5)	1/3325 (<0.1)	94% (56, 99)	<0.001
Month 12-24	**5/2980 (0.2)**	**0/2953 (0.0)**	**NE**	**NE**

CI=confidence interval; CSR=clinical study report; n=numbers of subjects with fractures; NE=not estimable; SAP=Statistical Analysis Plan

Note: N1=Number of subjects in either the primary efficacy analysis set (new, multiple new/worsening, and new/worsening vertebral fractures) or the full analysis set (clinical, nonvertebral, major nonvertebral, hip, and major osteoporotic fractures). Major nonvertebral fracture includes fractures of the pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm and hip. Major osteoporotic fractures include clinical vertebral fractures and fractures of the hip, forearm and humerus. Fractures associated with high trauma severity or pathologic fractures are excluded.

a. The Month 0 to 12 and Month 0 to 24 time intervals were prespecified in the 20070337 SAP and reported in the CSR. The Month 12 to 24 time interval is a new analysis.

b. Values represent placebo through Month 12, placebo/denosumab through Month 24, and denosumab from Months 12 to 24 (recognizing subjects received placebo through Month 12 prior to denosumab treatment).

c. Values represent romosozumab through Month 12, romosozumab/denosumab through Month 24, and denosumab from Months 12 to 24 (recognizing subjects received romosozumab through Month 12 prior to denosumab treatment).

d. Relative risk reduction is calculated from the risk ratio as 100 x (1 – risk ratio). Absolute risk reduction and risk ratio are based on Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables. Nominal p-values for vertebral fracture endpoints are based on a logistic regression model adjusting for age and prevalent vertebral fracture stratification variables.

e. Relative risk reduction is calculated from the hazard ratio as 100 x (1 –hazard ratio). Absolute risk reduction is based on inverse-weighted method adjusting for age and prevalent vertebral fracture stratification variables. Hazard ratio and nominal p-values for clinical, nonvertebral, major nonvertebral, hip, and major osteoporotic fractures are based on Cox proportional hazards model adjusting for age and prevalent vertebral fracture stratification variables.

Whilst the mentioned potential methodological deficiencies of this post-hoc analyses of the second-year fracture-incidences are acknowledged, the additional information provided however further supports the (general) assumption of persistence of the fracture-protective efficacy after cessation of romosozumab. Results provided indicate that the original co-primary efficacy analysis is not strongly dominated by month 12 outcome only. Similar to outcome for the Month 0-12 treatment period, the point estimate for the relative fracture risk reduction for the Month 12-24 study period (i.e. effect size) is smallest for the category of non-vertebral fractures.

Likewise, as regards investigation of maintenance of protective effect after cessation of romosozumab treatment under continued ALN treatment, it would seem most logical to take month 12 status as new baseline for data analysis, also in the ARCH trial. Whereas the CSR provides such information of ALN-controlled 12 months efficacy data, separate data analyses to support maintenance of persistent fracture-protective effect of romosozumab under ALN treatment was required. The Applicant provided the additional analyses separated by year- study time intervals as requested. See Table 19 below. It can be agreed to the Applicant that the statistical evaluation of fracture data collected after the treatment switch to alendronate is supporting the hypothesis, that extended fracture risk benefit can be achieved in the subsequent time period following romosozumab treatment cessation. However, such a finding should be differentiated from any benefit-claim directly associated with subsequent antiresorptive therapy, which is not a matter of primary assessment in this MAA. As for the FRAME trial, estimated effect size in both periods (Month 0-12, Month 12-24) seems least pronounced in the category of non-vertebral fractures.

Table 17: Subject Incidence Rates of Fracture Endpoints in 20110142 at Different Time Intervals

Fracture category Time point[a]	Incidence (n/N [%]) Alendronate [b]	 Romosozumab [c]	Relative risk reduction % (95% CI)	Nominal p-value
New vertebral [d]				
Month 0-12	85/1703 (5.0)	55/1696 (3.2)	36% (11, 54)	0.008
Month 0-24	147/1834 (8.0)	74/1825 (4.1)	50% (34, 62)	<0.001
Month 12-24	**69/1568 (4.4)**	**17/1573 (1.1)**	**75% (59, 85)**	**<0.001**
Clinical [e]				
Month 0-12	110/2047 (5.4)	79/2046 (3.9)	28% (4, 46)	0.027
Month 0-24	197/2047 (9.6)	146/2046 (7.1)	26% (9, 41)	0.005
Month 0 to Primary Analysis	266/2047 (13.0)	198/2046 (9.7)	27% (12, 39)	<0.001
Month 12-24	**94/1726 (5.4)**	**62/1739 (3.6)**	**35% (10, 53)**	**0.008**
Month 12 to Primary Analysis	**164/1726 (9.5)**	**115/1739 (6.6)**	**32% (14, 46)**	**0.001**
Nonvertebral [e]				
Month 0-12	95/2047 (4.6)	70/2046 (3.4)	26% (-1, 46)	0.057
Month 0-24	159/2047 (7.8)	129/2046 (6.3)	19% (-2, 36)	0.074
Month 0 to Primary Analysis	217/2047 (10.6)	178/2046 (8.7)	19% (1, 34)	0.037
Month 12-24	**68/1726 (3.9)**	**56/1739 (3.2)**	**18% (-17, 43)**	**0.26**
Month 12 to Primary Analysis	**127/1726 (7.4)**	**105/1739 (6.0)**	**19% (-5, 37)**	**0.12**
Hip [e]				
Month 0-12	22/2047 (1.1)	14/2046 (0.7)	36% (-26, 67)	0.19
Month 0-24	43/2047 (2.1)	31/2046 (1.5)	28% (-15, 54)	0.17
Primary Analysis	66/2047 (3.2)	41/2046 (2.0)	38% (8, 58)	0.015
Month 12-24	**19/1726 (1.1)**	**16/1739 (0.9)**	**15% (-65, 56)**	**0.63**
Month 12 to Primary Analysis	**42/1726 (2.4)**	**25/1739 (1.4)**	**40% (1, 63)**	**0.041**
Major osteoporotic [e]				
Month 0-12	85/2047 (4.2)	61/2046 (3.0)	28% (-1, 48)	0.053
Primary Analysis	209/2047 (10.2)	146/2046 (7.1)	32% (16, 45)	<0.001
Month 12-24	**71/1726 (4.1)**	**43/1739 (2.5)**	**41% (13, 59)**	**0.006**
Month 12 to Primary Analysis	**128/1726 (7.4)**	**78/1739 (4.5)**	**40% (21, 55)**	**<0.001**

ALN=alendronate; BMD=bone mineral density; CI=confidence interval; CSR=clinical study report; n=number of subjects with fractures; SAP=Statistical Analysis Plan

Note: N=Number of subjects in either the Primary Analysis set for vertebral fracture (new vertebral fractures) or the full analysis set (clinical, nonvertebral, hip fractures) for Month 0 to 12, Month 0 to 24, and Month 0 to Primary Analysis; N=Number of subjects randomized who received at least one open-label ALN dose for Month 12 to 24 and Month 12 to Primary Analysis.

a. The Month 0 to 12 and Month 0 to 24 time intervals and Primary Analysis were prespecified in the 20110142 SAP and reported in the CSR. The Month 12 to 24 time interval and the Month 12 through Primary Analysis are new analyses.

b. Values represent alendronate Month 12, Month 24, and through Primary Analysis.

c. Values represent romosozumab through Month 12, romosozumab/alendronate through Month 24, and alendronate from Months 12 to 24 and from Month12 to Primary Analysis (recognizing subjects received romosozumab through Month 12 prior to alendronate treatment).

d. Relative risk reduction is calculated from the risk ratio as 100 x (1 – risk ratio). Absolute risk reduction and risk ratio are based on Mantel-Haenszel method adjusted for age strata, baseline total hip BMD T-score (≤-2.5, >-2.5), and presence of severe vertebral fracture at baseline. Odds ratios are based on a logistic regression model adjusted for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline; nominal p-values for vertebral fracture are based on score test.

e. Relative risk reduction is calculated from the hazard ratio as 100 x (1 – hazard ratio). Absolute risk reduction is based on inverse-weighted method adjusting for age strata, baseline total hip BMD T-score (≤-2.5, >-2.5), and presence of severe vertebral fracture at baseline. Hazard ratio estimate and nominal p-values are based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.

Clinical Fracture endpoints Through Month 12 and Through Month 24

Table 18: Summary of Secondary Fracture Endpoints Through Month 12 and Through Month 24 in study 20070337

	Proportion of Women with Fracture		Absolute Risk Reduction (%) (95% CI)	Relative Risk Reduction (%) (95% CI)	Adjusted p-value[b]
	Placebo (%)	Romosozumab (%)			
Through month 12					
Clinical	90/3,591 (2.5)	58/3,589 (1.6)	1.2 (0.4, 1.9)	36 (11, 54)	0.008
Nonvertebral	75/3,591 (2.1)	56/3,589 (1.6)	0.8 (0.1, 1.4)	25 (-5, 47)	0.096
Major nonvertebral[d]	55/3,591 (1.5)	37/3,589 (1.0)	0.6 (0.1, 1.2)	33 (−2, 56)	0.096
New or worsening vertebral	59/3,322 (1.8)	17/3,321 (0.5)	1.3 (0.76, 1.77)	71 (51, 83)	0.096
Hip	13/3,591 (0.4)	7/3,589 (0.2)	0.3 (0.0, 0.6)	46 (−35, 78)	0.18
Major osteoporotic[e]	63/3,591 (1.8)	38/3,589 (1.1)	0.9 (0.3, 1.5)	40 (10, 60)	NA[c]
Multiple new/worsening vertebral	9/3,322 (0.3)	1/3,321 (<0.1)	0.24 (0.05, 0.43)	89 (13, 99)	NA[c]
Through month 24					
Clinical	147/3,591 (4.1)	99/3,589 (2.8)	1.4 (0.5, 2.4)	33 (13, 48)	0.096
Nonvertebral	129/3,591 (3.6)	96/3,589 (2.7)	1.0 (0.2, 1.9)	25 (3, 43)	0.057
Major nonvertebral[d]	101/3,591 (2.8)	67/3,589 (1.9)	1.1 (0.3, 1.8)	33 (9, 51)	0.096
New or worsening vertebral	84/3,327 (2.5)	22/3,325 (0.7)	1.86 (1.27, 2.46)	74 (58, 84)	0.096
Hip	22/3,591 (0.6)	11/3,589 (0.3)	0.4 (0.0, 0.7)	50 (−4, 76)	0.12
Major osteoporotic[e]	110/3,591 (3.1)	68/3,589 (1.9)	1.2 (0.5, 2.0)	38 (16, 54)	NA[c]
Multiple new/worsening vertebral	17/3,327 (0.5)	1/3,325 (< 0.1)	0.48 (0.23, 0.73)	94 (56, 99)	NA[c]

a. Nominal p-values based on logistic regression model (new or worsening and multiple new/worsening vertebral fracture) or Cox proportional hazards model (nonvertebral, major nonvertebral, hip, major osteoporotic) adjusted for age and prevalent vertebral fracture stratification factors.
b. Adjusted p-values are based on a sequential testing procedure and are to be compared to a significance level of 0.05.
c. NA: Endpoint was not part of sequential testing strategy; therefore, p-value adjustment is not applicable.
d. Pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm and hip
e. Clinical vertebral fractures and fractures of the hip, forearm and humerus

Table 19: Summary of Secondary and Select Exploratory Fracture Endpoints in study 20110142 Through Month 12 and Through Month 24

	Proportion of Women with Fracture		Absolute Risk Reduction (%) (95% CI)	Relative Risk Reduction (%) (95% CI)	Nominal p-value
	Alendronate (%)	Romosozumab (%)			
Through month 12					
Clinical	110/2,047 (5.4)	79/2,046 (3.9)	1.8 (0.5, 3.1)	28 (4, 46)	0.027
Non-vertebral	95/2,047 (4.6)	70/2,046 (3.4)	1.4 (0.1, 2.6)	26 (-1, 46)	0.057
Major non-vertebral[d]	88/2,047 (4.3)	59/2,046 (2.9)	1.6 (0.4, 2.7)	33 (6, 52)	0.019
New or worsening vertebral	101/1,703 (5.9)	67/1,696 (4.0)	2.0 (0.6, 3.5)	34 (11, 51)	0.006
Hip	22/2,047 (1.1)	14/2,046 (0.7)	0.3 (-0.3, 0.9)	36 (−26, 67)	0.19
Major osteoporotic	88/2,047 (4.2)	61/2,046 (3.0)	1.4 (0.3, 2.5)	28 (-1, 48)	0.053
Multiple new/worsening vertebral	21/1,703 (1.2)	20/1,696 (1.2)	<0.1 (-0.6, 0.8)	7 (-70, 50)	0.85
Through month 24					
Clinical	197/2,047 (9.6)	146/2,046 (7.1)	2.7 (0.8, 4.5)	26 (9, 41)	0.005
Non-vertebral	159/2,047 (7.8)	129/2,046 (6.3)	1.6 (-0.1, 3.3)	19 (-2, 36)	0.074
New or worsening vertebral	168/1,834 (9.2)	87/1,875 (4.8)	4.4 (2.8, 6.1)	48 (34,60)	<0.001
Hip	43/2,047 (2.1)	31/2,046 (1.5)	0.6 (-0.2, 1.4)	28 (−15, 54)	0.17
Multiple new/worsening vertebral	46/1,834 (2.5)	24/1,825 (1.3)	1.2 (0.3, 2.1)	48 (15, 68)	0.008

Sensitivity analyses demonstrated consistent results for both studies.

Like the co-primary endpoints, also selected secondary efficacy endpoints were tested in a fixed sequence approach to control for multiplicity. Accordingly, the remaining endpoints in the testing sequence were not formally tested for statistical significance. That means that a statistically significant difference in favour of romosozumab versus placebo could formally not be demonstrated for non-vertebral or hip fractures.
However, it is noted, that non-vertebral fracture accounted for the largest share (>85%) in the combined endpoint "clinical fracture" and statistical significance was demonstrated for this outcome.
Of note, forearm fractures, consisting predominantly of wrist fractures, were the most frequently reported type of non-vertebral fracture reported in both treatment groups.

Fracture data in study 20110142 at the time of primary analysis

Table 20: Subject Incidence of Clinical Fracture (symptomatic vertebral or non-vertebral in study 20110142 Through Primary Analysis with median follow-up time of 33 months. (Full Analysis Set - Primary Analysis)

	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)	Romosozumab 210 mg QM/ Alendronate 70 mg QW vs. Alendronate 70 mg QW/ Alendronate 70 mg QW
Clinical fracture through primary analysis			
Subject status			
Number of subjects	2047	2046	-
With fractures - n (%)	266 (13.0)	198 (9.7)	-
Hazard ratio [a]	-	-	0.73
SE	-	-	0.09
(95% CI)	-	-	(0.61, 0.88)
Nominal p-value	-	-	<0.001
Adjusted p-value			< 0.001

BMD = bone mineral density; CI = confidence interval; N = Number of subjects randomized; QM = every month; QW = weekly; SE = standard error
Hazard ratio < 1 favors romosozumab; SE represents the standard error of log (hazard ratio)
[a] The hazard ratio estimate is based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Missing values for clinical vertebral fractures are imputed by carrying forward the last nonmissing postbaseline value prior to the missing value.

Table 21: Subject Incidence of Non-vertebral Fracture Through Primary Analysis in study 20110142 (median follow-up time of 33 months, Full Analysis Set - Primary Analysis)

	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)	Romosozumab 210 mg QM/ Alendronate 70 mg QW vs. Alendronate 70 mg QW/ Alendronate 70 mg QW
Nonvertebral fracture through primary analysis			
Subject status			
Number of subjects	2047	2046	
With fractures - n (%)	217 (10.6)	178 (8.7)	
Hazard ratio [a]			0.81
SE			0.10
(95% CI)			(0.66, 0.99)
Nominal p-value (2-sided)			0.037
Nominal p-value (1-sided)			0.019
p-value (adjusted 2-sided)			0.040

BMD = bone mineral density; CI = Confidence interval; QM = every month; QW = every week; SE = standard error
Hazard ratio < 1 favors romosozumab; SE represents the standard error of log (hazard ratio)
[a] The hazard ratio estimate is based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.

Summary of non-vertebral fractures in pivotal PMO studies

The non-vertebral fracture data presented in Table 24 (study 20070337) and Table 25 (study 20070142) below are all the osteoporosis-related non-vertebral fractures as defined in the individual Statistical Analysis Plans (SAPs) for each study.

Table 22: Subject incidence, frequency, and location of osteoporotic Non-vertebral bone fracture through Month 12 and Month 24 in 20070337 (Full Analysis Set)

	Month 12		Month 24	
Bone fracture	Placebo (N=3591)	Romosozumab (N=3589)	Placebo/ denosumab (N=3591)	Romosozumab/ denosumab (N=3589)
	n (%)/n1			
Hip	13 (0.4)/13	7 (0.2)/7	22 (0.6)/22	11 (0.3)/11
Forearm (total)	29 (0.8)/39	23 (0.6)/29	55 (1.5)/74	42 (1.2)/52
Wrist	26 (0.7)/36	22 (0.6)/28	49 (1.4)/67	41 (1.1)/50
Rib	8 (0.2)/9	1 (<0.1)/1	14 (0.4)/15	3 (<0.1)/3
Humerus (total)	2 (<0.1)/2	5 (0.1)/5	6 (0.2)/6	12 (0.3)/12
Proximal humerus	1 (<0.1)/1	4 (0.1)/4	4 (0.1)/4	9 (0.3)/9
Pelvis	4 (0.1)/5	0	6 (0.2)/7	0
Leg (total)	13 (0.4)/14	10 (0.3)/13	19 (0.5)/25	16 (0.4)/22
Distal femur	0	1 (<0.1)/1	1 (<0.1)/1	2 (<0.1)/2
Lower leg with ankle	9 (0.3)/10	8 (0.2)/11	15 (0.4)/20	12 (0.3)/18
Ankle	7 (0.2)/8	7 (0.2)/9	13 (0.4)/16	10 (0.3)/12
Proximal tibia	1 (<0.1)/1	1 (<0.1)/1	2 (<0.1)/2	2 (<0.1)/3
Foot fracture	4 (0.1)/4	9 (0.3)/9	8 (0.2)/8	12 (0.3)/12

f. n=number of subjects with fracture. N=number of subjects randomized; n1=number of fractures

g. Note: Results are based on the Month 24 Analysis.

h. Note: Three individual fracture types were reported, carpus (1 romosozumab-treated subject at Months 12 and 24) sternum (2 placebo subjects and 1 romosozumab-treated subject at Months 12 and 24), and clavicle (1 subject in each treatment group at Month 12 and 2 subjects in each treatment group at Month 24), that were not included in any of the defined fracture subsets for 20070337 or 20110142. Details of the number of fractures can be found in the data sources below.

i. Note: Certain bone fracture subsets are included in this table. For example, in the placebo group at Month 12,

j. 13 subjects reported a leg fracture. Within this subgroup, 4 subjects experienced a leg fracture although not at the distal femur, and 9 subjects experienced a lower leg with ankle fracture, specifically, as an ankle fracture in 7 of 9 subjects and as a fracture of the proximal tibia in 1 of 9 subjects. In the case of the remaining subject, the specific location of the fracture in the lower leg was not specified

Table 23: Subject incidence, frequency, and location of osteoporotic Non-vertebral bone fracture through Month 12, Month 24, and Primary Analysis in 20110142 (Full Analysis Set)

Bone fracture	Month 12		Month 24		Primary Analysis[a]	
	ALN (N=2047)	Romo (N=2046)	ALN/ALN (N=2047)	Romo/ ALN (N=2046)	ALN/ALN (N=2047)	Romo/ALN (N=2046)
	n (%)/n1					
Hip	22 (1.1)/22	14 (0.7)/14	43 (2.1)/44	31 (1.5)/32	66 (3.2)/68	41 (2.0)/42
Forearm Wrist	42 (2.1)/62 38 (1.9)/58	33 (1.6)/47 29 (1.4)/41	59 (2.9)/86 52 (2.5)/77	52 (2.5)/73 47 (2.3)/66	73 (3.6)/107 61 (3.0)/90	65 (3.2)/90 60 (2.9)/83
Rib	10 (0.5)/11	5 (0.2)/5	16 (0.8)/18	8 (0.4)/9	23 (1.1)/25	13 (0.6)/13
Humerus Proximal humerus	11 (0.5)/11 10 (0.5)/10	5 (0.2)/5 5 (0.2)/5	19 (0.9)/20 18 (0.9)/19	12 (0.6)/12 11 (0.5)/11	31 (1.5)/31 28 (1.4)/28	20 (1.0)/20 17 (0.8)/17
Pelvis	8 (0.4)/12	1 (<0.1)/2	13 (0.6)/19	3 (0.1)/4	17 (0.8)/26	5 (0.2)/7
Leg (total) Distal femur Lower leg with ankle Ankle Proximal tibia	9 (0.4)/12 1 (<0.1)/1 8 (0.4)/11 4 (0.2)/6 4 (0.2)/4	14 (0.7)/17 1 (<0.1)/1 8 (0.4)/11 6 (0.3)/8 2 (<0.1)/2	21 (1.0)/27 4 (0.2)/4 12 (0.6)/16 7 (0.3)/9 5 (0.2)/5	24 (1.2)/29 5 (0.2)/5 11 (0.5)/16 7 (0.3)/10 3 (0.1)/3	29 (1.4)/35 7 (0.3)/7 14 (0.7)/18 8 (0.4)10 6 (0.3)/6	37 (1.8)/43 11 (0.5)/11 16 (0.8)/22 11 (0.5)/15 4 (0.2)/4
Foot fracture	3 (0.1)/3	1 (<0.1)/1	6 (0.3)/6	6 (0.3)/6	7 (0.3)/7	9 (0.4)/9

k. ALN=alendronate; n=number of subjects with fracture; N=number of subjects randomized; n1=number of fractures;
l. Romo=romosozumab
m. Note: Three individual fracture types were reported, carpus (1 ALN-treated subject at Primary Analysis), sternum
n. (1 ALN-treated subject at Month 12, Month 24, and Primary Analysis), and clavicle (1ALN-treated subject at
o. Month 12, 1 ALN-treated subject and 3 romo/ALN-treated subjects at Month 24, and 2 ALN-treated subjects and
p. 3 romoALN-treated subjects at Primary Analysis), that were not included in any of the defined fracture subgroups for 20070337 or 20110142. Details of the number of fractures can be found in the data sources below.
q. Note: Certain bone fracture subgroups are included in this table. For example, in the ALN group at Month 12,
r. 9 subjects reported a leg fracture. Within this subgroup, 1 subject experienced a leg fracture at the distal femur, and
s. 8 subjects experienced a lower leg with ankle fracture, specifically, as an ankle fracture in 4 of 8 subjects and as a fracture of the proximal tibia in 4 of 8 subjects.
t. a The Primary Analysis was performed on 464 subjects who experienced a clinical fracture after a median treatment time of 2.7 years (minimum to maximum: 1 day to 4.6 years).

In study 20070337, 5 additional non-vertebral fractures were reported up to month 12, which were not confirmed within 14 days by radiographs, other diagnostic imaging techniques or appropriate medical reports. Three of the additional fractures were reported in the placebo group (1 rib, 2 radius) and two in the romosozumab group (both rib). In study 20110142, 8 additional fractures were reported in six subjects in the alendronate treatment arm (3 femoral neck, 1 foot, 1 patella, 1 other, 2 radius) and 8 events in 7 subjects in the romosozumab arm (1 carpal, 2 femoral neck, 1 metatarsal, 1 other and 3 rib) up to month 12.

Figure 11: Time to First Non-vertebral Fracture Kaplan-Meier Curves (Full Analysis Set) (20070337 Final Analysis)

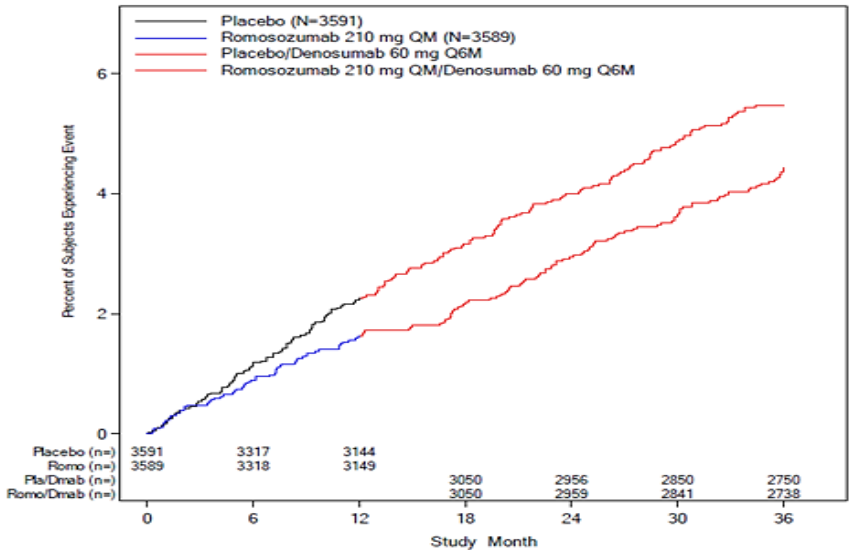
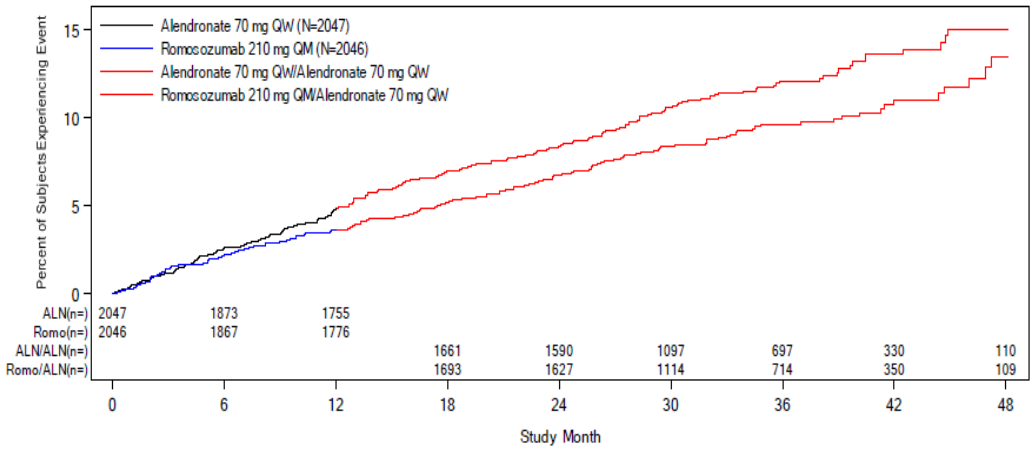


Figure 12: Time to First Non-vertebral Fracture Kaplan-Meier Curves (Full Analysis Set) (20110142 Primary Analysis)



The numbers of non-vertebral fracture events were generally low. In 20070337, hip fractures had occurred in totally 20 subjects through month 12 (romosozumab 0.2%, placebo 0.4%). The corresponding figures for study 20110142 through month 12 were 0.7% and 1.1%, respectively.

Table 24: Subject Incidence of Non-vertebral Fracture Through Month 12 by Region (Full Analysis Set; study 20070337)

	Placebo (N = 3591)	Romosozumab 210 mg QM (N = 3589)	Romosozumab 210 mg QM vs. Placebo
Primary analysis model with subgroup variable added			
Hazard ratio [b]			
Pt Est			0.75
SE			0.18
(95% CI)			(0.53, 1.06)
p-value			0.097
Treatment-by-subgroup interaction			
p-value			0.042
Qualitative interaction by Gail and Simon test			
p-value			0.47

A consistent treatment effect was found across all subgroup analyses in 20110142. However, in 20070337 at month 12, but not at month 24, a significant treatment-by-region interaction was noted for the non-vertebral fracture endpoint, and therefore also for the clinical fracture endpoint, as non-vertebral fractures accounted for the largest share of clinical fractures. The by-region interaction identified a regional difference in placebo fracture incidence (i.e., unexpected low fracture rate in the placebo group in Central/Latin America, the region with highest enrolment) that affected the non-vertebral fracture outcome for the study overall (Table 26). In a post hoc subgroup analysis that excluded Central/Latin America data to derive a patient subset from all other regions combined (rest-of-world), the non-vertebral fracture rate was 2.7% in the placebo group and 1.6% in the romosozumab group (RRR 42%, ARR 1.1%, p=0.012, post hoc). The Applicant has clarified that the baseline characteristics in the study are still balanced between the treatment groups in the rest-of-world subject subset, i.e. after excluding the Central/Latin America subjects. This needs to be seen in context of the FRAX risk differences at baseline. The 10-year probability of a major osteoporotic fracture according to the FRAX was generally lower in the region Central/Latin America compared to the rest of the study population.

Patient-reported and Clinician-reported Outcomes

No consistent or clinically meaningful differences in PRO/ClinRO endpoints were identified between the romosozumab and placebo or alendronate groups. Post-fracture data were obtained through at months 1, 2, and 3 for subjects who had a clinical fracture on study using the pre-fracture baseline for comparison.

Bone mineral density

Table 25: Bone Mineral Density Percent Change from Baseline at Month 12 in the Pivotal Fracture Studies (ANCOVA Model) (Primary Efficacy Analysis Set for BMD, LOCF)

	20070337			20110142		
	Placebo (N = 3591)	Romosozumab 210 mg QM (N = 3589)	Difference from Placebo	Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM (N = 2046)	Difference from Alendronate 70 mg QW
Lumbar spine						
n	3148	3151		1718	1722	
LS mean (SE)	0.4 (0.1)	13.1 (0.1)	12.7 (0.1)	5.0 (0.1)	13.7 (0.2)	8.7 (0.2)
(95% CI)	(0.24, 0.51)	(12.84, 13.26)	(12.44, 12.92)	(4.73, 5.21)	(13.36, 13.99)	(8.31, 9.09)
p-value			<0.001			<0.001
Adjusted p-value[a]			NA			<0.001
Total hip						
n	3210	3197		1781	1781	
LS mean (SE)	0.3 (0.1)	6.0 (0.1)	5.8 (0.1)	2.8 (0.1)	6.2 (0.1)	3.3 (0.1)
(95% CI)	(0.14, 0.37)	(5.90, 6.18)	(5.61, 5.96)	(2.67, 3.02)	(5.94, 6.39)	(3.03, 3.60)
p-value			<0.001			<0.001
Adjusted p-value[a]			NA			<0.001
Femoral neck						
n	3210	3197		1781	1781	
LS mean (SE)	0.3 (0.1)	5.5 (0.1)	5.2 (0.1)	1.7 (0.1)	4.9 (0.1)	3.2 (0.2)
(95% CI)	(0.08, 0.54)	(5.23, 5.71)	(4.94, 5.37)	(1.46, 1.98)	(4.65, 5.23)	(2.90, 3.54)
p-value			<0.001			<0.001
Adjusted p-value[a]			NA			<0.001

Based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction for Study 20070337, and adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline value, machine type, and baseline value-by-machine type interaction for Study 20110142
Missing values are imputed by carrying forward the last nonmissing postbaseline value prior to the missing value.
[a] Adjusted p-value for the secondary BMD endpoints in Study 20110142 was based on a sequential testing procedure.

In both studies, romosozumab increased DXA BMD through month 12 at all locations compared to placebo (20070337) and alendronate (20110142).

In the analyses through month 12 in study 20070337, treatment differences across demographic subgroups (i.e., age and geographic region) ranged from 12.0% to 14.4% for the lumbar spine and from 4.7% to 6.6% for the total hip and were more or less consistent with the treatment differences observed for the overall population (12.7% for lumbar spine and 5.8% for total hip at month 12). It is however noticed, that increase of BMD at total hip was most pronounced in the region Central/Latin America with a treatment difference of 6.6% at month 12. For the very same region no reduction in the non-vertebral fracture rate was seen in the romosozumab group compared to the placebo arm. This finding could question the relationship between fracture risk reduction and increasing BMD under treatment with romosozumab. Therefore, the Applicant was requested to discuss this further. The Applicant has clarified that Central/Latin American study patients is a subset where BMD-increase does not in 1 year translate to clinically relevant (non-vertebral) fracture risk reduction. According to the Applicant this could be due to the fact that the background fracture rate and fracture risk were too low to be able to detect a meaningful difference. As the fracture risk in the

Central/Latin American population was comparable to the fracture rate observed in premenopausal women, this might be a comprehensible explanation.

After transition to denosumab, the DXA BMD in the romosozumab/denosumab group continued to increase, albeit less than in the placebo/denosumab group; however, the total increase in DXA BMD at month 24 was higher in the romosozumab/denosumab arm. This indicates that the effect of denosumab is not potentiated by romosozumab treatment compared to placebo. The same pattern was seen with romosozumab/alendronate compared to alendronate alone.

In post hoc responder analyses demonstrated that romosozumab improved BMD from baseline to month 12 in 98.9% of subjects at the lumbar spine in 20070337 and in 98.4% in 20110142. In both studies, just over 68% of the romosozumab treated subjects had an increase from baseline in lumbar spine BMD at month 12 of ≥ 10%, irrespective of a lower baseline lumbar spine BMD T-score in 20110142.

Ancillary analyses

The percent change from baseline in DXA BMD at month 6 and month 18 was evaluated as part of predefined substudies (*Lumbar Spine and Proximal Femur DXA substudy [Imaging II substudy]* in 20070337 and *Imaging and PK/BTM/Biomarker Substudy* in 20110142).

Figure 13: Bone Mineral Density Percent Change from Baseline by Visit Least Squares Means and 95% CIs From ANCOVA Model (Imaging II Substudy Analysis Set, LOCF) Study 20070337 (24-Month Primary Analysis Period)

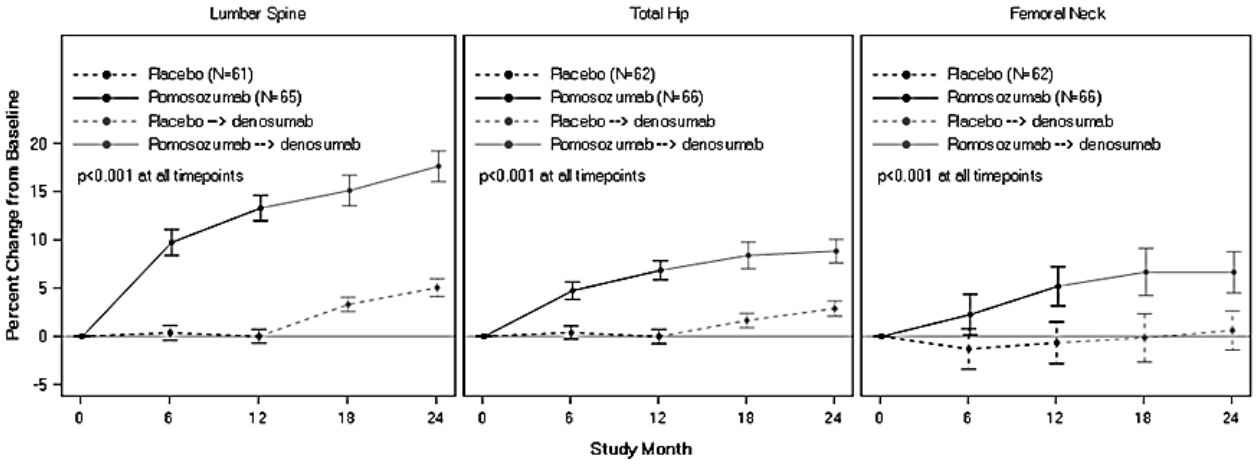
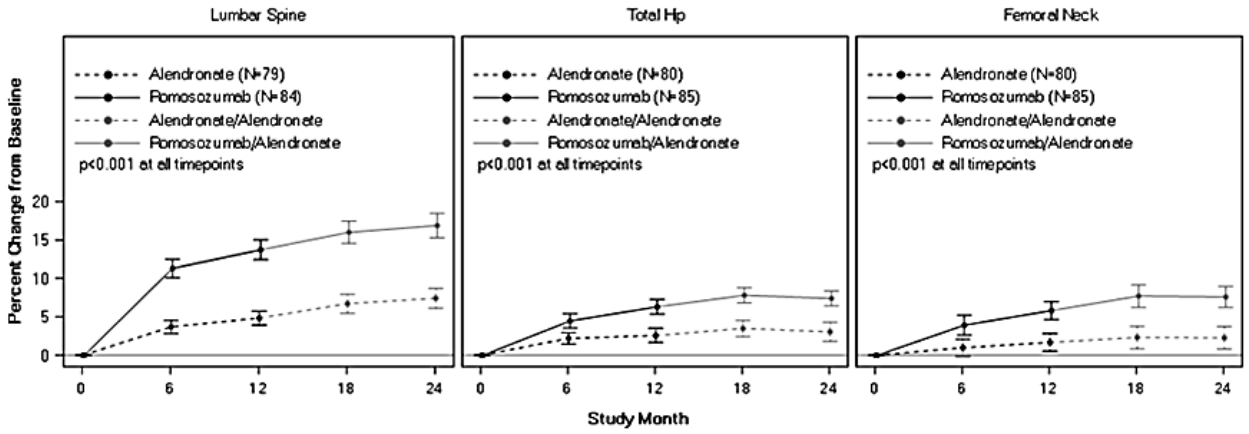


Figure 14: Bone Mineral Density: Percent Change from Baseline by Visit Least Squares Means and 95% CIs From ANCOVA Model (Substudy Imaging Efficacy Analysis Set, LOCF) Study 20110142 (Primary Analysis)



The results on DXA BMD up to month 24 are similar to the results of the significantly larger main studies. The findings are also consistent with pooled data from studies 20060326, 20101291 and 20120156 through 6 and 12 months in subjects treated with 210 mg romosozumab compared to placebo.

Forearm and Total Body DXA and HR-pQCT substudy (Imaging Substudy I)

A total of 95 randomized subjects from 20070337 enrolled, representing all regions except Central and Eastern Europe. Statistically significant increases in total body BMD were seen at all time points comparing romosozumab to placebo in the first 12 months and romosozumab/denosumab to placebo/denosumab month 12-24.

Romosozumab (months 6 and 12) and romosozumab/denosumab (months 18 and 24) did not have a significant impact on BMD in the forearm, as evaluated by DXA BMD at the distal 1/3 radius and total radius. BMD in the forearm was even lower in subjects who received 12 months of romosozumab treatment compared with those who received placebo. Consistent with the results for radius BMD by DXA, evaluation of the radius by HR-pQCT did not show significant differences in the double-blind period between romosozumab and placebo for volumetric BMD (total, cortical, trabecular).
Potential explanations to this finding could be the non-weight bearing nature of this skeletal site and the documented less responsivity of the distal radius for all pharmacological therapies for osteoporosis. Actually, even decreases in BMD at the distal radius during osteoporosis treatment have been reported in literature (Cosman et al, 2015). A conclusive interpretation of the fracture protective effect of romosozumab on forearm fractures remains however unclear due to the limited number of patients with forearm fractures in both 20070337 and the respective substudy.

At the distal tibia, romosozumab significantly increased total BMD (month 12), cortical BMD (month 12), and cortical thickness (month 6 and month 12) during the double-blind period compared with placebo, while the percent changes from baseline in trabecular BMD, trabecular bone volume to tissue volume, trabecular separation, and trabecular thickness did not differ significantly between the groups.

Imaging and PK/BTM/Biomarker substudy

Integral (total) and trabecular volumetric bone mineral density was measured by QCT in 76 subjects in the 20110142 substudy. Romosozumab increased integral (total) BMD and trabecular volumetric BMD at the lumbar spine to a greater extent than alendronate alone at all time points. It is however noted that increase

in BMD in the romosozumab group was largest during the first 6 months of treatment, again indicating a more pronounced effect of romosozumab in the beginning of the treatment. There was also a tendency to decreased BMD at month 24 compared to month 12 in the romosozumab group. The effects of romosozumab on lumbar spine strength as measured by FEA were consistent with the effects BMD as measured by QCT.

Bone Biopsy Substudy

The Bone biopsy substudy in 20070337 included 139 subjects and 154 biopsies.
Number of subjects: 16 romosozumab vs 18 placebo at month 2, 40 romosozumab vs 33 placebo at month 12 and 24 romosozumab/denosumab vs 23 placebo/denosumab at month 24.

Bone Histomorphometry Evaluation

Month 2 Cohort

15 subjects in the romosozumab vs 14 subjects in the placebo arm with quadruple fluorochrome labelling (double fluorochrome labelling at baseline and before month 2) were evaluated for histomorphometry at month 2. This allowed for comparison between baseline and month 2 within a single biopsy (within-subject comparison). In the *cancellous and endocortical compartments*, within-subject comparisons showed significant increases in single-label, double-label, and mineralizing surfaces and surface-based bone formation rates (BFR/BS) only in the romosozumab group. In the *intracortical compartment*, double-label surface also only significantly increased in the romosozumab group. In contrast, the MAR (mineral apposition rate) increased in the placebo group between baseline and month 2 but did not change significantly in the romosozumab group during that time period. These data suggest that romosozumab increased the surface extent of active bone formation (dL/BS) but not the rate at the level of the individual osteoblast (MAR). In *periosteal compartment*, no significant changes in histomorphometry parameters were noted in either group at month 2 (due to few double-labels and a reduced number of data points for MAR and BFR/BS).

Between-treatment comparisons of percent change from baseline to month 2 were consistent with the within-subject comparisons. Compared with placebo, romosozumab significantly increased single-label, double-label, and mineralizing surfaces and the BFR/BS in the *cancellous compartment*, double-label and mineralizing surfaces and the BFR/BS in the *endocortical compartment*, and double-label and mineralizing surfaces in the *intracortical compartment*. At month 2 in the *cancellous compartment*, the median percent change in mineralizing surface in the romosozumab group was 325.1% compared with 67.3% in placebo group. Similar changes were observed in BFR/BS at month 2 (median percent change of approximately 328% in daily and annual rates in the romosozumab group; median percent change of approximately 80% in daily and annual rates in the placebo group).

At month 2, bone structure parameters in the *cancellous compartment* (cancellous bone volume to tissue volume, trabecular thickness, trabecular number, and trabecular separation) did not differ significantly between the romosozumab and placebo groups.

Romosozumab significantly increased osteoid thickness and osteoid volume compared with placebo (static bone formation parameters).

A reduction in bone resorption was also evident at month 2, as indicated by significantly lower median eroded surface in the *cancellous* (romosozumab, 1.81%; placebo, 3.37%) and *endocortical compartments (*romosozumab, 1.58%; placebo, 6.27%) and a significantly lower median osteoclast surface in the *cancellous compartment* (romosozumab, 0%; placebo, 0.095%) in the romosozumab group.

Month 12 Cohort

Cancellous bone volume to tissue volume, trabecular thickness, wall thickness, and cortical thickness increased significantly in the romosozumab group compared with the placebo group at month 12.

However, dynamic and static bone formation parameters at month 12 demonstrated a decrease in bone formation secondary to the decrease in the rate of bone remodelling in the *cancellous compartment,* consistent with self-regulation of bone formation. All these parameters were significantly lower in the romosozumab arm, and mineralization lag time and formation period were significantly greater in the romosozumab group compared with the placebo group. These results are also supported by findings from bone formation marker, where elevated values are only detected during early romosozumab treatment phase. While on the one hand one could raise the concern that bone formation could in the worst case be inhibited for a longer time period (evaluation of histomorphometry parameters at month 24 did not reveal any significant differences between the romosozumab/denosumab and placebo/denosumab groups), it is however noted that bone formation markers increase again after 1 year in study 20060326.

In the *intracortical and endocortical compartments*, no significant changes were noted in the single-label surface, double-label surface, mineralizing surface, and surface-based bone formation rate in the romosozumab group compared with the placebo group at month 12. Eroded surface and osteoclast surface were significantly lower in the romosozumab group than in the placebo group, indicating sustained inhibition of bone resorption.

As no statistically significant difference to placebo was noted for bone formation parameters in the intracortical compartment (at month 2), concern was raised that this finding could be related to the fact that the most frequently reported type of non-vertebral fracture was forearm fractures. However, the Company clarified that changes to the cortical bone compartment result not only from effects at the intracortical but also at the periosteal and endosteal bone surfaces, and drug effects at any of those cortical surfaces can result in changes to cortical mass or structure. As described above, a positive effect on bone formation is observed in the endocortical surface at 2 months. This is supported by the finding that cortical thickness in biopsies of romosozumab treated patients was significantly thicker compared to placebo after 12 months.

Bone Biopsy Micro-CT Analysis

Micro-CT analyses were performed using bone biopsies from 71 subjects (39 romosozumab, 32 placebo) at month 12 and 38 subjects (18 romosozumab/denosumab, 20 placebo/denosumab) at month 24.

Romosozumab treatment for 12 months resulted in significant increases in trabecular BMD and trabecular bone volume, primarily due to increased trabecular thickness. Furthermore, a significantly lower trabecular bone pattern factor and trabecular bone surface to bone volume compared with the placebo group at month 12 was shown. The Company's argumentation that this indicates better connectivity and that there seem to be more concave surfaces is endorsed. Regardless of the methodology used (histomorphometry or micro-CT), there is no difference in trabecular number between placebo and romosozumab at month 12.

The Company did not discuss the clinical relevance of the findings. Therefore, such a discussion was requested with the Day 120 LoQ. Having considered the Applicant's response, it has to be commented that a more detailed overview on the different parameters evaluated with the aim to assess the quality of bone microstructure, e.g. trabecular number thickness, trabecular connectivity, cortical thickness s, etc. (not limited to these ones), including a discussion on the clinical meaning of the reported values for indeed achieving an improved strength, would have been expected. On the other hand, it is agreed that bone histomorphometry data are exploratory in nature and primarily used for safety reasons due to certain

limitations for example the fact that the samples represent a small fraction of the skeleton and may not be representative of other sites. Furthermore, the number of patients from who biopsies have been taken is small. Consequently, it is hard to draw any firm conclusions from the biopsies. It is also agreed that the presented parameters overall indicate an increased bone formation during the first weeks and a maintained decrease in bone resorption also during the late treatment phase, i.e. at month 12. It is therefore not considered reasonable to further pursue this issue and to ask for a more detailed discussion. It is also of interest that bone histomorphometry samples are taken at a non-weight bearing site, which may be a potential explanation to the fact that the effect of romosozumab in bone formation parameters is not as large at such sites as in e.g. vertebral bones.

Study 20110174 in male osteoporosis

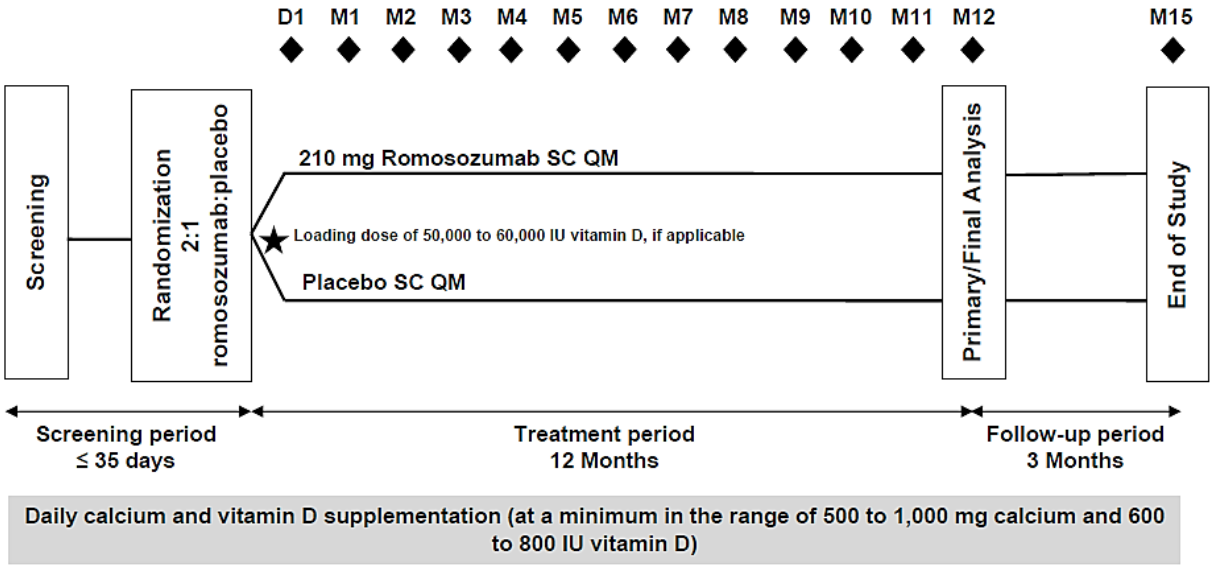
The phase 3 male osteoporosis bridging trial set included studies 20070337 and 20110174. The primary goal of the analyses utilizing this trial set was to allow for side-by-side comparison of the two studies with respect to BMD and BTMs to assess the consistency of efficacy results between these 2 pivotal studies. The comparisons of efficacy results were based on data from the first 12 months of each study. Methodology and results are discussed below.

Methods

Study design

20110174 was a randomized, double-blind, placebo-controlled study in men with osteoporosis.

Figure 15: Study Design and Treatment Schema



Study participants

This study was conducted at 31 centres in Europe, Latin America, Japan and North America.

Inclusion criteria

1 Ambulatory male subjects ≥ 55 years to ≤ 90 years of age, at the time of enrolment

2 Increased risk of fracture, defined as:

- BMD T-score ≤ -2.50 at the lumbar spine, total hip, or femoral neck, as assessed by the central imaging vendor at the time of screening, based on DXA scans OR
- BMD T-score ≤ -1.50 at the lumbar spine, total hip, or femoral neck, as assessed by the central imaging vendor at the time of screening, based on DXA scans and a history of fragility non-vertebral fracture or vertebral facture (thoracic or lumbar)

3 Subject has at least 2 evaluable vertebrae in the L1 to L4 region, as assessed by the principal investigator or designee

4 Subject has at least 1 evaluable hip, as assessed by the principal investigator or designee

Main Exclusion Criteria

1. BMD T-score ≤ -3.50 at the total hip or femoral neck, as assessed by the central imaging vendor at the time of screening, based on DXA scans
2. History of hip fracture
3. Use of anabolic steroid. Testosterone permitted provided not begun within 56 months prior to randomisation.

Additional exclusion criteria are generally the same as for study 20070337 with exception for exclusion criteria related to denosumab treatment and criteria not applicable for male subjects.

Treatments

The romosozumab dose 210 mg QM was based on the results from the phase 2 dose-ranging studies 20060326 and 20101291 in combination with PK/PD-data. No male subjects were included in these studies. However, there are no significant effects by gender according to the population PK analysis (section 3.3.1). As for the studies on postmenopausal women, protocol required supplementation with calcium/vitamin D as concomitant medication.

Outcomes/endpoints

Primary Endpoint

- The primary efficacy endpoint was percent change from baseline in DXA BMD at the lumbar spine at month 12.

Secondary Efficacy Endpoints

- The key secondary endpoints were percent change from baseline in DXA BMD at the femoral neck and total hip at month 12.
- Other secondary endpoints were percent change from baseline in DXA BMD at the lumbar spine, femoral neck, and total hip at month 6.

Exploratory Efficacy Endpoints

- Percent changes from baseline in the BTMs CTX and P1NP at months 1, 3, 6, and 12.
- Analysis of bone histology and histomorphometry parameters at month 12 (in a subset of subjects)

  In study 20110174, the percent change in lumbar spine BMD after 12 months of treatment is the primary endpoint as advised in the EMA guidelines on osteoporosis for bridging studies. BMD changes in

total hip and femoral neck are secondary endpoints and change in bone formation markers is included in the exploratory endpoints. However, effect on responder rates was not an endpoint.
For the two pivotal studies in postmenopausal women with osteoporosis, the proportion of subjects with any romosozumab induced increase of lumbar spine BMD from baseline as well as the proportion of subjects with such an increase of ≥10% were provided. The Applicant was asked to provide the corresponding numbers for the participants in 20110174. As in women, the responder rates were to include analyses based on all randomised subjects using a non-responder imputation in case data was missing**.** As requested, responder analyses have been provided, see below (Outcomes and estimations).

Sample size

A sample size of 225 subjects, 150 in the romosozumab arm and 75 subjects in the placebo arm was expected to provide > 99% power to show a difference between romosozumab and placebo in the primary and key secondary BMD endpoints. A high power at the planning stage is no issue, it is rather endorsed that the sample size was not smaller given the 2:1 allocation ratio and the importance to have a sufficient number of subjects in the control arm given also the assessment of e.g. safety.

Randomisation

Eligible subjects were randomised via IVRS to receive either romosozumab or placebo using a 2:1 allocation ratio. Randomisation was stratified by geographic region and it was expected that a minimum of 15 subjects was to be randomised from Japan.

Blinding (masking)

This was a double-blind study. Subjects received either romosozumab or matching placebo.

Statistical methods

Although differences between 20070337, 20110142 and 20110174 regarding e.g. primary endpoints the analysis approach as used in 20070337 and 20110142 for the analyses of BMD endpoints was used also here; i.e. an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) imputation. The sensitivity analyses planned comprised the primary analysis repeated based on the PP set and, at least for key secondary BMD endpoints, analyses were to be performed using a repeated measures model. The primary approach is not fully endorsed, and the sensitivity analysis based on a repeated measures model is not considered conservative in that it addresses the treatment effect if all patients would have been fully adherent. Having acknowledged the limited number of subjects who discontinued the study prior to month 12, no further analyses will however be requested.

The data cutoff date for the 12-month primary analysis was 27 January 2016. The SAP was amended once and after the primary analysis cutoff date. The changes made were accounted for and was generally endorsed. As for 20070337 and 20110142, the date for database lock and the breaking of randomisation codes had however not been found. The Applicant clarified the missing date that showed that (initial) unblinding in study 20110174 was conducted after approval of the (final) SAP. Further, the Applicant stated that the primary analysis snapshot reflected a complete and accurate copy of the clinical study database at the date of snapshot. Final SAP approval was 3 March 2016; the date for the primary analysis snapshot and approval to unblind was 11 March 2016. The final database lock occurred 6 June 2016.The primary analysis was performed after all subjects had had the opportunity to complete the month 12 visit. No interim analyses or sample size re-estimation were planned for this study.

The final analysis was to be performed after all subjects had had the opportunity to complete the month 15 visit. The primary objective of the final analysis was safety and the 3-month follow-up period was to provide the opportunity to monitor all subjects for adverse events and formation of anti-romosozumab antibodies.

The primary efficacy analysis subset included all randomised subjects who had a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement for each of the skeletal sites (lumbar spine, femoral neck, and total hip).

The primary endpoint, percent change from baseline in DXA BMD at the lumbar spine at month 12, was analysed using an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) imputation. The ANCOVA model included treatment, baseline DXA BMD value, baseline testosterone level, and the stratification factor of geographic region as main effects. Additional covariates of machine type (Hologic or Lunar) and machine type-by-baseline DXA BMD value interaction were also included in the model. A sensitivity analysis using the per protocol analysis subset was planned and has been performed.

To control multiplicity for assessment of the primary, key secondary endpoints, and other secondary endpoints, a combination of a hierarchical and simultaneous testing procedure was implemented. The hierarchical testing procedure had three steps:

1. Lumbar spine BMD percent change from baseline at 12 months

2. Total hip and femoral neck BMD percent change from baseline at 12 months

3. Lumbar spine, total hip and femoral neck BMD percent change from baseline at 6 months

The statistical inferences of the treatment effects in the second step was to be made only if the treatment effect on the primary efficacy endpoint was statistically significant using a 2-sided type 1 error rate of 0.05. The Hochberg procedure was employed to control the overall type 1 error for the second step in order to maintain the overall significance level at 0.05. The statistical inferences of the treatment effects in the third step, added in SAP version 2.0 (dated 03 March 2016), was to be made only when the treatment effects on both key secondary endpoints (in step 2) were statistically significant. The Hochberg procedure was employed to control the overall type 1 error also in the third step in order to maintain the overall significance level at 0.05.

Results

Recruitment

252 subjects were randomised.

Table 26: Subject Disposition and Investigational Product Completion in the 12-Month Double-blind Study Period: Study 20070337 (Women) and Study 20110174 (Men) (Randomized Subjects)

	Study 20070337 (Women)		Study 20110174 (Men)	
	Placebo (N = 3591) n (%)	Romosozumab 210 mg SC QM (N = 3589) n (%)	Placebo (N = 82) n (%)	Romosozumab 210 mg SC QM (N = 163) n (%)
Randomized	3591	3589	82	163
Completed the study	3205 (89.3)	3185 (88.7)	79 (96.3)	152 (93.3)
Completed IP	3130 (87.2)	3093 (86.2)	76 (92.7)	145 (89.0)
Discontinued IP	74 (2.1)	92 (2.6)	3 (3.7)	7 (4.3)
Never received IP	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued from the study	386 (10.7)	404 (11.3)	3 (3.7)	11 (6.7)
Completed IP	5 (0.1)	10 (0.3)	0 (0.0)	0 (0.0)
Discontinued IP	373 (10.4)	380 (10.6)	2 (2.4)	11 (6.7)
Never received IP	8 (0.2)	14 (0.4)	1 (1.2)	0 (0.0)

IP = Investigational product; N = Number of subjects randomized; QM = every month; SC = subcutaneous
Percentages based on number of subjects randomized
Subjects could continue on study after withdrawal from IP.

Baseline data

Table 27: Baseline Demographics: Study 20070337 (Women) and Study 20110174 (Men) (Randomized Subjects)

	Study 20070337 (Women)		Study 20110174 (Men)	
	Placebo (N = 3591)	Romosozumab 210 mg SC QM (N = 3589)	Placebo (N = 82)	Romosozumab 210 mg SC QM (N = 163)
Race - n (%)				
White	2052 (57.1)	2063 (57.5)	60 (73.2)	120 (73.6)
Asian	441 (12.3)	425 (11.8)	9 (11.0)	18 (11.0)
Black or African American	74 (2.1)	77 (2.1)	0 (0.0)	1 (0.6)
American Indian or Alaska Native	63 (1.8)	64 (1.8)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	59 (1.6)	60 (1.7)	0 (0.0)	1 (0.6)
Other	901 (25.1)	900 (25.1)	13 (15.9)	23 (14.1)
Geographic region - n (%)				
Asia Pacific	419 (11.7)	410 (11.4)	9 (11.0)	18 (11.0)
Central/Latin America	1534 (42.7)	1550 (43.2)	12 (14.6)	23 (14.1)
Europe	1547 (43.1)	1525 (42.5)	54 (65.9)	108 (66.3)
North America	91 (2.5)	104 (2.9)	7 (8.5)	14 (8.6)
Age (years)				
n	3591	3589	82	163
Mean	70.8	70.9	71.5	72.4
SD	6.9	7.0	6.9	7.4
Median	70.0	70.0	72.5	73.0
Min, Max	55, 90	55, 90	55, 85	56, 89
Age group - n (%)				
< 65 years	757 (21.1)	768 (21.4)	11 (13.4)	31 (19.0)
≥ 65 years	2834 (78.9)	2821 (78.6)	71 (86.6)	132 (81.0)
< 75 years	2470 (68.8)	2470 (68.8)	53 (64.6)	93 (57.1)
≥ 75 years	1121 (31.2)	1119 (31.2)	29 (35.4)	70 (42.9)

Subjects in study 20110174 were approximately 1.5 years older than the subjects in 20070337. 66% of the subjects in the study came from Europe compared to 42% in study 20070337.

Table 28: Summary of Baseline Characteristics: Study 20070337 (Women) and Study 20110174 (Men) (Randomized Subjects)

	Study 20070337 (Women)		Study 20110174 (Men)	
	Placebo (N = 3591)	Romosozumab 210 mg SC QM (N = 3589)	Placebo (N = 82)	Romosozumab 210 mg SC QM (N = 163)
Fracture history[a] - n (%)				
Yes	1451 (40.4)	1434 (40.0)	46 (56.1)	86 (52.8)
No	2140 (59.6)	2155 (60.0)	36 (43.9)	77 (47.2)
Lumbar spine BMD T-score				
n	3481	3498	82	163
Mean (SD)	-2.71 (1.04)	-2.72 (1.04)	-2.33 (1.41)	-2.22 (1.19)
Median	-2.78	-2.82	-2.66	-2.41
Min, Max	-5.8, 2.0	-5.5, 1.8	-5.2, 3.3	-5.3, 2.1
Total hip BMD T-score				
n	3590	3589	82	163
Mean (SD)	-2.46 (0.47)	-2.48 (0.47)	-1.92 (0.65)	-1.92 (0.59)
Median	-2.52	-2.53	-1.89	-1.97
Min, Max	-3.5, 0.1	-3.5, 0.1	-3.2, 0.1	-3.4, 0.5
Femoral neck BMD T-score				
n	3590	3589	82	163
Mean (SD)	-2.74 (0.29)	-2.76 (0.28)	-2.30 (0.52)	-2.34 (0.52)
Median	-2.72	-2.73	-2.40	-2.41
Min, Max	-3.5, -0.8	-3.6, -1.6	-3.3, -1.0	-3.4, -0.1

Table 29: 10 Year Probability of Fracture: Study 20070337 (Women) and Study 20110174 (Men) (Randomized Subjects)

	Study 20070337 (Women)		Study 20110174 (Men)	
	Placebo (N = 3591)	Romosozumab 210 mg SC QM (N = 3589)	Placebo (N = 82)	Romosozumab 210 mg SC QM (N = 163)
10-year probability of major osteoporotic fracture calculated with BMD - %				
n	3586	3577	80	163
Mean	13.360	13.444	8.639	8.993
SD	8.526	8.763	5.162	5.232
Median	10.915	10.810	7.225	7.740
Q1, Q3	7.120, 16.650	7.090, 17.020	4.690, 12.590	5.550, 11.720
Min, Max	2.65, 69.41	3.17, 69.69	1.79, 21.14	1.49, 32.96
10-year probability of hip fracture calculated with BMD - %				
n	3586	3577	80	163
Mean	5.889	5.871	3.639	3.978
SD	5.270	5.391	2.633	3.279
Median	4.370	4.280	2.985	3.250
Q1, Q3	2.800, 6.950	2.780, 6.970	1.570, 4.835	1.790, 4.890
Min, Max	0.27, 56.55	0.67, 57.89	0.25, 9.92	0.07, 22.59

Consistent with the differences in eligibility criteria, mean baseline BMD T-scores were higher in 20110174 than in 20070337 at all anatomical sites for both treatment groups. The percentage of subjects with a history of fractures was higher in 20110174.

Baseline 10-year fracture risk was lower in 20110174, but the distribution of individual subjects' 10-year probability of major osteoporotic fracture risk shows a considerable overlap with the distribution for 20070337.

Outcomes and estimation

Effect on bone mineral density (primary and secondary endpoints)

Table 30: Bone Mineral Density Percent Change From Baseline at Month 12: Study 20070337 (Women) and Study 20110174 (Men) (Primary Analysis Set for BMD, LOCF)

	Study 20070337 (Women)		Study 20110174 (Men)	
Percent Change From Baseline	Placebo (N = 3591)	Romosozumab 210 mg SC QM (N = 3589)	Placebo (N = 82)	Romosozumab 210 mg SC QM (N = 163)
Lumbar spine				
n	3148	3151	79	157
LS Mean (95% CI)	0.4 (0.2, 0.5)	13.1 (12.8, 13.3)	1.2 (0.2, 2.2)	12.1 (11.2, 13.0)
Difference from Placebo[a,b]		12.7 (12.4, 12.9)		10.9 (9.6, 12.2)
p-value		<0.001		<0.001
Total hip				
n	3210	3197	79	158
LS Mean (95% CI)	0.3 (0.1, 0.4)	6.0 (5.9, 6.2)	-0.5 (-1.1, 0.1)	2.5 (2.1, 2.9)
Difference from Placebo[a,b]		5.8 (5.6, 6.0)		3.0 (2.3, 3.7)
p-value		<0.001		<0.001
Femoral neck				
n	3210	3197	79	158
LS Mean (95% CI)	0.3 (0.1, 0.5)	5.5 (5.2, 5.7)	-0.2 (-1.0, 0.6)	2.2 (1.5, 2.9)
Difference from Placebo[a,b]		5.2 (4.9, 5.4)		2.4 (1.5, 3.3)
p-value		<0.001		<0.001

[a] For 20070337, based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction.
[b] For 20110174, based on ANCOVA model adjusting for treatment, baseline BMD value, machine type, machine type-by-baseline BMD value, baseline testosterone level, geographic region (stratification factor), and using a variance structure allowing for heterogeneity between treatment groups

The primary endpoint was met, as romosozumab increased lumbar spine BMD through month 12 compared to placebo. All p-values on tests of treatment-by-subgroup interactions were > 0.05 with the exception of baseline lumbar spine BMD T-score category (p = 0.0029). No qualitative interaction was detected. Romosozumab increased total hip and femoral neck BMD compared to placebo through month 12; however, the percent changes from baseline BMD in the romosozumab group were more modest in both total hip and femoral neck, resulting in a lower LS mean difference between romosozumab and placebo in 20110174 than in 20070337. The Applicant speculates that this may, in part, be due to the lower baseline BMD in 20070337. This can be supported by results of BMD T-score subgroups in the male osteoporosis study mentioned above. It is noted that the distribution of baseline lumbar spine BMD T-score and 10-year major osteoporotic fracture risk between Studies 20110174 and 20070337 have considerable overlap.

The magnitude of absolute BMD change from baseline was comparable between the romosozumab treatment arms of study 20110174 and the reference study 20070337 in lumbar spine, whereas the absolute BMD change to baseline in total hip and femoral neck were lower in male osteoporosis patients.

To be included in the analysis, subjects were required to have a baseline and at least one post-baseline assessment. Few subjects discontinued the study early i.e. prior to month 12; 11/163 (6.7%) in the romosozumab arm and 3/82 (3.7%) in the placebo group. Although more subjects in the romosozumab than

placebo arm, the proportion excluded from the primary analyses was identical in the two groups (3.7%). This implies that an "early" assessment, from month 6 or from the time-point of early discontinuation was carried forward for more subjects in the romosozumab arm than in the placebo arm. Although the use of LOCF can be questioned and the sensitivity analyses performed based on a repeated measure model is not considered very useful, the differences between the treatments are considered convincing.

As requested, the Applicant provided BMD responder analyses (for all three pivotal studies) based on all randomised subjects using non-responder imputation in case of missing data. The percentages of subjects with improved BMD (any increase from baseline) were higher in the romosozumab group than placebo group at all anatomical sites after 12 months of treatment. Below are excerpts from responses provided during the procedure. In the analyses in which a subject was to be classified as a responder only in case of ≥10% improvement from baseline, a statistically significant difference was shown for lumbar spine but not total hip or femoral neck. For lumbar spine the responder rate was 1.2% (1/82) in the placebo arm and 60.1% (98/163) in the romosozumab arm (p<0.001). For total hip and femoral neck respectively, there were no responders in the placebo group and in the romosozumab arm only 2/163 (1.2%) and 3/163 (1.8%), respectively.

Table 31: Summary of percent change from baseline in BMD at lumbar spine, total hip, and femoral neck in 20070337, 20110142, and 20110174 (Full Analysis Set, NRI)

	20070337[a] (Month 24 analysis)			20110142[b] (Primary Analysis)			20110174[c] (Month 12 Primary Analysis)		
	Placebo/ denosumab (N=3591) n/N1 (%)	Romosozumab/ denosumab (N=3589) n/N1 (%)	p-value[d]	ALN/ALN (N=2047) n/N1 (%)	Romosozumab/ ALN (N=2046) n/N1 (%)	p-value[e]	Placebo (N=82) n/N1 (%)	Romosozumab (N=163) n/N1 (%)	p-value[f]
Lumbar spine									
Improved									
Month 12	1665/3591 (46.4)	3107/3589 (86.6)	<0.001	1485/2047 (72.5)	1687/2046 (82.5)	<0.001	50/82 (61.0)	146/163 (89.6)	<0.001
Month 24	2627/3591 (73.2)	2836/3589 (79.0)	<0.001	1417/2047 (69.2)	1530/2046 (74.8)	<0.001	--	--	--
≥10% improvement									
Month 12	28/3591 (0.8)	2153/3589 (60.0)	<0.001	248/2047 (12.1)	1171/2046 (57.2)	<0.001	1/82 (1.2)	98/163 (60.1)	<0.001
Month 24	386/3591 (10.7)	2388/3589 (66.5)	<0.001	457/2047 (22.3)	1168/2046 (57.1)	<0.001	--	--	--
Total hip									
Improved									
Month 12	1681/3591 (46.8)	2999/3589 (83.6)	<0.001	1428/2047 (69.8)	1615/2046 (78.9)	<0.001	32/82 (39.0)	124/163 (76.1)	<0.001
Month 24	2453/3591 (68.3)	2820/3589 (78.6)	<0.001	1333/2047 (65.1)	1497/2046 (73.2)	<0.001	--	--	--
≥10% improvement									
Month 12	9/3591 (0.3)	523/3589 (14.6)	<0.001	55/2047 (2.7)	320/2046 (15.6)	<0.001	0/82 (0.0)	2/163 (1.2)	0.35
Month 24	79/3591 (2.2)	979/3589 (27.3)	<0.001	109/2047 (5.3)	436/2046 (21.3)	<0.001	--	--	--
Femoral neck									
Improved									
Month 12	1664/3591 (46.3)	2866/3589 (79.9)	<0.001	1208/2047 (59.0)	1497/2046 (73.2)	<0.001	35/82 (42.7)	109/163 (66.9)	<0.001
Month 24	2194/3591 (61.1)	2724/3589 (75.9)	<0.001	1163/2047 (56.8)	1421/2046 (69.5)	<0.001	--	--	--
≥10% improvement									
Month 12	46/3591 (1.3)	485/3589 (13.5)	<0.001	76/2047 (3.7)	297/2046 (14.5)	<0.001	0/82 (0.0)	3/163 (1.8)	0.15
Month 24	114/3591 (3.2)	834/3589 (23.2)	<0.001	88/2047 (4.3)	350/2046 (17.1)	<0.001	--	--	--

Fractures

In this study, fractures were reported as adverse events. In total, 6 fractures were reported as treatment emergent adverse events; 3 in the placebo group (N=81; 3.7%) (femur, humerus and upper limb) and 3 in the romosozumab group (N=163; 1.8%) (lumbar vertebra, rib, thoracic vertebra). No additional fracture was reported during the 3-month follow-up period in either group. The absolute number of fracture events in the study is far too small to draw any firm conclusions.

Ancillary analyses

Bone Biopsy Substudy

A total of 20 transiliac crest bone biopsy specimens were obtained from men with osteoporosis at 12 months (11 specimens in romosozumab group, 9 specimens in placebo group). Of the biopsies obtained, all were adequate for qualitative histology. All biopsies from placebo patients and 9 (81.8%) of biopsies from romosozumab patients were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments showed normal lamellar bone with no evidence of mineralization defects, woven bone, marrow fibrosis, or clinically significant marrow abnormality in patients treated with romosozumab. The presence of double-labelled surface, as evidence of active bone formation, was observed in the trabecular or cortical compartments for 88.9% (8/9) of patients in the romosozumab group and 77.8% (7/9) patients in the placebo group. In cancellous bone, histomorphometric analyses at month 12 revealed decreases in bone resorption parameters (percent eroded and osteoclastic surfaces) in the romosozumab group with no significant difference noted in bone formation and bone structure parameters compared with the placebo group.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary tables of main efficacy results in postmenopausal osteoporosis

Table 32a: Summary of efficacy for trial 20070337

Title: A multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of romosozumab treatment in postmenopausal women with osteoporosis		
Study identifier	Study No.: 20070337	
Design	A multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 months not applicable 12 months
Hypothesis	Romosozumab treatment for 12 months compared with placebo is effective in reducing the subject incidence of new vertebral fracture in postmenopausal women with osteoporosis. Romosozumab treatment for 12 months followed by denosumab treatment for 12 months compared with placebo followed by denosumab treatment is effective in reducing the subject incidence of new vertebral fracture in postmenopausal women with osteoporosis.	
Treatment groups	Romosozumab/Denosumab	Romosozumab 210mg SC QM for 12 months (M1-M12), Denosumab 60mg SC Q6M for 24 month (M12-M36); N=3589

	Placebo/Denosumab		Placebo SC QM for 12 months (M1-M12), Denosumab 60mg SC Q6M for 24 months (M12-M36); N=3591
Endpoints and definitions	Co-Primary endpoint	New vertebral fracture	Subject incidence of new vertebral fracture through month 12 and through month 24. New vertebral fractures occurred when there was ≥ 1 grade increase from the previous grade of 0 in any vertebra from T4 to L4 on the Genant Semiquantitative Scoring Method
	Secondary endpoints	Clinical fracture	Subject incidence of clinical fracture (non-vertebral fracture and clinical vertebral fracture)
		Non-vertebral fracture	Subject incidence of non-vertebral fracture
		New or worsening vertebral fracture	Subject incidence of new or worsening vertebral fracture. Worsening is defined as an increase of at least 1 grade on the semiquantitative scale
		Major non-vertebral fracture	Subject incidence of major non-vertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip)
		Hip fracture	Subject incidence of hip fracture
		Major osteoporotic fracture	Subject incidence of major osteoporotic fracture (hip, wrist, humerus, and clinical vertebral)
		Multiple new or worsening vertebral fracture	Subject incidence of multiple new or worsening vertebral fracture (⩾ 2 vertebrae from T4 to L4 with ⩾ 1 grade increase from the previous grade at the same visit)
		BMD	Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck
	Exploratory endpoint	New vertebral fracture through month 6	Subject incidence of new vertebral fracture
		Tooth loss	Subject incidence of tooth loss through month 12 and 24
		PRO and ClinRO	Changes from baseline through month 6, 12, 18 and 24
	Substudy endpoint	Lumbar spine and proximal femur DXA	
		Forearm and total body DXA and HR-pQCT	
		BTM and biomarker	Percent change from baseline in BSAP, OC, TRAP 5b, P1NP, and sCTX
		Bone biopsy	Bone histology, histomorphometry, and micro-CT parameters at months 2, 12, 24
		PK	Romosozumab serum concentrations at day 1, day 14, and months 1, 3, 6, 9, 12, and 13
Database lock	Study period cut-off date for the 24-month study was 14 December 2015. The date for the primary analysis snapshot and approval to unblind Amgen staff was 12 February 2016 and the final database lock was 10 March, 2017.		
Results and Analysis			
Analysis description	**Primary Analysis** ***Subject incidence of new vertebral fracture at month 12 and 24***		
Analysis population and time point description	Primary analysis set for vertebral fractures (All randomized subjects who have a baseline and ≥ 1 post-baseline evaluation of vertebral fracture at or before the time point under consideration, including subjects with missing baseline Genant semiquantitative scores whose first post-baseline spinal radiograph shows no fracture on the same vertebrae)		

Descriptive statistics and estimate variability	Treatment group	Placebo (Pbo) Month 12	Romosozumab (Romo) Month 12	Pbo/ Denosumab Month 24	Romo/ Denosumab Month 24
	Number of subjects	3322	3321	3327	3325
	Number (%) of patients with new vertebral fracture	59 (1.8)	16 (0.5)	84 (2.5)	21 (0.6)

Effect estimate per comparison	Co-Primary endpoint Month 12	Comparison groups	Romosozumab vs. Placebo
		ARR (%)	1.30
		95% CI	0.79, 1.80
		Risk ratio	0.27
		95% CI	0.16, 0.47
		RRR (%)	73
		95% CI	53, 84
		Odds ratio	0.27
		95% CI	0.15, 0.47
		p-value	<0.001
	Co-Primary endpoint Month 24	Comparison groups	Romo/Den vs. Pbo/Den
		ARR (%)	1.89
		95% CI	1.30, 2.49
		Risk ratio[1]	0.25
		95% CI	0.16, 0.40
		RRR (%)	75
		95% CI	60, 84
		Odds ratio[2]	0.24
		95% CI	0.15, 0.39
		p-value	<0.001
Notes	[1] Based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables [2] Based on logistic regression model adjusted for age and prevalent vertebral fracture stratification variables; p-value based on score test		
Analysis description	**Secondary Analysis** *Subject incidence of clinical, non-vertebral, new or worsening vertebral, major non-vertebral, hip, major osteoporotic and multiple new or worsening vertebral fracture*		
Analysis population and time point description	**Full analysis set** (all randomized subjects) for: (major)non-vertebral, clinical, major osteoporotic and hip fractures **Primary analysis set for vertebral fracture** for: new or worsening vertebral fracture and multiple new or worsening vertebral fractures		

Descriptive statistics and estimate variability	Treatment group	Pbo Month 12	Romo Month 12	Pbo/ Deno Month 24	Romo/Deno Month 24
	Number of subjects participating:				
	Clinical	3591	3589	3591	3589
	Nonvertebral	3591	3589	3591	3589
	New or worsening vertebral	3322	3321	3327	3325
	Major non-vertebral	3591	3589	3591	3589
	Hip	3591	3589	3591	3589
	Major osteoporotic	3591	3589	3591	3589
	Multiple new/worsening vertebral	3322	3321	3327	3325

	Number (%) of subjects with new fracture: Clinical Nonvertebral New or worsening vertebral Major non-vertebral Hip Major osteoporotic Multiple new/worsening vertebral	 90 (2.5) 75 (2.1) 59 (1.8) 55 (1.5) 13 (0.4) 63 (1.8) 9 (0.3)	 58 (1.6) 56 (1.6) 17 (0.5) 37 (1.0) 7 (0.2) 38 (1.1) 1 (<0.1)	 147 (4.1) 129 (3.6) 84 (2.5) 101 (2.8) 22 (0.6) 110 (3.1) 17 (0.5)	 99 (2.8) 96 (2.7) 22 (0.7) 67 (1.9) 11 (0.3) 68 (1.9) 1 (<0.1)
Effect estimate per comparison	Clinical fracture	Comparison groups	Romo vs. Pbo Month 12		Romo/Den vs. Plb/Den Month 24
		ARR (%)	1.2		1.4
		95% CI	0.4, 1.9		0.5, 2.4
		RRR (%)	36		33
		95% CI	11, 54		13, 48
		Nominal p-value	0.008		0.002
		Adjusted p-value	0.008		0.096
	Non-vertebral fracture	Comparison groups	Romo vs. Pbo Month 12		Romo/Den vs. Plb/Den Month 24
		ARR (%)	0.8		1.0
		95% CI	0.1, 1.4		0.2, 1.9
		RRR (%)	25		25
		95% CI	-5, 47		3, 43
		Nominal p-value	0.096		0.029
		Adjusted p-value	0.096		0.057
	New or worsening vertebral fracture	Comparison groups	Romo vs. Pbo Month 12		Romo/Den vs. Plb/Den Month 24
		ARR (%)	1.26		1.86
		95% CI	0.76, 1.77		1.27, 2.46
		RRR (%)	71		74
		95% CI	51, 83		58, 84
		Nominal p-value	< 0.001		< 0.001
		Adjusted p-value	0.096		0.096
	Major non-vertebral fracture	Comparison groups	Romo vs. Pbo Month 12		Romo/Den vs. Plb/Den Month 24
		ARR (%)	0.6		1.1
		95% CI	0.1, 1.2		0.3, 1.8
		RRR (%)	33		33
		95% CI	-2, 56		9, 51
		Nominal p-value	0.060		0.009
		Adjusted p-value	0.096		0.096
	Hip fracture	Comparison groups	Romo vs. Pbo Month 12		Romo/Den vs. Plb/Den Month 24
		ARR (%)	0.3		0.4
		95% CI	0.0, 0.6		0.0, 0.7

		RRR (%)	46	50
		95% CI	-35, 78	-4, 76
		Nominal p-value	0.18	0.059
		Adjusted p-value	0.18	0.12
	Major osteoporotic fracture	Comparison groups	Romo vs. Pbo Month 12	Romo/Den vs. Plb/Den Month 24
		ARR (%)	0.9	1.2
		95% CI	0.3, 1.5	0.5, 2.0
		RRR (%)	40	38
		95% CI	10, 60	16, 54
		Nominal p-value	0.012	0.002
		Adjusted p-value	NA	NA
	Multiple new or worsening vertebral fracture	Comparison groups	Romo vs. Pbo Month 12	Romo/Den vs. Plb/Den Month 24
		ARR (%)	0.24	0.48
		95% CI	0.05, 0.43	0.23, 0.73
		RRR (%)	89	94
		95% CI	13, 99	56, 99
		Nominal p-value	0.011	< 0.001
		Adjusted p-value	NA	NA

Analysis description	**Secondary Analysis** ***Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck***				
Analysis population and time point description	This analysis set includes all randomized subjects who have a baseline and ≥ 1 post-baseline evaluation at or before the time point under consideration in the study period.				
Descriptive statistics and estimate variability	Treatment group	Placebo (Pbo) Month 12	Romosozumab (Romo) Month 12	Pbo/ Denosumab Month 24	Romo/ Denosumab Month 24
	Number of subjects: Lumbar spine Total hip Femoral neck	 3148 3210 3210	 3151 3197 3197	 2877 2918 2918	 2861 2903 2903

Effect estimate per comparison		Comparison groups	Romo vs. Pbo Month 12	Romo/Den vs. Pbo/Den Month 24
	BMD % Change From Baseline Lumbar spine	LS mean	12.7	11.1
		95% CI	12.4, 12.9	10.8, 11.4
		p-value	<0.001	<0.001
	BMD % Change From Baseline Total Hip	LS mean	5.8	5.3
		95% CI	5.6, 6.0	5.1, 5.5
		p-value	<0.001	<0.001
	BMD % Change From Baseline Femoral neck	LS mean	5.2	4.9
		95% CI	4.9, 5.4	4.7, 5.2
		p-value	<0.001	<0.001

Table 33b: Summary of efficacy for trial 20110142

Title: A Multicenter, International, Randomized, Double-blind, Alendronate-controlled Study to Determine the Efficacy and Safety of Romosozumab in the Treatment of Postmenopausal Women With Osteoporosis			
Study identifier	Study No.: 20110142		
Design	A multicenter, international, randomized, double-blind, alendronate-controlled, parallel-group study		
Hypothesis	Romosozumab treatment for 12 months followed by alendronate treatment compared with alendronate treatment alone is effective in reducing the incidence of clinical fracture (non-vertebral fracture and clinical vertebral fracture) and new vertebral fracture in postmenopausal women with osteoporosis.		
Treatment groups	Romosozumab/Alendronate (ALN)		Romosozumab 210mg SC monthly (M1-M12)/ Alendronate 70mg orally every week; N= 2046
	Alendronate alone (Alendronate/Alendronate)		Alendronate 70mg orally every week; N= 2047
Endpoints and definitions	Primary endpoints	New vertebral fracture Clinical fracture	Subject incidence of new vertebral fracture through month 24 and subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) for the primary analysis period. The primary analysis period ended and the primary analysis was performed when clinical fracture events were confirmed for at least 330 subjects and all subjects completed the month 24 study visit. As more than 330 subjects had confirmed clinical fractures at the time each subject completed her month 24 visit, the primary analysis was based on all available data, which included 464 clinical fractures.
	Selected Secondary endpoints	Clinical fracture (month 12 and 24)	Subject incidence of clinical fracture (non-vertebral fracture and clinical vertebral fracture)
		Non-vertebral fracture (month 12 and 24)	Subject incidence of non-vertebral fracture
		New or worsening vertebral fracture (month 12 and 24)	Subject incidence of new or worsening vertebral fracture. Worsening is defined as an increase of at least 1 grade on the semiquantitative scale
		Hip fracture (month 12 and 24)	Subject incidence of hip fracture
		Multiple new or worsening vertebral fracture (month 12 and 24)	Subject incidence of multiple new or worsening vertebral fracture (≥ 2 vertebrae from T4 to L4 with ≥ 1 grade increase from the previous grade at the same visit)
		BMD	Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck
Study period	Study Period: First subject enrolled: 04 May 2012; last subject's last dose of double-blind investigational product: 22 February 2016; primary analysis data snapshot date: 27 February 2017.		
Results and Analysis			
Analysis description	**Primary Analysis** *Subject incidence of new vertebral fracture at month 24 and subject incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) for the primary analysis period (event-driven; mean follow-up period of approximately 32 months)*		

Analysis population and time point description	The **primary efficacy analysis set for vertebral fractures** (all randomized subjects who have a baseline and ≥ 1 post-baseline evaluation of vertebral fracture at or before the time point under consideration, including subjects with missing baseline Genant semiquantitative scores whose first post-baseline spinal radiograph shows no fracture on the same vertebrae) was used as the primary analysis set for new vertebral fractures at month 24. The **full analysis set** was used as the primary analysis set for clinical fractures through primary analysis. The primary analysis period was event-driven with a mean follow-up period of approximately 32 months.				
Descriptive statistics and estimate variability	Treatment group	Alendronate (ALN)/ALN Month 24	Romosozumab (Romo)/ALN Month 24	Alendronate (ALN)/ALN primary analysis	Romosozumab (Romo)/ALN primary analysis
	Number of subjects	1834	1825	2047	2046
	Number (%) of patients with ([1]new vertebral) fracture	147 (8.0)[1]	74 (4.1)[1]	266 (13.0)	198 (9.7)

Effect estimate per comparison	Primary endpoint Month 24 (new vertebral fracture)	Comparison groups	Romo vs. ALN
		ARR (%)	4.03
		95% CI	2.50, 5.57
		Risk ratio	0.50
		95% CI	0.38, 0.66
		RRR (%)	50
		95% CI	34, 62
		Odds ratio	0.48
		95% CI	0.36, 0.64
		p-value	<0.001
	Primary endpoint Clinical fracture (primary analysis)	Comparison groups	Romo vs. ALN
		Hazard ratio	0.73
		95% CI	0.61, 0.88
		p-value	<0.001
Notes	The hazard ratio estimate is based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.		
Analysis description	**Secondary Analysis** *Selected secondary endpoints: fractures: clinical, non-vertebral, hip, new or worsening vertebral, multiple new or worsening vertebral*		
Analysis population and time point description	The **primary efficacy analysis set for vertebral fractures** was used as the primary analysis set for the following endpoints: new, new or worsening, and multiple new or worsening vertebral fractures. The **full analysis set** was used as the primary analysis set for the following endpoints: non-vertebral fracture, clinical fracture, clinical vertebral fracture, all fracture, major non-vertebral fracture, major osteoporotic fracture and hip fracture**.** The **per protocol analysis set** for 12-month double-blind period The **per protocol analysis set** for the 24-month period.		

Descriptive statistics and	Treatment group	ALN Month 12	Romo Month 12	ALN/ALN Month 24	Romo/ALN Month 24

estimate variability	Number of subjects participating: Clinical Non-vertebral Hip New or worsening vertebral Multiple new/worsening vertebral		 2047 2047 2047 1703 1703	 2046 2046 2046 1696 1696	 2047 2047 2047 1834 1834	 2046 2046 2046 1825 1825
	Number (%) of subjects with new fracture: Clinical Non-vertebral Hip New or worsening vertebral Multiple new/worsening vertebral		 110 (5.4) 95 (4.6) 22 (1.1) 101 (5.9) 21 (1.2)	 79 (3.9) 70 (3.4) 14 (0.7) 67 (4.0) 20 (1.2)	 197 (9.6) 159 (7.8) 43 (2.1) 168 (9.2) 46 (2.5)	 146 (7.1) 129 (6.3) 31 (1.5) 87 (4.8) 24 (1.3)
Effect estimate per comparison	Clinical fracture	Comparison groups	Romo vs. ALN Month 12		Romo/ALN vs. ALN/ALN Month 24	
		ARR (%)	1.8		2.7	
		95% CI	0.5, 3.1		0.8, 4.5	
		RRR (%)	28		26	
		95% CI	4, 46		9, 41	
		Nominal p-value	0.027		0.005	
		Odds/Hazard Ratio	0.72		0.74	
	Non-vertebral fracture	Comparison groups	Romo vs. ALN Month 12		Romo/ALN vs. ALN/ALN Month 24	
		ARR (%)	1.4		1.6	
		95% CI	0.1, 2.6		-0.1, 3.3	
		RRR (%)	26		19	
		95% CI	-1, 46		-2, 36	
		Nominal p-value	0.057		0.074	
		Odds/Hazard Ratio	0.74		0.81	
	Hip fracture	Comparison groups	Romo vs. ALN Month 12		Romo/ALN vs. ALN/ALN Month 24	
		ARR (%)	0.3		0.6	
		95% CI	-0.3, 0.9		-0.2, 1.4	
		RRR (%)	36		28	
		95% CI	-26, 67		-15, 54	
		Nominal p-value	0.19		0.17	
		Odds/Hazard Ratio	0.64		0.72	
	New or worsening vertebral fracture	Comparison groups	Romo vs. ALN Month 12		Romo/ALN vs. ALN/ALN Month 24	
		ARR (%)	2.04		4.44	
		95% CI	0.59, 3.49		2.80, 6.08	
		RRR (%)	34		48	
		95% CI	11, 51		34, 60	
		Nominal p-value	0.006		< 0.001	
		Odds/Hazard Ratio	0.64		0.49	

	Multiple new or worsening vertebral fracture	Comparison groups	Romo vs. ALN Month 12	Romo/ALN vs. ALN/ALN Month 24
		ARR (%)	0.09	1.21
		95% CI	-0.64, 0.82	0.33, 2.10
		RRR (%)	7	48
		95% CI	-70, 50	15, 68
		Nominal p-value	0.85	0.008
		Odds/Hazard Ratio	0.94	0.51

Analysis description	**Secondary Analysis** *Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck*				
Analysis population and time point description	This analysis set includes all randomized subjects who have a baseline and ≥ 1 post-baseline evaluation at or before the time point under consideration in the study period.				
Descriptive statistics and estimate variability	Treatment group	Alendronate (ALN) Month 12	Romosozumab (Romo) Month 12	ALN/ALN Month 24 (Month 36)	Romo/ALN Month 24 (Month 36)
	Number of subjects: Lumbar spine Total hip Femoral neck	 1718 1781 1781	 1722 1781 1781	 1577 (1597) 1627 (1653) 1627 (1653)	 1571 (1593) 1622 (1653) 1622 (1653)

Effect estimate per comparison		Comparison groups	Romo vs. ALN Month 12	Romo/ALN vs. ALN/ALN Month 24 (Month 36)
	BMD % Change From Baseline Lumbar spine	LS mean	8.7	8.1 (7.4)
		95% CI	8.31, 9.09	7.58, 8.57 (6.84, 7.89)
		p-value	<0.001	<0.001
	BMD % Change From Baseline Total Hip	LS mean	3.3	3.8 (3.7)
		95% CI	3.03, 3.60	3.42, 4.10 (3.29, 4.02)
		p-value	<0.001	<0.001
	BMD % Change From Baseline Femoral neck	LS mean	3.2	3.8 (3.6)
		95% CI	2.90, 3.54	3.40, 4.14 (3.18, 3.97)
		p-value	<0.001	<0.001

Summary tables of main efficacy results in men with osteoporosis

Table 34 Summary of efficacy for trial 20110174

Title: A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of romosozumab with placebo in men with osteoporosis		
Study identifier	Study No: 20110174	
Design	This multicenter, randomized, double-blind, placebo-controlled study was designed to evaluate if treatment with romosozumab once every month (QM) for 12 months compared with placebo was effective in increasing BMD at the lumbar spine.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months + 3 months follow up not applicable not applicable

Hypothesis	Superiority		
Treatments groups	Romosozumab		210 mg sc QM for 12 months, n=163
	Placebo		Placebo sc QM for 12 months, n=82
Endpoints and definitions	Primary	Percent change from baseline in DXA BMD at the lumbar spine at month 12.	
	Secondary	Percent change from baseline in DXA BMD at the femoral neck and total hip at month 12	
		Percent change from baseline in DXA BMD at the lumbar spine, femoral neck, and total hip at month 6	
	Exploratory	Percent changes from baseline in the BTMs CTX and P1NP at months 1, 3, 6, and 12	
		Analysis of bone histology and histomorphometry parameters at month 12 in a subset of subjects	
Database lock	The primary analysis snapshot and approval to unblind was 11 March 2016. Final database lock was 6 June 2016.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Primary Efficacy Analysis Subset for each of the skeletal location (lumbar spine, femoral neck and total hip) included all randomized subjects who had a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement at the location of interest.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Romosozumab
	Number of subjects	79	157
	Lumbar spine (%change BMD)	1.2	12.1
	95% CI	0.2, 2.2	11.2, 13.0
	Total hip	-0.5	2.5
	95% CI	-1.1, 0.1	2.1, 2.9
	Femoral neck	-0.2	2.2
	95% CI	-1.0, 0.6	1.5, 2.9

Clinical studies in special populations

No clinical efficacy studies were performed in special populations. The subgroup analyses of the main studies are described under each study.

Table 37 summarises the number of subjects ≥65 years across the studies. In the controlled phase 2 and 3 studies, 43.2% of the subjects were 65 - <75 years old, 32.8% were 75 - <85 years old and 4.4% were ≥ 85 years old.

Table 35: Summary of subjects by age group for all clinical studies

	Age 65 to <75y		Age 75 to <85y		Age ≥85y	
	Control n/N (%)	Romosozumab n/N (%)	Control n/N (%)	Romosozumab n/N (%)	Control n/N (%)	Romosozumab n/N (%)
Phase 1 (PK studies)						
Controlled[a]						
20090378[b]	2/8 (25)	4/22 (18)	NA	NA	NA	NA
20060221[c]	1/12 (8)	9/36 (25)	0/12	2/36 (6)	NA	NA
20060223	7/10 (70)	14/30 (47)	0/10	6/30 (20)	0/10	0/30
20090153[c]	3/12 (25)	4/12 (33)	0/12	2/12 (17)	NA	NA
Noncontrolled						
20120277[d]	--	1/172 (0.6)	--	NA	--	NA
20150197[d]	--	5/188 (2.7)	--	NA	--	NA
20101180[d]	--	2/140 (1)	--	NA	--	NA
20090418[d]	--	0/145 (0)	--	NA	--	NA
20120274	--	5/62 (8.1)	--	0/62	--	0/62
20110227	--	11/24 (45.8)	--	3/24 (12.5)	--	0/24
20110253	--	21/60 (35.0)	--	10/60 (16.7)	--	0/60
Total in Phase 1(PK)	13/42 (31.0)	76/891 (8.5)	0/34	23/224 (10.3)	0/10	0/176
Phase 2 and Phase 3 clinical studies						
Controlled studies						
20070337[e]	1713/3591 (47.7)	1702/3589 (47.4)	1014/3591 (28.2)	1010/3589 (28.1)	107/3591 (3.0)	109/3589 (3.0)
20110142[e]	736/2047 (36.0)	734/2046 (35.9)	906/2047 (44.3)	910/2046 (44.5)	165/2047 (8.1)	163/2046 (8.0)
20110174[e]	42/82 (51.2)	62/163 (38.0)	28/82 (34.1)	65/163 (39.9)	1/82 (1.2)	5/163 (3.1)
20060326[f]	81/158 (51.3)	132/261 (50.6)	18/158 (11.4)	34/261 (13.0)	0/158 (0.0)	0/261 (0.0)
20080289[f]	96/218 (44.0)	83/218 (38.1)	62/218 (28.4)	79/218 (36.2)	12/218 (5.5)	6/218 (2.8)
20101291[f]	22/63 (34.9)	90/189 (47.6)	14/63 (22.2)	33/189 (17.5)	0/63 (0.0)	0/189 (0.0)
20120156[f]	14/53 (26.4)	103/241 (42.7)	14/53 (26.4)	44/241 (18.3)	2/53 (3.8)	2/241 (0.8)
Total in Phases 2 and 3	2704/6212 (43.5)	2906/6707 (43.3)	2056/6212 (33.1)	2175/6707 (32.4)	287/6212 (4.6)	285/6707 (4.2)
Overall Total	2717/6254 (43.4)	2982/7598 (39.2)	2056/6246 (32.9)	2198/6931 (31.7)	287/6222 (4.6)	285/6883 (4.1)

Analysis performed across trials (pooled analyses AND meta-analysis)

With the submitted dossier, an integrated summary of efficacy was provided. The objective of the analyses for this integrated summary of efficacy was to support the efficacy assessment of romosozumab in the treatment of osteoporosis in postmenopausal women and men with osteoporosis. This integrated statistical analysis plan (SAP) covers the efficacy assessment of romosozumab through the initial 12-month treatment period. In this integrated SAP, the objectives were:

• to assess the consistency of efficacy results during the initial 12-month treatment period across the two PMO pivotal studies (20070337 and 20110142), with respect to the fracture endpoints as well as bone mineral density (BMD) and bone turnover markers (BTMs)

• to summarize and compare efficacy of romosozumab 210 mg SC QM against placebo at month 6 and 12 (when available) and assess consistency of efficacy results in the three PMO supportive studies (20060326, 20101291 and 20120156), as measured by BMD and BTM endpoints

• to provide a dose-response efficacy profile of romosozumab doses compared with placebo in Studies 20060326 and 20101291 as measured by BMD and BTM endpoints, to support the dose regimen used in phase 3 studies

• to assess the consistency of efficacy results during the initial 12-month treatment period across the two pivotal studies (20070337 and 20110174),

In order to illustrate consistency of observed treatment effect in fracture data and BMD, several trial sets were defined to juxtapose important efficacy outcome data:

Phase 3 fracture trial set

The phase 3 fracture trial set included the Studies 20070337 and 20110142. The primary goal of the analyses utilizing this trial set was to allow for side-by-side comparison of PMO pivotal Studies 20070337 and 20110142 with respect to clinical endpoints of fractures, bone mineral density (BMD) and bone turnover markers (BTMs), to allow for assessment of consistency of efficacy results between the two pivotal studies.

Placebo-controlled trial set

The placebo-controlled trial set included placebo-controlled PMO Studies 20060326, 20101291 and 20120156. The objective of the analyses utilizing this trial set was to summarize and compare the efficacy of romosozumab 210 mg subcutaneously (SC) once monthly (QM) against placebo, as measured by BMD and BTM endpoints at 6 months and 12 months (when available) after study baseline.

Dose-ranging trial set

The dose-ranging trial set included the two multi-dose Studies 20060326 and 20101291. The objective of the analyses utilizing this trial set was to provide a dose-response efficacy profile of romosozumab doses compared with placebo as measured by BMD and BTM endpoints.

Phase 3 male osteoporosis bridging trial set

The phase 3 male osteoporosis bridging trial set included the Studies 20070337 and 20110174. The primary goal of the analyses utilizing this trial set was to allow for side-by-side comparison of pivotal Studies 20070337 and 20110174 with respect to bone mineral density (BMD) and bone turnover markers (BTMs), to assess the consistency of efficacy results between these two pivotal studies. The objective of this trial set is to support an indication for treatment of osteoporosis in men by bridging the efficacy of romosozumab in men with osteoporosis from Study 20110174 with results from the pivotal placebo-controlled registration Study 20070337 in women with osteoporosis.

No new hypotheses were to be tested for the phase 3 fracture trial set or the phase 3 male osteoporosis bridging trial set. The analysis of each study's endpoints was performed using the same approaches as specified in section 10 from each individual study SAP.

The hypothesis of the placebo-controlled trial set was that romosozumab 210 mg QM demonstrated superior efficacy compared with placebo, as measured by BMD and BTM endpoints.

The hypothesis of the dose-ranging trial set was that there was an increasing dose response in efficacy of romosozumab, as measured by BMD and BTM endpoints.

The conduct of integrated efficacy evaluation is generally acknowledged, the additional benefit for assessment is however limited. Efficacy data from the phase 3 fracture studies are presented side-by-side

and not integrated with each other due to the differences in the control group (placebo vs active control). The fracture studies are also not integrated with the supportive phase 2 and 3 studies.

For some parts of the assessment (e.g. comparison of FRAX-risk profiles of male/female study populations, region difference in baseline fracture risk), some of the tables produced were considered informative. In these cases, corresponding information/tables were taken from the integrated analyses report.

Supportive study 20120156

This study evaluated the non-inferiority of a 6-month treatment with romosozumab 210 mg administered every month (QM) using a 90 mg/mL concentration compared to a 70 mg/mL concentration. The study was conducted at 11 centres: 7 in Poland, 2 in the Czech Republic and 2 in the United States.

The *primary endpoint* was percent change from baseline in DXA BMD at the lumbar spine.

Table 36: Lumbar Spine Bone Mineral Density Percent Change from Baseline at Month 6 (ANCOVA Model) (Primary Efficacy Analysis Set, Observed Data) (20120156 Month 6 Analysis)

	Placebo (N = 46)	Romosozumab 70 mg/mL (N = 110)	Romosozumab 90 mg/mL (N = 117)
DXA BMD Lumbar Spine Month 6			
n	46	110	117
Estimate	0.8	9.6	9.2
95% CI	(-0.4, 2.1)	(8.8, 10.4)	(8.4, 10.0)
p-value[a]	0.1843	< 0.0001	< 0.0001
Difference from placebo[b]			
Estimate		8.8	8.4
95% CI		(7.3, 10.3)	(6.9, 9.9)
p-value		< 0.0001	< 0.0001
Difference from romosozumab 70 mg/mL[c]			
Estimate			-0.4
95% CI			(-1.5, 0.7)

ANCOVA = analysis of covariance; BMD = bone mineral density; CI = confidence interval; DXA = dual-energy X-ray absorptiometry; N = number of subjects with values at baseline and at ≥ 1 postbaseline visit; n = number of subjects with values at baseline and at the time point of interest.
[a] For the difference from baseline
[b] Based on ANCOVA model adjusting for treatment, and baseline lumbar spine BMD T-score.
[c] Based on ANCOVA model adjusting for treatment, and baseline lumbar spine BMD T-score. Treatment difference between romosozumab 90 mg/mL to romosozumab 70 mg/mL, which used romosozumab 70 mg/mL as the reference.

The mean treatment difference between romosozumab 90 mg/mL and romosozumab 70 mg/mL was -0.4%. Because the lower bound of the 1-sided 97.5% CI of the mean difference between the 2 romosozumab groups was -1.5%, which was greater than the pre-specified limit of -2.0%, the data supported the claim of non-inferiority. Together with the results from study 20120277 the equivalence of both treatment concentrations was confirmed. However, the applicant was encouraged to treat for full 12 months, due to the labelling duration of 12 months. This was based on the argument that the first 6 months of treatment account for ~70% of the treatment effect normally observed in 12 months. In general, the claim to show non-inferiority of 70mg/ml and 90mg/ml treatment was successfully demonstrated.

All fractures were reported as treatment-emergent adverse events. In the two placebo groups (N=52), 3 fractures (radius, humerus, patella) were reported. 2 fractures (radius, forearm) were reported in the romosozumab 70 mg/ml group (N=119) and 4 fractures (radius, foot, hand and spinal fracture) were

reported in the romosozumab 90 mg/ml group (N=123). The absolute number of events in each treatment group was too low to allow any firm conclusions.

Supportive study 20080289

This was a randomized, open-label, teriparatide (TPTD)-controlled study in postmenopausal women with osteoporosis at high risk for fracture after transition from < 3 years of treatment oral bisphosphonates.

It is agreed that it is of value to understand and document the effects of romosozumab in comparison to TPTD in women who have already been treated with antiresorptive agents such as bisphosphonates. A blinded treatment would have been strongly preferred.

Subjects were aged ≥ 55 to ≤ 90 years at randomization (mean age 71.5 years) and must have been taking an oral bisphosphonate at a dose approved for PMO, for a minimum of 3 years prior to screening, with the last year (of the previous 3 years prior to screening) treated with alendronate (70 mg weekly or equivalent).

The population is described as a "bisphosphonate pre-treated patient population". However, most of the patients were pre-treated with alendronate for 3 years prior to screening (92.7% and 88.1% for teriparatide and romosozumab, respectively). Literature indicates that anabolic responsiveness to teriparatide differs based on prior antiresorptive therapy, and that the use of alendronate may blunt the magnitude of the effect (Ettinger et al 2004, Finkelstein et al 2006, Black et al 2003, Gasser et al 2000, Graeff et al 2007). Therefore, generalizability of the results of study 20080289 to all bisphosphonate pre-treated patients cannot indisputably be concluded.

The *primary endpoint* was the percent change from baseline in DXA BMD at the total hip through month 12.

Table 37: Total Hip Bone Mineral Density by DXA Percent Change from Baseline Through month 12 (Repeated Measures Model) (Primary Efficacy Analysis Set, Observed Data) (20080289 Month 12 Final Analysis)

	Teriparatide 20 µg SC QD (N = 209)	Romosozumab 210 mg SC QM (N = 206)	Difference from Teriparatide[a]
Total hip bone mineral density percent change from baseline through month 12			
n	209	206	
LS Mean	-0.6	2.6	3.2
SE	0.2	0.2	0.3
(95% CI)	(-1.0, -0.2)	(2.2, 3.0)	(2.7, 3.8)
p-value			< 0.0001

BMD = bone mineral density; CI = confidence interval; DXA = dual-energy X-ray absorptiometry; LS = least squares; n = number of subjects with values at baseline and at ≥ 1 post baseline visit; N = number of subjects in the primary efficacy analysis set for DXA endpoints; QD = each day; QM = each month; SC = subcutaneously; SE = standard error

[a] Based on a repeated measures model adjusting for treatment, visit, baseline serum type 1 collagen C-telopeptide value, baseline BMD value, machine type, baseline BMD value-by machine type interaction, and using an unstructured variance covariance structure. The test through month 12 was based on the main effect of treatment and represents the average treatment effect at months 6 and 12.

Table 38: Selected secondary endpoints in study 20080289

	TPTD LS mean (95% CI)	Romosozumab LS mean (95% CI)	Difference from TPTD	P-value
DXA BMD at M12 Femoral neck	-0.2 (-0.8, 0.4)	3.2 (2.6, 3.8)	3.4 (2.6, 4.2)	<0.0001 [b]
DXA BMD at M12 Lumbar spine	5.4 (4.7, 6.1)	9.8 (9.0, 10.5)	4.4 (3.4, 5.4)	<0.0001 [b]

[b] without multiplicity analysis

Romosozumab increased total hip BMD compared to 20 µg QD TPTD through 12 months of treatment, indicating that previous treatment with bisphosphonates does not attenuate the romosozumab effect bone mineral density. There was no difference from baseline in total hip BMD with 12 months of TPTD treatment. As opposed to this, in study 20060326, 20 µg TPTD increased total hip BMD compared to placebo (1.3% vs -0.7; p<0.0001). The TPTD effect was comparable to the effect of romosozumab 70 mg QM and 140 mg Q3M, but lower than 140 mg QM and 210 mg QM. The main difference between the two studies was that in study 20060326, the use of bisphosphonates within a pre-specified time limit was an exclusion criterion.

Furthermore, romosozumab increased DXA BMD at 12 months in lumbar spine, femoral neck and total hip (p<0.0001 in all locations) and estimated strength by FEA at total hip (p<0.0001).

Concluding, it is agreed that romosozumab was superior in increasing BMD in postmenopausal women pre-treated with bisphosphonates (mainly alendronate) compared to teriparatide, during the first year of treatment following transition. The appropriateness to generalize results from alendronate to bisphosphonate pre-treatment is however questioned.

In this study, fractures were reported as adverse events. In the TPTD group, 8 fractures were reported and in the romosozumab group, there were 7 fractures reported.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The romosozumab clinical phase 2 and 3 programme consisted of three pivotal and four supportive studies. Two of the pivotal studies, 20070337 and 20110142, evaluated the effect of romosozumab in postmenopausal women, whereas the third, 20110174, was a bridging study to men with osteoporosis. The scope of study 20060326 was to find a dose level for future studies, to evaluate the effect of transition from romosozumab to antiresorptive medication and to evaluate romosozumab retreatment. Study 20101291 was a dose finding study exclusively in Japanese women. Study 20120156 compared two concentrations of romosozumab; 70 mg/mL and 90 mg/m. In study 20080289, romosozumab was compared to teriparatide after transition from ≥3 years of recent per oral bisphosphonate treatment.

Adherence to Scientific Advice

The applicant received scientific advice (SA) from the CHMP. Overall, the applicant did adhere to the CHMP scientific advices (see also section 1.1) as well as to the CHMP guideline on osteoporosis, specifically with regard to the clinical development programme, as summarised below:

Guideline on the evaluation of medical products in the treatment of primary osteoporosis 2006 (CHMP/EWP/552/95)

The primary variable should be based on the occurrence of new axial and peripheral fractures.

EMA Scientific Advice **EMA/CHMP/SAWP/868033/2011** 17 November 2011

Regarding Study 20070337, it was agreed that study endpoints are aligned to EU CHMP osteoporosis guideline. Regarding the active-controlled Study 20110142, CHMP concurred with the proposed patient population, and with alendronate as a comparator.

CHMP suggested conducting a study with a total duration of 3 years (in-line with the EU guideline requirements) in which 1 year of romosozumab treatment is followed by antiresorptive treatment (e.g. alendronate) for an additional 2 years. Assessment of primary efficacy after 12 months could be acceptable in order to determine the initial efficacy with continuation of the trial to further explore safety and confirm maintenance of effect after switching to the subsequent antiresorptive treatment.

EMA Follow-up Scientific Advice **EMA/CHMP/SAWP/352926/2013** 27 June 2013

CHMP concurred with the proposed multiple-dose study to demonstrate the non-inferiority of the 90 mg/mL PFS presentation compared with the 70 mg/mL glass PFS.

EMA Follow-up Scientific Advice **EMA/CHMP/SAWP/22643/2017** 26 Jan 2017

CHMP advised that an application for romosozumab may be initiated once 2-year follow-up data become available for Study 20110142, with 3-year data submitted during the licensing procedure. Further follow-up (3 to 5 years, as specified in guidelines) may be a post-licensing commitment, particularly if there are any signals of loss of efficacy or safety signals at the time of the MAA.

Dosing regimen

In study 20060326 and 20101291, there was a dose-dependent increase in lumbar spine bone mineral density (BMD) with romosozumab treatment (70 mg, 140 mg, 210 mg QM) through month 12 compared to placebo. In 20060326, romosozumab 140 mg and 210 mg given Q3M also increased lumbar spine BMD compared to placebo, but to a lower extent than the QM dosing.

The romosozumab treatment duration in the initial phase 2 study 20060326 was 24 months. Lumbar spine BMD continued to increase during the entire treatment period; however, the increase was largest during the first 6 months of treatment. This correlates with the transient increase in bone formation markers. However, the decrease in bone resorption markers was partly sustained through 12 months. Bone turnover markers (BTM) are further discussed in section3.3.2 (Pharmacodynamics).

Based on PK/PD data and the BTM and BDM data from study 20060326 and 20101291, the posology in the pivotal studies, as well as the proposed dosing regimen, was 210 mg SC QM for 12 months. This is endorsed.

The dose-response analysis (report 119384B) displays a clear dose-response relationship. However, several of the detected covariates are expected to be highly correlated and hence the covariate relationships should be interpreted with caution. The covariate relationships detected in the population PK analysis are considered more informative and an updated dose-response model is not expected to change the dosing recommendation.

In study 20101291, Japanese patients showed a differing response in both lumbar spine and total hip and even opposing effects were presented. These effects were explained by the applicant as confounded by study. However, this does not represent an acceptable explanation especially as also the PPK analysis including data for Japanese subjects from different studies showed a significant effect for Japanese patients. The applicant was asked to further address the differences seen for Japanese and was asked to provide an explanation for the opposite effects on lumbar spine and total hip. The Applicant provided a discussion concerning the claimed confounding by study effect for Japanese patients and further data to illustrate the differing effects seen for Japanese patients. The conclusion that the data was confounded by study was based on higher placebo response in study 20101291 including only Japanese patients resulting in lower response compared to placebo. The discussion provided by the Applicant can be followed and the conclusions are acceptable. The Applicant provided an overview of percent BMD change (for all three studies) and the absolute change for study 20070337 including the overall population and Japanese patients. The different trends for lumbar spine and total hip can be observed in percent BMD change (e.g. study 20070337: lumbar spine: Overall: 12.7% and Japanese 14.9%; total hip: Overall: 5.8% and Japanese: 4.8%). However, the effect is very small considering absolute BMD change (lumbar spine: Overall: 0.0992 and Japanese 0.102; total hip: Overall: 0.0385 and Japanese: 0.029). The Applicant provided literature references stating that this effect in Japanese patients has also been observed with other treatments for osteoporosis (denosumab, teriparatide). It is agreed that these changes are small and probably not clinically relevant. The overall discussion is acceptable.

In study 20120156, treatment effect between 210 mg romosozumab SC given QM as 3 x 1 ml of a 70 mg/ml solution and as 2x 2.17 ml of a 90 mg/mL solution was studied. The mean treatment difference between the romosozumab 90 mg/mL and romosozumab 70 mg/mL was -0.4%. Because the lower bound of the 1-sided 97.5% CI of the mean difference between the 2 romosozumab groups was -1.5%, which was greater than the pre-specified limit of -2.0%, the data supported the claim of non-inferiority. The mean differences from placebo were 8.8% and 8.4% for the romosozumab 70 mg/mL and romosozumab 90 mg/mL groups, respectively, which were both statistically significant ($p < 0.0001$). The claim to show non-inferiority of 70mg/ml and 90mg/ml treatment was successfully demonstrated.

Studies 20070337 and 20110142 – postmenopausal women with osteoporosis

Study 20070337 comprised of a 12-month double-blind, placebo-controlled study period and a 24-month open label denosumab follow-up period. 20110142 comprised of a 12–month double-blind, alendronate-controlled study period, followed by open label alendronate.
Study 20110142 was event-driven. The primary analysis was performed after a mean follow-up period of approximately 32 months.

The difference in the eligibility criteria regarding BMD T-score limits and fracture history between the two studies allowed inclusion of subjects with more severe osteoporosis in 20110142. The two studies are therefore not completely comparable.

Subjects with renal insufficiency were not explicitly excluded from the studies, but only 18 subjects in 20070337 and 11 in 20110142 had baseline eGFR <30 ml/min/1.73 m^2 (all in the range

15-<30 ml/min/1.73 m^2). The number of subjects with eGFR <30 ml/min/1.73 m^2 is considered too low to enable dose recommendations in this subpopulation.

Regarding planned analyses, the statistical analysis plans for study 20070337 and study 20110142 shared a number of features. The analyses performed were overall acceptable. The approach to missing data and missing data imputation however deserved clarifications and additional analyses were requested.

For analyses of the incidence of new vertebral fracture, a logistic regression model using last-observation-carried-forward was used. For both study 20070337 and study 20110142, the Applicant was requested to summarize the number and percentage of missing lateral spine x-ray assessments at each visit by study arm and to clarify in how many cases LOCF was used. The Applicant has clarified that LOCF imputation was only used at the vertebra level and not for completely missing x-rays. A summary of evaluable x-rays by nominal visit and treatment group (separately for each study) was presented. In study 20070337, the percentages of only partially available x-ray results per visit were all below 10%, in study 20110142 the percentages of only partially available x-ray results per visit were 11.6% for Month 12 and below 7% for Month 24. Irrespective of study, they were comparable between both treatment groups at all time-points. For other fracture endpoints time-to-event analyses were performed for which e.g. the analysis of clinical fracture it was stated that missing values were imputed by the use of the last non-missing observation; how LOCF was used in time-to-event analyses and further, how censoring was applied in case of missing assessments needed clarifications. In their response, the Applicant acknowledged that the term last observation carried forward (LOCF) in the context of Cox regression analyses was misleading and confirmed that established definitions for censoring and first occurrence of event were applied in time-to-event analyses; the censoring date for each study subject depended from her individual study duration and hence, that for patients dropping out earlier their actual study end date was taken into account in the analysis. For primary analyses of BMD endpoints, 10% to 20% of subjects were excluded depending on analysis time-point and in case of missing assessments, LOCF was used also here. Although reassuring that the proportion of subjects excluded were well balanced between randomised treatments irrespective of study, additional sensitivity analyses based on all randomised subjects were requested. In the sensitivity analyses now performed by the Applicant a control-based pattern multiple imputation approach for missing data was used. Although estimated treatment differences were smaller compared with the pre-planned initially presented analyses, they confirmed superior efficacy of the romosozumab arm versus the control arm in each of the studies (placebo in study 20070337 and alendronate in study 20110142). Regarding LOCF its use can be criticised in that it is not clear what treatment effect is targeted; it is neither the effect that would be observed if all patients would be fully adherent to treatment, nor the effect that would be observed if loss of benefit from active treatment after treatment drop-out is taken into account. In the primary BMD analysis set, subjects with assessments completely missing were ignored leading to non-negligible proportions of randomised subjects being excluded in the analyses; depending on analysis/time-point this concerned 12% to 20% of randomised subjects. Since the information in section 5.1 of the SmPC should be statistically compelling, not only in terms of degree of evidence presented, the Applicant was requested to amend the tables concerned. Therefore, in section 5.1 of the SmPC which had been proposed by the applicant,the BMD results were revised and based on ANCOVA analyses conducted on all randomised subjects using a control-based pattern multiple imputation approach for missing data.

The primary endpoint in study 20070337, the *subject incidence of new vertebral fracture* after romosozumab treatment compared with placebo, is aligned with CHMP guidance (CPMP/EWP/552/95 Rev. 2) and represents in principle the established measure of efficacy for the treatment of postmenopausal osteoporosis. The first component of the co-primary endpoint is considered suitable to analyse the efficacy of romosozumab in the time window of intended treatment duration, i.e. 0 - 12 months (induction of fracture-protective effect).

However, the second component of the co-primary endpoint, the *vertebral fracture incidence during the (first) 24-months* study period is not considered adequate to directly assess the maintenance of fracture protection after romosozumab cessation. This is because fracture events observed during the first year of treatment are counted again in this data analysis, and any relevant treatment effect already identified in the first year might suffice to reveal a significant result also for the co-primary 24-months analysis, even if there was no fracture protective effect after month 12. Against this background, one important comparison of interest concerns (new vertebral) fracture incidence observed exclusively in the second year during open-label denosumab treatment, i.e. setting a new baseline for the analysis at month 12 (cessation of romosozumab treatment). The Applicant provided the additional analyses as requested. Whilst the mentioned potential methodological deficiencies of this post-hoc analyses of the second-year fracture-incidences are acknowledged, the additional information provided however further supports the (general) assumption of persistence of the fracture-protective efficacy after cessation of romosozumab. Results provided indicate that the original co-primary efficacy analysis is not strongly dominated by month 12 outcome only. Similar to outcome for the Month 0-12 treatment period, the point estimate for the relative fracture risk reduction for the Month 12-24 study period (i.e. effect size) is smallest for the category of non-vertebral fractures.

The focus chosen in study 20110142 to primarily investigate fracture protection advantages of a romosozumab-alendronate (ALN) treatment sequence over an ALN-alone treatment after a treatment period of 24 months is not considered optimal from the romosozumab-licensure perspective. Instead, just as queried in relation for study 20070337 above, it would have been found most suitable to focus the assessment of treatment initiation of a protective effect on fracture data from the active-controlled phase (up to 12 months). As regards investigation of maintenance of protective effect after cessation of romosozumab treatment under continued ALN treatment, it would have seemed more adequate to take month 12 status as new baseline for data analysis, also in study 20110142. The Applicant provided the additional analyses separated by year- study time intervals as requested. It can be agreed with the Applicant, that the statistical evaluation of fracture data collected after the treatment switch to alendronate is supporting the hypothesis that extended fracture risk benefit can be achieved in the subsequent time period following romosozumab treatment cessation. However, such a finding should be differentiated from any benefit-claim directly associated with subsequent antiresorptive therapy, which is not a matter of primary assessment in this MAA. As for trial 20070337, estimated effect size in both periods (Month 0-12, Month 12-24) seems least pronounced in the category of non-vertebral fractures. Aside this non-optimality in definition of trial objective and primary endpoints, there is a high level of complexity coming from terminology and statistical analysis strategy, which aggravates reading and interpretation of the fracture data analyses. From a planning perspective, many conditions where set up to define when different analyses for different fracture endpoints were planned to be carried out, in varying analyses sets. Corresponding explanations are hard to follow, as throughout protocol, SAP and CSR the term "primary analysis" is used in a confusing manner, as it sometimes refers to the actual analysis of primary endpoints, but sometimes also just to the point in time when primary endpoints are evaluated (mentioned for the analyses of actual secondary endpoints).

A total of 16,716 subjects were screened for study 20070337 and 7,180 were randomized to the romosozumab 210 mg (3,589 subjects) and placebo (3,591 subjects) arm. These two groups were well balanced regarding baseline demographics and BMD, as expected. The 10-year probability of a major osteoporotic fracture, according to the FRAX, were similar between treatment groups, whereas generally lower in the region Central/Latin America (accounting for 43% of study population), reflecting a population with a lower fracture risk. This was driven by a substantially lower incidence of previous fractures, and a moderately lower incidence of parental hip fracture, current smoking status, secondary osteoporosis, and alcohol use. According to the Applicant, a number of reports in the scientific literature have indicated that

lower non-vertebral fracture risk and FRAX scores in women from the Central/Latin American region is not unusual when considering similar ages and T-scores of the population in other countries.

Efficacy data and additional analyses

Baseline demographics and disease characteristics in pivotal studies

The number of randomised subjects in 20070337 was 7,180 subjects and in 20110142 4,093 subjects. The male pivotal study, 20110174, was much smaller with 245 randomised subjects.

In all three studies, a substantial part (42-66%) of the subjects was included in Europe. The studies are considered relevant for the European population.

The treatment groups were well balanced regarding age, ethnicity, race and BMI in each study. The main differences between the three studies in baseline demographics was mean age (20070337 70.9 years; 20110142 74.3 years and 20110174 72.1 years) and smoking (46.1% never-smokers in 20110174 compared to 71.8% in 20070337 and 72.3% in 20110142).
The difference in mean age is considered secondary to the differences in eligibility criteria between the studies.

Due to eligibility criteria, mean baseline BMD T-scores at all locations were higher in 20110174 than in 20070337. This is discussed further below.

Fracture endpoints

Study 20070337 met its co-primary endpoints which were subject incidence of *new radiological vertebral fractures* compared with placebo through the 12-month double-blind period (0.5% vs 1.8%) and through month 24 after both groups transitioned to denosumab (0.6% vs 2.5%); $p<0.001$ at both time points. Vertebral fracture risk reduction persisted over the 24-month study period for subjects initially randomized to romosozumab, as romosozumab for 12 months followed by denosumab for 12 months significantly reduced the risk of new vertebral fractures compared with placebo for 12 months followed by denosumab for 12 months, with a relative risk reduction of 75% (95% CI: 60, 84) and absolute risk reduction of 1.89% (NNT=53).

Romosozumab also reduced the risk of *clinical fractures* (clinical vertebral and non-vertebral) compared to placebo at 12 months (adjusted $p=0.008$), but not at 24 months after adjustment for multiplicity.

Romosozumab numerically reduced the risk of *non-vertebral fractures* compared to placebo at 12 months and 24 months, however, the reduction was not statistically significant after adjustment for multiplicity.

In study 20110142, romosozumab treatment reduced subject incidence of *new vertebral fractures* compared to alendronate during the 12-month double-blind period (secondary endpoint) (3.2% vs 5.0%; $p=0.008$). Through 24 months, the incidence of new vertebral fractures with romosozumab/alendronate treatment compared to alendronate/alendronate (primary endpoint) (4.1% vs 8.0%; $p<0.001$).

The primary analysis in study 20110142 was performed after median follow-up time of 2.7 years (approximately 33 months). Romosozumab reduced the risk of *clinical fractures* through primary analysis (primary endpoint) compared to alendronate (9.7% vs 13.0%; nominal $p=0.027$).

Romosozumab/alendronate reduced the risk of *non-vertebral fractures* through primary analysis (not significant at 12 or 24 months) compared to alendronate alone (8.7% vs 10.6%); multiplicity adjusted $p=0.040$.

The incidence of fractures was higher in 20110142 than in 20070337. This was expected as the study population of 20110142 was older and had a more severe osteoporosis at baseline. The absolute numbers of fractures, especially non-vertebral fractures, were lower than estimated in 20070337 resulting in modest absolute risk reductions (1.3% at month 12, 1.9% at month 24).

Hip fractures are the most serious consequences of osteoporosis, associated with serious risks, permanent disability and also increased mortality. Differences in hip fractures between treatment groups were not statistically significant at any time points in any study. The low number of non-vertebral fracture events may impair the possibility to detect an effect of romosozumab subject incidence of such fractures.

In the remaining efficacy/safety studies, fractures were reported as adverse events. According to the EMA "Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003405.pdf) separate fracture data are not required for bridging studies.

The absolute number of fracture events in each study was too low for conclusions and the results were not consistent across studies.

In study 20070337, a predefined by-region subgroup analysis for the non-vertebral fracture endpoint through month 12 showed that in Central/Latin America (accounting for 43.0% of the randomized population), a lower than expected non-vertebral fracture rate (compared to the assumed rate of 3.5% used for sample size calculation) was observed in the placebo group in the first 12 months (1.2%), with no reduction seen in the romosozumab group (1.5%). In the Central/Latin America region, the absolute number of fractures was even higher in the romosozumab group (placebo: 19/1534) vs. romosozumab: 24/1550), but the corresponding statistical test for a qualitative interaction obviously lacked power due to the low event numbers and the rather small treatment difference in absolute terms. The Applicant also describes a non-vertebral fracture rate of 1.1% in the placebo group in North America, which was also lower than (overall) expected, and the impact of the trend to have better fracture protection under placebo on overall results is low, as the sample size in this region represents only 2.7% of the overall study population. In a post-hoc subgroup analysis that excluded Central/Latin America data to derive a patient subset from all other regions combined (rest-of-world), the non-vertebral fracture rate was 2.7% in the placebo group and 1.6% in the romosozumab group (RRR 42%, ARR 1.1%). As the baseline characteristics between treatment arms (placebo, romosozumab) are still balanced in the rest-of-world population after excluding the Central/Latin America region), this post-hoc analysis excluding Central/Latin America could be considered meaningful.

When looking on the FRAX data of the Central/Latin America population, a generally lower 10-year probability of major osteoporotic fractures and of hip fractures can be observed. These marked region differences in baseline FRAX probabilities aggravate a straight forward interpretation of fracture analysis outcome, in particular for the analyses of non-vertebral and clinical fractures. There were even more fractures in the romosozumab arm compared to the placebo arm in the central/Latin American population.

The Applicant has proposed a sequential treatment with romosozumab for 12 months followed by anti-resorptive therapy. Romosozumab increased BMD at the lumbar spine, total hip and femoral neck at Month 12 regardless of prior osteoporosis treatment in Study 20080289, 20110142, 20070337 and 20110174. A sequential approach is therefore accepted.

The appropriate timing for introducing romosozumab after a fracture has been discussed. Especially, it was considered unclear to what extent patients in romosozumab studies had recent osteoporotic fractures and which impact romosozumab might have on fracture healing if administered as early treatment. This post-fracture population is considered especially vulnerable for adverse events, and e.g. data for IV

bisphosphonate treatment suggests better efficacy when treatment is initiated >6 weeks after hip surgery compared to early treatment start.

To evaluate the timing of romosozumab initiation after a fracture, the gains in BMD in 67 subjects (20110142) and 29 subjects (20070337) following a non-vertebral fracture while on study were investigated. The mean time to next romosozumab dose was 23.0 days (median 14.0 days; range 0 to 197 days) in Study 20110142 and 16.0 days (median 13.0; range 0 to 66 days) in Study 20070337.
The mean percent change from baseline (95% CI) in lumbar spine BMD in 54 subjects with a non-vertebral fracture event through month 12 was 14.4 vs 13.7 in subjects without such a fracture event (n=1,572) in Study 2011042. The corresponding numbers for Study 20070337 were 13.5 (n=27) vs 12.9 (n=1,178). There was no indication of decreased anti-fracture efficacy for the remainder of the studies.
Furthermore, data from two fracture studies in rodents and cynomolgus monkeys did not indicate a different effect of romosozumab on bone strength or bone mass at the fracture site or other sites when given in connection with a fracture. Thus, so far, non-clinical and clinical data do not indicate a need for restricting the timing of initiation of romosozumab treatment after a fracture.

Additional analysis

Fracture events (New radiological vertebral, Clinical vertebral and non-vertebral, Non-vertebral, Hip fractures) for the studies 20110142 and 20070337 were calculated for a subpopulation that would have been included according to the restricted indication (severe osteoporosis in postmenopausal women at high risk of fracture) and contraindications (History of myocardial infarction or stroke) as proposed by the applicant during the procedure. These calculations are summarised below. Of note, this is a post-hoc analysis.

Table 39: Study 20110142 (severe PMO) results at month 12 (proposed target population)

Effect	Romosozumab n/N (%)	Alendronate n/N (%)
New radiological vertebral	50/1622 (3.1)	78/1621 (4.8)
Clinical vertebral and non-vertebral	75/1923 (3.9)	105/1920 (5.5)
Non-vertebral	67/1923 (3.5)	91/1920 (4.7)
Hip	14/1923 (0.7)	22/1920 (1.1)

Table 40: Effects Table for study 20070337 (less severe PMO) results at month 12 (patients representing proposed target population)

Effect	Romosozumab n/N (%)	Placebo n/N (%)
New radiological vertebral	11/1243 (0.9)	28/1262 (2.2)
Clinical vertebral and non-vertebral	30/1353 (2.2)	43/1383 (3.1)
Non-vertebral	29/1353 (2.1)	37/1383 (2.7)
Hip	3/1353 (0.2)	9/1383 (0.7)

Bone mineral density

In studies 20070337 and 20110174, the increase in BMD compared to baseline was higher in the romosozumab group than in the placebo group at all locations through month 12 and month 24; $p<0.001$ at all locations and time points.
Through month 12, percent change from baseline lumbar spine BMD was comparable between the studies; however, the percent changes from baseline BMD in the romosozumab group were more modest in both total hip and femoral neck, resulting in a lower LS mean difference between romosozumab and placebo in study 20110174. The Applicant has provided information indicating that there is no correlation between baseline weight and the difference in romosozumab effect on BMD in total hip and femoral neck between men and women, indicating that this difference is not explained by differences in mean weight between the studies. The Applicant speculates that the difference in effect may, in part, be due to the lower baseline BMD in study 20070337 caused by different inclusion criteria. No such differences were seen between study 20070337 and 20110142 despite the difference in baseline BMD. The reason for the difference between men and women in this context remains unclear.

Similarly, in study 20110142, romosozumab increased BMD compared to alendronate ($p<0.001$ at all locations and time points). This was consistent with the results in study 20060326, where the 210 mg QM dose was also associated with greater increases in BMD at the lumbar spine and total hip than the 2 active controls, alendronate and teriparatide.

In the analyses through month 12 in study 20070337, treatment differences across demographic subgroups (ie, age and geographic region) ranged from 12.0% to 14.4% for the lumbar spine and from 4.7% to 6.6% for the total hip and were more or less consistent with the treatment differences observed for the overall population (12.7% for lumbar spine and 5.8% for total hip at month 12). At month 36, romosozumab followed by denosumab resulted in continued increases in BMD at the lumbar spine, total hip, and femoral neck compared with placebo followed by denosumab. It is noted, that also in the Central/Latin American (CLA) population BMD-increase at month 12 was significant compared to placebo. The increase of BMD at total hip was even most pronounced in the region Central/Latin America with a treatment difference of 6.6% at month 12. For this same region, no reduction in the non-vertebral fracture rate was seen in the romosozumab group compared to the placebo arm. This finding could question the relationship between fracture risk reduction and increasing BMD under treatment with romosozumab.
The Applicant clarified on request that this was explained by the too low non-vertebral fracture risk and background fracture rate among the CLA population, representing about 43% of study population, rather than lack of efficacy. The median 10-year probability of major fractures and hip fractures in the CLA population were 7.26% and 3.02%, respectively, which was only slightly lower than the male fracture risk and about half of the risk of the "Rest of world"- population (i.e. after exclusion of the CLA population), where significant fracture risk reduction also in non-vertebral locations could be demonstrated.

Results of the Imaging Substudy I showed that Romosozumab (months 6 and 12) and romosozumab/denosumab (months 18 and 24) did not have a significant impact on BMD in the forearm, as evaluated by DXA BMD at the distal 1/3 radius and total radius. BMD in the forearm was even lower in subjects who received 12 months of romosozumab compared with those who received placebo. Consistent with the results for radius BMD by DXA, evaluation of the radius by HR-pQCT did not show significant differences in the double-blind period between romosozumab and placebo for volumetric BMD (total, cortical, trabecular). As potential reasons for this finding, the Applicant mentions the non-weight bearing nature of this skeletal site and the documented less responsivity of the distal radius for all pharmacological therapies for osteoporosis. Furthermore, even decreases in BMD at the distal radius during osteoporosis treatment

have been reported in literature (Cosman et al, 2015). A conclusive interpretation of the fracture protective effect of romosozumab on forearm fractures remains however unclear.

During the off-treatment phase of study 20060326, the effect on lumbar spine BMD of the initial romosozumab treatment was sustained only with follow-up treatment with denosumab. Retreatment after a period without treatment was comparable to the initial treatment, whereas the increase in BMD with romosozumab retreatment after denosumab was small in lumbar spine and lacking in total hip and femoral neck in this small number of subjects. This may in part be secondary to the effect on bone turnover markers with romosozumab retreatment after denosumab (see Dose-response study 20060326).
Study 20060326 is the only data source for both off-treatment and re-exposure to romosozumab and no efficacy conclusions can be made due to the limited number of study participants.

Bone biopsy studies

Evaluation of bone formation/resorption and structure parameters by histology, histomorphometry and micro-CT was performed at months 2, 12 and 24. At month 2, most dynamic and static bone formation parameters were elevated in the romosozumab group compared to placebo in the cancellous and endocortical compartments. In intracortical compartment, only double-label surface and mineralising surfaces increased. At month 2 in the cancellous compartment, the median %change in mineralizing surface in the romosozumab group was 325.1% compared with 67.3% in placebo group. The data suggest that romosozumab increases the surface extent of active bone formation but not the rate at the level of the individual osteoblast after 2 months. With regard to bone resorption parameters, a reduction was also evident in the cancellous and endocortical compartment.

In contrast, at month 12, dynamic and static bone formation parameters were significantly lower in the romosozumab group in the cancellous compartment. This decrease is probably secondary to the decrease in the rate of bone remodelling, consistent with self-regulation of bone formation. It is however acknowledged that at 12 months, bone structure parameters (trabecular thickness, bone volume to tissue volume, wall thickness, and cortical thickness) were significantly increased in the romosozumab compared to the placebo group. With regard to bone resorption, sustained inhibition was still seen after 1 year of treatment, which is also favourable.

The presented parameters overall indicate an increased bone formation during the first weeks and a maintained decrease in bone resorption also during the late treatment phase, i.e. at month 12. A more thorough discussion on the clinical relevance of the different parameters on a qualitative and quantitative level would have been expected. On the other hand, it is agreed that bone histomorphometry data are exploratory in nature and primarily used for safety reasons due to certain limitations for example the fact that the samples represent a small fraction of the skeleton and may not be representative of other sites. Furthermore, the number of patients from who biopsies have been taken is small. Consequently, it is hard to draw any firm conclusions from the biopsies. It is also of interest that bone histomorphometry samples are taken at a non-weight bearing site, which may be a potential explanation to the fact that the effect of romosozumab in bone formation parameters is not as large at such sites as in e.g. vertebral bones.

Study 20080289 - Switch study

In study 20080289, romosozumab increased total hip BMD measured by DXA (primary endpoint) compared to 20 µg QD TPTD through 12 months of treatment, indicating that previous treatment with bisphosphonates does not attenuate the romosozumab effect bone mineral density. Furthermore, all (key) secondary and exploratory endpoints were met for the ITT and PP analyses sets. Bone formation marker (P1NP) showed an initial superior effect compared to teriparatide but trended then back to baseline values while teriparatide

continued to increase. Bone resorption marker (CTX) slightly declined during the first 14 days with romosozumab and returned to baseline by month 3. With teriparatide, CTX increased and remained above baseline for the whole treatment period.

It is notable that in this study, there was no difference from baseline in total hip BMD with 12 months of TPTD treatment (LS mean -0.65). As opposed to this, in study 20060326, 20 µg TPTD increased total hip BMD compared to placebo (1.3% vs -0.7; p<0.0001). The TPTD effect was comparable to the effect of romosozumab 70 mg QM and 140 mg Q3M, but lower than 140 mg QM and 210 mg QM. The main difference between the two studies was that in study 20060326, the use of bisphosphonates within a pre-specified time limit was an exclusion criterion.

In study 20080289, most of the patients were pre-treated with alendronate (92.7% and 88.1% for teriparatide and romosozumab, respectively). Literature indicates that anabolic responsiveness to teriparatide differs based on prior antiresorptive therapy, and that the use of alendronate may blunt the magnitude of the effect. Generalizability of the results of study 20080289 to all bisphosphonate pre-treated patients cannot indisputably be concluded. The applicant proposed to address this in section 5.1 of the SmPC.

Additional expert consultation

CHMP requested an ad hoc expert meeting to obtain the opinion of experts in the field of osteoporosis, cardiology as well as geriatrics, and from patient representatives, on various aspects of the efficacy data and the issue of increased rate of CV events observed in studies with romosozumab. Questions were addressed to the ad hoc expert group. The corresponding answers are presented below:

Question 1

The target population of the most recently proposed indication for romosozumab (severe osteoporosis) was mainly studied in phase III PMO study 20110142. The AHEG is asked to comment on different aspects of the efficacy results from this study:

a. The incidences of vertebral and non-vertebral fractures were lower in the romosozumab compared to the alendronate group, but statistical significance was not reached for the difference in non-vertebral fractures at the end of romosozumab treatment at month 12. Please comment on the clinical relevance of these results, also considering that alendronate has been shown to be superior to placebo in reducing non-vertebral fractures in other studies.

There was clear evidence of efficacy with regard to reduction of new vertebral fractures in both pivotal trials 20070337 (FRAME study; romosozumab vs. placebo) and 20110142 (ARCH study; romosozumab vs. alendronate) at the 12 month time point as well as later time points.

While it was acknowledged that statistical significance was not yet reached for the reduction of non-vertebral fractures at the 12 month time points, i.e. at time of completion of the romosozumab treatment phase, this reached statistical significance at 33 month, also for hip fractures. The experts found it adequate to consider the overall longer term benefit beyond 12 months.

Also considering that the superiority outcome was achieved in comparison with alendronate in study 20110142 the experts found the efficacy of romosozumab to be very compelling.

b. Do you consider that romosozumab improves the treatment options in the proposed target population e.g. based on a unique mechanism of action, a clinically relevant

rapid increase of BMD and/or for patients previously treated with bisphosphonates, also taking into account data obtained with teriparatide and the fact that romosozumab has not been compared to denosumab or zoledronic acid in clinical studies?

According to the experts, the demonstrated efficacy (outlined above), accompanied by the rapid increase of BMD at various sites and its close correlation with a reduction in fracture risk (as evident in study 20070337), would constitute a valuable therapeutic option for patients with high risk of fracture.

In comparison with the only currently available osteoanabolic agent, teriparatide, advantages were seen e.g. regarding a better response of cortical bone, or when teriparatide is contraindicated. Although there was no direct comparison with e.g. denosumab or zoledronate, the chosen comparator alendronate is considered standard of care and, based on expected increases in bone mineral density (BMD), may not be assumed to be less efficacious than other bisphosphonates, such as zoledronate, according to some of the experts.

The applicant currently proposes the use in "severe osteoporosis . . . at high risk of fracture". The definition of this population might somewhat vary depending on country and guideline applied; in general it would be expected to comprise patients whose DEXA-measured BMD falls below a certain threshold and who have already experienced certain types of osteoporotic fracture. This was thought to represent an adequate population, with some experts finding it useful to also allow treatment of patients with a very high risk of fracture based on e.g. FRAX score and other estimates or e.g. a very low BMD.

A bridging study (study 20110174, BRIDGE study) was used to extrapolate fracture efficacy from the postmenopausal population to male patients based on similar increases in the surrogate parameter of BMD with a primary analysis after 12 months. This was in principle found to be adequate by design. However, as the increase in BMD in male patients was only about half of what was achieved with romosozumab in postmenopausal women for measurements at total hip (3.0 vs 5.8% placebo-corrected increase) and femoral neck (2.4 vs 5.2% placebo-corrected increase) the experts questioned whether efficacy in men should be accepted. Hypotheses regarding the reasons included the possibility of under-dosing in, on average, heavier male patients.

While intended for treatment-naïve patients, the experts did not discount the possibility of treating patients with romosozumab with prior exposure to anti-resorptive agents, in particular bisphosphonates.

Question 2

In PMO study 20110142, as well as in the bridging study in men and in the supportive study 20080289, there was an increased incidence of CV events in patients receiving romosozumab compared to the comparator (alendronate, placebo and teriparatide, respectively). The AHEG is asked to discuss the adequacy and the feasibility of the risk minimization measures proposed by the Applicant (as below) and to discuss any potential additional measures.

a. Contraindication in patients with previous MI or stroke

The experts shared the concern of an increase in CV events associated with romosozumab observed in some of the studies.

No evidence of a protective effect of alendronate to explain the difference is apparent, nor was another explanation identified by the experts. It was acknowledged that the increased relative risk of CV events was observed throughout the entire patient population without apparent significant differences between different subgroups. The views were split regarding the adequacy to contraindicate the use of romosozumab based on a history of an MI or stroke. While some experts found no scientific reason to specifically exclude patients with such a prior event from treatment, others found the restriction to be useful. Some experts proposed a warning instead of a contraindication. It was generally acknowledged that such a contraindication would reduce the CV risk in absolute terms, however the relative reduction of the risk associated with romosozumab treatment would appear to change little.

It was considered whether exclusion of patients with a fixed age cut-off, e.g. >75 years, could improve the risk profile sufficiently to justify exclusion of this population but this possibility was not supported by the majority of experts.

b. Information in the SmPC about the increased risk and a recommendation that "the prescribing physician should carefully evaluate the individual benefit-risk balance of using romosozumab treatment".

Experts supported the notion that treatment with romosozumab would be an individualized treatment decision; it was pointed out that the initiation of such therapy, for example in Germany and the UK, would most likely be in specialized centres in any case.

c. Post approval observational safety study

To further characterize cardiovascular risk associated with romosozumab, ideally a randomized controlled cardiovascular outcome trial would be preferred, but it was acknowledged, given the lack of enrichment of CV risk in romosozumab treated patients, that such a study would need to be very large. The experts had concerns whether the currently proposed observational study could satisfactorily adjust for the expected channelling bias of relatively higher CV risk patients away from romosozumab treatment. A proposal by the experts therefore was a randomized, non-blinded, registry-based type of study.

2.5.4. Conclusions on clinical efficacy

Efficacy and safety in postmenopausal women were assessed in two large pivotal studies, an alendronate-controlled study 20110142 (N=4,093) and a placebo-controlled study 20070337 (N=7,180). Subjects in Study 20110142 were on average 4 years older than subjects in Study 20070337 and had more severe osteoporosis according to the inclusion criteria. There was also a higher rate of history of hypertension in Study 20110142. Romosozumab was intended for a 12 months' time-limited treatment followed by anti-resorptive therapy. In both studies, patients were treated with romosozumab 210 mg SC once a month or with placebo/alendronate for 12 months in total. Thereafter, all subjects in study 20070337 received denosumab for additional 24 months. In study 20110142 all subjects were treated with alendronate until end of study. In the two pivotal studies romosozumab reduced the risk of new radiological vertebral fractures at 12 and 24 months compared to placebo (Study 20070337; 0.5% vs 1.8% through 12 months and 0.6% vs 2.5% through 24 months) and compared to alendronate (Study 20110142; 3.2% vs 5.0% through 12 months and 4.1% vs 8.0% through 24 months). In study 20110142, romosozumab also reduced the risk of clinical fractures (vertebral and non-vertebral) compared to alendronate at 12 months (3.9% vs 5.4%) and

compared to alendronate at the time point of primary analysis (9.7% vs 13.0%). Thus, the predefined primary endpoints were met. The effect on non-vertebral fractures (secondary endpoint) did not reach statistical significance in the placebo-controlled study 20070337. In Study 20110142, the effect of romosozumab was superior to alendronate for reducing the risk of non-vertebral fractures (11% vs 9%) and hip fractures (3.2% vs 2.0%) at the time of primary analysis at 33 months. Head to head comparisons of romosozumab with other potent antiresorptive treatments, such as zolendronic acid and denosumab, were not available which may be considered as a limitation. Therefore, sequential therapy of romosozumab followed by alendronate achieved benefit over current standard of care in both vertebral and non-vertebral fractures. Rapid BMD gains were achieved with romosozumab versus comparators (alendronate, teriparatide) in the first 12 months. The absolute risk reduction in non-vertebral fractures in PMO studies was small in both PMO studies, however, superiority in terms of fracture reduction across vertebral, clinical, and non-vertebral fractures over alendronate has been demonstrated in the presented trials.

2.6. Clinical safety

Introduction

The safety profile in the osteoporotic population was evaluated across 4 placebo-controlled studies over the 12-month treatment period between the romosozumab 210 mg group and placebo in the integrated analysis. In addition, with the emerging safety data from Study 20110142, the safety profile of romosozumab was evaluated in the integrated analysis across the 7 studies in the phase 2/3 program utilizing the following data presentation:

- Integrated data across all phase 2 and phase 3 studies (excluding Study 20110142) for the placebo group and the romosozumab 210 mg QM group
- Data from Study 20110142 for the alendronate group and the romosozumab 210 mg QM group
- Integrated data across all phase 2 and phase 3 studies including Study 20110142 for:

    -the integrated control groups (placebo, alendronate, teriparatide);

    -romosozumab 210 mg QM; and

    -total romosozumab groups (any dosing and frequency including every 3 months [Q3M]).

Discussions are focused on the following two sets:

12-month placebo-controlled osteoporosis safety analysis set: Subjects who were randomized and received at least 1 dose of romosozumab 210 mg QM or placebo in the 12-month placebo-controlled osteoporosis randomized analysis set.
The 12-month data for subjects in this analysis set are used to summarize safety endpoints.

Osteoporosis safety analysis set: Subjects who were randomized and received at least 1 dose of romosozumab (any dose or frequency) or control (placebo, alendronate, teriparatide) in the phase 2 and phase 3 osteoporosis studies. For this analysis set, 24-month data from 20060326, 12-month data from 20070337, 12-month data from 20080289, 12-month data from 20101291, 12-month data from 20110142, 12-month data from 20110174, and 6-month data from 20120156 were used to summarize safety endpoints and presented mostly as "exposure adjusted incidence rates".

Separate comprehensive integrated reports were provided for immunogenicity and cardiovascular safety.

Patient exposure

Safety data are submitted from an extensive safety database that includes 11553 subjects in 19 romosozumab clinical studies who received at least 1 dose of romosozumab (n = 7681) or placebo (n = 3872). Additionally, the integrated control group for the osteoporosis safety analysis set includes 6155 subjects who received placebo, alendronate, teriparatide, and/or denosumab. However, the number of male subjects with osteoporosis, who received at least 1 dose of romosozumab (n=163), is very limited. The majority of exposed subjects were older than 65 years, which is acceptable due to the generally late onset of osteoporosis. No paediatric patients were studied.

Table 41: Number of Subjects Receiving Treatment and Duration of Cumulative Exposure by Study Type (Overall Safety Analysis Set)

	Placebo			Romosozumab		
	≥ 1 Dose	≥ 6 Months	≥ 12 Months	≥ 1 Dose	≥ 6 Months	≥ 12 Months
Overall total exposure	3872	3588	3383	7681	6338	5863
Phase 1 studies[a]	50	2	0	945	3	0
Postmenopausal osteoporosis studies	3741	3506	3305	6573	6177	5712
Key phase 3 studies[b]	3576	3350	3200	5621	5263	5044
Additional phase 2 and 3 studies[c]	165	156	105	952	914	668
Male osteoporosis study[d]	81	80	78	163	158	151

[a] Includes Studies 20060220, 20060221, 20060223, 20090153, 20090378, 20090418, 20101180, 20110227, 20110253, 20120274, 20120277, and 20150197 for romosozumab exposure; 20060220, 20060221, 20090153, 20090378 for placebo.
[b] Includes 20070337 (12 months), and 20110142 (12 months) for romosozumab exposure; 20070337 (12 months) for placebo.
[c] Includes Studies 20060326 (24 months, 48 subjects who received romosozumab after 1 year of alendronate are included), 20080289 (12 months), 20101291 (12 months), and 20120156 (6 months) for romosozumab exposure and 20060326 (24 months), 20101291 (12 months), 20120156 (6 months) for placebo.
[d] Includes Study 20110174 (12 months).
Duration of cumulative study exposure is defined from the randomization or first dose date to the end of study or the end of analysis period, whichever comes first. There were an additional 27 subjects from Study 20060326 who received placebo in the initial 24 months and romosozumab 210 mg every month (QM) in the retreatment phase, but these subjects were excluded from this table.

Table 42: Osteoporosis Safety Analysis Set

All Studies (Including 20110142)		
Control[c] (N = 6155) n (%)	Romosozumab 210 mg QM[d] (N = 6358) n (%)	Romosozumab Total[e] (N = 6688) n (%)

Overview of adverse events

The total number of adverse events was generally comparable in the clinical studies between romosozumab and control groups. The number of treatment related AEs was somewhat higher in the Romosozumab group.

Table 43: Summary of Subject Incidence of Adverse Events (12-Month Placebo-controlled Osteoporosis Safety Analysis Set)

	20070337		20060326		20101291		20110174		Total	
	Placebo (N = 3576) n (%)	Romo 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romo 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romo 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romo 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romo 210 mg QM SC (N = 3858) n (%)
All treatment-emergent adverse events - n (%)	2863 (80.1)	2812 (78.5)	45 (90.0)	43 (84.3)	43 (68.3)	47 (74.6)	65 (80.2)	123 (75.5)	3016 (80.0)	3025 (78.4)
Serious adverse events	314 (8.8)	344 (9.6)	7 (14.0)	6 (11.8)	4 (6.3)	2 (3.2)	10 (12.3)	21 (12.9)	335 (8.9)	373 (9.7)
Leading to discontinuation of investigational product	96 (2.7)	106 (3.0)	2 (4.0)	2 (3.9)	0 (0.0)	1 (1.6)	1 (1.2)	5 (3.1)	99 (2.6)	114 (3.0)
Fatal adverse events	24 (0.7)	29 (0.8)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	2 (1.2)	26 (0.7)	31 (0.8)
Treatment-related treatment-emergent adverse events[a] - n (%)	496 (13.9)	596 (16.6)	6 (12.0)	7 (13.7)	1 (1.6)	1 (1.6)	7 (8.6)	19 (11.7)	510 (13.5)	623 (16.1)
Serious adverse events	13 (0.4)	16 (0.4)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	14 (0.4)	16 (0.4)
Leading to discontinuation of investigational product	48 (1.3)	55 (1.5)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	48 (1.3)	58 (1.5)
Fatal adverse events	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)

N = number of subjects in the analysis set; n = number of subjects reporting ≥ 1 event; QM = every month; Romo = romosozumab; SC = subcutaneously
[a] Includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product.

Table 44: Summary of Exposure-adjusted Incidence Rate of Treatment-emergent Adverse Events (Osteoporosis Safety Analysis Set)

	All Studies (Excluding 20110142)		Study 20110142		All Studies (Including 20110142)		
	Placebo[a] (N = 3822) n (r)	Romosozumab 210 mg QM[b] (N = 4318) n (r)	Alendronate 70 mg QW (N = 2014) n (r)	Romosozumab 210 mg QM (N = 2040) n (r)	Control[c] (N = 6155) n (r)	Romosozumab 210 mg QM[d] (N = 6358) n (r)	Romosozumab Total[e] (N = 6688) n (r)
All TEAEs	3047 (216.9)	3322 (208.1)	1584 (199.7)	1544 (188.3)	4858 (207.0)	4866 (201.4)	5157 (203.2)
Serious adverse event	341 (9.8)	400 (10.4)	278 (15.3)	262 (14.4)	650 (11.7)	662 (11.7)	701 (11.4)
Leading to discontinuation of investigational product	102 (2.8)	126 (3.2)	64 (3.3)	70 (3.7)	184 (3.2)	196 (3.3)	208 (3.3)
Fatal adverse events	26 (0.7)	32 (0.8)	21 (1.1)	30 (1.5)	47 (0.8)	62 (1.0)	63 (1.0)
Treatment-related TEAEs[f]	521 (15.9)	716 (20.2)	310 (18.1)	299 (17.2)	888 (16.9)	1015 (19.2)	1078 (18.9)
Serious adverse event	14 (0.4)	16 (0.4)	12 (0.6)	13 (0.7)	26 (0.4)	29 (0.5)	30 (0.5)
Leading to discontinuation of investigational product	50 (1.4)	65 (1.6)	35 (1.8)	27 (1.4)	92 (1.6)	92 (1.6)	94 (1.5)
Fatal adverse events	1 (<0.1)	1 (<0.1)	3 (0.2)	0 (0.0)	4 (<0.1)	1 (<0.1)	1 (<0.1)

N = Number of subjects in the analysis set, n = Number of subjects Q3M = every 3 months; QM = every month; QW = every week; r = exposure-adjusted incidence rate per 100 subject-years; SC = subcutaneously; TEAE = treatment-emergent adverse event
Alendronate-treated subject 14248015041 had a fatal non-treatment-related serious adverse event of pneumonia that had an incorrect death flag in the primary analysis snapshot and was not included in the exposure-adjusted incidence rate of fatal events.
[a] Includes Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months).
[b] Includes Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months).
[c] Includes placebo from Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months), alendronate from Studies 20060326 (12 months) and 20110142 (12 months), and teriparatide from studies 20060326 (12 months), and 20080289 (12 months).
[d] Includes Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months), 20101291 (12 months), 20110142 (12 months), 20110174 (12 months), and 20120156 (6 months).
[e] Includes romosozumab QM and Q3M from Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months, all data), 20101291 (12 months), 20110142 (12 months), 20110174 (12 months), and 20120156 (6 months).
[f] Includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product.

Common adverse events

Table 45: Treatment-emergent Adverse Events Occurring ⩾ 2% in Total Romosozumab 210 mg QM and More Frequently Than in Total Placebo by Preferred Term (12-month Placebo-Controlled Osteoporosis Safety Analysis Set)

	20070337		20060326		20101291		20110174		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romosozumab 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romosozumab 210 mg QM SC (N = 3858) n (%)
Number of subjects reporting adverse events	2863 (80.1)	2812 (78.5)	45 (90.0)	43 (84.3)	43 (68.3)	47 (74.6)	65 (80.2)	123 (75.5)	3016 (80.0)	3025 (78.4)
Nasopharyngitis	439 (12.3)	460 (12.8)	7 (14.0)	9 (17.6)	8 (12.7)	20 (31.7)	22 (27.2)	35 (21.5)	476 (12.6)	524 (13.6)
Arthralgia	434 (12.1)	468 (13.1)	3 (6.0)	2 (3.9)	2 (3.2)	0 (0.0)	7 (8.6)	8 (4.9)	446 (11.8)	478 (12.4)
Headache	208 (5.8)	235 (6.6)	8 (16.0)	5 (9.8)	1 (1.6)	2 (3.2)	6 (7.4)	10 (6.1)	223 (5.9)	252 (6.5)
Muscle spasms	140 (3.9)	163 (4.6)	0 (0.0)	3 (5.9)	2 (3.2)	0 (0.0)	5 (6.2)	3 (1.8)	147 (3.9)	169 (4.4)
Cough	117 (3.3)	130 (3.6)	2 (4.0)	5 (9.8)	0 (0.0)	0 (0.0)	1 (1.2)	5 (3.1)	120 (3.2)	140 (3.6)
Oedema peripheral	67 (1.9)	86 (2.4)	1 (2.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	69 (1.8)	86 (2.2)
Neck pain	54 (1.5)	80 (2.2)	1 (2.0)	1 (2.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	56 (1.5)	81 (2.1)

N = number of subjects in the analysis set; n = Number of subjects reporting ≥ 1 event; QM = every month; SC = subcutaneously
Preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using Medical Dictionary for Regulatory Activities version 19.1.
The preferred terms asthenia and dyslipidemia were removed based upon clinical review; these events are not confirmed by objective laboratory data. The subject incidence of these events are similar between the romosozumab and placebo groups.

Table 46: Exposure-adjusted Incidence Rate of Treatment-emergent Adverse Events by Preferred Term (Occurring ⩾ 2 Per 100 Subject-years in Total Romosozumab Group and More Frequently Than in Control) (Osteoporosis Safety Analysis Set).

	All Studies (Excluding 20110142)		20110142		All Studies (Including 20110142)		
Preferred Term	Placebo[a] (N = 3822) n (r)	Romosozumab 210 mg QM[b] (N = 4318) n (r)	Alendronate 70 mg QW (N = 2014) n (r)	Romosozumab 210 mg QM (N = 2040) n (r)	Control[c] (N = 6155) n (r)	Romosozumab 210 mg QM[d] (N = 6358) n (r)	Romosozumab Total[e] (N = 6688) n (r)
Number of subjects reporting treatment-emergent adverse events	3047 (216.9)	3322 (208.1)	1584 (199.7)	1544 (188.3)	4858 (207.0)	4866 (201.4)	5157 (203.2)
Nasopharyngitis	483 (14.4)	578 (15.7)	218 (11.9)	213 (11.7)	730 (13.4)	791 (14.3)	885 (14.9)
Headache	226 (6.4)	271 (7.0)	110 (5.9)	105 (5.6)	351 (6.2)	376 (6.5)	400 (6.4)
Cough	123 (3.5)	151 (3.8)	55 (2.9)	74 (3.9)	191 (3.3)	225 (3.9)	249 (3.9)
Dyspepsia	68 (1.9)	80 (2.0)	50 (2.6)	54 (2.8)	125 (2.2)	134 (2.3)	146 (2.3)
Injection site pain	46 (1.3)	87 (2.2)	24 (1.2)	32 (1.7)	72 (1.2)	119 (2.0)	137 (2.2)
Cataract	55 (1.5)	79 (2.0)	35 (1.8)	49 (2.6)	94 (1.6)	128 (2.2)	138 (2.1)
Oedema peripheral	70 (1.9)	87 (2.2)	38 (2.0)	34 (1.8)	110 (1.9)	121 (2.1)	129 (2.0)

N = Number of subjects in the analysis set, n = Number of subjects; Q3M = every month; QM = every month; QW = every week; r = exposure-adjusted incidence rate per 100 subject-years; SC = subcutaneously
Preferred terms are sorted by descending order of the exposure-adjusted incidence rate in the total romosozumab group and control group, and coded using Medical Dictionary for Regulatory Activities version 19.1.
[a] Includes Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months).
[b] Includes Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months).
[c] Includes placebo from Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months), alendronate from studies 20060326 (12 months) and 20110142 (12 months), and teriparatide from studies 20060326 (12 months) and 20080289 (12 months).
[d] Includes Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months), 20101291 (12 months), 20110142 (12 months), 20110174 (12 months), and 20120156 (6 months).
[e] Includes romosozumab QM and Q3M from Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months, all data), 20101291 (12 months), 20110142 (12 months), 20110174 (12 months), and 20120156 (6 months).

The most common adverse events were nasopharyngitis, headache, cough, arthralgia, dyspepsia and oedema peripheral and muscle spasms with no striking differences between treatment groups. The pattern of common and treatment associated adverse events presents similarly in the male osteoporosis population. Injection site pain and cataracts seem to be more common in the Romosozumab group. Nasopharyngitis (13.6% vs 12.6%), arthralgia (12.4% vs 11.8%), headache (6.5% vs 5.9%), muscle spasms (4.4% vs 3.9%), neck pain (2.1% vs 1.5%), cataract (2.0% vs 1.5%), injection site pain (1.8% vs 1.2%), injection site erythema (1.5% vs 0.2%), sinusitis (1.4% vs 0.8%), and injection site pruritus (0.7% vs 0.2%) are proposed to be labelled in the SmPC with a frequency "common" or "very common".

MedDRA System Organ Class	Adverse Reaction	Frequency Category
Infections and infestations	Nasopharyngitis	Very Common
	Sinusitis	Common
Immune system disorders	Hypersensitivity[a]	Common
	Rash	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Rare
	Erythema multiforme	Rare
Metabolism and nutrition disorders	Hypocalcaemia[b]	Uncommon
Nervous system disorders	Headache	Common
	Stroke[c]	Uncommon
Eye disorders	Cataract[d]	Common
Cardiac disorders	Myocardial infarction[c]	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	Very Common
	Neck pain	Common
	Muscle spasms	Common
General disorders and administration site conditions	Injection site reactions[e]	Common

a. See sections 4.3 and 4.4.
b. Defined as albumin adjusted serum calcium that was below the lower limit of normal. See sections 4.3 and 4.4.
c. See section "Myocardial infarction and stroke" below.
d. At 12months in pooled placebo controlled studies, cataract frequency was 1.5% in placebo group versus 2.1% in romosozumab group.
e. Most frequent injection site reactions were pain and erythema.

Serious adverse events

Table 47: Most Frequent (⩾ 0.2% in Total Romosozumab or Placebo Groups) Serious Adverse Events by Preferred Term (12-month Placebo-Controlled Osteoporosis Safety Analysis Set)

	20070337		20060326		20101291		20110174		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romo 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romo 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romo 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romo 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romo 210 mg QM SC (N = 3858) n (%)
Number of subjects reporting serious treatment-emergent adverse events	314 (8.8)	344 (9.6)	7 (14.0)	6 (11.8)	4 (6.3)	2 (3.2)	10 (12.3)	21 (12.9)	335 (8.9)	373 (9.7)
Pneumonia	10 (0.3)	19 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	10 (0.3)	21 (0.5)
Angina unstable	3 (<0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.6)	3 (<0.1)	8 (0.2)
Hypertension	5 (0.1)	8 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	8 (0.2)
Cardiac failure congestive	4 (0.1)	7 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	7 (0.2)
Chronic obstructive pulmonary disease	15 (0.4)	6 (0.2)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	16 (0.4)	7 (0.2)
Lung neoplasm malignant	6 (0.2)	7 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)	7 (0.2)
Osteoarthritis	15 (0.4)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	15 (0.4)	7 (0.2)
Acute myocardial infarction	4 (0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	6 (0.2)
Atrial fibrillation	4 (0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	6 (0.2)
Cardiac failure	1 (<0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (<0.1)	6 (0.2)
Death	5 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.6)	6 (0.2)	6 (0.2)
Non-cardiac chest pain	0 (0.0)	4 (0.1)	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.6)	2 (<0.1)	6 (0.2)
Cerebrovascular accident	7 (0.2)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	7 (0.2)	5 (0.1)
Cholelithiasis	8 (0.2)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.2)	5 (0.1)
Urinary tract infection	7 (0.2)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	7 (0.2)	5 (0.1)
Femur fracture	7 (0.2)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	8 (0.2)	4 (0.1)
Femoral neck fracture	8 (0.2)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.2)	3 (<0.1)

N = number of subjects in the analysis set; n = number of subjects reporting ≥ 1 event; QM = every month; Romo = romosozumab; SC = subcutaneously
Preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using Medical Dictionary for Regulatory Activities version 19.1.

Table 48: Exposure-adjusted Incidence Rate of Treatment-emergent Serious Adverse Events by Preferred Term (≥ 0.2 per 100 Subject-years in the Romosozumab 210 mg QM or Total Romosozumab Groups) (Osteoporosis Safety Analysis Set

	All Studies (Excluding 20110142)		20110142		All Studies (Including 20110142)		
Preferred Term	Placebo[a] (N = 3822) n (r)	Romosozumab 210 mg QM[b] (N = 4318) n (r)	Alendronate 70 mg QW (N = 2014) n (r)	Romosozumab 210 mg QM (N = 2040) n (r)	Control[c] (N = 6155) n (r)	Romosozumab 210 mg QM[d] (N = 6358) n (r)	Romosozumab Total[e] (N = 6688) n (r)
Number of subjects reporting serious treatment-emergent adverse events	341 (9.8)	400 (10.4)	278 (15.3)	262 (14.4)	650 (11.7)	662 (11.7)	701 (11.4)
Pneumonia	10 (0.3)	22 (0.5)	17 (0.9)	16 (0.8)	29 (0.5)	38 (0.6)	41 (0.6)
Osteoarthritis	15 (0.4)	8 (0.2)	5 (0.3)	6 (0.3)	21 (0.4)	14 (0.2)	17 (0.3)
Femur fracture	8 (0.2)	4 (<0.1)	12 (0.6)	11 (0.6)	20 (0.3)	15 (0.3)	15 (0.2)
Acute myocardial infarction	4 (0.1)	6 (0.1)	2 (0.1)	8 (0.4)	6 (0.1)	14 (0.2)	14 (0.2)
Chronic obstructive pulmonary disease	16 (0.4)	8 (0.2)	10 (0.5)	5 (0.3)	26 (0.4)	13 (0.2)	13 (0.2)
Cholelithiasis	8 (0.2)	6 (0.1)	6 (0.3)	5 (0.3)	15 (0.3)	11 (0.2)	13 (0.2)
Atrial fibrillation	4 (0.1)	9 (0.2)	4 (0.2)	3 (0.2)	8 (0.1)	12 (0.2)	13 (0.2)
Cerebrovascular accident	7 (0.2)	6 (0.1)	7 (0.4)	6 (0.3)	14 (0.2)	12 (0.2)	13 (0.2)
Urinary tract infection	7 (0.2)	5 (0.1)	8 (0.4)	8 (0.4)	15 (0.3)	13 (0.2)	13 (0.2)
Radius fracture	6 (0.2)	4 (<0.1)	12 (0.6)	8 (0.4)	19 (0.3)	12 (0.2)	12 (0.2)
Cardiac failure	1 (<0.1)	7 (0.2)	5 (0.3)	5 (0.3)	6 (0.1)	12 (0.2)	12 (0.2)
Hypertension	5 (0.1)	9 (0.2)	4 (0.2)	1 (<0.1)	9 (0.2)	10 (0.2)	11 (0.2)
Angina unstable	3 (<0.1)	8 (0.2)	2 (0.1)	2 (0.1)	5 (<0.1)	10 (0.2)	11 (0.2)
Transient ischaemic attack	1 (<0.1)	5 (0.1)	2 (0.1)	6 (0.3)	4 (<0.1)	11 (0.2)	11 (0.2)
Femoral neck fracture	8 (0.2)	4 (<0.1)	12 (0.6)	5 (0.3)	20 (0.3)	9 (0.2)	9 (0.1)
Cardiac failure congestive	4 (0.1)	7 (0.2)	5 (0.3)	2 (0.1)	9 (0.2)	9 (0.2)	9 (0.1)

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N = number of subjects in the analysis set; n = number of subjects; Q3M = every 3 months; QM = every month; QW = every week; r = exposure-adjusted incidence rate per 100 subject-years; Romo = romosozumab

Preferred terms are sorted by descending order of the exposure-adjusted incidence rate in the total romosozumab group and control group, and coded using Medical Dictionary for Regulatory Activities version 19.1.

[a] Includes Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months).

[b] Includes Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months).

[c] Includes placebo from Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months), alendronate from Studies 20060326 (12 months) and 20110142 (12 months), and teriparatide from Studies 20060326 (12 months) and 20080289 (12 months).

[d] Includes Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months), 20101291 (12 months), 20110142 (12 months), 20110174 (12 months), and 20120156 (6 months).

[e] Includes romosozumab QM and Q3M from Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months, all data), 20101291 (12 months), 20110142 (12 months), 20110174 (12 months), and 20120156 (6 months).

The total numbers of serious adverse events were somewhat higher for romosozumab compared to placebo but somewhat lower compared to alendronate in study 20110142.

Deaths

Table 49: Treatment-emergent Fatal Adverse Events by System Organ Class and Preferred Term (12-month Placebo-Controlled Osteoporosis Safety Analysis Set); (>1 event)

	20070337		20060326		20101291		20110174		Total	
System Organ Class Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romosozumab 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romosozumab 210 mg QM SC (N = 3858) n (%)
Number of subjects reporting fatal treatment emergent adverse events	24 (0.7)	29 (0.8)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	2 (1.2)	26 (0.7)	31 (0.8)
Cardiac disorders	5 (0.1)	7 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	5 (0.1)	8 (0.2)
Cardio-respiratory arrest	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	3 (<0.1)
Myocardial infarction	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)
Cardiac arrest	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Cardiac failure congestive	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Congestive cardiomyopathy	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Angina pectoris	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (<0.1)	8 (0.2)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	8 (0.2)
Lung neoplasm malignant	0 (0.0)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Adenocarcinoma gastric	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Breast cancer	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hepatocellular carcinoma	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Ovarian cancer	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Bronchial carcinoma	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Colorectal cancer	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Metastases to pleura	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
General disorders and administration site conditions	7 (0.2)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.6)	8 (0.2)	7 (0.2)
Death	5 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.6)	6 (0.2)	6 (0.2)
Multiple organ dysfunction syndrome	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Sudden death	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Injury, poisoning and procedural complications	1 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	3 (<0.1)
Brain contusion	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Post procedural haemorrhage	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Subarachnoid haemorrhage	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

Craniocerebral injury	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Vascular disorders	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)
Circulatory collapse	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Deep vein thrombosis	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hypovolaemic shock	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Nervous system disorders	3 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	1 (<0.1)
Ruptured cerebral aneurysm	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Cerebrovascular accident	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	0 (0.0)
Ischaemic stroke	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Gastrointestinal disorders	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Lower gastrointestinal haemorrhage	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Intestinal ischaemia	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

N = Number of subjects in the analysis set
n = Number of subjects reporting ≥ 1 event
System organ classes and preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using MedDRA version 19.1.

Table 50: Subject Incidence of Treatment-emergent Fatal Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set - 20110142 Primary Analysis)

	Double-blind Period	
System Organ Class Preferred Term	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM (N = 2040) n (%)
No.of subjects reporting fatal TEAEs	21 (1.0)	30 (1.5)
Cardiac disorders	3 (0.1)	9 (0.4)
Infections and infestations	5 (0.2)	5 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.1)	4 (0.2)
Nervous system disorders	2 (<0.1)	3 (0.1)
Vascular disorders	0 (0.0)	3 (0.1)
General disorders and administration site conditions	5 (0.2)	2 (<0.1)
Injury, poisoning and procedural complications	0 (0.0)	2 (<0.1)
Respiratory, thoracic and mediastinal disorders	2 (<0.1)	1 (<0.1)
Hepatobiliary disorders	1 (<0.1)	0 (0.0)

Figure 16: Time to First Occurrence of Adverse Event Leading to Death Through Month 12 (Safety Analysis Set) (20110142 Primary Analysis)

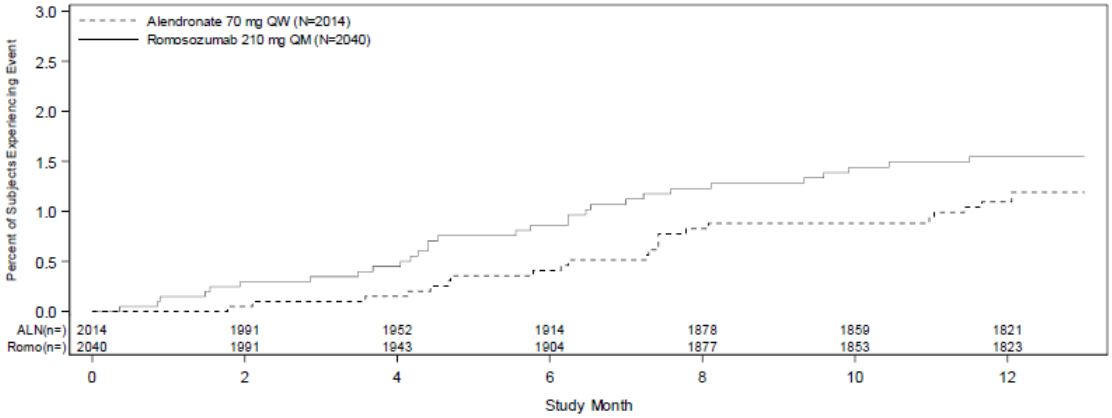
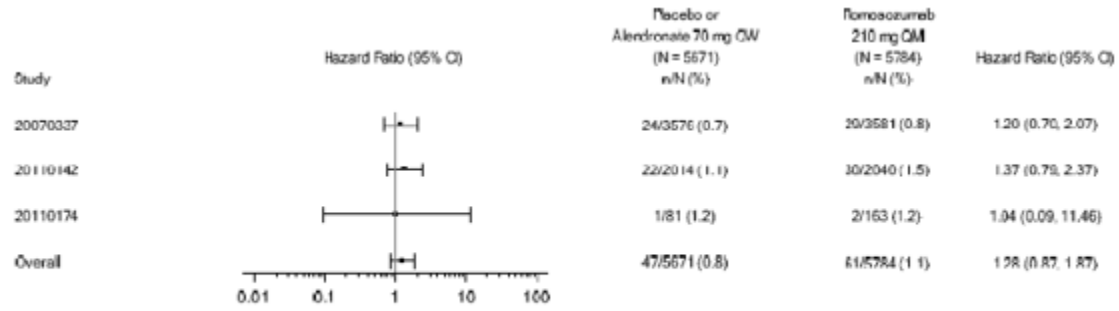


Figure 17: Time to first occurrence of AE leading to death through Month 12 (Safety Analysis Set; 20070337, 20110142 and 20110174)



AE=adverse event; CI=confidence interval; N=number of subjects in Safety Analysis Set; QM=every month; QW=every week

Fatal events in age subgroups

Figure 18: Subgroup analysis of baseline Characteristics: Time to First Occurrence of Adverse Event Leading to death through Month 12 (Safety Analysis Set) (20070337, 20110142, 20110174)

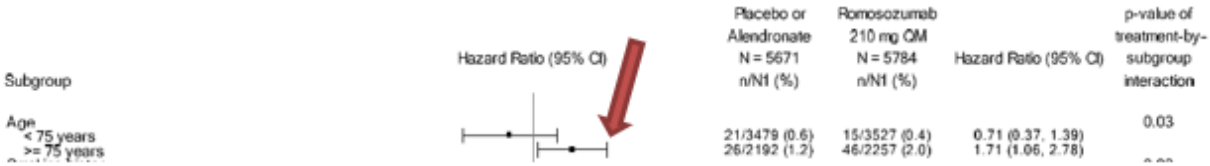


Table 51: Treatment-emergent Fatal Adverse Events through Month 12 in subjects ≥75 years* and <75 Years by System Organ Class (Safety Analysis Set) (20070337, 20110142, 20110174)

	N (%) of Subjects															
Study	20070337 (FRAME)				20110174 (BRIDGE)				20110142 (ARCH)				Total			
Age Group	<75 years		≥75 years		<75 years		≥75 years		<75 years		≥75 years		<75 years		≥75 years	
Treatment	PBO	ROM	PBO	ROM	PBO	ROM	PBO	ROM	ALN	ROM	ALN	ROM	C	ROM	C	ROM
SOC N	2461	2464	1115	1117	53	93	28	70	965	970	1049	1070	3479	3527	2192	2257
Any fatal AE	16 (0.7)	10 (0.4)	8 (0.7)	19 (1.7)	0 (0.0)	0 (0.0)	1 (3.6)	2 (2.9)	5 (0.5)	5 (0.5)	16 (1.5)	25 (2.3)	21 (0.6)	15 (0.4)	25 (1.1)	46 (2.0)
Cardiac disorders	3 (0.1)	3 (0.1)	2 (0.2)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.1)	3 (0.3)	2 (0.2)	6 (0.6)	4 (0.1)	6 (0.2)	4 (0.2)	11 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.1)	5 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	4 (0.4)	3 (<0.1)	5 (0.1)	3 (0.1)	7 (0.3)

* The number of fatal adverse events in the control group of the subgroup of patients ≥75 years was corrected from n=25 to n=26 during the procedure.

In the pooled pivotal trials, there was a numerical imbalance in fatal events with HR 1.20 and 1.37 in the two large PMO studies. In the subgroup of patients ≥75 years fatal adverse events occurred stat. significantly more often under romosozumab treatment as compared to control (either alendronate or placebo), fatal events occurred in 46 (2.0%) patients treated with Romosozumab and 26 (1.2%) of controls, HR 1.71 (1.06-2.78). The imbalance was mainly due to fatal cardiovascular events and neoplasms.

Baseline co-morbidities/risk factors between treatment groups within each age subgroup, were not consistently favouring control or romosozumab groups. It was also not possible to identify age specific other risk factors for fatal events that would be specific for Romosozumab group.

There are numerous variables that can play a role in the fatal outcome of an event and the causality to romosozumab is not possible to determine in individual cases. However, an osteoporosis drug that reduces fractures in older population would be expected to possibly reduce all-cause mortality, not the opposite.

Other significant adverse events

Based on the mechanism of action, the pharmacologic profile of romosozumab, potential class effects of bone-forming agents, observations made during the nonclinical and clinical program, and Agency feedback, additional adverse event evaluations were conducted. Adverse events of interest included hypocalcaemia, hypersensitivity, injection site reactions, malignancies, hyperostosis, osteoarthritis, atypical femoral fractures and osteonecrosis of the jaw. Independent adjudication of serious cardiovascular events was pre-specified in the 3 pivotal phase 3 studies. The events are summarised in the tables below and are thereafter discussed one by one.

Table 52: Summary of Treatment-emergent Adverse Events of Interest and Adjudicated Adverse Events (12-Month Placebo-controlled Osteoporosis Safety Analysis Set)

	20070337		20060326		20101291		20110174		Total	
	Placebo (N = 3576) n (%)	Romo 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romo 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romo 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romo 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romo 210 mg QM SC (N = 3858) n (%)
Hypocalcemia										
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events potentially related to hypersensitivity										
Adverse events	247 (6.9)	242 (6.8)	4 (8.0)	4 (7.8)	4 (6.3)	3 (4.8)	4 (4.9)	8 (4.9)	259 (6.9)	257 (6.7)
Serious adverse events	0 (0.0)	6 (0.2)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	6 (0.2)
Injection site reaction										
Adverse events	104 (2.9)	188 (5.2)	2 (4.0)	3 (5.9)	1 (1.6)	2 (3.2)	3 (3.7)	9 (5.5)	110 (2.9)	202 (5.2)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant or unspecified tumours										
Adverse events	55 (1.5)	50 (1.4)	2 (4.0)	1 (2.0)	0 (0.0)	1 (1.6)	2 (2.5)	3 (1.8)	59 (1.6)	55 (1.4)
Serious adverse events	41 (1.1)	35 (1.0)	1 (2.0)	1 (2.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.6)	42 (1.1)	38 (1.0)
Hyperostosis										
Adverse events	28 (0.8)	18 (0.5)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (0.8)	18 (0.5)
Serious adverse events	5 (0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	1 (<0.1)
Osteoarthritis										
Adverse events	316 (8.8)	285 (8.0)	5 (10.0)	0 (0.0)	0 (0.0)	10 (15.9)	4 (4.9)	8 (4.9)	325 (8.6)	303 (7.9)
Serious adverse events	17 (0.5)	7 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	17 (0.5)	8 (0.2)
Adjudicated positive atypical femoral fracture										
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Serious adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Adjudicated positive osteonecrosis of the jaw										
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = number of subjects in the analysis set; n = number of subjects reporting ≥ 1 event; QM = every month; Romo = romosozumab; SC = subcutaneously
Hypersensitivity and malignancy include only treatment-emergent adverse events as a result of a narrow search/scope in standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ).
Hypocalcemia, injection site reaction, hyperostosis, and osteoarthritis include only treatment-emergent adverse events as a result of Amgen-defined MedDRA search strategies.
Atypical femoral fracture and osteonecrosis of the jaw were not adjudicated in Study 20101291.
Preferred terms are coded using MedDRA version 19.1.

Table 53: Summary of Exposure-adjusted Incidence Rate of Treatment-Emergent Adverse Events of Interest (Osteoporosis Safety Analysis Set)

	All Studies (Excluding 20110142)		20110142		All Studies (Including 20110142)		
	Placebo[a] (N = 3822) n (r)	Romosozumab 210 mg QM[b] (N = 4318) n (r)	Alendronate 70 mg QW (N = 2014) n (r)	Romosozumab 210 mg QM (N = 2040) n (r)	Control[c] (N = 6155) n (r)	Romosozumab 210 mg QM[d] (N = 6358) n (r)	Romosozumab Total[e] (N = 6688) n (r)
Hypocalcemia							
Adverse events	0 (0.0)	4 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)	5 (<0.1)	5 (<0.1)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events potentially related to hypersensitivity							
Adverse events	266 (7.6)	284 (7.4)	118 (6.3)	122 (6.5)	401 (7.1)	406 (7.1)	450 (7.3)
Serious adverse events	1 (<0.1)	6 (0.1)	2 (0.1)	3 (0.2)	3 (<0.1)	9 (0.2)	9 (0.1)
Injection Site Reaction							
Adverse events	110 (3.1)	244 (6.3)	53 (2.8)	90 (4.8)	170 (2.9)	334 (5.8)	375 (6.1)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant or unspecified tumours							
Adverse events	60 (1.7)	61 (1.5)	28 (1.5)	31 (1.6)	92 (1.6)	92 (1.5)	95 (1.5)
Serious adverse events	43 (1.2)	42 (1.0)	20 (1.0)	25 (1.3)	64 (1.1)	67 (1.1)	69 (1.1)
Hyperostosis							
Adverse events	30 (0.8)	20 (0.5)	12 (0.6)	2 (0.1)	42 (0.7)	22 (0.4)	28 (0.4)
Serious adverse events	5 (0.1)	1 (<0.1)	2 (0.1)	0 (0.0)	7 (0.1)	1 (<0.1)	1 (<0.1)
Osteoarthritis							
Adverse events	328 (9.5)	325 (8.4)	146 (7.8)	138 (7.4)	487 (8.7)	463 (8.1)	493 (8.0)
Serious adverse events	17 (0.5)	9 (0.2)	6 (0.3)	8 (0.4)	24 (0.4)	17 (0.3)	20 (0.3)
Adjudicated positive atypical femoral fracture							
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Serious adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Adjudicated positive osteonecrosis of the jaw							
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of subjects in the analysis set; n = Number of subjects reporting ≥ 1 event; Q3M = every 3 months; QM = every month; QW = every week;
r = Exposure-adjusted incidence rate per 100 subject-years
Hypersensitivity and malignancy include only treatment-emergent adverse events as a result of a narrow search/scope in standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ).
Hypocalcemia, injection site reaction, hyperostosis, and osteoarthritis include only treatment-emergent adverse events as a result of Amgen-defined MedDRA search strategies.
Atypical femoral fracture and osteonecrosis of the jaw were not adjudicated in Studies 20101291 and 20120156.
Preferred terms are coded using MedDRA version 19.1.
[a] Includes Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months).
[b] Includes Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months), 20101291 (12 months), 20110174 (12 months), and 20120156 (6 months).
[c] Includes placebo from Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20110174 (12 months) and 20120156 (6 months), alendronate from Studies 20060326 (12 months) and 20110142 (12 months), and teriparatide from studies 20060326 (12 months) and 20080289 (12 months).
[d] Includes Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months), 20101291 (12 months), 20110142 (12 months), 20110174 (12 months), and 20120156 (6 months).
[e] Includes romosozumab QM and Q3M from Studies 20070337 (12 months), 20060326 (24 months), 20080289 (12 months, all data), 20101291 (12 months), 20110142 (12 months), 20110174 (12 months), and 20120156 (6 months).

Hypocalcaemia

The 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 increased demands for calcium for matrix mineralization. Four subjects (< 0.1%), all in the romosozumab 210 mg group had a hypocalcaemia adverse event in the Osteoporosis Safety Analysis Set. In the alendronate-controlled Study 20110142, during the 12-month double-blind period, 1 (< 0.1%) adverse event of hypocalcaemia (preferred term) was reported in each treatment group.

Only few adverse events of hypocalcaemia were reported as adverse events in the clinical studies. However, transient decrease in S-calcium has been observed in patients receiving romosozumab; see section "laboratory findings" below. Hypocalcaemia is proposed as an identified risk for romosozumab, it is included

in SmPC as a warning in section 4.4 and is listed as an undesirable effect in Section 4.8 with a frequency "uncommon" (Defined as albumin adjusted serum calcium that was below the lower limit of normal) in the table in section 4.8. This risk is further increase in patients with renal impairment; see section safety in special populations.

Hypersensitivity and injection site reactions

Overall, when hypersensitivity cases were medically reviewed across the 12-month placebo-controlled osteoporosis safety analysis set, there were no anaphylactic reactions reported that were attributable to romosozumab. In Study 20070337, the subject incidence of potential anaphylactic reactions was generally similar between both treatment groups and both study periods.

In the 12-month placebo-controlled osteoporosis population, the most frequently reported (> 0.5%) adverse events were rash (romosozumab: 1.1%; placebo: 0.9%), dermatitis allergic (0.7%; 0.8%), eczema (0.6%; 0.8%), rhinitis allergic (0.6%, 0.7%), urticaria (0.5%, 0.6%), and dermatitis (0.4%, 0.8%).

Adverse events potentially related to hypersensitivity led to discontinuation from investigational product for 11 (0.3%) subjects in the total romosozumab group and 6 (0.2%) subjects in the placebo group.

Serious adverse events corresponding to terms potentially related to hypersensitivity reactions were reported for 6 (0.2%) subjects in the total romosozumab group (all in Study 20070337, and 1 (< 0.1%) subject in the placebo group (Study 20060326).

In study 20110142, serious adverse events potentially related to hypersensitivity were reported for 3 (0.1%) subjects in the romosozumab group and 2 (< 0.1%) subjects in the alendronate group. One subject had angioedema. Hypersensitivity is proposed to be labelled as an adverse event for romosozumab, section 4.8 in the SmPC. Also warnings in section 4.4 is proposed and endorsed.

There was an imbalance of injection site reactions to the disadvantage of romosozumab in all pivotal studies and this is a common adverse drug reaction for romosozumab included under Section 4.8 Unidesirable Effects of the SmPC. No serious adverse events of injection site reactions were reported in the pivotal studies. The most frequent reactions were injection site pain and injection site erythema.

Malignant or unspecified tumours

Although sclerostin expression has been reported in a limited number of soft tissue and bone tumours, there is no current evidence that the presence or absence of sclerostin is related to malignant potential. There are no reports of an increased cancer incidence in patients with sclerosteosis or van Buchem disease. Although the high-dose group in the 2-year rat bioassay, performed by the applicant reported osteosarcomas in two rats these findings were not attributed to romosozumab exposure: no other study parameters showed precursor osteoblastic changes, and also because of its low incidence largely matching with historical background data for osteosarcomas.

In the 12-month placebo-controlled osteoporosis safety analysis set, adverse events of malignant or unspecified tumors were reported for 1.4% of subjects in the total romosozumab treatment group and 1.6% of subjects in the placebo group; serious adverse events were reported for 1.0% and 1.1% of subjects, respectively. Preferred terms reported for ≥ 0.2% of subjects in either treatment group were basal cell carcinoma (0.3%, 0.5%) and lung neoplasm malignant (0.2%, 0.2%).
The subject incidences of lymphomas and leukemia were low and balanced between the romosozumab and placebo groups. Similar pictures were observed in the Osteoporosis Safety Analysis Set (exposure-adjusted

incidence rate per 100 subject-years of adverse events of malignant or unspecified tumors was 1.5 in the total romosozumab and romosozumab 210 mg groups and 1.6 in the integrated control group) and the male osteoporosis set (romosozumab: 1.8%; placebo: 2.5%).

In the re-exposed group (Romosozumab Retreatment Period, Month 36-48), malignancies were reported for 6 subjects (3.6%), of which 5 were subjects who had received romosozumab during the first 2 years of the study (breast cancer, invasive ductal breast carcinoma, lung neoplasm malignant, squamous cell carcinoma of lung, and squamous cell carcinoma of skin): the first 4 events were considered serious adverse events. No adverse event of malignancy was considered by the investigator to be related to investigational product, and the incidences between romosozumab and placebo were similar: [3.6% [5 subjects] versus 3.7% [1 subject with thyroid cancer]]. This can be accepted.

The applicant also further investigated the small difference in deaths observed in the 12-month Placebo-Controlled Osteoporosis Safety Analysis Set that was driven by fatal malignant lung cancer (4 subjects (0.1%) in the romosozumab 210mg QM SC treatment group [N=3581] compared with 0 in the placebo treatment group [N=3576])

The individual case reports of these four patients reveal strong risk factors for developing the disease, such as long-term smoking, and COPD that would make a connection of romosozumab in the development of the disease unlikely. A certain deficiency in the applicant's line of argumentation is the lack of comparison regarding the occurrence of risk factors between treatment and placebo arm. The applicant furthermore presented tables discussing incidences and exposure adjusted incidences of lower respiratory tract malignancies in the 12 months placebo-controlled osteoporosis with no imbalances identified to placebo and alendronate treatment.

In addition, the applicant investigated, as requested, whether, after cessation of treatment, increased incidences of malignancies in general could be observed. This was evaluated for extension phases of studies 20070337, 20110142, 20060326, 20101291, and 20120156. No evidence was found that patients who had previously been treated with romosozumab have a higher probability to develop a malignancy after cessation of treatment, as compared to placebo and or control. This diminishes uncertainty regarding a potential association between romosozumab long term exposure and the development of malignancies.

Cataracts:

Table 54: Treatment-emergent Cataracts Adverse events by Preferred Term (12-month Placebo-controlled Osteoporosis Safety Analysis Set)

	20070337		20060326		20101291		20110174		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romosozumab 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romosozumab 210 mg QM SC (N = 3858) n (%)
Number of subjects reporting treatment-emergent narrow-scope cataract adverse events	56 (1.6)	74 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.3)	1 (1.2)	3 (1.8)	57 (1.5)	81 (2.1)
Cataract	54 (1.5)	70 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.3)	1 (1.2)	3 (1.8)	55 (1.5)	77 (2.0)
Cataract operation	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)
Cataract operation complication	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Cataract nuclear	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

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N = Number of subjects in the analysis set
n = Number of subjects reporting ≥ 1 event
Cataracts adverse events include only treatment-emergent adverse events as a result of Amgen-defined MedDRA search strategies.
Preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using MedDRA version 20.1.

Table 55: Treatment-emergent Cataracts Adverse events by Preferred Term for subjects without prior history of cataracts (12-month Placebo-controlled Osteoporosis Safety Analysis Set)

	20070337		20060326		20101291		20110174		Total	
Preferred Term	Placebo (N = 2923) n (%)	Romosozumab 210 mg QM SC (N = 2890) n (%)	Placebo (N = 44) n (%)	Romosozumab 210 mg QM SC (N = 41) n (%)	Placebo (N = 54) n (%)	Romosozumab 210 mg QM SC (N = 56) n (%)	Placebo (N = 67) n (%)	Romosozumab 210 mg QM SC (N = 142) n (%)	Placebo (N = 3088) n (%)	Romosozumab 210 mg QM SC (N = 3129) n (%)
Number of subjects reporting treatment-emergent narrow-scope cataract adverse events	38 (1.3)	59 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.4)	0 (0.0)	3 (2.1)	38 (1.2)	65 (2.1)
Cataract	38 (1.3)	57 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.4)	0 (0.0)	3 (2.1)	38 (1.2)	63 (2.0)
Cataract nuclear	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Cataract operation	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

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N = Number of subjects in the analysis set
n = Number of subjects reporting ≥ 1 event
Cataracts adverse events include only treatment-emergent adverse events as a result of Amgen-defined MedDRA search strategies.
Preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using MedDRA version 20.1.

Cataracts were frequent and occurred more frequently in the romosozumab arm in clinical studies in patients without prior history of cataracts. The baseline characteristics were balanced between romosozumab and placebo patients in the cataract analysis sets.

Even if the available non-clinical data presented by the applicant do not indicate that sclerostin or romosozumab have a direct action in the lens in the eye, for example changes in calcium concentration may be a risk factor for cataracts. Cataracts are labelled in the SmPC.

Hyperostosis

Patients with genetic disorders such as sclerosteosis and van Buchem disease that result in a life-long absence and/or decrease of sclerostin have an increase in both bone density and bone mass. Neurologic sequelae due to hyperostosis in these patients with the genetic absence of sclerostin include nerve compression, facial paralysis, deafness, visual changes, and headache from increased intracranial pressure.

Audiology substudy

Study 20070337 included an audiology substudy of 498 subjects to assess the effect of romosozumab treatment for 12 months compared with placebo on the incidence of hearing loss (defined as subjects meeting the American Speech-Language-Hearing Association criteria for ototoxicity), and mean change from baseline in hearing threshold (assessed as change from baseline in pure tone average; defined as [1] loss of ≥ 20 dB at any single frequency or [2] loss of ≥ 10 dB at any 2 adjacent frequencies or [3] loss of response at 3 consecutive frequencies where responses were previously obtained). The subject incidence of hearing loss at baseline was similar between romosozumab and placebo groups, and no significant difference in average change in hearing threshold was observed between the romosozumab and placebo groups at month 12 as assessed by the mean change from baseline in pure tone average.

BMD T-Scores

The human genetic diseases sclerosteosis and van Buchem disease stem from lifelong sclerostin deficiency and can result in a markedly increased BMD. No excessive increases in BMD were observed in clinical studies. The subject incidence of maximum post-baseline T-score > 2 at the lumbar spine was < 0.1% (1 subject) in the romosozumab group and <0.1% (1 subject) in the placebo group. No subject had a maximum post-baseline T-score > 2 at the total hip or femoral neck.

The overall data do not give strong support that hyperostosis would be a potential risk with romosozumab treatment of skeletally mature osteoporosis patients.

Osteoarthritis

Current literature supports a role of canonical Wnt signalling in the maintenance of articular cartilage and that dysregulation of the pathway could negatively affect cartilage health. Sclerostin is expressed in articular cartilage but its role in maintenance of cartilage health is unclear. In a nonclinical rodent model of osteoarthritis, Sci-Ab at doses up to 7 times the clinical dose of 210 mg QM on a mg/kg basis increased bone mass as anticipated, with no effects on cartilage thickness or area (Roudier et al, 2013)
In the 12-month placebo-controlled osteoporosis safety analysis set, adverse events of osteoarthritis were reported for 7.9% of subjects in the total romosozumab treatment group and 8.6% of subjects in the placebo group; serious adverse events were reported for 0.2% and 0.5%, respectively. Osteoarthritis adverse events (preferred terms) reported for ≥ 0.5% of subjects in either treatment group were osteoarthritis (romosozumab: 5.2%; placebo: 6.0%), spinal osteoarthritis (2.4% each group), and arthritis (0.5%; 0.3%).

Results for the osteoporosis safety analysis set were generally similar to the 12-month placebo-controlled osteoporosis safety analysis set. The exposure-adjusted incidence rates per 100 subject-years of adverse events of osteoarthritis were 8.0 in the total romosozumab group, 8.1 in the romosozumab 210 mg group, and 8.7 in the integrated control group; serious adverse events occurred at rates of 0.3, 0.3, and 0.4, respectively.
Overall, clinical data does neither suggest elevated incidences of osteoarthritis in romosozumab women, nor lead to a faster progression of the disease as evaluated in Study 20070337, which included an osteoarthritis substudy of 343 subjects where no significant progression of osteoarthritis of the knee was observed for subjects in the romosozumab group compared with the placebo group at month 12, as assessed by the change from baseline in the WOMAC total and subscale scores.

Tumor Necrosis Factor-Mediated Inflammatory Adverse Events

Sclerostin has been proposed as having a role as a negative regulator of TNF-α production in synovium, and expression of sclerostin has been shown in synoviocytes from patients with rheumatoid arthritis (Wehmeyer et al, 2016). However, the findings of this paper are in conflict with other studies that do not indicate a role of sclerostin in regulation of TNF-α-mediated inflammation (Chen et al, 2013; Marenzana et al, 2013). There is also little data to suggest a role for sclerostin in another disease, ankylosing spondylitis, a condition where TNF-α is thought to play a role.

For the 12-month placebo-controlled osteoporosis safety analysis set, the subject incidence of treatment-emergent TNF-mediated inflammatory adverse events was 0.3% in the romosozumab group and 0.4% the placebo group. Results for the osteoporosis safety analysis set were generally similar to the 12-month placebo-controlled osteoporosis safety analysis set. The exposure-adjusted incidence rate per 100 subject-years of adverse events of TNF-mediated inflammatory diseases was 0.4 in the total romosozumab and romosozumab 210 mg groups and 0.5 in the integrated control group. The exposure-adjusted incidence rates per 100 subject-years were 8.2 in the total romosozumab group, 9.2 in the romosozumab 210 mg group, and 10.7 in the integrated control group for subjects with a prior history of a TNF-mediated inflammatory disease. In the male osteoporosis Study 20110174, the subject incidence of treatment-emergent TNF-mediated inflammatory adverse events was 1.2% (2 subjects) in the romosozumab group and 0.0% the placebo group. On the whole TNF mediated inflammatory adverse events show a similar pattern of incidence as osteoarthritis with no relevant differences between romosozumab treated patients vs. placebo and/or control.

Sarcopenia

Theoretically, sarcopenia may be associated with sclerostin inhibition. Reduced muscle weight was recently reported in a study in sclerostin knock-out mice. The basis for this finding is unclear as sclerostin is not expressed in skeletal muscle. However, the weight of evidence from other nonclinical studies support that sclerostin deficiency or inhibition does not negatively affect muscle mass (Section 3.4.10 of Module 2.6.2, Pharmacology Written Summary). Sarcopenia is not reported in patients with sclerosteosis (Hamersma et al, 2003). In the 12-month placebo-controlled osteoporosis safety analysis set, adverse events of sarcopenia (narrow and broad scope) were reported for 5.8% of subjects in the total romosozumab group and 5.8% of subjects in the placebo group.
Sarcopenia adverse events (preferred terms) reported for ≥ 0.5% of subjects in either treatment group were asthenia (romosozumab: 2.2%; placebo: 2.2%), fatigue (1.3%; 1.5%), weight decreased (0.6%; 0.3%), muscle contracture (0.6%; 0.5%), muscular weakness (0.5% each), and musculoskeletal stiffness (0.5%; 0.5%). Although an evaluation of muscle size or performance was not performed, lean tissue mass was calculated for 83 subjects in Study 20070337 who participated in the Forearm and Total Body dual-energy X-ray absorptiometry (DXA) and high-resolution peripheral quantitative computed tomography (HR pQCT Imaging I) substudy.
The data indicate that the decrease in lean tissue mass measured by DXA was observed in a substudy of romosozumab treated patients in study 20070337 [romosozumab 210mg once a month for 1 year/ decrease in lean tissue mass (-1.6%) relative to the placebo group] was a consequence of an increase in bone mass and not of a decrease in muscle mass.

Atypical femoral fracture

In the 12-month placebo-controlled osteoporosis safety analysis set, 1 subject in the romosozumab group had a positively adjudicated serious adverse event of AFF. The event occurred after 3.5 months of romosozumab treatment and the patient had a history of prodromal pain and a low screening vitamin D level.

In study 20110142, positively adjudicated AFF cases were identified during the open-label alendronate treatment period for 2 subjects in the romosozumab/alendronate group and 4 subjects in the alendronate/alendronate group during the primary analysis period. The 2 subjects in the romosozumab/alendronate group who had AFFs during the open-label alendronate treatment period (Subjects 35007008 and 68001053) experienced these events 655 and 492 days, respectively, after the first dose of alendronate. One additional positively adjudicated adverse event of AFF was noted for Study 20110142 (Subject 14228003174) after the snapshot date of 27 February 2017. This 79-year old Asian woman received romosozumab for 12 months (2013 to 2014) followed by alendronate (2014 to 2016), and partially withdrew consent in 2016. The subject had a serious adverse event of right femur fracture after a fall on 2017 (day 1360) during the primary analysis period.

Atypical femur fractures are identified risk for other antiresorptive anti-osteoporotic agents and the risk is known to increase with increased treatment duration. They seldom occur during the first years of treatment and the evidence for other agents has been obtained post-marketing. Because inhibition of bone resorption is a component of the dual effect of romosozumab, there is a potential concern for increased risk of AFF.

For romosozumab, one event occurred during romosozumab treatment and three additional events in patients who had received romosozumab and then received alendronate, which is a confounding factor. Following completion of romosozumab therapy, transition to other antiresorptive therapy is recommended in the current SmPC proposal for romosozumab and any postmarketing follow up of this risk will also be confounded.

However, based on the mechanism of action it is reasonable to conclude that romosozumab treatment has contributed to the AFF events that occurred in the clinical programme. Proposed warning text in SmPC section 4.4 is endorsed.

Osteonecrosis of the jaw (ONJ)

Osteonecrosis of the jaw has been observed with the use of antiresorptive agents. Preclinical data gives some support that romosozumab would not be associated with ONJ. However, none of these studies examined effects of romosozumab followed by another antiresorptive agent.

In the 12-month placebo-controlled osteoporosis safety analysis set (excluding Study 20101291, for which events were not adjudicated), 1 subject in the romosozumab group and no placebo subject had a positively adjudicated case of ONJ. This case had continuous use of a maladaptive fitting denture. One additional positively adjudicated case of ONJ was identified in the romosozumab group of Study 20070337 after the double-blind period (subject was taking denosumab at the time). This case occurred after the administration of 1 dose of denosumab in a subject who had a prior non-serious adverse event of periodontitis.

To date, in Study 20110142, there are a total of 3 positively ONJ events, all of which occurred during the open-label alendronate treatment period: 2 events occurred in the romosozumab/alendronate group and 1 occurred in the alendronate/alendronate group.

To date, a total of four cases of ONJ have been reported in the Romosozumab clinical programme, one during romosozumab treatment and three during following denosumab/alendronate treatment. This information should be included in the SmPC, in the table in section 4.8. Following completion of 1-year romosozumab therapy, transition to other antiresorptive therapy is recommended. Recommendations regarding oral hygiene are considered appropriate for romosozumab treated patients as for oral antiresorptive agents for osteoporosis in section 4.4 of the SmPC.

Infections

The subject incidence of infections was generally similar between treatment groups. The most frequently reported adverse events in the total romosozumab or placebo treatment groups were nasopharyngitis (13.6%, 12.6%), viral upper respiratory tract infection (5.4%, 6.0%), and influenza (4.6%, 5.0%). Events of rare and potentially opportunistic events reported only in the romosozumab 210 mg QM group were 1 event each of *Mycobacterium avium* complex infection (grade 3) and Cryptococcal pneumonia (grade 3). Pulmonary disease caused by *Mycobacterium avium* complex infection usually occurs in patients with chronic lung disease or deficient cellular immunity; however, it can affect persons without predisposing conditions, particularly elderly women.

Table 56: Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (12-month Placebo-Controlled Osteoporosis Safety Analysis Set)

System Organ Class Preferred Term	20070337 Placebo (N = 3576) n (%)	20070337 Romoso-zumab 210 mg QM SC (N = 3581) n (%)	20060326 Placebo (N = 50) n (%)	20060326 Romoso-zumab 210 mg QM SC (N = 51) n (%)	20101291 Placebo (N = 63) n (%)	20101291 Romoso-zumab 210 mg QM SC (N = 63) n (%)	20110174 Placebo (N = 81) n (%)	20110174 Romoso-zumab 210 mg QM SC (N = 163) n (%)	Total Placebo (N = 3770) n (%)	Total Romoso-zumab 210 mg QM SC (N = 3858) n (%)
Number of subjects reporting serious treatment-emergent adverse events	314 (8.8)	344 (9.6)	7 (14.0)	6 (11.8)	4 (6.3)	2 (3.2)	10 (12.3)	21 (12.9)	335 (8.9)	373 (9.7)
Infections and infestations	46 (1.3)	67 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	6 (3.7)	48 (1.3)	73 (1.9)
Pneumonia	10 (0.3)	19 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	10 (0.3)	21 (0.5)
Urinary tract infection	7 (0.2)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	7 (0.2)	5 (0.1)
Cellulitis	2 (<0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	5 (0.1)
Bronchitis	1 (<0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	4 (0.1)
Sepsis	1 (<0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	4 (0.1)
Urinary tract infection bacterial	3 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	3 (<0.1)
Pneumonia bacterial	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	3 (<0.1)	2 (<0.1)
Appendicitis	2 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (<0.1)	2 (<0.1)
Erysipelas	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)
Staphylococcal infection	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Diverticulitis	3 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	1 (<0.1)

A numerical imbalance in serious adverse events of infections in the largest pivotal placebo-controlled study 20070337 was noted. 1.9% in the romosozumab group and 1.3% in the placebo group. In the male osteoporosis Study 2011017, serious adverse events in the system organ class of infections and infestations occurred at rates of 3.7% in the romosozumab group and 2.5% in the placebo group. However, no imbalance was evident in the study 20110142.

Table 57: Exposure-adjusted Incidence Rate of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Osteoporosis Safety Analysis Set)

System Organ Class Preferred Term	All Studies (Excluding 20110142) Placebo[a] (N = 3822) n (r)	All Studies (Excluding 20110142) Romosozumab 210 mg QM[b] (N = 4318) n (r)	20110142 Alendronate 70 mg QW (N = 2014) n (r)	20110142 Romosozumab 210 mg QM (N = 2040) n (r)	All Studies (Including 20110142) Control[c] (N = 6155) n (r)	All Studies (Including 20110142) Romosozumab 210 mg QM[d] (N = 6358) n (r)	All Studies (Including 20110142) Romosozumab Total[e] (N = 6688) n (r)
Infections and infestations	48 (1.3)	76 (1.9)	48 (2.5)	47 (2.4)	103 (1.8)	123 (2.1)	133 (2.1)
Pneumonia	10 (0.3)	22 (0.5)	17 (0.9)	16 (0.8)	29 (0.5)	38 (0.6)	41 (0.6)
Urinary tract infection	7 (0.2)	5 (0.1)	8 (0.4)	8 (0.4)	15 (0.3)	13 (0.2)	13 (0.2)
Cellulitis	2 (<0.1)	5 (0.1)	3 (0.2)	1 (<0.1)	5 (<0.1)	6 (0.1)	7 (0.1)

There was a numerical imbalance in serious adverse events of infections in the pivotal placebo-controlled studies, even when adjusted for patient years. The imbalance was marginally higher in subgroup of patients >75 years and the frequency of these events was overall somewhat higher in these patients, as shown in table 5. Pneumonia was the most frequent type of infection; however, when adjusted for patient years, no imbalance was evident.

There is no clear biologic plausibility for increased risk of especially pneumonia, however, some effects on haematology parameters and white blood count were seen both in preclinical and clinical studies.

Nasopharyngitis and sinusitis are currently the only type of infection that is proposed to be included in the Romosozumab SmPC. The CHMP considers that the data on serious infection should be taken into account

when discussing the benefit/risk of romosozumab especially in patients >75 years. Serious infection is included in the RMP as an important potential risk and also included as an endpoint for any further PASS studies of Romosozumab.

Cardiovascular disorders

Because sclerostin expression has been identified in the aorta and in vascular calcified foci, there is a theoretical concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification. There is no reported increase in early onset vascular mineralization or cardiovascular disease in patients with sclerosteosis and van Buchem disease. Please also see data and discussion in the non-clinical section of this report.

The primary endpoints in Studies 20070337 and 20110142 were not designed as cardiac outcome studies during which serious cardiac events are prospectively collected as the primary endpoints of the study. An external, independent adjudication of cardiovascular serious adverse events by Duke Clinical Research Institute (DCRI) in the 3 pivotal phase 3 studies (Studies 20070337, 20110142, and 20110174) in the romosozumab clinical program was pre-specified in the respective protocols and Clinical Events Classification (CEC) Charter. Per protocol, Studies 20070337, 20110142, and 20110174 specified independent adjudication of serious adverse events meeting a predefined list of terms reflecting potential cardiovascular events. Potential cardiovascular serious adverse events were captured from fatal adverse event reports, investigator-identified cardiovascular serious adverse events, and from a predefined list of preferred terms of possible cardiovascular serious adverse events. Only serious adverse events meeting the predefined list of terms were systematically sent for adjudication.

In order to confirm the results, a second review of all adverse event data in Studies 20070337, 20110142, and 20110174 by the TIMI (Thrombolysis in Myocardial Infarction) Study Group to identify potential cardiovascular adverse events. This approach included re-adjudication by TIMI of all deaths and other serious adverse events previously adjudicated by DCRI, blinded to treatment and DCRI adjudication result.

Table 58: Treatment-emergent <u>Serious</u> Adverse Events by System Organ Class and Preferred Term (12-month Placebo-Controlled Osteoporosis Safety Analysis Set)

	20070337		20060326		20101291		20110174		Total	
System Organ Class Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romosozumab 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romosozumab 210 mg QM SC (N = 3858) n (%)
Cardiac disorders	39 (1.1)	48 (1.3)	1 (2.0)	0 (0.0)	2 (3.2)	1 (1.6)	1 (1.2)	6 (3.7)	43 (1.1)	55 (1.4)

Table 59: Exposure-adjusted Incidence Rate of Treatment-emergent <u>Serious</u> Adverse Events by System Organ Class and Preferred Term (Osteoporosis Safety Analysis Set)

	All Studies (Excluding 20110142)		20110142		All Studies (Including 20110142)		
System Organ Class Preferred Term	Placebo[a] (N = 3822) n (r)	Romosozumab 210 mg QM[b] (N = 4318) n (r)	Alendronate 70 mg QW (N = 2014) n (r)	Romosozumab 210 mg QM (N = 2040) n (r)	Control[c] (N = 6155) n (r)	Romosozumab 210 mg QM[d] (N = 6358) n (r)	Romosozumab Total[e] (N = 6688) n (r)
Cardiac disorders	43 (1.2)	62 (1.5)	34 (1.8)	40 (2.1)	80 (1.4)	102 (1.7)	109 (1.7)

Table 60: Exposure-adjusted Incidence Rate of Treatment-Emergent Adverse Events of Ischaemic Heart Disease (Osteoporosis Safety Analysis Set), irrespective of adjudication status

	All Studies (Excluding 20110142)		20110142		All Studies (Including 20110142)		
Preferred Term	Placebo[a] (N = 3822) n (r)	Romosozumab 210 mg QM[b] (N = 4318) n (r)	Alendronate 70 mg QW (N = 2014) n (r)	Romosozumab 210 mg QM (N = 2040) n (r)	Control[c] (N = 6155) n (r)	Romosozumab 210 mg QM[d] (N = 6358) n (r)	Romosozumab Total[e] (N = 6688) n (r)
Number of subjects reporting treatment-emergent adverse events of ischemic heart disease	44 (1.2)	47 (1.2)	18 (0.9)	34 (1.8)	63 (1.1)	81 (1.4)	83 (1.3)

Table 61: Exposure-adjusted Incidence Rate of Treatment-Emergent Adverse Events of Central Nervous System Haemorrhages and Cerebrovascular Conditions (Osteoporosis Safety Analysis Set), irrespective of adjudication status

	All Studies (Excluding 20110142)		20110142		All Studies (Including 20110142)		
Preferred Term	Placebo[a] (N = 3822) n (r)	Romosozumab 210 mg QM[b] (N = 4318) n (r)	Alendronate 70 mg QW (N = 2014) n (r)	Romosozumab 210 mg QM (N = 2040) n (r)	Control[c] (N = 6155) n (r)	Romosozumab 210 mg QM[d] (N = 6358) n (r)	Romosozumab Total[e] (N = 6688) n (r)
Number of subjects reporting treatment-emergent adverse events of central nervous system haemorrhages and cerebrovascular conditions	38 (1.1)	46 (1.1)	32 (1.7)	44 (2.3)	73 (1.2)	90 (1.5)	95 (1.5)

In study 20110142, there were more events for Romosozumab compared to alendronate in both Ischaemic Heart Disease and CNS Haemorrhages and Cerebrovascular Conditions, irrespective of adjudication status.

Of note, the numbers of reported AEs irrespective of adjudication status in tables above are higher (approximately double) than the numbers for adjudicated cases of same disorder (data presented in tables below). For example, 34 ischemic heart disease events were reported but only 16 cardiac ischemic events were adjudicated for Romosozumab in study 20110142.

Presentation of adjudicated positive CV events:

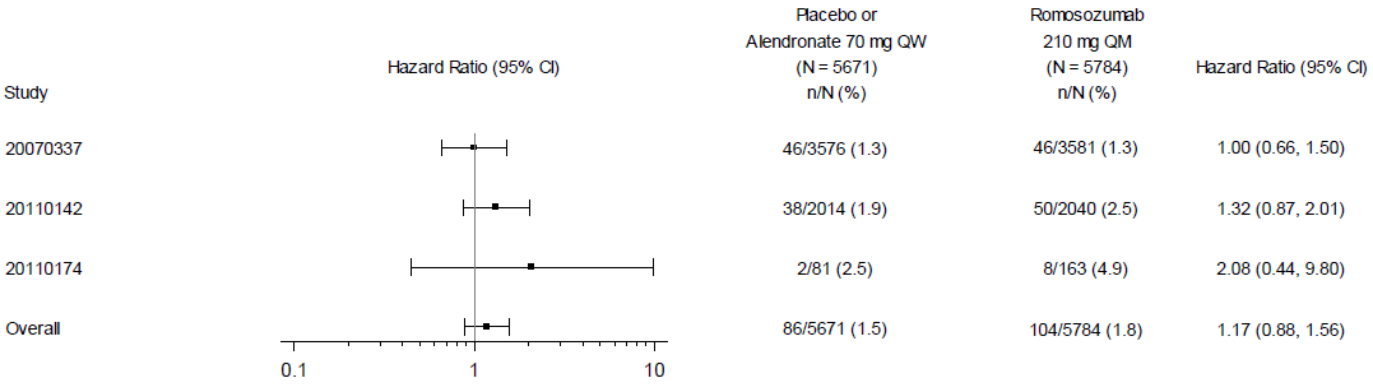
Serious Cardiovascular Adverse Events

12-month Double-blind Period: The incidence of positively-adjudicated cardiovascular serious adverse events through month 12 across the 3 pivotal studies was 1.8% for romosozumab vs 1.5% for control (placebo or alendronate)

Table 62: Exposure-adjusted Incidence Rate of Adjudicated Positive Serious Cardiovascular Adverse Events by Category (Osteoporosis Safety Analysis Set)

	20110174		20070337		20110142	
Category	Placebo (N = 81) n (r)	Romosozumab 210 mg SC QM (N = 163) n (r)	Placebo (N = 3576) n (r)	Romosozumab 210 mg SC QM (N = 3581) n (r)	Alendronate 70 mg QW (N = 2014) n (r)	Romosozumab 210 mg SC QM (N = 2040) n (r)
Any adjudicated positive cardiovascular serious adverse event	2 (2.5)	8 (5.2)	46 (1.4)	46 (1.4)	38 (2.0)	50 (2.6)
Death	1 (1.2)	2 (1.3)	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.9)
Cardiac ischemic event	0 (0.0)	3 (1.9)	16 (0.5)	16 (0.5)	6 (0.3)	16 (0.8)
Cerebrovascular event	1 (1.3)	3 (1.9)	11 (0.3)	10 (0.3)	7 (0.4)	16 (0.8)

Figure 19: Time to First Occurrence of Positively-adjudicated Serious Cardiovascular Event ***Through Month 12*** **(Safety Analysis Set) (Meta-analyses of Studies 20070337, 20110142, and 20110174)**



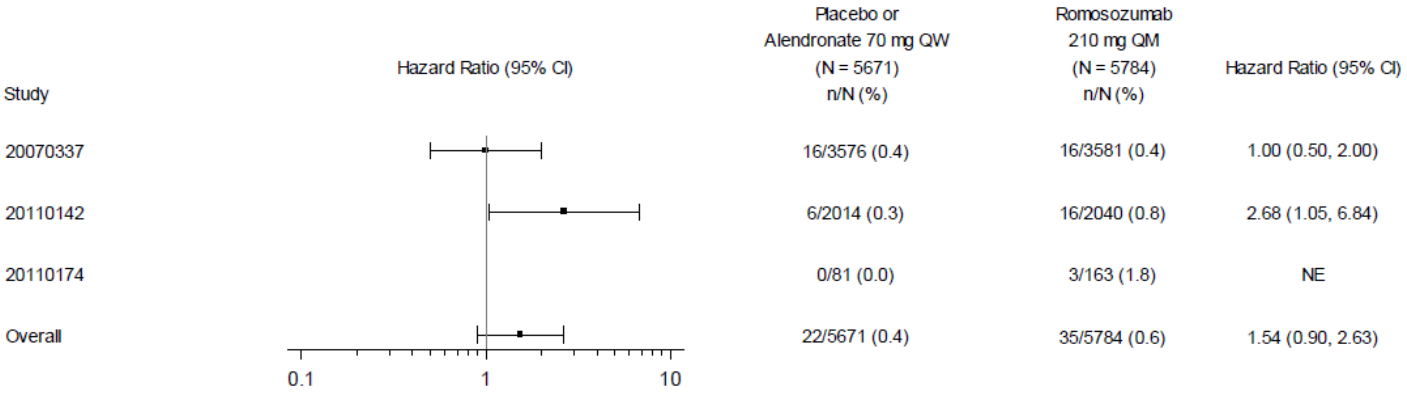
N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period
NE = Not estimable
Hazard ratio and 95% CI are based on Cox proportional hazards model; overall estimates are based on Cox proportional hazards model stratified by study comparing romosozumab versus 'control' (either placebo or alendronate).
Study 20070337 used 1:1 randomization allocation ratio between romosozumab and placebo.
Study 20110142 used 1:1 randomization allocation ratio between romosozumab and alendronate.
Study 20110174 used 2:1 randomization allocation ratio between romosozumab and placebo.

Through Follow-up Period

The incidence of positively-adjudicated cardiovascular serious adverse events through the follow-up period was 4.7% for the romosozumab/follow-on therapy (denosumab or alendronate) group vs 4.4% for the control (placebo or alendronate)/follow-on therapy (denosumab or alendronate) group.

Serious Cardiac Ischaemic Events

Figure 20: Time to First Occurrence of Positively-adjudicated Serious Cardiac Ischaemic Event Through Month 12 (Safety Analysis Set) (Studies 20070337, 20110142, and 20110174)

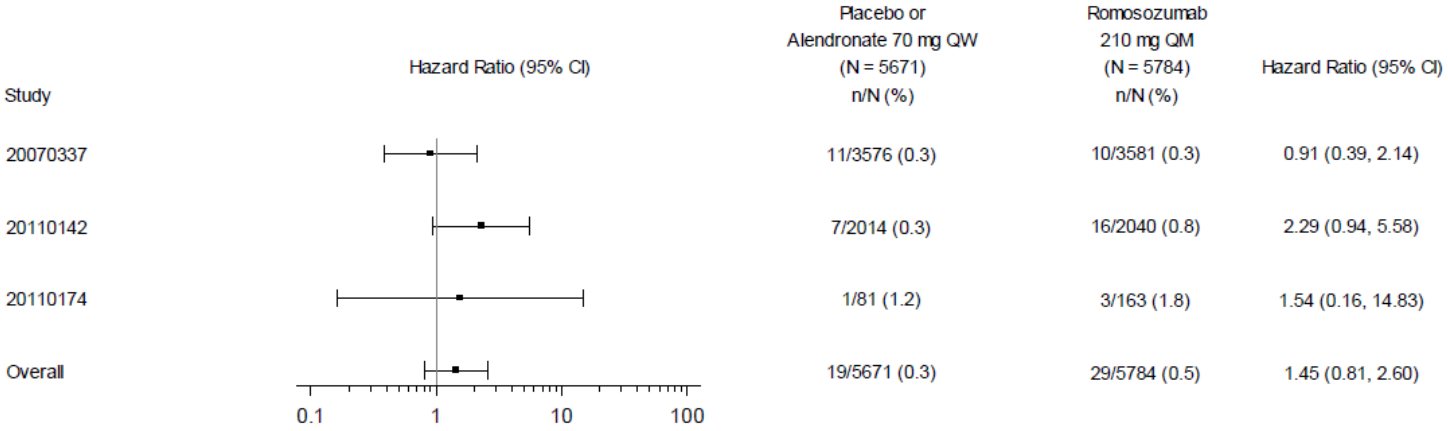


Through Follow-up Period

The incidence of positively-adjudicated serious cardiac ischaemic events through the follow-up period was 1.2% for the romosozumab/follow-on therapy (denosumab or alendronate) group vs 1.0% for the control (placebo or alendronate)/follow-on therapy (denosumab or alendronate) group; HR: 1.18 (95% CI: 0.83, 1.67).

Serious Cerebrovascular Events

Figure 21: Time to First Occurrence of Positively-adjudicated Serious Cerebrovascular Event Through Month 12 (Safety Analysis Set) (Studies 20070337, 20110142, and 20110174)



Through Follow-up Period

The incidence of positively-adjudicated serious cerebrovascular events through the follow-up period was 1.6% for the romosozumab/follow-on therapy (denosumab or alendronate) group vs 1.1% for the control (placebo or alendronate)/follow-on therapy (denosumab or alendronate) group; HR: 1.41 (95% CI: 1.02, 1.94)

Major Adverse Cardiovascular Events (MACE)

The results for the time to the first occurrence of MACE-2 (defined as adverse event leading to all-cause death, and positively-adjudicated serious myocardial infarction or serious stroke) in the double-blind period and through the follow-up period for Studies 20070337, 20110142, and 20110174 were similar to those for MACE-1 (defined as positively-adjudicated Cardiovascular Event Leading to Death, Serious Myocardial Infarction or Stroke).

12-month Double-blind Period

Figure 22: Time to First Occurrence of Adverse Event Leading to Death, Positively Adjudicated Serious MI or Stroke (MACE-2)Through Month 12 (Safety Analysis set) (20070337, 20110142 and 20110174)

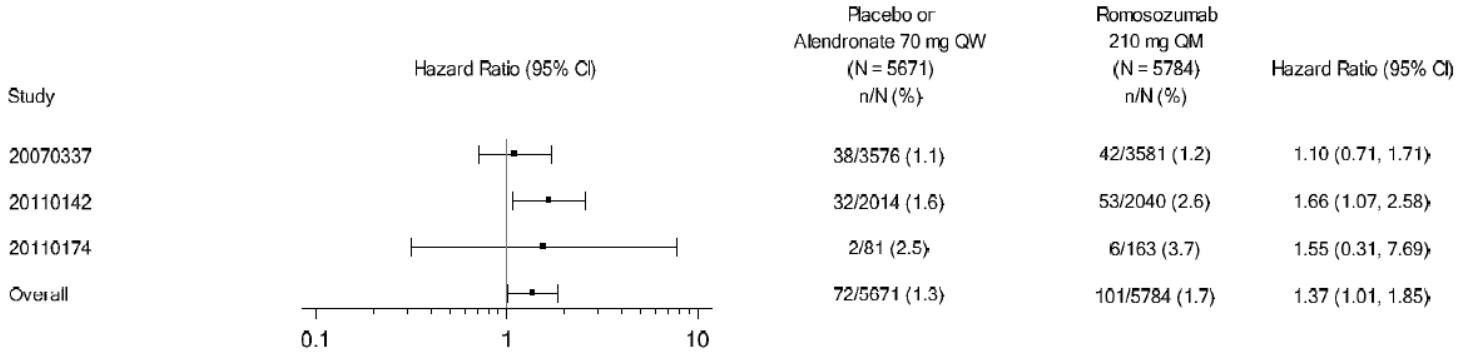
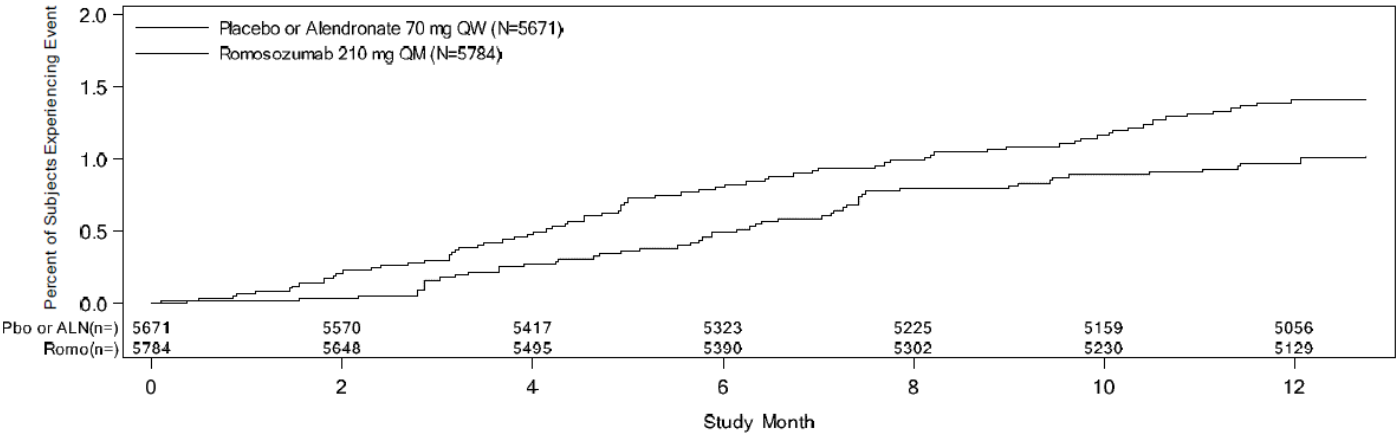


Figure 23: Time to First Occurrence of Positively Adjudicated CV Event Leading to Death, Serious MI or Stroke (MACE-1) Through Month 12 (Safety Analysis set) (20070337, 20110142 and 20110174)



N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period

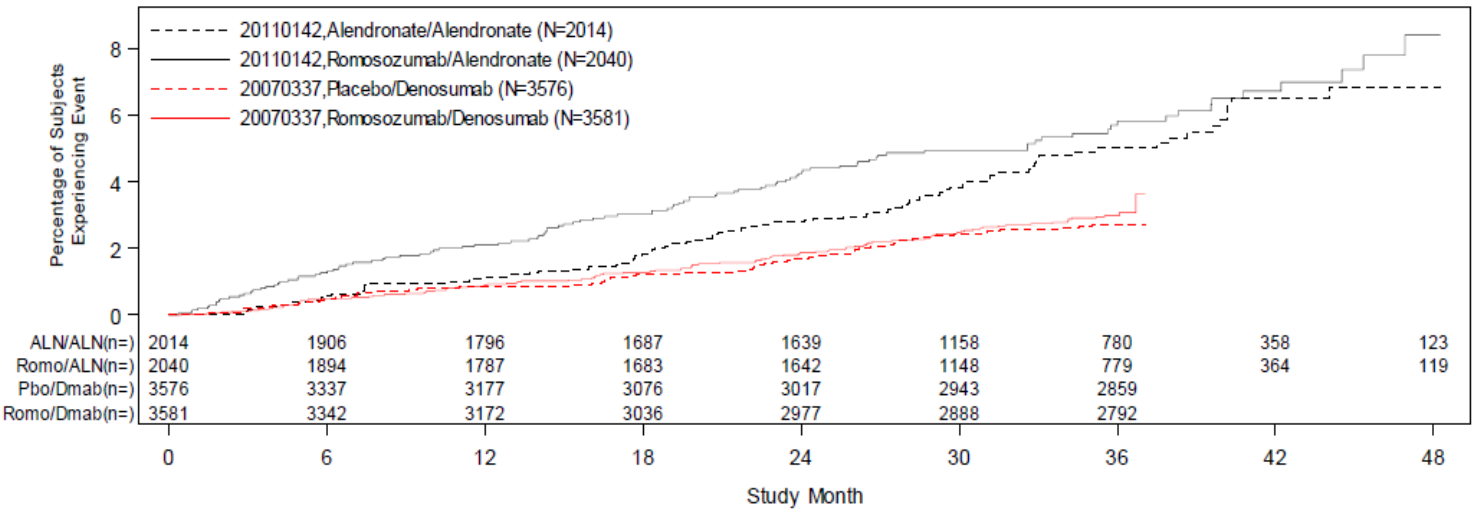
n = Number of subjects at risk for event at time point of interest

Study 20070337 used 1:1 randomization allocation ratio between romosozumab and placebo. Study 20110142 used 1:1 randomization allocation ratio between romosozumab and alendronate. Study 20110174 used 2:1 randomization allocation ratio between romosozumab and placebo.

Through Follow-up Period

Regarding positively adjudicated MACE events, the imbalance noted in study 20110142 double blinded treatment period, persisted at least through month 24.

Figure 24: Time to First Occurrence of Positively-adjudicated Cardiovascular Serious Adverse Event Leading to Death, Serious Myocardial Infarction or Stroke Through Follow-up Period (Safety Analysis Set) (Studies 20070337 and 20110142)



N = Number of subjects in the safety analysis set. n = Number of subjects at risk for event at time point of interest

Study 20070337 used 1:1 randomization allocation ratio between romosozumab and placebo. Subjects received open-label denosumab after the 12-month double blinded period. Study 20110142 used 1:1 randomization allocation ratio between romosozumab and alendronate. Subjects received open-label alendronate after the 12-month double blinded period.

The timepoint for Study Month 36 is set at Study Day 1082 (Study Day 1096 - 14 days).

Risk of cardiovascular events in a proposed new target population

In response to the concerns of the CHMP, the Applicant has evaluated the cardiovascular risk profile of romosozumab in a new target population with severe osteoporosis and high risk for fracture and excluding patients with no history of myocardial infarction [MI] or stroke.

In data from the Swedish National Health Register presented by the Applicant, exclusion of patients with a history of MI/stroke did bring the baseline risk of MI or stroke in an osteoporosis post-fracture population to a level similar to the general osteoporosis population.

Baseline Characteristics Across the 3 Phase 3 Studies

Table 63: Summary of Baseline Cardiovascular Risk Factors (Safety Analysis Set) (Studies 20070337, 20110142, and 20110174)

	20110174		20070337		20110142	
	Placebo (N = 81)	Romo 210 mg (N = 163)	Placebo (N = 3576)	Romo 210 mg (N = 3581)	Alendronate 70 mg QW (N = 2014)	Romo 210 mg (N = 2040)
Age (years)						
Mean (SD)	71.4 (6.9)	72.4 (7.4)	70.8 (6.9)	70.9 (7.0)	74.2 (7.5)	74.4 (7.5)
Median	72.0	73.0	70.0	70.0	75.0	75.0
Q1, Q3	67.0, 76.0	67.0, 79.0	65.0, 76.0	65.0, 76.0	69.0, 80.0	69.0, 80.0
Min, Max	55, 85	56, 89	55, 89	55, 90	55, 90	55, 90
Age group - n (%)						
< 75 years	53 (65.4)	93 (57.1)	2461 (68.8)	2464 (68.8)	965 (47.9)	970 (47.5)
≥75 years	28 (34.6)	70 (42.9)	1115 (31.2)	1117 (31.2)	1049 (52.1)	1070 (52.5)
Smoking history - n (%)						
Current/Former	51 (63.0)	81 (49.7)	1037 (29.0)	982 (27.4)	591 (29.3)	533 (26.1)
Never	30 (37.0)	82 (50.3)	2539 (71.0)	2599 (72.6)	1423 (70.7)	1506 (73.8)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Any history of cardiovascular risk factor - n (%)	58 (71.6)	126 (77.3)	2717 (76.0)	2667 (74.5)	1607 (79.8)	1625 (79.7)
History of hypercholesterolemia	32 (39.5)	63 (38.7)	1408 (39.4)	1379 (38.5)	674 (33.5)	708 (34.7)
History of hypertension	44 (54.3)	83 (50.9)	1919 (53.7)	1890 (52.8)	1227 (60.9)	1248 (61.2)
History of diabetes	32 (39.5)	55 (33.7)	1252 (35.0)	1227 (34.3)	658 (32.7)	664 (32.5)
History of CV disease	54 (66.7)	108 (66.3)	2331 (65.2)	2327 (65.0)	1456 (72.3)	1497 (73.4)
History of central nervous system vascular disorder	10 (12.3)	15 (9.2)	190 (5.3)	173 (4.8)	183 (9.1)	147 (7.2)
Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)						
< 15 mL/min/1.73 m^2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
15 - < 30 mL/min/1.73 m^2	0 (0.0)	0 (0.0)	8 (0.2)	10 (0.3)	7 (0.3)	4 (0.2)
30 - < 60 mL/min/1.73 m^2	13 (16.0)	21 (12.9)	625 (17.5)	734 (20.5)	476 (23.6)	508 (24.9)
60 - < 90 mL/min/1.73 m^2	55 (67.9)	111 (68.1)	2526 (70.6)	2406 (67.2)	1189 (59.0)	1257 (61.6)
≥ 90 mL/min/1.73 m^2	13 (16.0)	31 (19.0)	416 (11.6)	431 (12.0)	342 (17.0)	270 (13.2)
Missing	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)

CV = cardiovascular; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; HLGT = High-level Group Terms; MedDRA = Medical Dictionary for Regulatory Activities; QW = once every week; Romo = romosozumab; SD = standard deviation; SOC = system organ class.
N=Number of subjects who receive at least 1 dose of investigational product.
History of cardiovascular risk factors were assessed based on the Medical History eCRF relating to history of diabetes, hypertension, hypercholesterolemia, cardiac disorder SOC, vascular disorder SOC and central nervous system vascular disorders HLGT in MedDRA version 19.1. Subjects can have more than 1 cardiovascular risk factor. Therefore, subject incidences may not sum to the total.
For Studies 20070337 and 20110142, baseline eGFR was reported by the central laboratory, and for Study 20110174, Baseline eGFR (mL/min/1.73 m^2) = 175 * serum creatinine (mg/mL) $^{-1.154}$ * age $^{-0.203}$ *

An imbalance in positively-adjudicated cardiovascular serious adverse events was observed between treatment groups in the pivotal, active-comparator-controlled study in postmenopausal women with osteoporosis (Study 20110142). This imbalance was observed specifically for serious cardiac ischemic and

cerebrovascular events, with a higher incidence in the romosozumab group compared with the alendronate group. These findings had not been observed in the placebo-controlled study in postmenopausal women with osteoporosis (Study 20070337).

These divergent findings in 2 large randomized, controlled studies (balanced placebo-controlled and numerically-imbalanced active-controlled) lead to assessment of the overall clinical program, preclinical data, epidemiology, and biological plausibility.

Between the studies, the most pronounced difference was in age: subjects in Study 20110142 were on average 4 years older than subjects in Study 20070337 and 2 years older than subjects in Study 20110174. To determine whether age helped clarify the discrepancy seen between the studies in the risk of positively-adjudicated cardiovascular serious adverse events, the Applicant evaluated the safety risk using age-matched cohorts for the 2 pivotal phase 3 studies; however, the difference in age alone did not appear to explain the observed discrepancy between the 2 studies. Other differences between the studies included a somewhat higher rate of history of hypertension and, influenced by that, history of cardiovascular disease in Study 20110142 compared with the other 2 studies.

Presence of possible confounding factors in the male osteoporosis study was assessessed in detail. In the romosozumab group, more subjects had a CV-related past medical history (77.3% vs placebo 71.6%), while the Baseline use of CV-related concomitant medications and use of prior CV-related medications were lower in the romosozumab group (57.1% vs placebo 61.7%, and 57.7% vs placebo 65.4%, respectively). The study 20110174 was limited in size, only 244 men were randomized. A small numerical difference between treatment groups was noted in baseline "any history of cardiovascular risk factor" (72.2% and 76.1% in the placebo and romosozumab groups, respectively). However, smoking was not included in these numbers and was more common in the placebo group 63.0% vs 49.7%. Also renal impairment GFR <60 was numerically more common at baseline in placebo group as well as diabetes and hypertension. As the Applicants points out, the CV related medications were also higher in the placebo group. In light of these numbers, it seems actually that more patients in placebo group had multiple CV risk factors than in the romosozumab group.

In summary, it is considered very unlikely that any imbalance in important CV risk factors at baseline would be a significant confounder in study 20110174, explaining the imbalance in the results.

Table 64: Cardiovascular-related Baseline Medications (Safety Analysis Set) (Studies 20070337, 20110142, and 20110174)

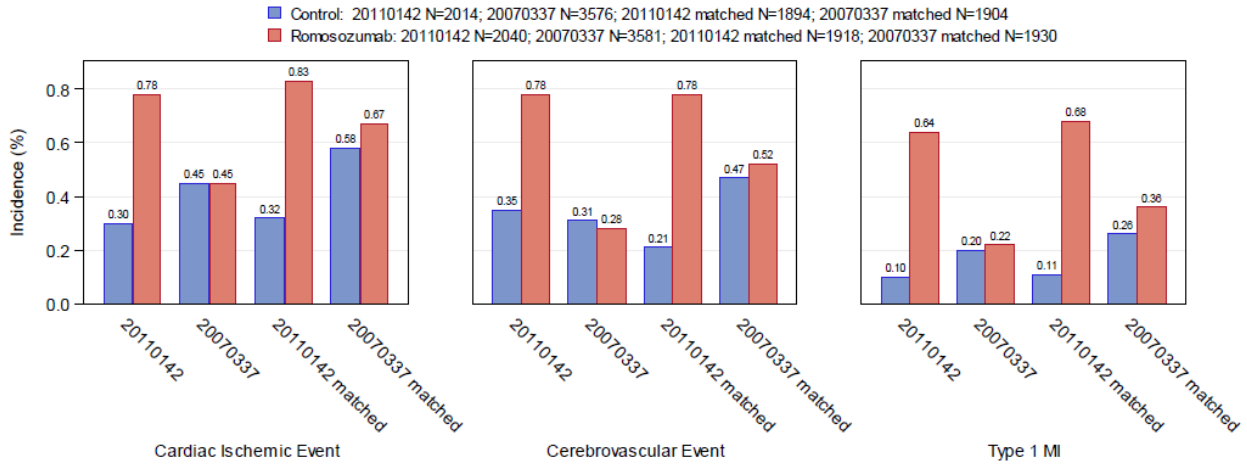
	20110174		20070337		20110142	
	Placebo (N = 81) n (%)	Romosozumab 210 mg SC QM (N = 163) n (%)	Placebo (N = 3576) n (%)	Romosozumab 210 mg SC QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg SC QM (N = 2040) n (%)
Subjects with cardiovascular-related baseline medications	53 (65.4)	94 (57.7)	2065 (57.7)	2018 (56.4)	1238 (61.5)	1253 (61.4)
Aspirin	24 (29.6)	45 (27.6)	713 (19.9)	751 (21.0)	436 (21.6)	449 (22.0)
Anti-platelet therapy	28 (34.6)	46 (28.2)	755 (21.1)	801 (22.4)	472 (23.4)	483 (23.7)
Both aspirin and anti-platelet therapy	24 (29.6)	45 (27.6)	713 (19.9)	751 (21.0)	436 (21.6)	449 (22.0)
Beta-Blockers Beta-Blocking agents	21 (25.9)	39 (23.9)	729 (20.4)	716 (20.0)	478 (23.7)	518 (25.4)
Anticoagulants	31 (38.3)	47 (28.8)	815 (22.8)	837 (23.4)	558 (27.7)	578 (28.3)
Angiotensin II receptor antagonists	15 (18.5)	23 (14.1)	600 (16.8)	578 (16.1)	374 (18.6)	347 (17.0)
Statins	31 (38.3)	45 (27.6)	943 (26.4)	913 (25.5)	475 (23.6)	497 (24.4)
ACE Inhibitors	20 (24.7)	29 (17.8)	702 (19.6)	730 (20.4)	490 (24.3)	531 (26.0)

ACE = angiotensin converting enzyme; SC = subcutaneous; QM = once every month; QW = once every week.
N=Number of subjects who received at least 1 dose of investigational product.
Included baseline medications started on or before Study Day 1.
Medications are coded using WHO Drug Dictionary 2016Q2 for Study 20070337 WHO Drug Dictionary 2016Q4 for Study 20110142, and WHO Drug Dictionary 2015Q4 for Study 20110174.

Exploration of the Potential Impact of Age and Other Cardiovascular Risk Factors in Study 20110142 vs Study 20070337

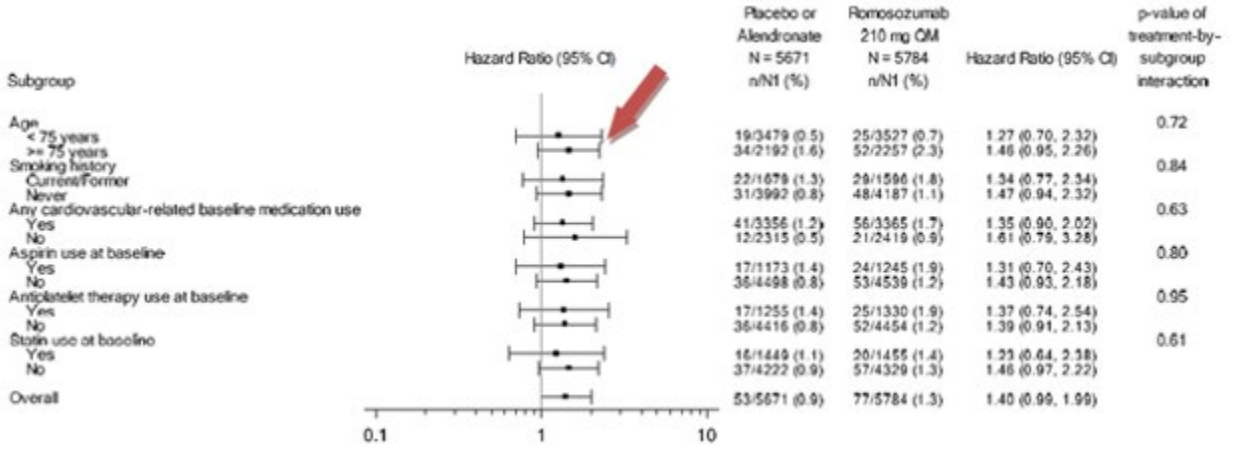
Because the main difference in known cardiovascular risk differences between the populations in Studies 20070337 and 20110142 was an older mean age of 4 years in Study 20110142, Amgen created 20070337 and 20110142 cohorts that matched baseline age distribution. A total of 3848 of the 4093 subjects enrolled in Study 20110142 were age-matched to subjects enrolled in Study 20070337). Age-matched cohorts still yielded discordant cardiovascular serious adverse event results between the 2 studies, as shown in Figure below. Similar results were observed when the 2 populations were matched for age and modified-RUTH score (used to identify osteoporotic women with CV risk in Raloxifene use for the heart-study (Keech et al, 2005).

Figure 25: Age-matched Subject Incidence of Positively-adjudicated Cardiovascular Serious Adverse Events by Cardiac Category and Study in the 12-Month Double-blind Period (Safety Analysis Set) (Studies 20070337 and 20110142)



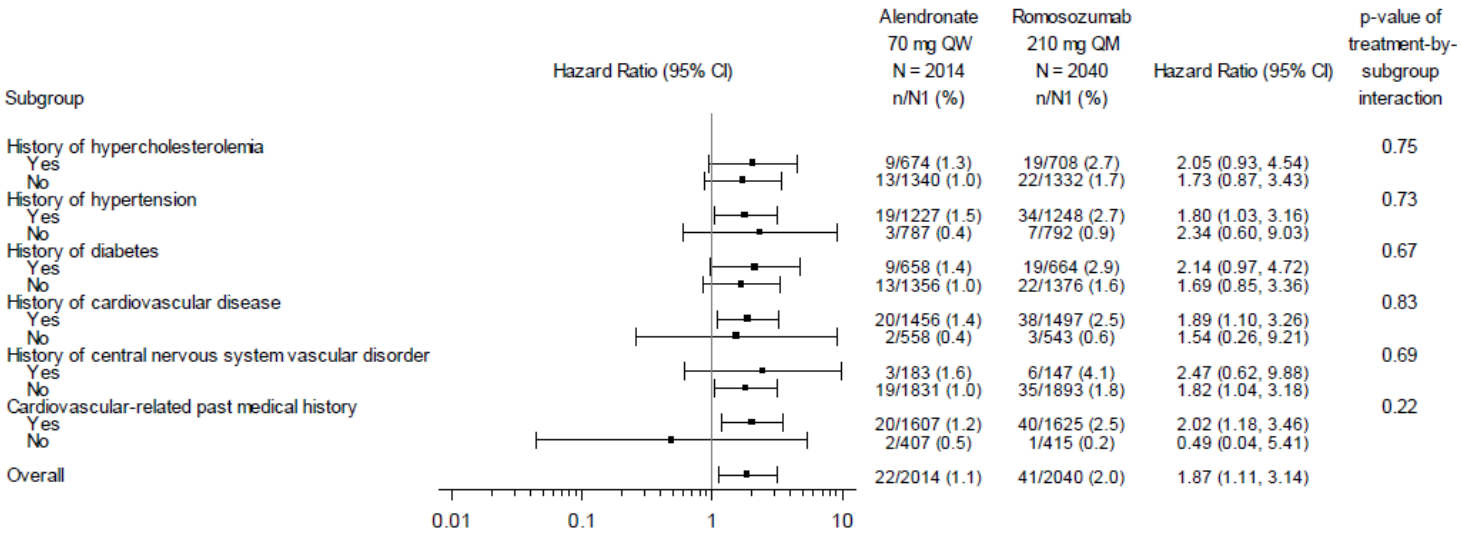
N = Number of subjects in the safety analysis set
Control arm is placebo for 20070337 study and Alendronate 70 mg QW for 20110142 study
Subjects from Studies 20070337 and 20110142 w ere matched by age

Figure 26: Subgroup Analyses of Baseline Characteristics: Time to First Occurrence of Positively Adjudicated CV Events leading to Death, Serious MI or Stroke through month 12 (Safety Analysis Set) (Studies 20070337, 20110142, and 20110174)



The age-matched cohorts still yielded discordant cardiovascular serious adverse event results between the 2 studies. Similar results were observed when the 2 populations were matched for age and modified-RUTH score. However, interestingly matched (=overall higher) age and RUTH score seem to drive a difference between romosozumab and placebo in study 20070337 for cardiac ischemic events and Type 1 MI. Subgroups divided by age at least seem to show a certain trend that romosozumab could be more harmful for subjects as old or older than 75 years in terms of onset of serious CV events leading to death, serious MI, and serious stroke.

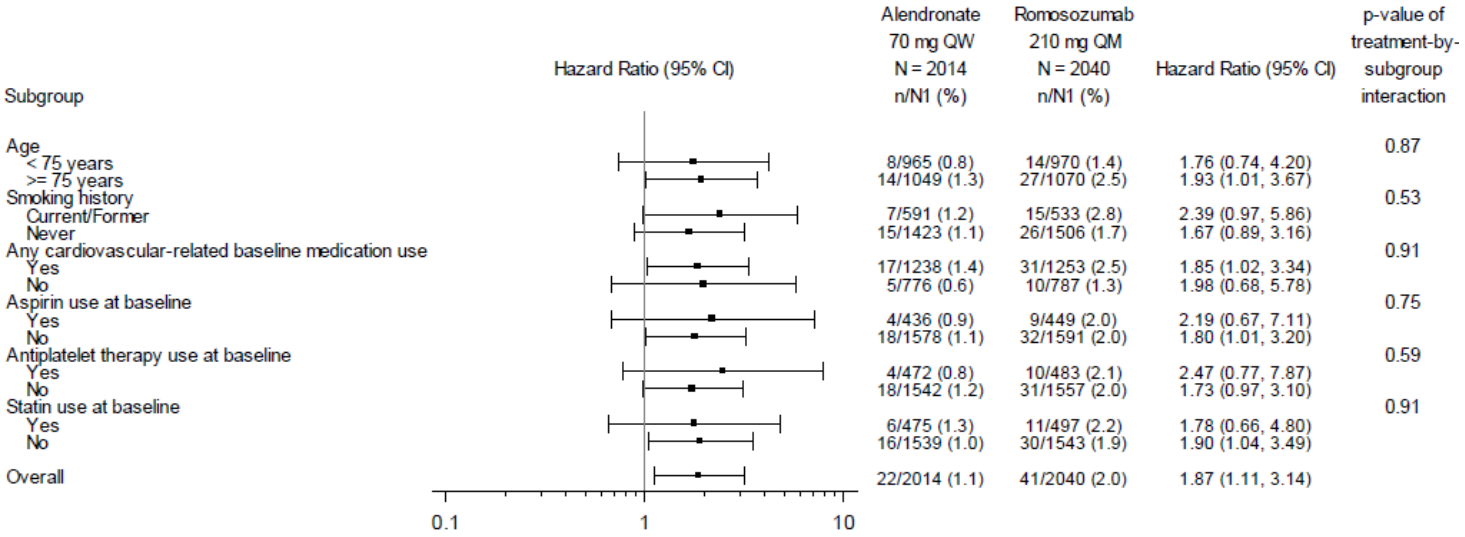
Figure 27: Medical History Subgroup Analyses: Time to First Occurrence of Positively-adjudicated Cardiovascular Event Leading to Death, Serious Myocardial Infarction or Stroke (MACE-1) Through Month 12 (Safety Analysis Set) (Study 20110142 Primary Adhoc Analysis)



N = Number of subjects who received ≥ 1 dose of active investigational product; N1 = Number of subjects in the subgroup
Hazard ratio and 95% CI based on the Cox proportional hazard model.

An increased risk in major adverse cardiovascular events in study 20110142 was noted in all subgroups regardless of previous CV related medical history. However, the absolute incidences of these events were lower in patients without history of CV risk factors and there was also a tendency to somewhat lower increase in the risk measured by hazard ratios.

Figure 28: Medication History Subgroup Analyses: Time to First Occurrence of Positively-adjudicated Cardiovascular Event Leading to Death, Serious Myocardial Infarction or Stroke (MACE-1) Through Month 12 (Safety Analysis Set) (Study 20110142 Primary Adhoc Analysis)



N = Number of subjects who received ≥ 1 dose of active investigational product; N1 = Number of subjects in the subgroup
Hazard ratio and 95% CI based on the Cox proportional hazard model.

Studies 20110142 and Study 20070337 had different inclusion/exclusion criteria regarding osteoporosis severity (T-scores and fractures). Only 14% of all included patients in these two pivotal PMO studies had overlapping inclusion criteria. Consequently, these two pivotal studies represent largely different osteoporosis populations. The patients in study 20110142 were older and had a more severe osteoporosis disease. A discrepancy in some safety results, such as treatment emergent MI and stoke events, between studies is thus not totally unexpected.

Literature Review and Epidemiology Assessment

One explanation for the difference between the 2 studies could be that alendronate exerts a protective effect against cardiovascular events in humans. The applicant evaluated the literature in animals and humans to further explore this hypothesis in detail in the Application (not included in this AR). Based on the assessment of clinical and preclinical studies in animals and humans, early cardiovascular events (ie, within 3 to 6 months of dosing) were observed with romosozumab, while the literature would suggest any possible cardioprotective effects of alendronate would be seen after longer term observations.

Thus, the CHMP agrees with the Applicant that based on the available evidence thus far, that a consistent cardioprotective effect of alendronate has not been demonstrated.

Genetic Conditions with Absent or Reduced Sclerostin

Patients with sclerosteosis or van Buchem disease, or those heterozygous for the SOST mutations (resulting in total loss or reduction in sclerostin), can serve as a model of what may be expected in subjects treated

with a sclerostin inhibitor such as romosozumab. A literature review did not identify any association of increased risk or notable trend in cardiovascular disease in patients who suffer from sclerosteosis or van Buchem disease and have significantly reduced or absent sclerostin activity. In addition, genome-wide association studies have failed to identify genetic associations between the SOST gene and cardiovascular risk.

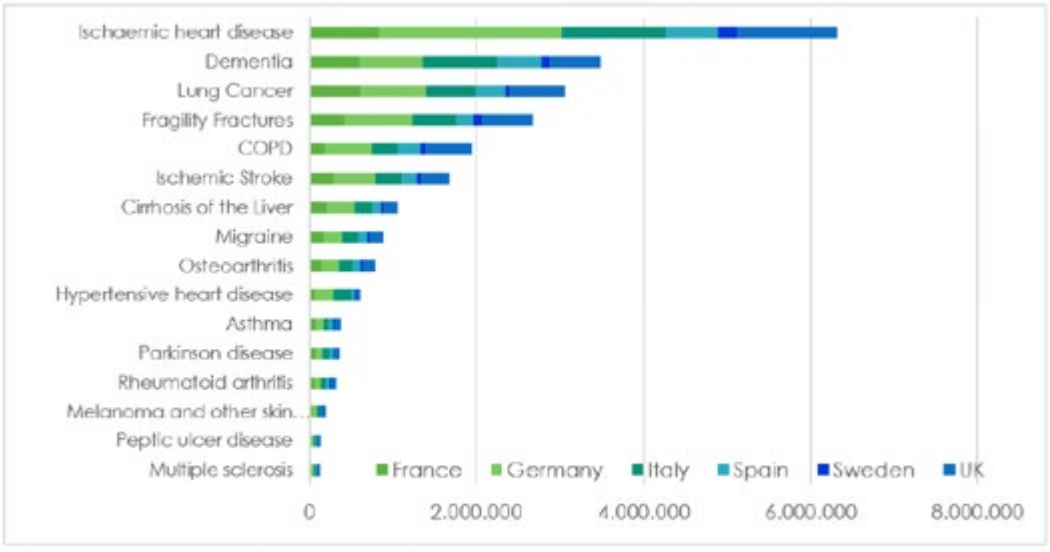
Summary of Epidemiology of Serious Cardiovascular Events

Overall, the incidence rates of positively-adjudicated cardiovascular serious adverse events reported among subjects in the 3 phase 3 studies (Studies 20070337, 20110142, and 20110174), including subjects receiving romosozumab, appear to be similar to or lower than those reported from population-based studies of the general population and of patients with osteoporosis. Specifically, incidence rates of cerebrovascular events were lower, and incidence rates of cardiac ischaemic events were comparable, among subjects who received romosozumab compared with the general or osteoporotic female populations. For subjects who received alendronate, incidence rates of both cerebrovascular and cardiac ischaemic events were lower than the incidence rates in the general or osteoporotic female populations. Reported incidence rates from population-based studies and clinical study data suggest that there is not an excess in the incidence of cardiovascular serious adverse events observed among subjects who received romosozumab in the clinical studies compared with what might be expected, based on review of epidemiological evidence.

Direct comparisons of reported incidence rates from population-based studies and clinical study data are challenging to make because of numerous confounding factors, including differences in patient characteristics such as: age and other clinical risk factors; regional differences; time frame of assessments; cardiovascular outcome definitions and ascertainment methodologies; statistical methodology; and being part of a clinical study population.

Burden of disease and unmet need

Figure 29: Country distribution to total DALYs by disease in EU6 in 17 selected diseases



COPD=chronic obstructive pulmonary disease; DALY=Disability-Adjusted Life Year

Fractures may significantly impair the quality of life. However, the DALY estimates presented by the Applicant demonstrate that ischaemic heart disease (the important safety concern with romosozumab) outweighs clearly other disease groups.

CV risk factors analysis

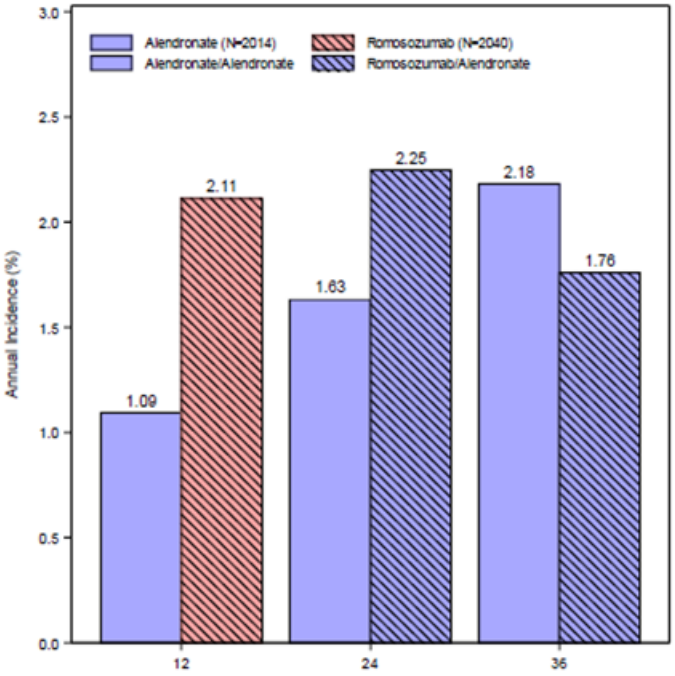
Various post hoc subgroup analyses based on CV risk factors (e.g., osteoporosis severity, diabetes, and smoking) were conducted and did not identify a subpopulation at consistently increased relative risk of CV SAEs with administration of romosozumab.

Among these subgroup analyses, the CV imbalance was analysed for the subgroup of older osteoporosis subjects. There was a slight numerical increase in the HRs for the incidence of MACE-1 in the older age group (≥75 years) between treatment arms compared to that from the younger age group (<75 years) in 20070337 and the meta-analysis, but all p-values for treatment by subgroup interactions were nonsignificant.

When further evaluating the annual incidence rates in 20110142, it was noted that the number of CV events was lowest in the first year in the ALN group, with an increase in the rate of these events in this group in subsequent years. The risk of CV events increases with age, therefore a tendency to increased rate during four years of follow-up would not be unexpected in any cohort.

In contrast, the rate of CV events for subjects treated with romosozumab was highest during the actual treatment year and the year after followed by a decline. This pattern could be expected in a randomized trial if romosozumab treatment is associated with CV events.

Figure 30: Annual incidence of positively adjudicated MACE-1 in Study 20110142



N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period
The incremental KM incidences are the annual incremental changes of KM estimates at Month 12, Month 24 and Month 36.

Finally, in a new subgroup analysis of the 3 pivotal studies, HRs for the positively-adjudicated MACE-1 was determined for subjects with or without a prior history of MI or stroke. This analysis indicated that the

relative risk of a MACE-1 was consistent regardless of prior history of stroke or MI (1.59 [0.62, 4.10] vs. 1.38 [0.95, 2.02], respectively). As expected, the absolute risk was consistently greater (but with small differences) for subjects with a prior history of stroke or MI, regardless of treatment group. Within the romosozumab group, 3.7% of subjects with a prior history of stroke or MI had a positively adjudicated MACE-1 compared with 1.2% of subjects without a prior history of stroke or MI (for control group, 2.2% of subjects with a prior history and 0.9% of subjects without a prior history).

2.6.1. Laboratory findings

Table 65: Subject Incidence of Laboratory CTCAE Grade ≥ 2 in the Placebo Control Period (12-month Placebo-Controlled Osteoporosis Safety Analysis Set)

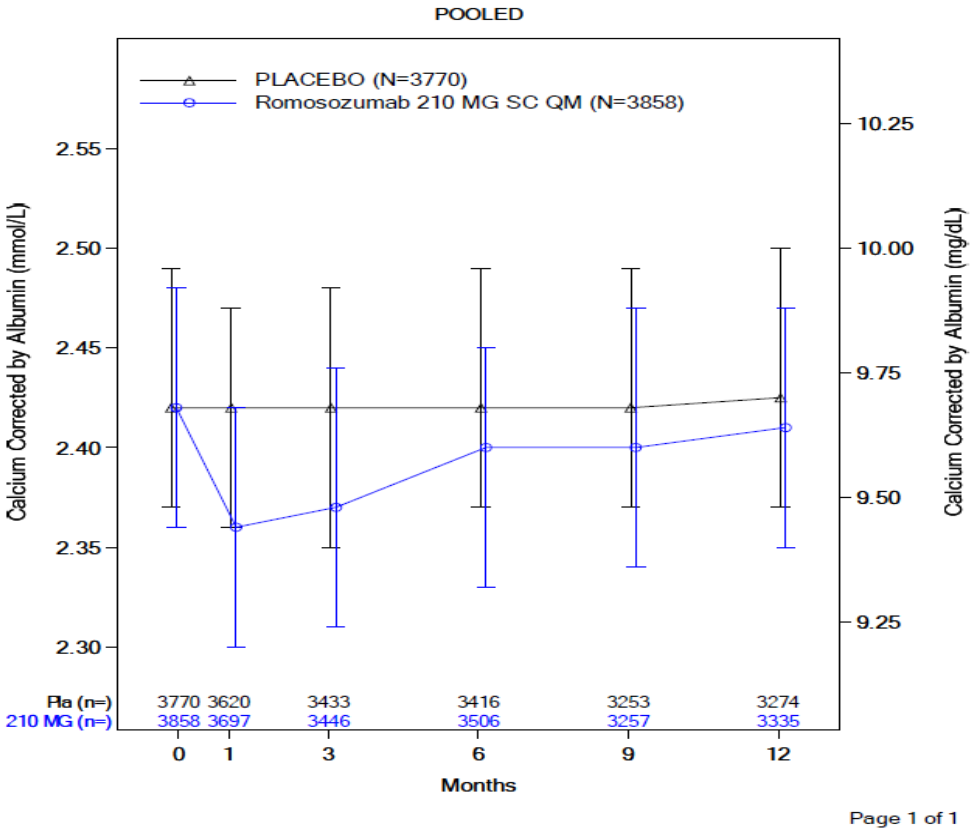
			20070337		20060326		20101291		20110174		Total	
Laboratory Parameters	Relationship to Normal	Grade	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romosozumab 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romosozumab 210 mg QM SC (N = 3858) n (%)
Bicarbonate	Below	Grade 2	44 (1.2)	57 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	3 (1.8)	46 (1.2)	60 (1.6)
Magnesium	Above	Grade 3	3 (<0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	4 (0.1)
	Below	Grade 2	9 (0.3)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.2)	5 (0.1)
		Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (<0.1)
Calcium (Corrected)	Above	Grade 2	7 (0.2)	5 (0.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.2)	5 (0.1)
	Below	Grade 2	1 (<0.1)	8 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (<0.1)	9 (0.2)
		Grade 4	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Phosphorus	Below	Grade 2	5 (0.1)	19 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	6 (3.7)	7 (0.2)	25 (0.6)
		Grade 3	4 (0.1)	5 (0.1)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	2 (2.5)	5 (3.1)	6 (0.2)	11 (0.3)
Creatinine	Above	Grade 2	13 (0.4)	13 (0.4)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (0.3)	14 (0.4)
Aspartate Amino Transferase	Above	Grade 2	36 (1.0)	15 (0.4)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	38 (1.0)	15 (0.4)
		Grade 3	5 (0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	3 (<0.1)
		Grade 4	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Alanine Amino Transferase	Above	Grade 2	41 (1.1)	23 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	41 (1.1)	23 (0.6)
		Grade 3	10 (0.3)	5 (0.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.3)	5 (0.1)
Alkaline Phosphatase	Above	Grade 2	8 (0.2)	10 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	8 (0.2)	11 (0.3)
		Grade 3	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Total Bilirubin	Above	Grade 2	8 (0.2)	15 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.7)	0 (0.0)	11 (0.3)	15 (0.4)
		Grade 3	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)

Albumin	Below	Grade 2	14 (0.4)	15 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	14 (0.4)	16 (0.4)
		Grade 3	2 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	1 (<0.1)
Glucose	Above	Grade 2	171 (4.8)	177 (4.9)	1 (2.0)	1 (2.0)	0 (0.0)	2 (3.2)	0 (0.0)	6 (3.7)	172 (4.6)	186 (4.8)
		Grade 3	71 (2.0)	55 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	71 (1.9)	58 (1.5)
		Grade 4	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
	Below	Grade 2	11 (0.3)	19 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	12 (0.3)	19 (0.5)
Hemoglobin	Below	Grade 2	46 (1.3)	37 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)	1 (1.2)	0 (0.0)	47 (1.2)	39 (1.0)
		Grade 3	4 (0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	4 (0.1)
		Grade 4	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Platelets	Below	Grade 2	3 (<0.1)	3 (<0.1)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	4 (0.1)
		Grade 3	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
White Blood Cells	Below	Grade 2	49 (1.4)	69 (1.9)	0 (0.0)	3 (5.9)	6 (9.5)	4 (6.3)	1 (1.2)	0 (0.0)	56 (1.5)	76 (2.0)
		Grade 3	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)
Total Neutrophils	Below	Grade 2	78 (2.2)	67 (1.9)	2 (4.0)	2 (3.9)	7 (11.1)	3 (4.8)	1 (1.2)	1 (0.6)	88 (2.3)	73 (1.9)
		Grade 3	8 (0.2)	9 (0.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.6)	9 (0.2)	10 (0.3)
		Grade 4	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Lymphocytes	Below	Grade 2	74 (2.1)	72 (2.0)	0 (0.0)	0 (0.0)	1 (1.6)	2 (3.2)	2 (2.5)	2 (1.2)	77 (2.0)	76 (2.0)
		Grade 3	5 (0.1)	12 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	12 (0.3)

N = Number of subjects in the analysis set
The maximum toxicity grade is based on the Common Terminology Criteria for Adverse Events, version 3.0

Serum Calcium

Figure 31: Calcium Corrected by Albumin by Visit in Standard and Conventional Units Median and Interquartiles (12-month Placebo-Controlled Osteoporosis Safety Analysis Set)



Lab data was not collected for 20110174 study at month 3 and month 9.
N = Number of subjects in the analysis set
n = Number of subjects with observed data
Normal ranges are 2.07-2.64, 2.075-2.650 in mmol/L.

In Study 20110142, mild and transitory decreases in serum albumin-corrected calcium were observed in both the romosozumab and alendronate treatment groups. Mild decreases in phosphorus in both treatment groups were also observed throughout the primary analysis period.

Other (sub) Studies

Study 20070337 included a calcium substudy comprising 1687 subjects to characterize the subject incidence of hypocalcaemia (defined as albumin-corrected serum calcium level < 7.5 mg/dL) associated with the first romosozumab 210 mg dose along with daily calcium and vitamin D supplementation. On study day 14, no hypocalcaemic values were observed for any subject in either treatment group.

In Phase 1 Study 20110227, the administration of romosozumab resulted in a greater decrease in serum calcium level in subjects with stage 4 and stage 5 CKD than in healthy subjects. (see section "renal impairment") The mean percent change from baseline for albumin-adjusted calcium reached a nadir on day 15 in healthy subjects (−1.9%).

Study 20110142 included a substudy in which other parameters (calcium, iPTH, sclerostin, and phosphate) were analysed. Serum calcium was evaluated for 151 subjects in the romosozumab/alendronate group and

140 subjects in the alendronate/alendronate group who participated in the BTM substudy. There was a decrease in corrected serum calcium levels at months 1 and 3; the median percent change from baseline was -2.8% and -2.5%, respectively, for subjects who received romosozumab and -1.7% and -1.0% for subjects who received alendronate.

Phosphorus

Because romosozumab increases bone formation, there is an increased demand for phosphorus, in addition to calcium, to support bone matrix mineralization. Decreases in phosphorus levels with romosozumab treatment were observed both in the 12-month placebo-controlled osteoporosis safety analysis set and in the male osteoporosis Study 20110174.

In Study 20110142, at month 1, the median percent change in phosphorus level was -6.4% in the romosozumab group and -3.5% in the alendronate group. Phosphorous levels remained below baseline through month 30, returning to near baseline levels by month 36 (median percent change from baseline was -2.9% in the romosozumab/alendronate group and 0.5% in the alendronate/alendronate group).

Median phosphorous values remained within the normal range. With the exception of month 1, no differences in the phosphorus levels between treatment groups were statistically significant.

Table 66: Subject Incidence of Calcium and phosphorus Laboratory Value Shifts Away From Baseline by ≥ 2 Grades (12-month Placebo-Controlled Osteoporosis Safety Analysis Set)

	20070337		20060326		20101291		20110174		Total	
Laboratory Parameters	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 81) n (%)	Romosozumab 210 mg QM SC (N = 163) n (%)	Placebo (N = 3770) n (%)	Romosozumab 210 mg QM SC (N = 3858) n (%)
Calcium (Corrected)										
Decrease	2 (<0.1)	8 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (<0.1)	9 (0.2)
Increase	2 (<0.1)	2 (<0.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	2 (<0.1)
Phosphorus										
Decrease	9 (0.3)	24 (0.7)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	2 (2.5)	8 (4.9)	11 (0.3)	33 (0.9)

Serum Intact Parathyroid Hormone and Urinary Calcium

Because romosozumab increases bone formation, there may be compensatory responses in iPTH as a result of calcium demands from bone matrix mineralization. In the Phase 1 Study 20110227, the administration of romosozumab resulted in a greater increase in iPTH in subjects with stage 4 and stage 5 CKD than in healthy subjects

Study 20070337

Study 20070337 included an iPTH and urinary calcium substudy comprising 656 subjects to characterize serum iPTH concentration and urinary calcium excretion through month 12. The median percentage change from baseline in iPTH was 29% in the romosozumab group and 4% in the placebo group at month 6 and 27% in the romosozumab group and 8% in the placebo group at month 12. Differences between romosozumab and placebo were statistically significant at both time-points (nominal p-value < 0.001 from Wilcoxon rank-sum test without multiplicity adjustment).

Corresponding median percentage change from baseline in estimated 24-hour urinary calcium excretion values were −16.8% in the romosozumab group and 3.0% in the placebo group at month 6, and −15.9% in the romosozumab group and −7.6% in the placebo group at month 12. Differences between romosozumab and placebo for urinary calcium excretion were statistically significant at 6 months (nominal p-value < 0.001

from Wilcoxon rank-sum test without multiplicity adjustment) but not at 12 months (nominal p-value = 0.10 from Wilcoxon rank-sum test without multiplicity adjustment).

Study 20110142

In the BTM and biomarker substudy of Study 20110142, iPTH was analyzed for 67 subjects in the romosozumab/alendronate group and 64 subjects in the alendronate/alendronate group. At baseline, the median iPTH value was 4.83 pmol/L (45.60 pg/mL) in the romosozumab group and 4.80 pmol/L (45.25 pg/mL) in the alendronate group. Beginning with month 1, the median iPTH values increased (7.52 pmol/L and 6.37 pmol/L, respectively). The median percent change in iPTH at month 1 was 60.1% in the romosozumab group and 34.7% in the alendronate group, which was statistically significant (nominal p-value < 0.006 using the Wilcoxon rank-sum test). The median iPTH values were statistically significantly higher in the romosozumab through month 6.

Study 20110174

The levels of iPTH increased at month 6; the median percent change from baseline was 39.4% for subjects who received romosozumab and 3.6% for subjects who received placebo. Levels of iPTH decreased from month 6 to month 12 for subjects in the romosozumab group, such that the median percent change from baseline at month 12 was 18.7% for the romosozumab group and 5.7% for the placebo group.

In patients with end-stage renal disease, previous publications have described a relationship among increased PTH levels and cardiovascular risk (Block et al, 2004; Floege et al, 2011). In the romosozumab clinical development program, PTH levels were only collected in a subset of subjects who experienced very few cardiovascular events. Given the lack of convincing evidence in non-chronic kidney disease patients to suggest that there is a relationship between PTH levels and cardiovascular events it seems not likely that an analysis of PTH levels/changes and cardiovascular events could be contributory to the understanding of the cardiovascular results in the romosozumab clinical program.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Absolute values and changes from baseline in vital signs were provided in individual study reports and were not integrated. Analysis of vital signs (mean values of systolic and diastolic blood pressures, pulse rate, body temperature, body weight, and BMI) in individual studies demonstrated no clinically important effect of romosozumab.

There is a low likelihood for delayed cardiac repolarization due to human ether-a-go-go-related gene (hERG) channel blockade with romosozumab, primarily based on its physical size of approximately 150 kD and the low potential for large protein therapeutics (especially monoclonal antibodies) to interfere with cardiac ion channels in vivo, including hERG-mediated current (Vargas et al, 2008). There were no romosozumab-related electrocardiographic changes in conscious telemetry-instrumented cynomolgus monkeys following single IV doses up to 300 mg/kg followed by 14 days of monitoring. Area under the concentration-time curve and maximum serum concentration (Cmax) exposure margins achieved were up to 32-fold and 210-fold, respectively, to clinical exposures at 210 mg QM. 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 300 mg/kg IV.

ECGs were not done in pivotal phase 3 studies. Analysis of ECG results in individual studies in which they were analysed demonstrated no clinically important effect of romosozumab.

In study 20060326, ECG was collected at baseline and during Romosozumab treatment at month 1, 3, 9 and 12. No subject had QTcF > 500 msec. Two subjects (140 mg QM and 140 mg Q3M) had QTcF between 480 and 500 msec at the month 3 visit, 2 subjects (210 mg QM and 210 mg Q3M) had QTcF between 480 and 500 msec at the month 9 visit, 1 subject (70 mg QM) had QTcF between 480 and 500 msec at the month 12 visit. Three subjects in the combined romosozumab group had Bazett's corrected QTc (QTcB) > 500 msec (1 subject in the 210 mg QM group at month 9 and 2 subjects in the 70 mg QM group at month 12) None of these subjects had adverse events of cardiac arrhythmia, hypocalcaemia, hypokalaemia, or hypomagnesemia, and all of these subjects had a cardiac history that could potentially account for these findings.

The clinical data in Studies 20070337, 20110142, and 20110174 did not indicate any relevant changes in mean blood pressure and heart rate. Mean values were comparable between treatment arms at baseline and throughout each of the studies. In Studies 20070337 and 20110142, the number of subjects with positively-adjudicated serious cardiovascular events during the 12-month double-blind period, and systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg, was generally comparable between treatment groups or was fewer in the romosozumab group.

Safety in special populations

Renal impairment

Based on the totality of the data, dose adjustment for patients with RI is not proposed by the Applicant.

Treatment-emergent adverse events by baseline eGFR rate and preferred term are provided for the 12-month placebo-controlled osteoporosis safety analysis set for Studies 20060326 and 20070337. No safety analyses were performed for subgroups by RI in Study 20110142 or in the male osteoporosis Study 20110174.

Table 67: Treatment-emergent Adverse Events by Baseline eGFR and Preferred Term (12-month Placebo-Controlled Osteoporosis Safety Analysis Set, Study 20060326)

	30 - < 60 mL/min/1.73m^2		60 - < 90 mL/min/1.73m^2		≥ 90 mL/min/1.73m^2	
Preferred Term	Placebo (N = 7) n (%)	Romosozumab 210 mg QM SC (N = 6) n (%)	Placebo (N = 31) n (%)	Romosozumab 210 mg QM SC (N = 30) n (%)	Placebo (N = 12) n (%)	Romosozumab 210 mg QM SC (N = 15) n (%)
Number of subjects reporting adverse events	6 (86)	6 (100)	28 (90)	23 (77)	11 (92)	14 (93)

Table 68: Treatment-emergent Adverse Events by Baseline eGFR and Preferred Term (12-month Placebo-Controlled Osteoporosis Safety Analysis Set, Study 20070337)

	15 - < 30 mL/min/1.73m^2		30 - < 60 mL/min/1.73m^2		60 - < 90 mL/min/1.73m^2		≥ 90 mL/min/1.73m^2	
Preferred Term	Placebo (N = 8) n (%)	Romosozumab 210 mg QM SC (N = 10) n (%)	Placebo (N = 625) n (%)	Romosozumab 210 mg QM SC (N = 734) n (%)	Placebo (N = 2526) n (%)	Romosozumab 210 mg QM SC (N = 2406) n (%)	Placebo (N = 416) n (%)	Romosozumab 210 mg QM SC (N = 431) n (%)
Number of subjects reporting adverse events	8 (100)	9 (90)	507 (81)	569 (78)	2015 (80)	1881 (78)	332 (80)	353 (82)

In the osteoporosis safety analysis set, adverse events were assessed based on baseline eGFR categories of 15 to < 30, 30 to < 60, 60 to < 90, and ≥ 90 mL/min/1.73 m2 (no subject had an eGFR < 15 mL/min/1.73 m2 at baseline. The exposure adjusted incidence rate per 100 subject-years of adverse events for the total romosozumab group was 365.9 for subjects with eGFR ≥ 15 to < 30 mL/min/1.73 m2 (vs 1371.8 for placebo); 202.2 for subjects with eGFR ≥ 30 to < 60 mL/min/1.73 m2. (vs 233.7 for placebo); 201.6 for subjects with ≥ 60 to < 90 mL/min/1.73 m2 (vs 217.6 for placebo); and 243.3 for subjects with eGFR ≥ 90 mL/min/1.73 m2 (vs 215.6 for placebo).

Numerical differences were noted but are likely because of the small number of subjects in some subgroups, for example 14 subjects in the romosozumab group and 8 subjects in the placebo group for subjects with eGFR ≥ 15 to < 30 mL/min/1.73 m2.

Phase 1 Study 20110227

Phase 1 Study 20110227 was conducted in 24 subjects (8 healthy subjects and 8 subjects each with stage 4 RI or stage 5 CKD requiring haemodialysis) to investigate the pharmacokinetics, pharmacodynamics, and safety of romosozumab in subjects with RI. Romosozumab was administered at single doses of 210 mg.

The most common adverse events were hypocalcaemia (5 subjects [1 subject with stage 4 RI, 4 subjects with stage 5 CKD requiring haemodialysis]) and secondary hyperparathyroidism (4 subjects [4 subjects with stage 4 RI]); all of these events were CTCAE **≤** grade 2 except 1 subject with stage 5 CKD requiring haemodialysis who had a grade 3 non-serious adverse event of asymptomatic hypocalcaemia reported on 2 separate occasions. The administration of romosozumab resulted in a greater decrease in serum calcium level and a greater compensatory physiological increase in iPTH in subjects with stage 4 RI and stage 5 CKD requiring haemodialysis than in healthy subjects.

The mean percent change from baseline for albumin-adjusted calcium reached a nadir on day 15 in healthy subjects (−1.9%) and by day 22 for subjects with stage 4 RI (−4.8%) and subjects with stage 5 CKD requiring haemodialysis (−12.9%). The albumin-adjusted calcium levels then returned toward baseline levels.

Hepatic Impairment

Monoclonal antibodies are not eliminated via hepatic metabolic mechanisms; therefore, no studies have been conducted in subjects with hepatic impairment.

Elderly

A subgroup analysis of adverse events by age groups (< 65 years, ≥ 65 years to 74 years; ≥ 75 years to 84 years; and ≥ 85 years) using the 12-month placebo-controlled osteoporosis safety analysis set was provided as well as adverse events by age (< 75 years, ≥ 75 years) in Study 20110142.

Table 69: Treatment-emergent Adverse Events by Age Group Category (<65, 65-74, 75-84 and ≥ 85 Years) and Preferred Term (12-month Placebo-Controlled Osteoporosis Safety Analysis Set)

	< 65 years		≥ 65 - 74 years		≥ 75 - 84 years		≥ 85 years	
Preferred Term	Placebo (N = 814) n (%)	Romosozumab 210 mg QM SC (N = 833) n (%)	Placebo (N = 1791) n (%)	Romosozumab 210 mg QM SC (N = 1822) n (%)	Placebo (N = 1059) n (%)	Romosozumab 210 mg QM SC (N = 1089) n (%)	Placebo (N = 106) n (%)	Romosozumab 210 mg QM SC (N = 114) n (%)
Number of subjects reporting adverse events	627 (77.0)	650 (78.0)	1450 (81.0)	1417 (77.8)	853 (80.5)	865 (79.4)	86 (81.1)	93 (81.6)

Overall, there were no notably different trends between romosozumab or placebo/control treatment groups in the incidence of TEAEs by these four age categories. Observed increases with romosozumab versus placebo/control tended to be small, not always consistent across age categories, and often associated with higher incidences in corresponding placebo/control groups. A small number of subjects in some AE categories, especially in the ≥85 years age group, limited the interpretation of these data.

Geographic Region

Subjects in Western Europe and Australia/New Zealand had the highest incidence of adverse events (88.1% romosozumab, 89.3% placebo), followed by North America (84.9%, 81.4%), Asia Pacific (83.6%, 80.6%), Central/Latin America (76.2%, 77.7%), and Central and Eastern Europe (73.7%, 78.2%). Despite regional differences in the incidence of individual adverse events, the incidence of individual adverse events was similar between treatment groups within a region (≤ 5% difference for nearly all adverse events and regions).

Race

In summary no meaningful influence of race on romosozumab associated risk could be noted. The only uncertainty pertains to the high incidence of osteoarthritis in the Japanese dose finding study that was not found in any other subgroup. This is however not of primary interest regarding the European population.

Body Mass Index

In general, adverse events by preferred term were reported with similar frequency in the romosozumab and placebo groups within each BMI subgroup, and these incidences were similar to those seen in the overall population. However, regarding the overall number of subjects reporting adverse events it is noted that patients in the "slimmest" group (BMI ≤ 22.5 kg/m2) are the only group exhibiting a higher overall incidence as placebo. The difference is however minimal and does not give rise to concern.

Immunological events

Immunogenicity in Clinical Studies with Romosozumab

In phase 2 and phase 3 clinical studies of osteoporosis in postmenopausal women, the incidence of developing anti-romosozumab antibodies was 18.6% (1162 of 6244) across all doses studied. The safety profiles of the subjects who tested positive for binding antibodies were evaluated. The safety profiles assessed included adverse events potentially related to hypersensitivity, injection site reaction or autoimmune disorder related symptoms in subjects who tested positive for binding and neutralizing ADA in the PMO safety analysis set. Anti-romosozumab antibodies were not tested in subjects randomized to placebo.

The incidence of hypersensitivity events in the romosozumab dosed groups were comparable between subjects who were positive for anti-romosozumab binding and neutralizing antibodies (7.5% and 5.4%) and for those subjects who were negative for anti-romosozumab binding antibodies (7.8% and 7.6%); and in the placebo group (7.6%).

The incidence of autoimmune related disorders in the romosozumab dosed groups were comparable between subjects who were positive for anti-romosozumab binding and neutralizing antibodies (0.7% and 0.0%) and for those subjects who were negative for anti-romosozumab binding antibodies (0.8% and 0.7%); and in the placebo group (0.9%). Adverse events potentially related to autoimmune disorders were generally similar for

subjects who received romosozumab, regardless of binding or neutralizing ADA status, as well as for subjects who received placebo.

The site reactions were more common in the romosozumab dosed subjects (8.2%) than placebo dosed groups (3.1%) but no association of anti-romosozumab binding (8.3%) and neutralizing antibodies (15.7%) was noted with the date of onset of the injection site reaction when compared to antibody negative subjects (6.2% and 7.7%) for the romosozumab dosed groups

Additionally, the treatment- emergent hypersensitivity events, injection site reactions, and autoimmune disorders were assessed the 210mg QM romosozumab dosed and placebo groups and found to be comparable between subjects who were positive for anti-romosozumab binding and neutralizing antibodies and negative for anti-romosozumab binding antibodies.

In Study 20110174, the number of subjects reporting treatment-emergent adverse events was 9.9% for placebo (8/81), 10.0% for antibody negative (13/130), 12.5% for binding antibody positive (4/32), and 0% for neutralizing antibodies (0/1).

In Study 20110142, the number of subjects reporting treatment-emergent adverse events was 9.7% for alendronate (195/2014), 10.6% for antibody negative (174/1639), 9.5% for binding antibody positive (30/316), and 8.3% for neutralizing antibodies (1/12).

These data indicate no effect of anti-romosozumab antibodies on the safety of romosozumab.

Safety related to drug-drug interactions and other interactions

No studies on potential drug-drug interactions were conducted with romosozumab due to the fact that no PK drug-drug interactions are expected with romosozumab administration. Romosozumab is a monoclonal antibody that binds specifically to sclerostin, and there are no known mechanisms or previous PK or pharmacodynamics experience whereby romosozumab may precipitate PK drug-drug interactions.

Discontinuation due to AES

The overall number of discontinuations was balanced between romosozumab and integrated control groups. There were no marked differences in reasons for discontinuations in the preferred term level and no preferred term was reported by more than 5 subjects in any treatment group.

In the 12-month placebo-controlled osteoporosis population, adverse events leading to discontinuation from the study were reported for 46 (1.2%) subjects in the total romosozumab group and 50 (1.4%) of subjects in the placebo group. During the 12-month double-blind treatment period of the alendronate-controlled Study 20110142, adverse events led to withdrawal from the study for 30 (1.5%) subjects who received romosozumab and 27 (1.3%) subjects who received alendronate.

Longer-term Follow-up

Study 20070337

This study included a 12-month treatment phase, during which subjects received romosozumab or placebo. This was followed by a 12-month open-label denosumab follow-up period, and a 12-month open-label denosumab extension period through month 36.

Table 70: Summary of Subject Incidence of Adverse Events (Safety Analysis Set) (20070337 Month-24 Analysis)

	12-Month Double-blind Period		24-Month Study Period	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Placebo/ Denosumab 60 mg Q6M (N = 3576) n (%)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3581) n (%)
All adverse events	2850 (79.7)	2806 (78.4)	3069 (85.8)	3053 (85.3)
Serious adverse events	312 (8.7)	344 (9.6)	540 (15.1)	565 (15.8)
Leading to discontinuation of IP	94 (2.6)	103 (2.9)	110 (3.1)	122 (3.4)
Leading to discontinuation from study	50 (1.4)	44 (1.2)	56 (1.6)	52 (1.5)
Fatal adverse events	23 (0.6)	29 (0.8)	47 (1.3)	52 (1.5)

IP = investigational product; N = Number of subjects who received at least one dose of investigational product in the double-blind period; Q6M = every 6 months; QM = every month

The subject incidence rates for the 24-month study period include all events that occurred in the double-blind period and, in addition, all events that occurred in the open-label period for those subjects who received at least one dose of denosumab. Events occurring during the first 12-month study period are also included in the 12-month placebo-controlled osteoporosis safety analysis set pooled results and the osteoporosis population pooled results.

Table 71: Subject Incidence of Adverse Events of Interest (Safety Analysis Set, 20070337 Month-24 Analysis)

	12-Month Double-blind Period		24-Month Study Period	
Event of Interest	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Placebo/ Denosumab 60 mg Q6M (N = 3576) n (%)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3581) n (%)
Hypocalcemia				
Adverse events	0 (0.0)	1 (<0.1)	3 (<0.1)	6 (0.2)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypersensitivity				
Adverse events	245 (6.9)	242 (6.8)	331 (9.3)	314 (8.8)
Serious adverse events	0 (0.0)	7 (0.2)	3 (<0.1)	7 (0.2)
Injection site reactions				
Adverse events	104 (2.9)	187 (5.2)	106 (3.0)	188 (5.2)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancy				
Adverse events	69 (1.9)	59 (1.6)	100 (2.8)	105 (2.9)
Serious adverse events	43 (1.2)	37 (1.0)	69 (1.9)	65 (1.8)
Hyperostosis				
Adverse events	27 (0.8)	19 (0.5)	40 (1.1)	35 (1.0)
Serious adverse events	5 (0.1)	1 (<0.1)	6 (0.2)	6 (0.2)
Osteoarthritis				
Adverse events	315 (8.8)	281 (7.8)	431 (12.1)	396 (11.1)
Serious adverse events	17 (0.5)	7 (0.2)	27 (0.8)	13 (0.4)
Adjudicated positive ONJ				
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	2 (<0.1)
Serious adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Adjudicated positive AFF				
Adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Serious adverse events	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)

Study 20110142

Subjects were randomized (1:1) to receive romosozumab 210 mg subcutaneously (SC) monthly or alendronate 70 mg orally every week for the 12–month double-blind period. After the initial 12-month study period, subjects received alendronate while remaining blinded to their initial treatment assignment.

Table 72: Summary of Subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set – 20110142 Primary Analysis)

	Double-blind Period		Primary Analysis Period	
	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM (N = 2040) n (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2014) n (%)	Romo 210 mg QM/ Alendronate 70 mg QW (N = 2040) n (%)
All treatment-emergent adverse events	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Serious adverse events	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Leading to discontinuation of investigational product	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
Leading to discontinuation from study	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)
Fatal adverse events	21 (1.0)	30 (1.5)	90 (4.5)	90 (4.4)

Table 73: Summary of Subject Incidence of Treatment-emergent Adverse Events of Interest (Safety Analysis Set - 20110142 Primary Analysis)

	Double-blind Period		Primary Analysis Period	
Event of Interest	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM (N = 2040) n (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2040) n (%)
Hypocalcaemia				
Adverse events	1 (<0.1)	1 (<0.1)	1 (<0.1)	4 (0.2)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events potentially related to hypersensitivity				
Adverse events	118 (5.9)	122 (6.0)	185 (9.2)	205 (10.0)
Serious adverse events	2 (<0.1)	3 (0.1)	4 (0.2)	7 (0.3)
Injection site reactions				
Adverse events	53 (2.6)	90 (4.4)	53 (2.6)	90 (4.4)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant or unspecified tumors				
Adverse events	28 (1.4)	31 (1.5)	85 (4.2)	84 (4.1)
Serious adverse events	20 (1.0)	25 (1.2)	59 (2.9)	61 (3.0)
Hyperostosis				
Adverse events	12 (0.6)	2 (<0.1)	27 (1.3)	23 (1.1)
Serious adverse events	2 (<0.1)	0 (0.0)	3 (0.1)	1 (<0.1)
Osteoarthritis				
Adverse events	146 (7.2)	138 (6.8)	268 (13.3)	247 (12.1)
Serious adverse events	6 (0.3)	8 (0.4)	11 (0.5)	24 (1.2)
Adjudicated positive osteonecrosis of the jaw				
Adverse events	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Serious adverse events	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Adjudicated positive atypical femoral fracture				
Adverse events	0 (0.0)	0 (0.0)	4 (0.2)	2 (<0.1)
Serious adverse events	0 (0.0)	0 (0.0)	4 (0.2)	2 (<0.1)

Study 20060326

Subjects were randomized in a 1:1:1:1:1:1:1:1 ratio to receive 1 of 5 double-blind dosing regimens of romosozumab or placebo for 24 months (or open-label alendronate (ALN) or open-label teriparatide for the first 12 months). This 24-month treatment phase was followed by re-randomization to a 12-month extension phase with denosumab or placebo; followed by a 12-month retreatment phase with romosozumab 210 mg QM, followed by a 24-month open-label follow-on phase with no intervention or zoledronic acid.

The overall percentage of subjects with adverse events up to month 24 was similar in the total romosozumab group (96.1%) and the total placebo group (96.0%). There was no dose-dependent trend seen in the overall incidence of adverse events across the romosozumab groups (92% to 100%).

Table 74: Summary of Subject Incidence of Adverse Events (Safety Analysis Set) (Events Started After Month 24 Visit Are Excluded) (20060326 Month 24 Interim Analysis)

	Placebo	Romosozumab SC					
	Total (N = 50) n (%)	70 mg QM (N = 50) n (%)	140 mg Q3M (N = 52) n (%)	140 mg QM (N = 49) n (%)	210 mg Q3M (N = 53) n (%)	210 mg QM (N = 51) n (%)	Total (N = 255) n (%)
All	48 (96.0)	50 (100.0)	48 (92.3)	46 (93.9)	53 (100.0)	48 (94.1)	245 (96.1)
Serious	9 (18.0)	9 (18.0)	8 (15.4)	8 (16.3)	5 (9.4)	6 (11.8)	36 (14.1)
Fatal	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Leading to discontinuation from study	0 (0.0)	2 (4.0)	1 (1.9)	1 (2.0)	1 (1.9)	0 (0.0)	5 (2.0)
Leading to discontinuation of IP	3 (6.0)	3 (6.0)	3 (5.8)	3 (6.1)	2 (3.8)	3 (5.9)	14 (5.5)

IP = investigational product; N = subjects who received at least one dose of IP; QM = every month; Q3M = every 3 months; SC = subcutaneously
Includes only treatment-emergent adverse events started on or before the end of the first 24 months period.

Up to 24 months, adverse events occurring more frequently across the combined romosozumab groups compared with placebo (≥ 5 percentage points difference) and occurring in ≥ 10% of subjects in the total romosozumab group included nasopharyngitis (29.4% romosozumab, 24.0% placebo), pain in extremity (14.5%, 8.0%), and urinary tract infection (11.0%, 6.0%). Injection site pain occurred more frequently in the total romosozumab group (7.8%) than in the placebo group (0.0%).

In study 20060326, a total of 255 patients received romosozumab at different doses for 24 months. No dose-dependent trend was seen in the overall incidence of adverse events across the romosozumab groups and the overall incidence of AE:s seemed comparable with the incidences seen in the 12-month osteoporosis set. However, this study was considerably smaller. The proposed dosing regimen is 210 mg for 12 months.

Study 20060326 is the only data source for both off-treatment and re-exposure to romosozumab. At months 36 to 48, a total of 167 subjects received re-treatment with romosozumab. One serious MI occurred in the study during re-treatments period. Due to the limited number of patients receiving re-treatment, no firm conclusions on safety of re-treatment can be made.

Other safety results of interest

Study 20080289 (Transition from Bisphosphonate Therapy)

Study 20080289 was a multicentre, randomized, open-label, 12-month teriparatide-controlled study in 436 postmenopausal women with osteoporosis (safety analysis set of 432 subjects) who were transitioning from bisphosphonate therapy.

The percentages of subjects reporting adverse events were (148 of 214 subjects [69.2%]) for the teriparatide group and (164 of 218 subjects [75.2%]) for the romosozumab group. Injection site reactions were observed more frequently with romosozumab (7.8%) compared with teriparatide (2.8%), which led to study drug discontinuation for 1 subject in the romosozumab group. Hypercalcaemia was reported more frequently with teriparatide (10.3%) compared to romosozumab (0.9%).

Numerically, there were more AEs of nervous system disorders (20 vs 14%), cardiac disorders (5.0 vs 3.7%) and vascular disorders (7.3 vs 3.3%) in the romosozumab group.

Serious cardiac disorders were reported in 2.3% for Romosozumab and 0.9% for teriparatide. One serious cerebrovascular accident, one ischaemic stroke and one transient ischaemic attack were reported in the Romosozumab group vs none in the teriparatide group. CV events were not adjudicated in this study.

Study 20120156 (70 mg/mL and 90 mg/mL Formulations)

Study 20120156 was a phase 3, multicentre, randomized, multiple dose study to evaluate the non-inferiority of romosozumab at a 90 mg/mL concentration (proposed for commercial use) compared with a 70 mg/mL concentration (used in other phase 3 studies) in postmenopausal women with osteoporosis.

All 294 randomized subjects received ≥ 1 dose of investigational product with a median number of 6 doses in all 3 treatment groups. At months 6 and 9, the incidence of adverse events and serious adverse events was comparable among the 3 treatment groups (placebo, romosozumab 90 mg/mL, and romosozumab 70 mg/mL).

Table 75: Treatment-Emergent Adverse Events of Potentially Related to Hypersensitivity by Preferred Term (Safety Analysis Set) (20120156 Final Analysis)

	Placebo			Romosozumab		
Preferred term	70 mg/ml (N = 26) n (%)	90 mg/ml (N = 26) n (%)	Total (N = 52) n (%)	70 mg/ml (N = 119) n (%)	90 mg/ml (N = 123) n (%)	Total (N = 242) n (%)
Number of subjects reporting treatment-emergent adverse events of hypersensitivity	1 (3.8)	2 (7.7)	3 (5.8)	3 (2.5)	14 (11.4)	17 (7.0)

The overall incidence of anti-romosozumab binding antibodies had similar incidence between the concentration groups.

In this relatively small study 20120156, hypersensitivity reactions were more common in the romosozumab 90 mg/mL (proposed for commercial use) group (11.4%) compared with the romosozumab 70 mg/mL (used in other phase 3 studies) group (2.5%). 2 subjects with injection site hypersensitivity and 1 subject with erythema withdrew from investigational product due to these events; there were no hypersensitivity related withdrawals in the other groups.

The reported incidence of hypersensitivity reactions in 90 mg/mL group in study 20120156 was also higher than for romosozumab in the 12-Month placebo-controlled osteoporosis safety analysis set (257 cases,

6.7%). The rationale for development of 90mg/mL formulation for patient convenience is acknowledged. However, overall, the clinical experience of 90mg/mL formulation is at this time point very limited with only 123 patients exposed for 6 months.

Hypersensitivity is an identified risk for Romosozumab. The current safety data showed no anaphylactic reactions that were attributable to romosozumab 90mg/mL or 70mg/mL concentrations. Any new serious events related to hypersensitivity should be followed post-marketing.

Device-related Adverse Event Data

Device-related adverse events were collected in 5 phase 1 studies; other clinical studies did not collect relationship of adverse events to device on the adverse event case report form. The 5 phase 1 studies comprised 539 subjects who received romosozumab using 1 of 3 drug product presentations:

* a glass prefilled syringe (PFS) containing 70 mg/mL of romosozumab

* a resin PFS containing 90 mg/mL of romosozumab (the planned commercial product)

* an autoinjector containing 90 mg/mL of romosozumab

All 5 studies were single-dose studies. The planned commercial product was presented in a single-use resin PFS and prefilled autoinjector/pen containing 90 mg/mL romosozumab with a 1.17 mL deliverable volume. Administration was to be performed by an individual trained in injection technique. Subjects administered the 210 mg dose by resin PFS received a total of 2 injections per dose and subjects administered the dose using a glass PFS received a total of 3 injections per dose. The majority of subjects who participated in studies in which device-related adverse events were collected received the drug product planned for commercial use. A total of 121 subjects received 363 injections of romosozumab using the glass PFS and 344 subjects received 688 injections of romosozumab using the resin PFS. The remaining 74 subjects received romosozumab via autoinjector/pen.

Somewhat higher incidence of device-related adverse events (almost all injection site reactions) occurred in the 90 mg/mL group vs the 70 mg/mL group.

Table 76: Number (Percentage) of Subjects with Device-related Adverse Events by Study (Phase 1 Studies 20120277, 20150197, 20110227, 20090418, 20120274)

	Drug Product and Device		
Study Number	70 mg/mL Glass PFS	90 mg/mL CZ Resin PFS	90 mg/mL Autoinjector
20120277	2/87 (2.3)	7/85 (8.2)	—
20150197	—	15/188 (8.0)	—
20110227	0/24 (0)	—	—
20090418	—	1/71 (1.4)	1/74 (1.4)
20120274	0/10 (0)	—	—
Total	2/121 (1.7)	23/344 (6.7)	1/74 (1.4)

CZ = Crystal Zenith; PFS = prefilled syringe

Post marketing experience

N/A

2.6.2. Discussion on clinical safety

Safety data were submitted from an extensive safety database that includes 11553 subjects in 19 romosozumab clinical studies who received at least 1 dose of romosozumab (n = 7681) or placebo (n = 3872). Additionally, the integrated control group for the osteoporosis safety analysis set includes 6155 subjects who received placebo, alendronate, teriparatide, and/or denosumab. In contrast, the number of male subjects with osteoporosis, who received romosozumab (n=163), is very limited.

The total number of adverse events was generally comparable in the clinical studies between romosozumab and control groups in pooled datasets. The number of treatment related AEs was somewhat higher in the romosozumab group. The most common adverse events were nasopharyngitis, headache, cough, arthralgia, dyspepsia and peripheral oedema and muscle spasms with no striking differences between treatment groups. Injection site pain and cataracts seem to be more common in the romosozumab group. Of these, nasopharyngitis (13.6% vs 12.6%), arthralgia (12.4% vs 11.8%), headache (6.5% vs 5.9%), muscle spasms (4.4% vs 3.9%), neck pain (2.1% vs 1.5%), cataract (2.0% vs 1.5%), injection site pain (1.8% vs 1.2%), injection site erythema (1.5% vs 0.2%), sinusitis (1.4% vs 0.8%), and injection site pruritus (0.7% vs 0.2%) were proposed to be labelled in the SmPC with a frequency "common" or "very common". The total number of serious adverse events was somewhat higher for romosozumab compared to placebo but somewhat lower compared to alendronate in study 20110142.

In the pooled pivotal trials, there was a numerical imbalance in fatal events with HR 1.20 and 1.37 in the two large PMO studies. In study 20070337 patients 75 years of age and older had a significantly increased risk of death in general in the romosozumab arm as compared to alendronate (19 vs 8 cases; HR 2.4 [95%CI 1.03-5.40]). This difference in patients 75 years and older vs control (alendronate or placebo) was also observed in the safety analysis set of all pivotal trials (20070337,20110142,20110174) (46 vs. 26 cases, HR 1.71 [95%CI 1.06,2.78]).The imbalance was mainly due to fatal cardiovascular events and neoplasms. Baseline co-morbidities/risk factors between treatment groups within each age subgroup, were not consistently favouring control or romosozumab groups. It was also not possible to identify age specific other risk factors for fatal events that would be specific for the romosozumab group. There are numerous variables that can play a role in the fatal outcome of an event and the causality to romosozumab is not possible to determine in individual cases. However, an osteoporosis drug that reduces fractures in older population would be expected to possibly reduce all-cause mortality, not the opposite.

Based on the mechanism of action, class effects of bone-forming agents and CHMP feedback, adverse events of interest for romosozumab included hypocalcaemia, hypersensitivity, injection site reactions, malignancies, hyperostosis, osteoarthritis, atypical femoral fractures and osteonecrosis of the jaw. Independent adjudication of serious cardiovascular events was pre-specified in the 3 pivotal phase 3 studies.

Cardiovascular events

During the development program, an imbalance in positively-adjudicated cardiovascular serious adverse events was observed between romosozumab (2.5%) and alendronate (1.9%) in Study 20110142. This imbalance was due specifically to serious cardiac ischemic (0.8% vs 0.3%) and serious cerebrovascular (0.8% vs 0.3%) events. Death, serious MI or serious stroke (MACE) occurred in 53/2040 (2.6%) patients treated with romosozumab compared to 32/2014 (1.6%) patients treated with alendronate, HR 1.7 (95%CI 1.1-2.6). An imbalance in major adverse CV events noted in study 20110142 12-month double blinded treatment period persisted at least through month 24 in the follow-up period.

Among these subgroup analyses, the CV imbalance was analysed for the subgroup of older osteoporosis subjects. There was a slight numerical increase in the HRs for the incidence of MACE-1 in the older age group (≥75 years) between treatment arms compared to that from the younger age group (<75 years), but all p-values for treatment by subgroup interactions were nonsignificant.

These findings were not apparent in the larger, placebo-controlled study (Study 20070337); MACE HR 1.1 (95%CI 0.7-1.7). In the smaller placebo-controlled male osteoporosis study, the imbalance in positively-adjudicated cardiovascular events was again observed between treatment groups, MACE HR 1.6 (95%CI 0.3-7.7) despite the fact that the prevalence of diabetes and smoking was higher in the placebo treatment arm. However, number of subjects in this male study was limited resulting in broad CIs.

Numerical imbalance in cardiovascular events was also noted in Study 20080289 compared to teriparatide in subjects who transitioned from bisphosphonate therapy (safety analysis set of 432 subjects). Serious cardiac disorders were reported in 2.3% for romosozumab and 0.9% for teriparatide.

The divergent findings regarding CV events in the two large pivotal studies were of concern. There was no bias in baseline characteristics within each randomized 3 clinical studies. However, the populations in each study were quite different: Subjects enrolled in Study 20110142 were on average 4 years older than in Study 20070337 and had a more severe osteoporosis defined by the entry criteria. Other differences among the studies included a somewhat higher rate of history of hypertension and cardiovascular disease in Study 20110142 compared with the other 2 studies. Men are known to have an increased CV risk compared to women. While many CV events occurred also in study 20070337, the incidence in the placebo group was lower than in the studies showing imbalance in CV events.

Adjudication process could reduce the number of events in studies and lead to possibly false low incidences of these events (but similarly in both treatment and comparator groups). For example, in study 20070337, a total of 342 cardiac disorders were reported but only 86 were reported as serious and were sent for adjudication. In addition, events sent to adjudication could fail adjudication (204 SAEs out of 524 in total) due to missing information only.

Osteoporosis and cardiovascular disease have overlapping risk factors and are associated conditions in epidemiological studies. The discrepancy seen between the studies in the risk of positively-adjudicated cardiovascular serious adverse events might be explained by a combination of factors that are associated with osteoporosis severity and cardiovascular risk but numerically difficult to capture in a detailed review of small differences in medical history, baseline cardiovascular-related medications, general medical history and in an exploration of the potential impact of age alone and other cardiovascular risk factors separately. Studies 20110142 and Study 20070337 had different inclusion/exclusion criteria regarding osteoporosis severity (T-scores and fractures). Only 14% of all included patients in these two pivotal PMO studies had overlapping inclusion criteria. Consequently, these two pivotal studies represent largely different osteoporosis populations. The patients in study 20110142 were older and had a more severe osteoporosis disease. A discrepancy in some safety results, such as treatment emergent MI and stoke events, between studies is thus not totally unexpected.

When further evaluating the annual incidence rates in study 20110142, it was noted that the number of CV events was lowest in the first year in the ALN group, with an increase in the rate of these events in this group in subsequent years. The risk of CV events increases with age, therefore a tendency to increased rate during four years of follow-up would not be unexpected in any cohort. In contrast, the rate of CV events for subjects treated with romosozumab was highest during the actual treatment year and the year after followed by a

decline. This pattern could be expected in a randomized trial if romosozumab treatment is associated with CV events.

One explanation for the difference between the 2 studies that was explored was that alendronate would be protective against cardiovascular events in humans. However, based on the available evidence thus far, a consistent cardioprotective effect of alendronate has not been demonstrated. Direct comparisons of reported incidence rates from population-based studies and clinical study data are challenging to make because of numerous confounding factors, including differences in patient characteristics such as: age and other clinical risk factors; regional differences; time frame of assessments; cardiovascular outcome definitions and ascertainment methodologies; statistical methodology; and being part of a clinical study population.

In response to the concerns of the CHMP, the Applicant has explored the cardiovascular risk profile of romosozumab in a new proposed target population with a larger need for osteoporosis treatment and a relatively lower risk for cardiovascular events than the broad study population, i.e. subjects with severe osteoporosis and with no history of MI or stroke. Approximately 40% of the subjects in Study 20070337 and the entire population in Study 20110142 are considered to have severe osteoporosis.

By excluding subjects with a history of MI/stroke from the post-fracture population in studies 20070337 and 20110142 when calculating event rates, the excess MACE/1,000 patients in the romosozumab versus control arm decreased from 23 excess events to 3. The corresponding number in a population without established cardiovascular disease (CVD) was 2 excess MACE/1,000 patients. Such reductions of the absolute risk for MI/stroke are expected, as subjects with previous MI/stroke are at high risk for subsequent cardiovascular events. The calculated absolute risk difference of MACE is small in the revised proposed target population that would have been included according to the restricted indication (severe osteoporosis in postmenopausal women at high risk of fracture) and contraindications (History of myocardial infarction or stroke) as proposed by the applicant during the procedure. However, the relative risk for MACE in romosozumab versus control treated subjects is largely unchanged (4.4% vs 2.6% in the population with previous MI/stroke, 1.4% vs 0.9% in the population without MI/stroke and 0.8% vs 1.2% in the population without established CVD, for romosozumab versus control respectively), as described below.

Table 77: Effects Table for study 20110142 (severe PMO) results at month 12 (proposed target population)

Effect	Romosozumab n/N (%)	Alendronate n/N (%)
AE:s of Ischaemic heart disease	31/1916 (1.6)	15/1890 (0.8)
CNS Haemorrhages and cerebrovascular conditions	41/1916 (2.1)	29/1890 (1.5)
Death (all)	27/1916 (1.4)	20/1890 (1.1)
Adjudicated MACE	37/1916 (1.9)	17/1890 (0.9)

Table 78: Effects Table for study 20070337 (less severe PMO) results at month 12 (patients representing proposed target population)

Effect	Romosozumab n/N (%)	Placebo n/N (%)
AE:s of Ischaemic heart disease	14/1352 (1.0)	23/1376 (1.7)
CNS Haemorrhages and cerebrovascular conditions	15/1352 (1.1)	16/1376 (1.2)
Death (all)	10/1352 (0.7)	8/1376 (0.6)
Adjudicated MACE	9/1352 (0.7)	13/1376 (0.9)

Other events of interest

Clinically significant **hypersensitivity** reactions, including angioedema, erythema multiforme, and urticaria occurred in the romosozumab group in clinical trials. Hypersensitivity was proposed to be labelled as an adverse event for romosozumab, section 4.8 in the SmPC. Also warnings in section 4.4 were proposed and endorsed by the CHMP. In study 20120156, hypersensitivity reactions were more common in the romosozumab 90 mg/mL (proposed for commercial use) group 11.4% group compared with the romosozumab 70 mg/mL (used in other phase 3 studies) group 2.5%. 2 subjects with injection site hypersensitivity and 1 subject with erythema withdrew from investigational product due to these events; there were no hypersensitivity related withdrawals in the other groups. Romosozumab 70 mg/mL was used in pivotal phase 3 studies. However, higher concentration of 90 mg/mL were proposed for commercial use. Hypersensitivity reactions were more common with romosozumab 90 mg/mL in study 20120156. A higher incidence of **device-related adverse events** (almost all injection site reactions) occurred in the 90 mg/mL group vs the 70 mg/mL group in study 20120156. The rationale for development of 90mg/mL formulation for patient convenience is acknowledged. However, overall, the clinical experience of 90mg/mL formulation is at this time point very limited with only 123 patients exposed for 6 months. Hypersensitivity is an identified risk for Romosozumab. The current safety data showed no anaphylactic reactions that were attributable to romosozumab 90mg/mL or 70mg/mL concentrations. Any new serious events related to hypersensitivity should be followed post-marketing.

Concerning **malignancies***,* no case of osteosarcoma (potential signal from rat studies, however occurred therein within level of background incidence) was noted. However, due to the typically long time between onset of symptoms (bone pain) and diagnosis, this incidence might have been underestimated. Although sclerostin expression has been reported in a limited number of soft tissue and bone tumours, there is no current evidence that the presence or absence of sclerostin is related to malignant potential.

Patients with the genetic absence of sclerostin may have neurologic sequelae due to **hyperostosis** including nerve compression and deafness. In an audiology substudy, no significant difference in average change in hearing threshold was observed between the romosozumab and placebo groups at month 12. No subjects had a markedly increased BMD post-baseline in clinical studies. The overall data do not give strong support that hyperostosis would be a potential risk with romosozumab treatment of skeletally mature osteoporosis patients.

Both pivotal PMO studies included a 12-month treatment phase, during which subjects received romosozumab or placebo/comparator; followed by an open label treatment phase with denosumab/alendronate. **Osteonecrosis of the jaw (ONJ)** and **atypical femur fractures (AFF)** are known AEs associated with longer term exposure of antiresorptive medications. These events occurred in romosozumab/denosumab, alendronate/romosozumab and alendronate/alendronate treatment groups but not in the placebo/denosumab group that had shortest total exposure of antiresorptive treatment.

There was a numerical imbalance in serious adverse events of infections in the pivotal placebo-controlled studies, even when adjusted for patient years. The imbalance was marginally higher in subgroup of patients >75 years and the frequency of these events was overall somewhat higher in these patients, as shown in table 5. Pneumonia was the most frequent type of infection; however, when adjusted for patient years, no imbalance was evident. There is no clear biologic plausibility for increased risk of especially pneumonia, however, some effects on haematology parameters and white blood count has seen both in preclinical and clinical studies.

Nasopharyngitis and sinusitis are currently the only type of infection that is proposed to be included in the Romosozumab SmPC. Serious infection is included in the RMP as an important potential risk and also included as an endpoint for any possible further PASS studies of romosozumab.

A total of 167 subjects received re-treatment with romosozumab in Study 20060326. One serious MI occurred in the study during re-treatments period. Due to the limited number of patients, no firm conclusions on safety of re-treatment can be made.

Laboratory findings

The 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 increased demands for calcium for matrix mineralization. Romosozumab administration was associated with transient decreases in serum calcium in pivotal PMO Studies 20070337 and Study 20110174. S-calcium was measured at month 1 in these studies. However, in phase 1 study, the mean percent change from baseline for albumin-adjusted calcium reached a nadir on day 15 in healthy subjects. This means that the lowest S-Ca values may not have been captured in the pivotal trials. Only few adverse events of hypocalcaemia were reported as adverse events in the clinical studies. However, transient decrease in S-calcium has been observed in patients receiving romosozumab. Hypocalcaemia is proposed as an identified risk for romosozumab, and to be included in SmPC as a warning in section 4.4 and with a frequency "uncommon" (Defined as albumin adjusted serum calcium that was below the lower limit of normal). This risk is further increased in patients with renal impairment, see below. Lipids were not collected in the 3 pivotal phase 3 studies. Romosozumab treatment is associated with decreases in s-phosphorus. Romosozumab treatment is associated with increase in iPTH and decrease in urinary calcium excretion. These changes may be related to the decrease in s-Ca. The changes seem to persist throughout the treatment period.

No limitations in the use of romosozumab are proposed by the applicant, except a warning that these patients are at risk of developing hypocalcaemia. It is noted that there were only a few patients with baseline GFR 15-30 mL/min/1.73 m2; 14 subjects in the romosozumab group and 8 subjects in the placebo group in the entire osteoporosis safety analysis set. A phase 1 Study 20110227 was conducted in 8 healthy subjects and 8 subjects each with stage 4 RI or stage 5 CKD requiring haemodialysis. Hypocalcaemia was reported in >30% of the subjects with 4 RI or stage 5 CKD after a single dose. The administration of romosozumab resulted in a greater decrease in serum calcium level and a greater increase in iPTH in 4RI and 5CDK than in healthy subjects. In patients with end-stage renal disease, previous publications have described a relationship among increased PTH levels and cardiovascular risk (Block et al, 2004; Floege et al, 2011). It is also noted that patients with renal impairment <30 / mL/min/1.73 m2 have an elevated risk for CV events.

Immunogenicity

Antidrug antibody formation after romosozumab treatment seems to be a common phenomenon. About 7.9% (66 of 832) of subjects developed binding antibodies after at least 1 dose of romosozumab. All ADA positive subjects showed a persistent binding response with a positive result at the last time point tested. Neutralizing antibodies were detected in 2.1% (18 of 832) of all romosozumab dosed subjects. Not surprisingly, in repeat dose settings the incidence of binding antibodies in subjects repeatedly dosed with romosozumab is more common than in a single dose setting (pooled 210 mg QM 19.1% (758 of 3959)). Interestingly however is the lower incidence of neutralizing antibodies (0.8% (31 of 3959), respectively. In general incidences of binding and neutralizing antibodies are very comparable in osteoporosis patients across analysis sets and populations. Though limited by low patient numbers, a retreatment phase with romosozumab does not lead to a higher immunogenic potential in terms of ADA formation. Also, pre- or interim treatment with

denosumab does not seem to be associated with a different ADA formation incidence. The incidence of pre-existing romosozumab ADA is considered low with a low magnitude of immune response (close to cut off) In general neither incidence no magnitude of this finding suggests a clinically meaningful effect. Cross reactivity is one potential explanation.

The applicant investigated adverse events which can reasonably be associated with immunogenicity regarding their incidence rates according to binding and neutralizing ADA status, namely injection site reactions, hypersensitivity, and autoimmune disorders. The only possible correlation could be identified for positive neutralizing antibodies status and the incidence of injection site reactions, at least when looking at exposure adjusted data for the PMO: (incidence rate for positive neutralizing antibody status [14.3] negative status [7.0] placebo group [3.1]).
In general, as opposed to binding antibody status, positive neutralizing antibody status more clearly increases the overall (exposure adjusted) incidence rate of adverse events (positive 18.1 vs negative 13.9), however this could also be associated with the small group size of neutralizing antibody positive patients (n=62 vs n=1137 in the negative group). When looking at absolute incidence numbers, no trend is observed for either injection site reactions or absolute numbers of AE in the PMO.
In the male osteoporosis population binding antibody status more clearly affects the incidence of adverse events (81.3% positive anti-romosozumab antibody test at any time vs 74% with negative ADA status). Trends supporting an influence of immunogenicity on specific AE are also observed for hypersensitivity (12.5% binding antibody positive/10.0% of binding antibody negative/9.9% of subjects in the placebo) and injection site reaction (9.4% of binding antibody positive, 4.6% binding antibody negative, and 3.7% placebo). The influence on safety of neutralizing antibodies could not be assessed due to their rare incidence (only one subject remaining at month 15).
The influence of binding antibodies on safety is potentially larger in male osteoporosis patients than for PMO patients, where only neutralizing antibodies exhibit a visible influence on injection site reactions.

Additional expert consultation

The CHMP requested an ad hoc expert meeting to obtain the opinion of experts in the field of osteoporosis, cardiology as well as geriatrics, and from patient representatives, on various aspects of the efficacy data and the issue of increased rate of CV events observed in studies with romosozumab. Questions were addressed to the ad hoc expert group. For the corresponding answers please **see 2.5.3 "Discussion on clinical efficacy", section "Additional expert consultation" of this report**.

2.6.3. Conclusions on the clinical safety

An increased risk of cardiovascular serious adverse events associated with the use of romosozumab was noted in the clinical programme with an increase in adjudicated major adverse cardiovascular events (MACE, defined as all-cause death, and positively-adjudicated serious myocardial infarction or serious stroke) in the pivotal study 20110142. In this study, MACE occurred in 53/2040 (2.6%) patients treated with romosozumab compared to 32/2014 (1.6%) patients treated with alendronate, HR 1.7 (95%CI 1.1-2.6). In addition, in the smaller placebo-controlled male osteoporosis study, an imbalance in positively-adjudicated cardiovascular events was observed between treatment groups with a MACE HR of 1.6 (95%CI 0.3-7.7). These findings were not seen in the larger, placebo-controlled study (Study 20070337); adjudicated MACE HR 1.1 (95%CI 0.7-1.7). Therefore, the most important risk of romosozumab is the association of its use with serious cardiovascular events.
In addition, in study 20070337 patients 75 years of age and older had a significantly increased risk of death

in general in the romosozumab arm as compared to placebo (19 vs 8 cases; HR 2.4 [95%CI 1.03-5.40]), which was also the case for the pooled safety data.
In general, in other aspects romosozumab displayed a risk profile that resembles in many respects the risk profile of placebo, and hence, the underlying disease.

2.7. Risk Management Plan

The CHMP and PRAC, having considered the data submitted in the application were of the opinion that due to the concerns identified with this application, the risk management plan version 0.6 which was submitted in response to the 4th joint CHMP/PRAC Day 180 List of Outstanding Issues Assessment Report, cannot be agreed at this stage.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant declared that romosozumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers romosozumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union. However, in light of the negative recommendation, new active substance status is not applicable at this stage.

2.10. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

However, due to the aforementioned concerns a satisfactory package leaflet cannot be agreed at this stage.

2.10.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Osteoporosis is defined as a disease characterised by low bone mass and microarchitectural deterioration of bone tissue and a consequent increase in fracture risk. Romosozumab is a humanized immunoglobulin G2 (IgG2) monoclonal antibody that binds and inhibits sclerostin. Sclerostin is a negative regulator of signalling in osteoblast-lineage cells which result in inhibition of osteoblast-mediated bone formation and stimulation of osteoclast-mediated bone resorption. 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 treatment changes expression of regulators of osteoclast activity, thereby decreasing bone resorption. The aim of the treatment is to prevent fractures. Romosozumab was intended to be given as SC monthly injections for 12 months.

Romosozumab was intended for treatment of osteoporosis in postmenopausal women (PMO) and also in adult men at increased risk of fractures.
However, the male indication was not further pursued during the procedure.
Furthermore, during the procedure, the applicant also considered to limit the use to treatment of severe postmenopausal osteoporosis at high risk of fractures. This was considered as an attempt to enrich the intended target population with the more severe forms of osteoporosis, although there may be no universally recognized definition to distinguish these populations.

3.1.2. Available therapies and unmet medical need

Bisphosphonates and denosumab are the most common antiresorptive medications prescribed for osteoporosis treatment. Teriparatide has a mainly anabolic mechanism of action. There is a need for new treatment alternatives. In Europe, 22 million women and 5.5 million men were estimated to have osteoporosis in 2010 and 3.5 million possibly related fractures were sustained. Most fractures occur at the spine, wrist and hip. The vast majority of osteoporotic fractures occur in postmenopausal women and the incidence increases markedly with age.

3.1.3. Main clinical studies

Three studies were considered pivotal in this application:

20070337: placebo controlled study in less severe PMO (N=7180)

20110142: alendronate-controlled study in severe PMO (N=4093)

20110174: placebo controlled bridging study in men with osteoporosis (N=245)

All these studies included a randomized, double-blind 12 months treatment phase with romosozumab vs placebo or alendronate. The PMO studies were followed by an open-label follow-up phase: patients in study 20070337 received denosumab up to 24 additional months and patients in study 20110142 received alendronate for a mean 20 additional months.

Supportive studies included study 20080289 which was a teriparatide-controlled study in patients with previous bisphosphonate use; study 20060326 which was a dose-ranging placebo- and active-controlled

study (teriparatide or alendronate) with off-treatment and re-treatment phases; study 20101291 which was dose-ranging placebo-controlled study in Japanese women; and Study 20120156, which was a placebo-controlled non-inferiority study testing romosozumab at different concentrations.

3.2. Favourable effects

Study 20070337:

Study 20070337 met its co-primary endpoints as romosozumab reduced the subject incidence of new *radiological vertebral fractures* compared with placebo during the 12-month double-blind period with n = 16 (0.5%) for romosozumab vs 59 (1.8%) for placebo and through month 24 (0.6% vs 2.5%) after both groups transitioned to denosumab, p<0.001 at both time points.

Romosozumab significantly reduced the risk for *clinical fractures* (including symptomatic vertebral and non-vertebral fractures) compared to placebo (1.6% vs 2.5%, adjusted p=0.008) at 12 months, but not at 24 months after adjustment for multiplicity.

A lower incidence of *non-vertebral fractures* in the romosozumab arm was noted at 12 months (1.6% vs 2.1%) and 24 months, however, the reductions were not statistically significant after adjustment for multiplicity.

An increase in *DXA BMD* from baseline was markedly higher in the romosozumab group than in the placebo group at month 12 at the lumbar spine (13% vs 0.4%), total hip (6.0% vs 0.3%) and femoral neck (5.5% vs 0.3%); p<0.001 at all locations. The DXA BMD in the romosozumab treated group continued to increase during denosumab treatment, albeit somewhat less than in the placebo/denosumab group. The largest increase in BMD in the romosozumab group occurred during the first 6 months.

Study 20110142:

Study 20110142 met both of its two primary endpoints as romosozumab followed by alendronate reduced subject incidence of new radiological vertebral fractures through month 24 and clinical (includes symptomatic vertebral and non-vertebral) fractures trough primary analysis period compared to alendronate only.

The subject incidence of new *radiological vertebral fractures* through 12 months was lower in the romosozumab group compared to the alendronate group (3.2% vs 5.0%, p=0.008). New vertebral fractures through month 24 occurred in 4.1% of patients with romosozumab/alendronate treatment vs 8.0% with alendronate/alendronate treatment (p<0.001).

This study was event-driven and the primary analysis was performed after median follow-up time of approximately 32 months. Romosozumab reduced the risk of *clinical fractures* at the time point of primary analysis compared to alendronate (9.7% vs 13.0%, nominal p<0.001)

A reduction in *non-vertebral fractures was* not statistically significant at 12 (3.4% vs 4.6%) or at 24 months. At the time point of primary analysis, romosozumab/alendronate had reduced non-vertebral fractures compared to alendronate alone (8.7% vs 10.6%), multiplicity adjusted p=0.040.

Romosozumab increased *DXA BMD* compared with alendronate at the lumbar spine, (14% vs 5.0%), total hip (6.2% vs 2.8%) and femoral neck (4.9% vs 1.7%) at 12 months, p<0.001 at all locations. The differences remained significant at 24 months.

3.3. Uncertainties and limitations about favourable effects

Despite the study size, the absolute numbers of non-vertebral fractures were moderate resulting in modest absolute risk reductions. In study 20070337 at month 12, hip fractures had occurred in 7/3589 (0.2%) romosozumab patients vs 13/3591(0.4%) on placebo. In study 20110142 at month 12, hip fractures had occurred in 14/2046 (0.7%) romosozumab patients vs 22/2047 (1.1%) on alendronate.

A by-region subgroup analysis showed lack of efficacy in Central/Latin America (43% of the randomised subjects) and North America (2.7%, very few fractures in total). Central/Latin America patients had lower than expected fracture rates in the placebo group probably indicative of a lower baseline fracture risk in this subpopulation. The marked region differences in baseline FRAX probabilities hamper a straight forward interpretation of fracture analysis outcome, in particular for the analyses of non-vertebral and clinical fractures. Study 20060326 (N=255) is the only data source for both off-treatment and re-exposure to romosozumab and due to limited number of patients in multiple treatment arms, no firm efficacy conclusions can be made.

In addition to a pre-filled syringe, which has been used in the pivotal phase III studies, the applicant also did seek a marketing authorization for an auto-injector/pen for the administration of romosozumab. Study 20090418 was intended to show bioequivalence of the pre-filled syringe and the autoinjector/pen in healthy volunteers. Although the Applicant did show that the two devices were bioequivalent for the primary PK parameters and similar for PD markers, there were device complaints arising in two subjects after the injection with the auto-injector/pen. The use errors occurring in the usability tests could be attributed to participants not fully reading the IFU. The PIL and IFU were revised and the results of the readability test were indicative of acceptable performance.

3.4. Unfavourable effects

The extensive safety database included 11553 subjects in 19 romosozumab clinical studies who received at least 1 dose of romosozumab (n = 7681) or placebo (n = 3872). Additionally, the integrated control group for the osteoporosis safety analysis set includes 6155 subjects who received placebo, alendronate, teriparatide, and/or denosumab. The overall number of discontinuations was balanced between romosozumab and integrated control groups.

The most common adverse events were nasopharyngitis, headache, cough, arthralgia, dyspepsia and peripheral oedema with no striking differences between treatment groups. At 12 months, injection site reactions (5.2% vs 2.9%), muscle spasms (4.4% vs 3.9%) and neck pain (2.1% vs 1.5%) were more common in the romosozumab group vs placebo. Cataracts (2.1% vs 1.6%) were more common in the romosozumab group vs control and were included in the proposed SmPC.

The number of fatal adverse events was 0.8% in the romosozumab group compared to 0.7% in placebo group in the 12-month Placebo-Controlled Osteoporosis Safety Analysis Set. In the alendronate-controlled study 20110142, the number of fatal adverse events was higher in the romosozumab group with 30 (1.5%) compared to alendronate 21 (1.0%). The exposure-adjusted incidence rate of fatal Treatment-emergent Adverse Events (in the Osteoporosis Safety Analysis Set) in all studies, including 20110142, was n = 63 (1.0 per 100 subject-years) in the romosozumab group and 47 (0.8 per 100 subject-years) in the control group. The overall numerical imbalance in fatal events was mainly due to fatal cardiac disorders and neoplasms in the romosozumab group.
In study 20070337, patients 75 years of age and older had a significantly increased risk of death in general in the romosozumab arm as compared to alendronate (19 vs 8 cases; HR 2.4 [95%CI 1.03-5.40]). This

difference in patients 75 years and older vs control (alendronate or placebo) was also observed in the safety analysis set of all pivotal trials (20070337,20110142,20110174) (46 vs. 26 cases, HR 1.71 [95%CI 1.06,2.78]).

Cardiovascular events

Independent adjudication of serious cardiovascular events was pre-specified in the 3 pivotal studies. An imbalance in positively-adjudicated cardiovascular serious adverse events was observed between romosozumab (2.5%) and alendronate (1.9%) in Study 20110142. This imbalance was due specifically to serious cardiac ischaemic (0.8% vs 0.3%) and serious cerebrovascular (0.8% vs 0.3%) events. Death, serious MI or serious stroke (MACE) occurred in 53/2040 (2.6%) patients treated with romosozumab compared to 32/2014 (1.6%) patients treated with alendronate, HR 1.7 (95%CI 1.1-2.6). An imbalance in major adverse CV events noted in the 12-month double-blinded treatment period persisted at least through month 24 in the follow-up period.

In the larger, placebo-controlled study (Study 20070337) the adjudicated MACE HR was 1.1 (95%CI 0.7-1.7).
In the smaller placebo-controlled male osteoporosis study, a tendency to imbalance in positively-adjudicated cardiovascular events was again observed between treatment groups, MACE HR 1.6 (95%CI 0.3-7.7, broad CI due to few subjects). Some imbalance in cardiovascular events was also noted at 12 months in study 20080289, compared to teriparatide in subjects who transitioned from bisphosphonate therapy (safety analysis set of 432 subjects). Serious cardiac disorders were reported in 2.3% for romosozumab and 0.9% for teriparatide.

Other events of interest

A difference over placebo in the incidence of serious infections and infestations was noted in study 20070337 (romosozumab 1.9% vs. placebo 1.3%). The difference is mainly driven by cases of serious pneumonia (romosozumab 0.5% vs. placebo 0.3%), which were in both treatment groups almost exclusively identified in the largest trial 20070337 in osteoporotic women. Serious infections are included in the RMP as an important potential risk.

Romosozumab administration was associated with transient decreases in serum calcium. In study 20070337, there was a decrease in corrected serum calcium levels. Median change from baseline was -2.2% at month 1 and -1.0% at month 12, for subjects who received romosozumab vs 0% for subjects who received placebo. Only few adverse events of hypocalcaemia (5 subjects, < 0.1%) were reported as adverse events in romosozumab-treated patients in pivotal studies. Romosozumab treatment was also associated with decreases in s-phosphorus. The median percent change from baseline was -5.1% vs 0% for placebo at month 1 and -5.4% vs -2.3% at month 12. In the Serum iPTH and Urinary Calcium substudy analysis set of study 20070337, the median percentage increase from baseline in iPTH was 29% in the romosozumab group and 4% in the placebo group at month 6, and 27% vs 8% at month 12. The median percent decrease in estimated 24-hour urinary calcium excretion was -16.8% in the romosozumab group and 3.0% in the placebo group at month 6 and -15.9% vs -7.6% at month 12. These changes may be secondary to the decrease in s-Ca.

Total numbers of AEs related to hypersensitivity were balanced between romosozumab and placebo. Serious hypersensitivity was, however, more common in romosozumab treated patients vs placebo (0.2% vs <0.1%). Osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF) are known AEs associated with longer term exposure of antiresorptive medications. Some events occurred in romosozumab/denosumab,

alendronate/romosozumab and alendronate/alendronate treatment groups but not in the placebo/denosumab group that had the shortest total exposure of active treatments.

3.5. Uncertainties and limitations about unfavourable effects

Romosozumab is a first-in-class monoclonal antibody binding to and inhibiting sclerostin. Sclerostin is constitutively expressed in the aorta and upregulated in foci of vascular calcification. However, a weight of evidence assessment of all available non-clinical data indicates no obvious mechanistic association between sclerostin inhibition and vascular calcification or promotion of atherosclerosis, in normal and/or diseased tissue. Further non-clinical testing is, thus, not likely to contribute to the overall benefit / risk assessment in humans.

Findings regarding adjudicated CV events in the two large pivotal studies were somewhat divergent. The two large pivotal studies 20110142 and 20070337 had different inclusion/exclusion criteria regarding osteoporosis severity (T-scores and fractures), with overlapping inclusion criteria in only 14% of the subjects. Various post hoc subgroup analyses based on CV risk factors (e.g., osteoporosis severity, diabetes, and smoking) were conducted and did not identify a subpopulation at consistently reduced relative risk of CV SAEs with administration of romosozumab.

In response to the concerns of the CHMP, the Applicant has during the procedure investigated the cardiovascular risk profile of romosozumab in a new proposed target population with a larger need for osteoporosis treatment and a potentially relatively lower risk for cardiovascular events than the broad study population, i.e. subjects with severe osteoporosis and with no history of MI or stroke. By excluding subjects with a history of MI/stroke from the post-fracture population in studies 20070337 and 20110142, the calculated absolute number of CV events in this population in the romosozumab versus control arm would decrease. However, the relative risk for MACE in romosozumab versus control treated subjects is still largely unchanged.

Neoplasms were detected in the overall number of deaths in the 12 months placebo controlled osteoporosis set where a malignant lung neoplasm was reported (romosozumab: 4 [0.1%] subjects, placebo: 0 subjects) and also in the retreatment period of phase 2 study 20060326, where malignancies were reported for 6 subjects (3.6%), of which 5 were subjects who had received romosozumab during the first 2 years of the study. The individual case reports of these four patients reveal strong risk factors for developing the disease, such as long term smoking, and COPD that would make a connection of romosozumab in the development of the disease unlikely.

In the entire osteoporosis safety analysis set, there were only a few patients with baseline GFR 15-30 mL/min/1.73 m2; 14 subjects in the romosozumab group and 8 subjects in the placebo group. A phase 1 Study 20110227 was conducted in 8 healthy subjects and 8 subjects each with stage 4 RI or stage 5 CKD requiring haemodialysis. Hypocalcaemia was reported in >30% of the subjects with CKD stage 4 or 5 after a single dose. The administration of romosozumab resulted in a greater decrease in serum calcium level and a greater increase in iPTH in subjects with CKD stage 4 or 5 than in healthy subjects.

During the procedure, after careful assessment of the available data, the CHMP had seriously questioned whether the Benefit/Risk of romosozumab for male osteoporosis patients is comparable to the Benefit/Risk of female patients. However, as the Applicant chose not to pursue the male indication further before final decision, no formal conclusion by the CHMP was stated.

3.6. Effects Table

Tables 83 and 84 below are based on the data from the pivotal trials (thus including the originally proposed entire study populations). The results for long-term benefit achieved with sequential therapy at the time of primary analysis are described above.

Tables based on post-hoc analyses in a subpopulation according to the restricted target population proposed during the procedure are presented in the sections "Discussion on Clinical Efficacy" and "Discussion on Clinical Safety".

Table 79: Effects Table for study 20110142 (severe PMO population) results

Effect	Romosozumab n/N (%)	Alendronate n/N (%)	Nominal / exploratory p-value	Absolute risk Difference (%)	Numbers needed to treat or harm
Favourable reduction of fracture events at month 12					
New radiological vertebral	55/1696 (3.2)	85/1703 (5.0)	0.008	-1.8	54
Clinical vertebral and non-vertebral	79/2046 (3.9)	110/2047 (5.4)	-0.0-27	-1.8	56
Non-vertebral	70/2046 (3.4)	95/2047 (4.6)	0.057	-1.4	71
Hip	14/2046 (0.7)	22/2047 (1.1)	NS	-0.3	333
Favourable reduction of fracture events at primary analysis approx. at month 33 (All patients received alendronate after month 12)					
Clinical vertebral and non-vertebral	198/2046 (9.7)	266/2047(13.0)	<0.001	Not available as subjects have various exposure at primary analysis	
Non-vertebral	178/2046(8.7)	217/2047(10.6)	0.037		
Hip	41/2046 (2.0)	66/2047(3.2)	0.015		
Unfavourable (cardiovascular) events at month 12					
AEs of ischaemic heart disease	34/2040 (1.7)	18/2014 (0.9)	0.035	0.77	129
CNS haemorrhages and cerebrovascular conditions	44/2040 (2.2)	32/2014 (1.7)	NS	0.57	175
Death (all)	30/2040 (1.5)	22/2014 (1.1)	NS	0.38	265
Adjudicated MACE	53/2040 (2.6)	32/2014 (1.6)	0.028	1.0	99

Abbreviations: MACE = all-cause death, and positively-adjudicated serious myocardial infarction or serious stroke; NS = Not statistically significant
For New radiological vertebral fracture, the absolute risk reduction was based on the Mantel-Haenszel method adjusted for age strata, Baseline total hip BMD T-score (⩽ -2.5, > -2.5), and presence of severe vertebral fracture at Baseline.
For other fracture types the absolute risk difference is based on inverse variance weighted method adjusting for age strata, baseline total hip BMD T-score (⩽ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.
For cardiovascular events, the absolute risk difference is based on raw risk differences between the treatment groups.
p-values are all nominal and two-sided based on the corresponding test on ratios, i.e. Hazard ratios based on a Cox-model for "clinical vertebral and non-vertebral", non-vertebral and hip fracture and odds ratios based on a logistic regression model for new radiological vertebral fractures.

Table 80: Effects Table for study 20070337 (less severe PMO population) - results at month 12

Effect	Romosozumab n/N (%)	Placebo n/N (%)	Nominal / exploratory p-value	Absolute risk Difference (%)	Numbers needed to treat or harm
Favourable fracture events					
New radiological vertebral	16/3321 (0.5)	59/3322 (1.8)	<0.001	-1.30	77
Clinical vertebral and non-vertebral	58/3589 (1.6)	90/3591 (2.5)	0.008	-1.2	83
Non-vertebral	56/3589 (1.6)	75/3591 (2.1)	NS	-0.8	125
Hip	7/3589 (0.2)	13/3591 (0.4)	NS	0.3	333
Unfavourable (cardiovascular) events					
AEs of ischaemic heart disease	39/3581 (1.1)	41/3576 (1.1)	NS	-0.1	1741
CNS haemorrhages and cerebrovascular conditions	33/3581 (0.9)	35/3576 (1.0)	NS	-0.1	1748
Death (all)	29/3581 (0.8)	24/3576 (0.7)	NS	0.14	722
Adjudicated MACE	42/3581 (1.2)	38/3576 (1.1)	NS	0.1	907

Abbreviations: MACE = all-cause death, and positively-adjudicated serious myocardial infarction or serious stroke; NS = Not statistically significant
For New radiological vertebral fracture, the absolute risk reduction was based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables.
For other fracture types the absolute risk difference is based on inverse variance weighted method adjusting for age strata, baseline total hip BMD T-score ($\leqslant$ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.
For cardiovascular events, the absolute risk difference is based on raw risk differences between the treatment groups.
p-values are all nominal and two-sided based on the corresponding test on ratios, i.e. Hazard ratios based on a Cox-model for "clinical vertebral and non-vertebral", non-vertebral and hip fracture and odds ratios based on a logistic regression model for new radiological vertebral fractures.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Radiological vertebral fractures are common findings in postmenopausal women but they are frequently asymptomatic (in approximately 60%). A typical symptomatic vertebral fracture causes acute pain and decreased mobility that may last about one month. BMD is a surrogate marker for osteoporosis severity and included in the osteoporosis definition by the WHO criteria. Fractures that require surgery are the most severe aspect of osteoporosis. Surgery is sometimes necessary for wrist fractures and other fractures, however hip fractures in particular are associated with serious risks, permanent disability and also increased mortality.

Romosozumab is a first-in-class monoclonal antibody. Romosozumab reduced the risk of new radiological vertebral fractures at 12 and 24 months compared to placebo and to alendronate in two pivotal studies. Romosozumab also reduced the risk of clinical fractures compared to placebo at 12 months and compared to alendronate at the time point of primary analysis. Thus, the predefined primary endpoints were met.

The effect on non-vertebral fractures (secondary endpoint) did not reach statistical significance in the placebo controlled study 20070337. In 43.0% of the randomized population (Central/Latin America) no reduction in non-vertebral fractures was observed in the romosozumab group after 12 months. Moreover, a significant reduction in hip fractures, one of the most severe aspects of osteoporosis, could not be demonstrated even after 36 months in study 20070337. In the study performed in patients with severe osteoporosis (study 20110142), the effect on non-vertebral fractures was superior to alendronate.

Alendronate is considered as 1st line osteoporosis therapy in many EU countries and has data of reducing the risk of vertebral and hip-fractures vs placebo in previous studies. However, there is no direct comparison of the effect size with other potent antiresorptive treatments (e.g. denosumab, zoledronic acid) available.

An increased risk of cardiovascular serious adverse events was noted in the clinical programme with an increase in adjudicated MACE events (myocardial infarction, stroke and death) observed in 2 of 3 pivotal studies: between romosozumab and alendronate in the pivotal study 20110142 as well as in the smaller placebo-controlled male study. In addition, in study 20110142 patients 75 years and older had a significantly increased risk of death in general in the romosozumab arm as compared to alendronate. This significantly increased incidence in patients older than 75 was also observed (for romosozumab vs. alendronate or placebo as comparator) in the safety analysis set of all pivotal trials (20070337, 20110142, 20110174).

Patients with severe osteoporosis (included in study 20110142) are generally at higher risk for CV events. However, already the osteoporosis population overall has a higher risk of CV events compared to the general population. No sub-population has been identified in which there is no increased relative risk of major adverse cardiac events (MACE) with romosozumab (even if it is acknowledged that the number of events in some sub-groups is low and the data should be interpreted with some caution). The Applicant had proposed a contraindication in patients with previous MI or stroke due to their increased baseline risk of CV events. It is agreed that patients with a history of MI or stroke are an easily identifiable and homogeneous population and at greatest absolute risk of a subsequent event. However, it is questionable if this would reduce the risk to an acceptable level considering that the mechanism behind the increased risk is not known and no subgroup without an increased risk has been identified.

The Applicant had proposed several post authorisation safety studies (PASS). These were intended to evaluate adherence to the risk minimization measures and the effectiveness of the educational materials

intended for implementation in the EU (for both HCPs prescribing romosozumab and patients being prescribed romosozumab), and to further characterize the CV risk. The latter PASS, however, was considered not likely to obtain further information related to the risk beyond what is available from randomized clinical studies.

3.7.2. Balance of benefits and risks

Taken together, the CHMP considers that the effect of sequential treatment with romosozumab followed by antiresorptive therapy appears to be of clinically relevant magnitude for the proposed target population of postmenopausal women with severe osteoporosis, but that the increased risk of MACE in the proposed target population was of major concern. An increased mortality in patients 75 and older was also concerning. In subjects with less severe osteoporosis, where there might be a lower absolute risk of MACE, the efficacy of romosozumab was less convincing, e.g., a statistically significant benefit on non-vertebral fractures and hip fractures could not be shown. The proposed risk minimisation activities (such as warnings, contraindications) were not considered to remove (or satisfactorily limit) this risk, in particular considering that the underlying cause and mechanism of action for the increased risk is not known and no subgroup without an increased risk has been identified.

Therefore, the benefits are not considered to outweigh the risks in the considered target populations.

3.8. Conclusions

The overall B/R of Evenity is negative.

Divergent positions are appended to this report.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Evenity in the treatment of severe osteoporosis in postmenopausal women at high risk of fracture, the CHMP considers by majority decision that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product. The CHMP considers that:

Whereas the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated:

- The increased risk of MACE in study 20110142 representing the proposed target population of postmenopausal women with severe osteoporosis is a major concern. The proposed risk minimisation activities (warnings, contraindications) are not considered to satisfactorily reduce the risk considering that the mechanism is not known and no subgroup without an increased risk of MACE has been identified. In addition, in the pooled safety data set, an increased risk of all cause mortality in patients 75 years of age and older was documented.
- The efficacy of Evenity (romosozumab) for the treatment of osteoporosis appears to be of clinically relevant magnitude in the proposed target population of postmenopausal women with severe osteoporosis. In subjects with less severe osteoporosis, where there might be a lower absolute risk of MACE, the efficacy of romosozumab is less convincing, e.g., a statistically significant benefit on non-vertebral fractures and hip fractures could not be shown.

Therefore, the benefits are not considered to outweigh the risks in any of the proposed target populations.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

5. Re-examination of the CHMP opinion of 27 June 2019

Following the CHMP conclusion that Evenity was not approvable based on concerns with an increase of cardiovascular events and an adverse outcome in elderly in some of the studies and a smaller reduction of fracture risk in less severe osteoporosis, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant:

Introduction

In their "grounds for re-examination" the applicant brought forward their arguments in support of the approval of therapy with romosozumab. The applicant defined a proposed population based on BMD (T< -2.5) and a previous fragility fracture, or 'severe osteoporosis' according to the WHO definition.

During the re-examination several letters were submitted to the Agency, which were brought to the attention of the CHMP for transparency, advocating the approval of the product.

5.1. Grounds for re-examination - Safety

The grounds for refusal were as follows:

The increased risk of MACE in study 20110142 representing the proposed target population of postmenopausal women with severe osteoporosis is a major concern. The proposed risk minimisation activities (warnings, contraindications) are not considered to satisfactorily reduce the risk considering that the mechanism is not known and no subgroup without an increased risk of MACE has been identified. In addition, in the pooled safety data set, an increased risk of all-cause mortality in patients 75 years of age and older was documented.

Imbalance in all-cause mortality in study 20110142

The Applicant, in their grounds for re-examination, addressed the concerns with the mortality imbalance as follows:

The Applicant concludes that all-cause mortality in this study is driven by the imbalance in MI and stroke: As shown in Table 81, in 20070337, a total of 24 placebo subjects (0.7%) vs 29 romosozumab subjects (0.8%) had a fatal adverse event (AE), whereas in 20110142 this was 22 ALN subjects (1.1%) vs 30 romosozumab subjects (1.5%).

All fatal AEs in these studies were adjudicated by Duke Clinical Research Institute (DCRI) and were confirmed as either CV or non-CV-related deaths according to the Charter. These were further classified according to the underlying causes. Deaths which could not be confirmed to be CV related were assumed to be CV in the analysis.

Table 81: Subject incidence of all-cause mortality by classification in the 12-month Double-Blind Period in 20070337 and 20110142

Study	20070337		20110142	
Category	**Placebo**	**Romosozumab 210mg QM**	**ALN 70mg QW**	**Romosozumab 210mg QM**
	(N=3576) n (%)	(N=3581) n (%)	(N=2014) n (%)	(N=2040) n (%)
All-cause death	24 (0.7)	29 (0.8)	22 (1.1)	30 (1.5)[a]
Death CV related	9 (0.3)	6 (0.2)	5 (0.2)	10 (0.5)
Acute MI	1 (<0.1)	1 (<0.1)	0 (0.0)	3 (0.1)
Heart failure	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Other CV	0 (0.0)	4 (0.1)	1 (<0.1)	0 (0.0)
Stroke	2 (<0.1)	0 (0.0)	2 (<0.1)	2 (<0.1)
Sudden cardiac	6 (0.2)	0 (0.0)	2 (<0.1)	5 (0.2)
Death non-CV related	9 (0.3)	12 (0.3)	10 (0.5)	12 (0.6)
Accidental (unintentional injury)	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)
Chronic lower respiratory disease	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhage (not intracranial)	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)
Infection	1 (<0.1)	0 (0.0)	4 (0.2)	5 (0.2)
Malignant neoplasm	4 (0.1)	10 (0.3)	3 (0.1)	5 (0.2)
Other non-CV death	0 (0.0)	0 (0.0)	2 (<0.1)	0 (0.0)
Suicide	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Undetermined	6 (0.2)	11 (0.3)	7 (0.3)	7 (0.3)

CV=cardiovascular; DCRI=Duke Clinical Research Institute; MI=myocardial infarction; N=Number of randomized subjects who received at least 1 dose of investigational product; QM=every month; QW=every week

[a] Of the all-cause deaths (30 events), 29 events were adjudicated by DCRI and categorized as specified in the table. The unadjudicated case was Subject 14256004126 who had a fatal femoral neck fracture, which was not considered in the categorization.

The incidence of non-CV deaths in the 12-month Double-Blind Period was generally balanced in both studies with the majority of deaths in both studies attributable to malignancies (22 of 43 cases). In 20070337, malignancy-related deaths were slightly higher in the romosozumab group (10 [0.3%]) compared to the placebo group (4 [0.1%]). Review of these deaths showed that these were primarily driven by lung neoplasms. All subjects with malignant lung neoplasms were current or former smokers, the time to onset was short (47 to 132 days after first treatment of romosozumab (as presented in the Day 120 Response to Questions) and the overall incidence of fatal and nonfatal lung neoplasms was balanced between treatment groups. These data support a lack of effect of romosozumab on non-CV mortality compared to either placebo or ALN.

With regards to CV mortality (Table 81, "CV death" + "Undetermined"), in 20070337 was generally balanced 17 romosozumab-treated subjects (0.5%) and 15 placebo-treated subjects (0.4%) experiencing positively-adjudicated CV deaths. In 20110142, the incidence of fatal CV events was 17 romosozumab subjects (0.8%) compared to 12 ALN subjects (0.6%). Of these, 5 romosozumab subjects compared to 2 ALN subjects were fatal MIs or strokes. The incidence of non-MI or non-stroke fatal CV events was balanced (9 romosozumab and 8 ALN).

When reviewed by age groups (Table 82), an imbalance in death specifically in subjects ≥75 years old is observed in both 20070337 and 20110142 during the 12-month Double-Blind Period, which was no longer apparent in the Overall Study Period. In 20070337 imbalances were driven by the non-CV death category (0.0 vs 0.5%), which was driven by 4 malignancy deaths and the Undetermined death category (0.2% in

placebo vs 0.7% in romosozumab). Similarly, in 20110142 the imbalance in all-cause death was driven by the Undetermined (0.3% vs 0.6%) and confirmed CV (0.8% vs 1.3%) death categories.

The trend in CV vs non-CV deaths in the 2 pivotal studies was generally consistent regardless of age. Furthermore, the small number of events limits the ability to draw specific conclusions, particularly when those numbers become even smaller when split by age groups.

In conclusion, the differences in mortality seen at the end of the 12-month Double-Blind Period in 20110142 is primarily accounted for by a higher number of fatal MI and strokes in romosozumab-treated subjects compared to ALN-treated subjects. This aligns with the imbalance seen for the total number of MI and stroke (fatal and nonfatal). Importantly, there is no increased risk of mortality beyond that related to the imbalance in overall MI and stroke.

Table 82: Subject incidence of fatal adjudicated AEs in the 12-month Double-Blind Period in 20070337 and 20110142 by age

Study	20070337		20110142	
Treatment	**Placebo n/N (%)**	**Romosozumab n/N (%)**	**ALN n/N (%)**	**Romosozumab n/N (%)**
Overall	24/3576 (0.7)	29/3581 (0.8)	22/2014 (1.1)	30/2040 (1.5)[a]
<75 years	16/2461 (0.7)	10/2464 (0.4)	5 /965 (0.5)	5/970 (0.5)
CV Death	7	4	4	3
CV Death	3	1	0	2
Undetermined	4	3	4	1
Non-CV Death	9	6	1	2
Malignancies	4	6	0	0
Other	5	0	1	2
≥75 years	8/1115 (0.7)	19/1117 (1.7)	17/1049 (1.6)	25/1070 (2.3)[a]
CV Death	8	13	8	14
CV Death	6	5	5	8
Undetermined	2	8	3	6
Non-CV Death	0	6	9	10
Malignancies	0	4	3	5
Other	0	2	6	5

AE=adverse event; ALN=alendronate; CV=cardiovascular; DCRI=Duke Clinical Research Institute; N=number of subjects in the analysis set (overall, <75 years, and ≥75 years); n=number of subjects who reported ≥1 event.
[a] Includes 1 (DCRI) unadjudicated case (Subject 14256004126 who had a fatal femoral neck fracture) which was not considered in the categorization in the table.
categorization in the table.

Discussion and Conclusion by CHMP:

The 12-month double blind period was the period during which differences in cardiovascular outcome became most evident; in the view of the CHMP, analysis of this time period is appropriate.

Non-CV deaths were higher with romosozumab than with comparator (24 v 19), with a striking difference in death due to malignancy (15 v 7). Based on time to onset, this could be a chance finding as was assumed in the original procedure.

'Undetermined death' was assumed to be CV-death. The absolute numbers of subjects and percentages are small in these groupings. On the one hand it may be argued that addition of the 'undetermined' group masks an effect, on the other hand it may be argued that classifying 'undetermined' as 'CV-death' is a conservative approach that may be regarded as acceptable.

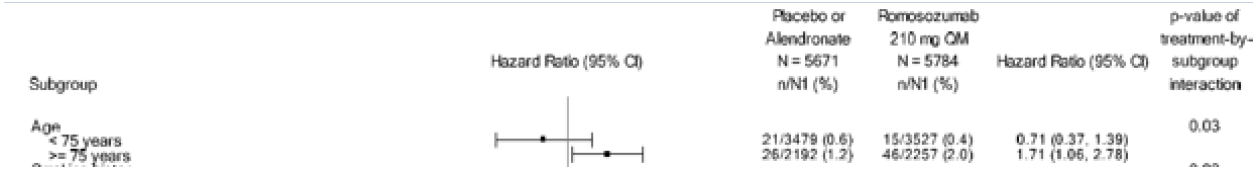
Also CV deaths and "undetermined" deaths were higher with romosozumab (16 v 14 and 18 v 13 respectively). After exclusion of the MI/stroke related cases, mortality still disfavoured romosozumab in both trials (20070337: 28 v 21 and 20110142: 25 v 20).

Subgroup of elderly above 75 years

The differences in mortality were also apparent in the subgroup of elderly above 75 years and observed in both trials. One-year all-cause mortality in elderly (≥75 years) was 19 vs 8 in Study 20070337 and 25 v 17 in Study 20110142 for Romosozumab vs control, respectively. Although the results point in the same direction possibly suggesting a safety signal, it may be accepted that it is difficult to make firm conclusions because of the small number of subjects (n=105, less than 1%) affected (either in total or in subgroups).

The applicant did not address this issue within the re-examination procedure. The pooled safety data set referred to in the included subjects in study 174, i.e. men. Analysis was presented and assessed in the initial part of the procedure, as shown:

Figure 32: Subgroup analysis of baseline Characteristics: Time to First Occurrence of Adverse Event Leading to death through Month 12 (Safety Analysis Set) (20070337, 20110142, 20110174)



It is agreed that the meta-analysis that combines results of studies with different designs and that put placebo and alendronate as 'same' control is not appropriate; therefore the forest plot of figure 32 above is considered to be not appropriate.

More detailed analyses of data from placebo-controlled studies showed the following:

Of 7628 unique subjects in the 12-month placebo-controlled osteoporosis safety analysis set [studies 174 & 337 and 2 phase II studies], 57 deaths (0.7% of subjects overall: 0.8% of total romosozumab group and 0.7% of placebo group) were reported.

Among subjects who received romosozumab, 31 deaths (0.8% of subjects) were reported; fatal adverse events reported for 2 or more subjects in the total romosozumab group included lung neoplasm malignant (reported for 4 subjects), cardiorespiratory arrest (reported for 3 subjects), myocardial infarction (reported for 2 subjects), and death not otherwise specified (reported for 6 subjects). The 4 subjects with fatal malignant lung neoplasm were all current or former smokers, 1 subject had a history of basal cell carcinoma, and 1 subject reported a family history of unspecified cancer.

Among subjects who received placebo, 26 deaths (0.7% of subjects) were reported; fatal adverse events reported for 2 or more subjects included myocardial infarction, angina pectoris, and cerebrovascular accident (reported for 2 subjects each) and death not otherwise specified (reported for 6 subjects). Treatment-related fatal adverse events were reported for 1 subject in each treatment group (deep vein thrombosis in the romosozumab group and sudden death [cause unknown] in the placebo group.

The causes of the deaths were consistent with what is expected for the subject population enrolled in these studies.

Study 20110142 used alendronate as an active control, and thus was not included in the 12-month placebo-controlled osteoporosis safety analysis set. In this study, in which the average age was more than 3 years older than the placebo-controlled population,

- 30 (1.5%) subjects in the romosozumab group and 21 (1.0%) subjects in the alendronate group had fatal adverse events during the double-blind period. Adverse events (preferred terms) resulting in death, which occurred in ≥2 subjects in the romosozumab group, were acute myocardial infarction (3 subjects), cardiac failure (2 subjects), and uro-sepsis (2 subjects).
- 21 (1.0%) subjects in the alendronate group had fatal adverse events during the 12-month double-blind treatment period. Preferred terms reported for ≥2 subjects in the alendronate group included pneumonia (3 subjects), cerebrovascular accident (2 subjects), death (2 subjects), and sudden death (2 subjects).

Comparison between the romosozumab and alendronate arms is made difficult by the alendronate arm having 4 subjects whose cause of death is recorded as 'death' or 'sudden death' instead of a more definite cause such as 'acute myocardial infarction' as in the romosozumab arm.

For a discussion on the caveats with subgroup analyses, reference is made to publications of Altman and colleagues (Analysis by categorizing or dichotomizing continuous variables is inadvisable: an example from the natural history of unruptured aneurysms. Naggara O, Raymond J, Guilbert F, Roy D, Weill A, Altman DG. AJNR Am J Neuroradiol. 2011 Mar;32(3):437-40; The problem of subgroup analyses: an example from a trial on ruptured intracranial aneurysms. Naggara O, Raymond J, Guilbert F, Altman DG. AJNR Am J Neuroradiol. 2011 Apr;32(4):633-6) and comments further below.
In the case of 'death of those >75yrs', the answer to most questions posed to establish whether or not a subgroup effect is present is 'no' i.e. it is difficult to claim credibility for the finding of the subgroup analysis. A similar approach is also described by Ioannidis & Guyatt and colleagues (in: How to Use a Subgroup Analysis. Users' Guides to the Medical Literature. Sun X et al. JAMA. 2014;311(4):405-411). Similarly, following CHMP guidance (EMA/CHMP/539146/2013, Jan 2019), it is concluded that the interpretation of an effect in those >75yrs old requires great caution, nonetheless, a signal of risk is described. It could suggest that the mortality is related to frailty, which might be difficult to capture in a clinical trial.

Imbalance in MI and stroke without identified biological mechanism

To address the CHMP's concern regarding the increased risk of MACE in 20110142, the Applicant had presented in the original MAA during the review an assessment of the data. The Applicant considerd that the divergent results in the 2 pivotal fracture studies have introduced important uncertainty regarding the existence and magnitude of any CV risk and this differed from the CHMP view that the imbalance observed in 20110142 or the meta-analysis conclusively established the identified risk.

Possible principle causes for the observation in study 142 could include:

i. Increased risk of a cardiovascular event consequent to exposure to romosozumab
ii. Decreased risk of a cardiovascular event consequent to exposure to alendronate
iii. a random low event rate creating spurious imbalance in the context of background low absolute risk of cardiovascular events
iv. more background cardiovascular disease in women with severe osteoporosis [the population of study 142 compared to those is study 337] contributing to 'noise'.
v. other, unidentified cause

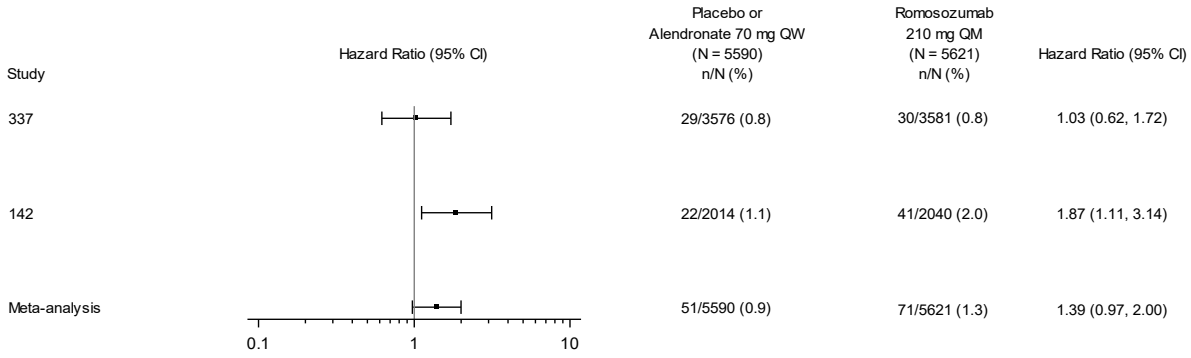
Clinical and nonclinical evaluations have not identified a mechanism by which romosozumab may exert an effect on the CV system and no subgroup can be identified in whom there is increased relative risk vs the entire study population.

Incidence in MACE in the 2 pivotal studies

The prespecified endpoint for the DCRI adjudication was the subject incidence of positively-adjudicated CV serious adverse events (SAEs), with subcategories that captured, among others, cardiac ischemic and cerebrovascular events, as well as CV death.

A posthoc analysis of the composite of MI, stroke, or CV death, ie, MACE, was performed to understand the CV safety profile, in line with the EMA reflection paper (EMEA/ CHMP/15404/2007). As shown in Figure 33, the subject incidence of MACE in the placebo-controlled study 20070337 was 0.8% in both the romosozumab-treated (30 subjects) and placebo-treated (29 subjects) groups. Conversely, in 20110142, 2.0% (41 subjects) of romosozumab-treated subjects compared to 1.1% (22 subjects) of ALN-treated subjects experienced a positively-adjudicated MACE in the 12-month Double-Blind Period.

Figure 33: Meta-analyses: Time to first occurrence of positively-adjudicated cardiovascular adverse event leading to death, serious myocardial infarction, or stroke through Month 12



N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period
Hazard ratio and 95% CI are based on Cox proportional hazards model; meta-analysis estimates are based on Cox proportional hazards model stratified by study comparing romosozumab versus 'control' (either placebo or alendronate).
Study 337 used 1:1 randomization allocation ratio between romosozumab and placebo.
Study 142 used 1:1 randomization allocation ratio between romosozumab and alendronate.
Death events include fatal events adjudicated as cardiovascular-related or undetermined.

While the applicant refered to an EMA reflection paper (Reflection paper on benefit risk assessment methods in the context of evaluation of marketing authorisation applications of medicinal products for human use. EMEA/CHMP/15404/2007, 19 Mar 2008), in which post hoc analyses are described under benefit where companies are invited to consider the impact of a post hoc analysis the current issue, however, is one of safety. Therefore the CHMP considers the Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015) as more relevant to the subject. It describes among others that as a general rule, assuming a comparison against a placebo or standard of care (SOC), the evidence based on the cardiovascular safety profile should be planned to obtain an upper limit of the confidence interval (UCL - 95%, two sided) for the Hazard Ratio (HR) below 1.8 in the event that HR≈1.

Interpretation of estimates of treatment effects

For study 20070337, no increase in incidence of MACE was observed in the 12-month Double-Blind Period with romosozumab treatment compared to placebo (0.8% in both treatment groups), translating into a 1.03 HR (95% CI: 0.62, 1.72). In contrast, the HR for MACE in 20110142 was 1.87 (95% CI: 1.11, 3.14), with 1.1% in the ALN arm and 2.0% in the romosozumab arm, corresponding to an absolute risk difference of 0.9%. A priori, there was no reason to expect the effect of romosozumab on CV risk would differ between these 2 studies. As each study contributed a modest number of events, it is possible the estimated HRs of CV risk from each study may reflect random high and/or random low bias and the true association between romosozumab and CV risk, if any, is reflected by a magnitude of risk somewhere in between.

One approach to identifying a plausible estimate is from a meta-analysis of the 2 studies. However, heterogeneity in baseline risk, different comparator arms in each study, and inconsistencies in the data from study 20110142 suggest that the results of a simple meta-analysis that equally weights the data from the 2 studies should be interpreted with caution.

It is agreed that the submitted studies were not designed to look for cardiovascular events.

The number of cardiovascular events is small over the time period examined; it is known that hazard ratios may be dis-informative in the presence of few events and where it cannot be shown that there is a constant proportion of hazard between the two study arms (because of small numbers), as is the case here.

The meta-analysis technique employed by the company is not considered appropriate; the forest plot in Figure 33 above is considered to be misleading. A more appropriate meta-analysis technique to combine results of different study designs and with different comparators would have been the network meta-analysis, as conducted by the FDA for the Evenity application in North America.

Uncertainties regarding the imbalance in MI and stroke from the ALN-controlled study

The rate of MACE in the control arms of both pivotal studies

Despite higher baseline CV risk in 20110142, the rate of MACE in the control arms of both pivotal studies aligns through 12 months:

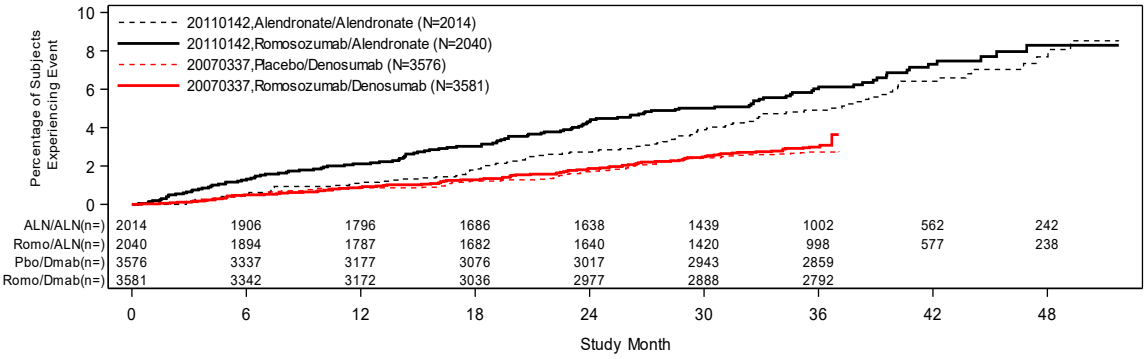
The CV-related medical history and CV-related baseline concomitant medications of the study populations enrolled in studies 20070337 and 20110142 were generally balanced between the treatment groups within each study.

However:

- subjects in 20110142 were on average approximately 3.5 years older than subjects in 20070337 and the population in 20110142 had higher prevalence rates of comorbidities than in 20070337, highlighted by the higher incidence rates of SAEs in 20110142 compared to 20070337. Prevalence rates of CV-related medical histories were generally balanced between the treatment groups within each study.
- subjects in 20110142 were more likely to have hypertension, history of coronary artery disease (ischemic heart disease, MI), and history of cerebrovascular disease (ischemic stroke or transient ischemic attack) than in 20070337.

Consistent with the higher rates of all SAEs observed in 20110142 compared to 20070337 and increased prevalence of comorbidities and risk factors that might influence the occurrence of CV events, the patient population in 20110142 would be expected to have a higher incidence of serious CV events than the patient population in 20070337 in both treatment groups. However, in contrast, the ALN-treated subjects in 200110142 had similar incidence of MACE in particular in the first 12 months of treatment (Figure 34), including two episodes of 3 months during which no MACE was reported. The US Food and Drug Administration (FDA) investigated whether there might be a cardioprotective effect of ALN by conducting an exploratory network meta-analysis to indirectly estimate the HR of MACE for ALN from 20110142 vs placebo from 20070337 during the first year of the 2 studies. Their analysis yielded a HR of 0.55 (95% CI: 0.27, 1.14) for ALN vs placebo. However, this exploratory network analysis cannot definitively address the CV risk of ALN, as a review of the literature and placebo-controlled ALN studies does not suggest a cardioprotective effect of ALN (US FDA, Multi-disciplinary review and evaluation [Biologics License Application 761062], 2019).

Figure 34: Kaplan-Meier plot of time to first MACE in the Overall Study Period (Safety Analysis Set) (DCRI Adjudication of 20070337 and 20110142)



N = Number of subjects in the safety analysis set

n = Number of subjects at risk for event at time point of interest

Study 20070337 used 1:1 randomization allocation ratio between romosozumab and placebo. Subjects received open-label denosumab after the 12-month double blinded period.

Study 20110142 used 1:1 randomization allocation ratio between romosozumab and alendronate. Subjects received open-label alendronate after the 12-month double blinded period.

The timepoint for study month 36 is set at study day 1082 (study day 1096 - 14 days).

Death events include fatal events adjudicated as cardiovascular-related or undetermined.

Program: f-km-eos-337-142-duke.sas

Output: f14-06-002-001-011-km-mace-eos-337-142-duke.rtf (Date Generated: 08MAY18 18:15) Source Data: adam.adttes, adam.adsl

This phenomenon is not observed over the longer duration of study follow-up (median 36 months) despite all subjects receiving ALN. In fact, during the Overall Study Period, the cumulative incidence of MACE in the ALN arm is consistent with the population in 20110142 being older and having higher rates of pre-existing CV risk factors. As can be seen in Figure 34, rather than continue to align with the rate of events in 20070337, it closes the gap with the treatment arm in 20110142 that received romosozumab.

During the original procedure the assessment of the CHMP agreed with the applicant that there was an acceptable balance between arms of each study as described above. Subjects in study 142 had more severe osteoporosis (with more consequence such as fracture) compared to subjects in study 337. There is a known association between severity of osteoporosis and cardiovascular disease (and vice versa) and so the findings of the company with regards to more evidence of cardiovascular disease in study 142 may be considered as not unexpected.

A signal of cardiovascular risk was also noted in study 20110174 (study of men with osteoporosis), as shown in the following table

Table 2. Subject Incidence of Positively-adjudicated Cardiovascular Serious Adverse Events by Layers and Study in the 12-month Double-blind Period (Safety Analysis Set) (Studies 20070337, 20110142, and 20110174)

	20110174		20070337		20110142	
Category (Layer 1) Layer 2 Layer 3	Placebo (N = 81) n (%)	Romosozumab 210 mg SC QM (N = 163) n (%)	Placebo (N = 3576) n (%)	Romosozumab 210 mg SC QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg SC QM (N = 2040) n (%)
Number of subjects reporting treatment-emergent adjudicated positive cardiovascular serious adverse event	2 (2.5)	8 (4.9)	46 (1.3)	46 (1.3)	38 (1.9)	50 (2.5)
Cardiac ischemic event	**0 (0.0)**	**3 (1.8)**	**16 (0.4)**	**16 (0.4)**	**6 (0.3)**	**16 (0.8)**
Angina	0 (0.0)	2 (1.2)	7 (0.2)	7 (0.2)	1 (<0.1)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.6)	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Type 1 (spontaneous)	0 (0.0)	1 (0.6)	7 (0.2)	8 (0.2)	2 (<0.1)	13 (0.6)
Type 2 (secondary)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	3 (0.1)	3 (0.1)
Type 4a (peri-PCI)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Type 4b (stent thrombosis)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
PCI or coronary bypass graft, without MI or angina	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular event	**1 (1.2)**	**3 (1.8)**	**11 (0.3)**	**10 (0.3)**	**7 (0.3)**	**16 (0.8)**
Stroke	1 (1.2)	3 (1.8)	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)
Hemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)	3 (0.1)
Ischemic stroke	1 (1.2)	3 (1.8)	10 (0.3)	2 (<0.1)	6 (0.3)	10 (0.5)
Undetermined stroke	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	1 (<0.1)	0 (0.0)
TIA	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)	0 (0.0)	3 (0.1)
CV Death	**1 (1.2)**	**2 (1.2)**	**15 (0.4)**	**17 (0.5)**	**12 (0.6)**	**17 (0.8)**
CV-Related[a]	0 (0.0)	1 (0.6)	9 (0.3)	6 (0.2)	5 (0.2)	10 (0.5)
Acute myocardial infarction	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)	3 (0.1)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Other cardiovascular	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	1 (<0.1)	0 (0.0)
Stroke	0 (0.0)	0 (0.0)	2 (<0.1)	0 (0.0)	2 (<0.1)	2 (<0.1)
Sudden cardiac	0 (0.0)	1 (0.6)	6 (0.2)	0 (0.0)	2 (<0.1)	5 (0.2)
Undetermined	1 (1.2)	1 (0.6)	6 (0.2)	11 (0.3)	7 (0.3)	7 (0.3)

A signal of cardiovascular risk was also noted in study 20080289; this was a randomized, open-label, 12-month, teriparatide-controlled study in 436 postmenopausal women with osteoporosis at high risk for fracture after transition from < 3 years of treatment oral bisphosphonates. Serious cardiac disorders were reported in 2.3% for Romosozumab and 0.9% for teriparatide. One serious cerebrovascular accident, one ischaemic stroke and one transient ischaemic attack were reported in the Romosozumab group vs none in the teriparatide group. It is noted that cardiovascular events were not adjudicated in this study.

Although studies 20110174 and 20080289 are not decisive with regards to cardiovascular risk, CHMP considered that the outcomes add to uncertainty.

Over time, the Kapplan-Meier curves (Figure 34) seem to cross; however this is only after 48 months. It could be interpreted as a fading unfavourable effect of romosozumab. Importantly, after 36 months less than half of the subjects were still in the trial, suggesting much uncertainty; at the time-point after 48 months only about 12% were still at risk.

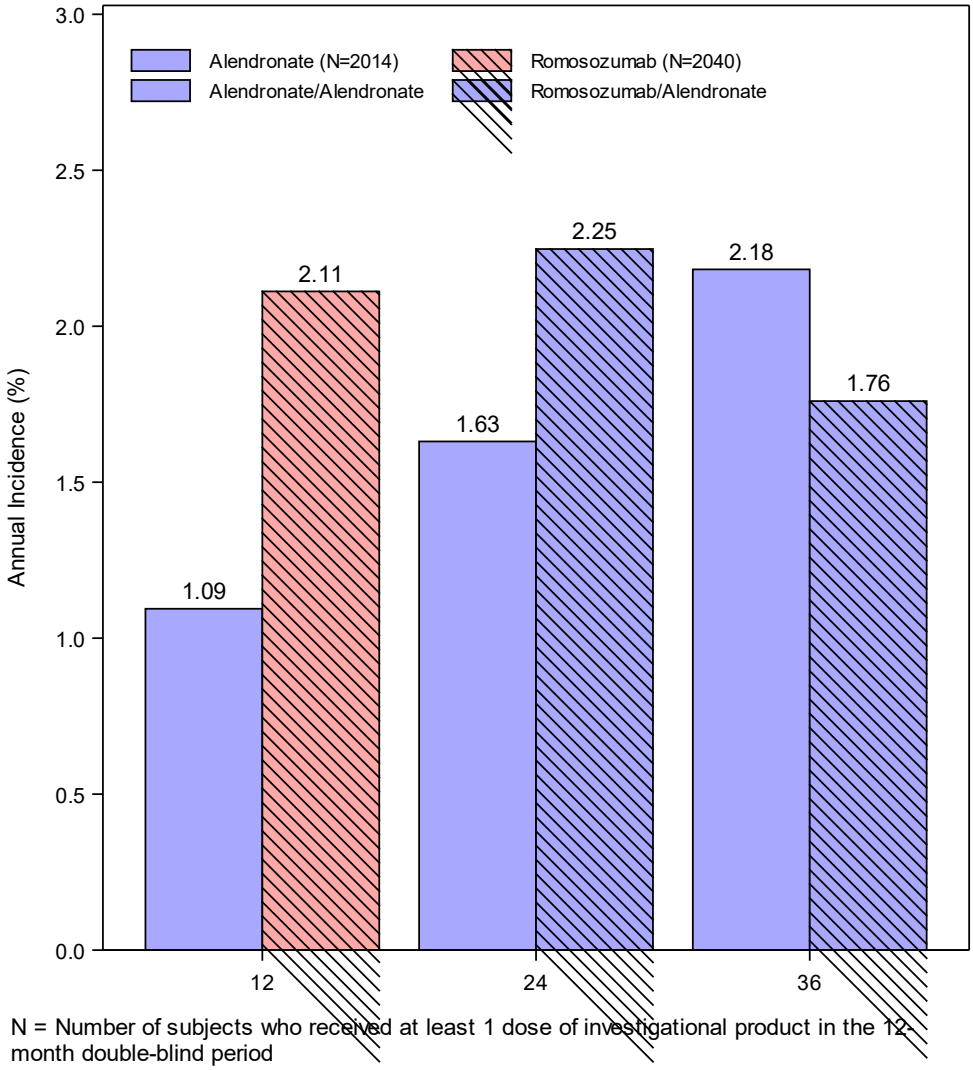
Event rate for the ALN arm

A standard assumption in the analysis of event-driven endpoints is a constant hazard rate over the course of follow-up. This assumption translates into the testable statistical hypothesis of proportion hazards between 2 arms in the Cox proportional hazard model used to estimate the HR for the treatment effect. It was noted that this assumption does not hold for the ALN arm in 20110142 for both the 12-month Double-Blind Period and Overall Study Period, where an increasing hazard is observed over time (Figure 34), with the lowest annualized rate of MACE observed in the first 12 months (1.1%) and a doubling of this rate by year 3 (2.2%).

The Kaplan-Meier curve for time to first MACE in the ALN-treated group (Figure 34) further illustrates this inconsistency in event rate across the duration of the study. This behaviour is not consistent with the biologic

mechanism of CV events, where the rate of events would not be expected to increase substantially over a time period of only 3 years.

Figure 35: Annual incidence of MACE in 20110142 (DCRI adjudication of 20110142)



N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period
The incremental KM incidences are the annual incremental changes of KM estimates at Month 12, Month 24 and Month 36.
Data of this figure also shown in Figure 30, in section "CV risk factors analysis" In2.6 Clinical Safety

For comparison, the constant rate of events that would be expected are seen in cardiovascular outcome trials; two representative examples are the SAVOR study in 16,492 Type 2 diabetes patients mean age 65 years and 14% of subjects ≥75 years of age and, CAMELLIA study in 12,000 obese patients with median age 64 (interquartile range: 58 to 69).

As shown in Figure 35, for the treatment arm in 20110142, romosozumab followed by ALN, the annual incidence in MACE remains constant. The Kaplan-Meier curve further illustrates this linear behaviour (Figure 34). In fact, if romosozumab were to affect CV outcomes adversely, then in both 20070337 and 20110142, the rate would be expected to change after this switch at Month 12 to denosumab or ALN, respectively.

Thus, the imbalance in MACE observed in 20110142, is primarily observed during the first 12 months when subjects were treated with either romosozumab or ALN. During this time period, 41 romosozumab-treated subjects (2.0%) and 22 ALN-treated subjects (1.1%) experienced at least 1 MACE, a difference of 19 subjects.

Thus, the applicant argued during the re-examination of the opinion, that in the context of a low background absolute risk, the potential for random low event rates creating spurious imbalances should be considered.

Discussion and Conclusion by CHMP

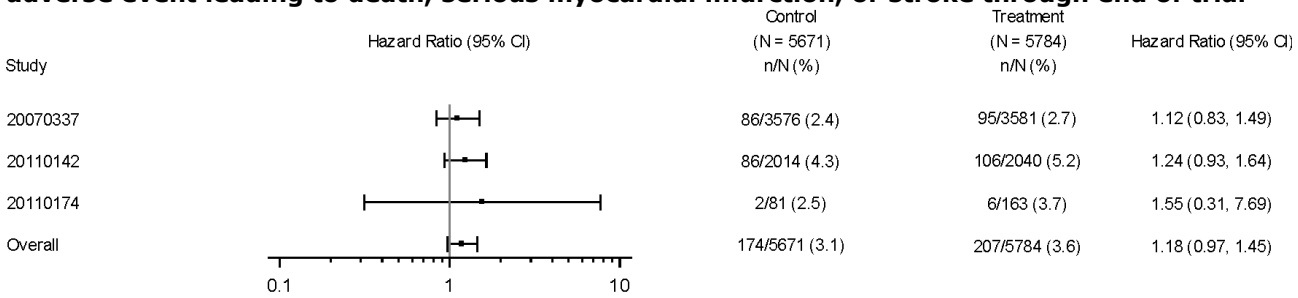
The Applicant has provided a meta-analysis of the adjudicated MACE events in the first year in both pivotal trials (Figure 33). This analysis results in a Hazard ratio of 1.39 (0.97; 2.00) and an absolute risk difference of 0.4% (romosozumab 1.3% v comparator 0.9%). The increased incidence of MACE was not observed in 20070337, HR 1.03 (95% CI: 0.62, 1.72), but only in 20110142; HR 1.87 (95% CI: 1.11, 3.14). However, in the view of the CHMP the meta-analysis techniques employed by the applicant were not considered appropriate. A more appropriate meta-analysis technique to combine results of different study designs and with different comparators would have been the network meta-analysis, as conducted by the FDA for the Evenity application in North America.

CHMP agreed with the Applicant that the meta-analysis of the studies is of little help in understanding the diverging observations. The Applicant suggested that the difference could be attributed to chance, but also explored other explanations. It is noted that the absolute risk of MACE was higher in the latter trial (1.6% v 0.8%). Subjects in 20110142 were on average approximately 3.5 years older than subjects in 20070337 and the population in 20110142 had higher prevalence rates of comorbidities than in 20070337, e.g. hypertension (61 v 53%) and ischaemic heart disease (13.6 vs 9.2%), suggesting higher CV risk. The observed rate of MACE in the control arms of trial 337 (PBO) and trial 142 (ALN) was similar (0.8%). Based on the higher CV risk, the number of MACE events in the comparator arm (ALN) in the first year of trial 142 is lower than expected and/or in trial 337 higher than expected.

In comparison with placebo, ALN could be cardioprotective; however, the applicant was not able to provide evidence for that, nor did an FDA review of the literature (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761062Orig1s000MultidisciplineR.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761062Orig1s000TOC.cfm) and placebo-controlled ALN studies suggest a cardioprotective effect of ALN. As FDA's network meta-analysis seems to be based only on trial 142 and 337, it is therefore subject to the same potential chance events that hamper understanding of the differences between the trials.
Another hypothesis could be a temporary CV benefit from ALN. While this would explain the observations in the 142 comparator group, no such phenomenon is observed in the 142 romosozumab group. In that case, the data suggest that romosozumab antagonises any temporary CV benefit from ALN.

CHMP agreed with the Applicant that the rate of MACE in CV outcomes trials e.g in type 2 diabetes is rather constant if no CV-effective pharmacological treatment is given. To correct for any short-term chance effects, the Applicant provided a simulation in which the HR for MACE was based on a control-group with ALN using data from year 1, 2 and 3. However, it remained unclear why this approach would be essentially different from a MACE analysis of the entire trial as presented in an analysis in the original assessment of the procedure.

Figure 36: Meta-analyses: Time to first occurrence of positively-adjudicated cardiovascular adverse event leading to death, serious myocardial infarction, or stroke through end of trial



Based on the meta-analysis, it could be argued that the upper limit of the confidence interval of 1.8 as a commonly used threshold (Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)) has been exceeded. However, the submitted studies were not designed to look for cardiovascular events. The number of cardiovascular events is small over the time period examined; it is known that hazard ratios may be dis-informative in the presence of few events and where it cannot be shown that there is a constant proportion of hazard between the two study arms (because of small numbers), as is the case here.

In conclusion, in the view of the CHMP there still seems to be a trend of an adverse effect on MACE through treatment with romosozumab, which is observed both in placebo and alendronate controlled trials. The effect size in trial 142 could be a random high; but, as discussed above, it is difficult to attribute the complete observations to chance.

Possible identification of a CV risk factor through subgroup analyses that drives the imbalance

The CHMP in its grounds for refusal stated that: "….. no subgroup without an increased risk [of MACE] has been identified".

The applicant in its responses stated that subgroup analyses were based on categorization of subjects defined by the well-established CV risk factors. As expected, they did show higher incidence of events in the high-risk subgroup compared to the low-risk subgroup. Yet, the relative risk of events between treatment arms was generally consistent within all subgroups and no subgroup was identified with consistently higher or lower estimated HRs. In the view of the applicant, the lack of a subgroup effect raises additional doubt about whether the risk is accurately reflected by the 20110142 estimate. Study 20110142 appeared to be at greater baseline CV risk than study 20070337, based on a higher age and prevalence of CV risk factors, comorbidities and concomitant medications. If this higher total CV risk contributed to a further increase in risk associated with romosozumab use, then it should be expected that a greater relative risk would be observed in the subset of subjects at highest CV risk in either study. On the contrary, all subsets of 20070337 consistently showed a lack of association between romosozumab and CV events. A subpopulation of 20070337 was not identified such that the magnitude of effect observed in 20110142 could be replicated or confirmed. In addition, relative risks seen in the subgroup analyses of 20110142 were generally similar to the results from the full study population.

The issue of interpretation of subgroup analyses is also described in: Guideline on the investigation of subgroups in confirmatory clinical trials, EMA/CHMP/539146/2013, Jan 2019. (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-

confirmatory-clinical-trials_en.pdf) In this document, the CHMP describes the need for consistency, credibility, biological plausibility and replication; the CHMP advice is essentially similar to that advised by Altman and colleagues, above.

The subgroup analyses were assessed in the original assessment. The company presented separate subgroup analyses for studies 337 and 142; the analyses for study 337 are pre-specified whereas those for study 142 are 'ad hoc' i.e. post hoc. For study 337 all subgroups lie on the line of unity based on baseline [general] characteristics and baseline cardiovascular risk factors. In study 142, exposure to romosozumab [compared to alendronate] is associated with a shift rightwards away from the line of unity i.e. apparent higher risk of MACE, as described, associated with exposure to romosozumab based on medical history and medication history.

In the view of CHMP, in study 142, subgroup analysis was

- 'ad hoc' (understood to be 'post hoc')
- Direction not specified
- Not based on small numbers of subgroups i.e. many subgroups displayed
- Not large effect / broad confidence intervals
- Not consistent with subgroup analysis of study 337
- Not [apparently] supported by a biological rationale

For the above reasons CHMP considered it difficult to give credibility for a particular subgroup effect of romosozumab in study 142. A general effect may be present.

Potential biological mechanism for MACE

In general, the mechanisms underlying MI and stroke events and CV risk factors are reasonably well understood. However, for romosozumab, no causal mechanistic association between sclerostin and/or romosozumab and CV risk could be identified, despite dedicated nonclinical studies specifically conducted to examine any potential effects as well as an extensive analysis of our own and publicly available genetic, nonclinical, and clinical data for sclerostin and/or romosozumab . These studies included evaluations obtained from young and aged ovariectomized animals and in normal and diseased animal models, as well as ex vivo human atherosclerotic plaques.

Nonclinical evidence

The nonclinical data considered during the assessment for a potential mechanistic association between sclerostin, romosozumab, and CV risk, and the findings are summarized below.

- There was no evidence of any treatment-related adverse effects on the CV system following treatment with romosozumab in the young or aged monkey in studies up to 12 months duration, or in the rat in studies of up to 98 weeks duration (Studies 105781, 107426, 107903 and 107895). These studies included CV telemetry studies and assessment for any increase in the incidence of tissue calcification in rats in a lifetime study and aortic mineralization in aged ovariectomized monkeys.

- The key events which lead to MI and stroke, namely plaque rupture, plaque erosion, increased thrombogenesis, and vasospasm, and the key pathological mediators underlying each of these (combined and modified from Crea and Libby, 2017; Ford et al, 2017; Pasterkamp et al, 2017; Hellings et al, 2010; Naghavi et al, 2003) were also evaluated. There was extensive data to support this evaluation in either normal and/or diseased tissues.
- There was no evidence that any of the key pathological processes leading to MI and stroke were affected by the inhibition of sclerostin in either normal and/or diseased tissues. Specific to this assessment, pivotal dedicated studies included assessment of sclerostin expression in 144 advanced human atherosclerotic plaques, which showed that sclerostin expression did not correlate with various plaque features associated with atherosclerosis or MACE or with the patient's medical history of CV events pre- and post-removal of the plaques assessed.
- In addition, inhibition of sclerostin did not affect atheroprogression in the apolipoprotein E knock out atherosclerosis mouse model, neither sclerostin nor romosozumab induced vasospasm in human coronary arteries and romosozumab did not induce platelet activation.

In summary despite intensive preclinical study there was no evidence to support sclerostin or romosozumab impacting any mechanism known to be related to MI and stroke.

Genetic evidence

In addition to nonclinical data, genetic data were also evaluated for any evidence of a potential mechanistic association between sclerostin, romosozumab and CV risk are summarized below.

- Sclerosteosis and Van Buchem's patients are completely deficient in sclerostin or have low levels of sclerostin respectively. Sclerosteosis patients typically have a shortened lifespan but at least 5 have lived for more than 50 years, without reported CV effects. There are no reports of clinical or radiological involvement of the central or peripheral CV system or CV effects in sclerosteosis patients (Hamersma et al, 2003) and no mention of CV issues in a clinical management plan (Beighton et al, 2013). Van Buchem's patients have a normal lifespan but similarly there are no reports of CV effects and no mention of CV issues in a clinical management plan (Beighton et al, 2013). A genome-wide association study was conducted to assess for any association between a common sclerostin single nucleotide polymorphism (SNP) that is strongly associated with both sclerostin expression and BMD, and a risk of stroke or MI (Study 150655). This SNP was strongly associated with lower sclerostin expression, higher BMD, and lower risk of OP and fracture, as expected from the pharmacology, but had no significant association with the risk of MI or stroke.
- In Feb 2019, a non-peer reviewed pre-publication manuscript became available online (Bovijn et al, 2019, http://dx.doi.org/10.1101/531004), which claims there is an association between sclerostin SNPs and CV risk. In the view of the applicant, there are several scientific deficiencies in this manuscript, including non-standard analysis approaches, which are open to differential interpretation, and that the conclusion of an association with CV events is based on the combined effect of 2 non-independent SNPs and cross-cohort data but, individually, the association with CV events is inconsistent between cohorts and sometimes between the 2 SNPs within the same cohort. In view of the applicant, these analyses have a high potential to overestimate the evidence of an association with CV risk through "double counting" the effects of dependent SNPs.

Overall biological plausibility

Sclerostin is constitutively expressed in the aorta (Brunkow et al, 2001; Chouinard et al, 2016; Didangelos et al, 2010) and upregulated in foci of vascular and valvular calcification (Brandenburg et al, 2013; Kramann et al, 2013; Rukov et al, 2016; Zhu et al, 2011). Sclerosteosis is the clinical model of absence of sclerostin expression. It is a rare, progressive disorder in which bone overgrowth causes facial distortion and cranial nerve dysfunction. The intracranial pressure usually becomes elevated and sudden death often occurs in adulthood. In patients with sclerosteosis or van Buchem disease (homozygous for sclerostin gene [SOST]), there is no evidence of early onset vascular calcification or increased cardiovascular risk in the literature or through written communications with a key scientific expert for the disease state (Beighton, 2011c; Beighton, 2011d). However, experience may be limited as survival into old age has been unusual. In conclusion, althouth the presence of sclerostin receptor in the aorta and calcification centers has been shown. Its role, if any, in the process of atherosclerosis is uncertain. With regard to the results from the Bovijn study (see above), although it seems to show a relation between sclerostin SNPs associated reduction of fractures, and in the same patients an increase in CV risk, the magnitude of this increase in risk remains uncertain, and its relevance for above issue remains inconclusive.

5.1.1. Risk management aspects

Regarding the risk management activities proposed for romosozumab, CHMP concluded in their grounds for refusal that "the proposed risk minimisation activities (warnings, contraindications) are not considered to satisfactorily reduce the risk". In particular:

- Subgroup analyses of 20110142 could not identify populations in which the relative risk of MACE was neutral or considerably reduced.
- The Applicant proposed a contraindication in patients with a history of MI or stroke. However, the estimated relative risks for MACE and all-cause mortality would have remained largely unchanged.

Considering the conflicting data from the 2 studies and the small number of overall events in total, there is uncertainty as to whether the results from 20110142 represent a true drug-related effect or not. It has not been possible to identify a plausible mechanism by which romosozumab would impact the risk of MI and stroke and no specific subgroups were identified from the clinical data as being at higher relative risk. Therefore, it follows that any risk mitigation measures can only address the absolute risk rather than the relative risk. It should be noted that for the individual patient, it is their absolute risk that is relevant in a benefit-risk assessment.

In the following sections, the Applicant addressed the CHMP's concerns in more detail by discussing the proposed risk minimization activities and their anticipated effectiveness. The Applicant has also proposed additional activities utilizing the Patient Support Program (PSP) and the post-authorization safety study (PASS) to further enhance the existing proposal.

Current Risk Management Plan and proposed enhancements

Based on the detailed assessment of the CV events in the pivotal studies, the Applicant considered the risk of MI and stroke a potential risk as, based on the data it can neither be concluded nor excluded that MI and

stroke are drug related. Despite this, the Applicant during the procedure has accepted the risk as an "identified" risk in the EU Risk Management Plan (RMP) as a precautionary approach.

The current EU RMP encompasses both routine and additional pharmacovigilance (PV) and RMMs. These include:

- Labeling with contraindications and warnings and precautions
- Patient Alert Card
- Prescriber Guide
- Letter to cardiologists and neurologists
- PASS
- Use of detailed follow-up questionnaires for postmarketing reports of MI and stroke.

These measures are designed to educate and inform the patient and the relevant physicians with a view to optimize benefit-risk assessments, including in the event of an acute CV event and encourage appropriate communication between the HCPs. In addition, a key objective is to ensure detailed oversight of emerging data to be able to identify an emerging safety signal as quickly as possible. When viewed as a whole, these measures will provide appropriate risk minimization and PV oversight as summarized briefly below:

- **The SmPC is utilized to prevent use in those with the highest absolute risk** and provide information to support the physician in the individual benefit-risk assessments to ensure that for patients treated with romosozumab, the benefit risk is positive.
- **The prescribing physicians and patients are fully informed** such that the individual benefit risk is carefully assessed and understood before treatment is initiated - via the Patient Alert Card, Prescriber Guide, SmPC, and dedicated website.
- **The prescribing physician is sufficiently experienced** to assess benefit risk and oversee treatment - limit prescribing to OP specialists.
- **Rapid medical intervention in event of MI or stroke is facilitated** to optimize outcome - via awareness of patient and treating physician through Patient Alert Card, Prescriber Guide, SmPC and dedicated website.
- **The care and communication in event of MI or stroke are optimized** – via letter to cardiologists and neurologists to provide them with the relevant information and Patient Alert Card, as well as dedicated website.
- **Effectiveness of RMMs is measured** – via PASS.
- **An emerging safety signal is identified early** – via routine PV activities, including questionnaires, and via PASS.
- **Risk of MI and stroke is further assessed and described – via PASS**

The RMMs as discussed above have already been assessed by the PRAC and were considered to be adequate, yet the Applicant is proposing 2 further enhancement to the EU RMP:

1. Additional activities to be added to the currently proposed PASS
2. Utilizing the PSP

- The distribution and use of the Patient Alert Card will be further leveraged through connection with the PSP. The Patient Alert Card will be both included in the Patient Welcome Kit that will be provided to each patient by the physician at initial prescription and added it to the PSP website with the possibility of downloading additional copies of the Patient Alert Card.

- For patients participating in the nurse support phone call program of the PSP (currently planned in UK, Ireland, Germany and Spain), the nurse will have a conversation with patient/caregiver:
    - as to whether the Patient Alert Card 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 Patient Alert Card – will provide evidence of effectiveness.

The CHMP agreed with the Applicant that labelling (see below) and education of the prescribers are the most important means to optimize the use of romosozumab in subjects who may have the best individual benefit/risk ratio. A PASS can clarify if these measures are effective as intended.

It is not expected that measures aimed at better care for subjects taking romosozumab with a (non-fatal) MACE event will have a substantial impact. Instead, these patients will have the usual approach for these emergencies and use of romosozumab will barely be considered (and it will not influence diagnostic or treatment decision in any way).

The PASS is discussed further below.

Labelling

During the initial review of the MAA for romosozumab, the Applicant addressed the concerns of CHMP regarding the benefit risk of the indicated population by proposing substantial changes to the label. These changes have been maintained as the Applicant considers them sufficient to enable OP specialists to exclude patients with the highest baseline CV risk.

Contraindication of patients with a history of MI and stroke

The strongest predictor of a subsequent MI or stroke is a recent MI or stroke. The risk of a further event is highest in the first year and continues to decrease with time, thereafter. The proposal to contraindicate romosozumab in all patients with a history of MI or stroke regardless of when those events occurred represents a conservative approach to manage the absolute risk of CV events. Feedback on the appropriateness of this contraindication as a RMM was provided by the experts at both Ad hoc expert (AHEG) meetings, where it was generally acknowledged that such a contraindication would reduce the CV risk in absolute terms.

For the remaining population of patients without history of MI or stroke, there are risk factors (eg, age, diabetes, renal impairment, smoking) overlapping both osteoporotic fractures and CV disease, yet their influence on each of these conditions is different. Accordingly, published data demonstrates that the 2 risks weakly correlate at a population level. Studies considering smaller samples showed that these shared risk factors can explain only a limited level (maximum up to approximately 10%) of the variance in the CV and fracture risk (Kawińska-Hamala et al, 2017; Tasić et al, 2015). This is further confirmed in a large epidemiological study of UK Biobank showing in female patients that prior fragility fracture impact on CV-related hospitalization over 5 years (MI or ischemic heart disease) was not significant (Paccou et al, 2018).

- Additional advice provided in Section 4.4 "Special warnings and precautions for use"

To optimize the individual benefit risk, the Applicant proposed wording as outlined below in the EU SmPC Section 4.4 "Special warnings and precautions for use" to ensure that prescribers and patients are informed

of the risks in order to make appropriate treatment decisions at an individual patient level (see proposed text below).

- Restricting prescribing to OP specialized HCP

The Applicant considered that assessment of the individual benefit-risk balance would be best managed by OP specialized HCPs and thus proposed that romosozumab treatment should be initiated and supervised by specialist physicians experienced in the management of OP. This will enable appropriate selection of patients for whom the benefits from fracture risk reduction clearly outweigh the risk of MACE. This will be achieved by the proposed cautionary information in the SmPC and further enhanced through educational materials (Prescriber Guide and Patient Alert Card as specified in the EU RMP).

Proposed key information in SmPC to mitigate CV risk:

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis.

[…]

4.3 Contraindications

[…]

- History of myocardial infarction or stroke (see section 4.4)

4.4 Special warnings and precautions for use

Myocardial infarction and stroke

In pooled randomised controlled studies, an increase in serious cardiovascular events (myocardial infarction and stroke) has been observed in romosozumab treated patients compared to controls (see section 4.8).

EVENITY is contraindicated in patients with previous myocardial infarction or stroke (see section 4.3).

When determining whether to use EVENITY for an individual patient, consideration should be given to her fracture risk over the next year and her cardiovascular risk based on risk factors (e.g. established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, age). EVENITY should only be used if the benefit outweighs the risk.

Patients who develop symptoms suggestive of myocardial infarction or stroke during EVENITY treatment should undergo a prompt medical evaluation and discontinuation of therapy should be considered, based on an individual benefit-risk assessment.

[…]

CHMP agreed with the Applicant and the experts at both AHEG meetings that a contraindication in subjects with a history of stroke or myocardial infarction would reduce the CV risk in absolute terms. In addition, subjects with a history of TIA, cardiovascular revascularisation or hospitalisation for unstable angina may also be considered to have 'established CV disease'; however, these conditions are less well defined and only limited data available form the trials, nevertheless the use of romosozumab in these circumstances is

cautioned in special warnings. The second AHEG noted that subjects with a history of stroke or MI are easy to identify, but recent events are associated with the highest risk. In that respect, the proposal can be seen as conservative.

An initial proposal entailed assessment of the CV risk by OP specialists based on medical history, signs and symptoms, and potentially laboratory investigations of lipids, glycaemia and renal function if not yet available. The second AHEG concluded that besides adequate history taking no further mandatory specifc CV screening program would be adequate.

To these effects, the company proposed:

- PASS activities to further explore cardiovascular risk;
- Risk minimisation measures such as warnings in the PI texts and alerts to patients and prescribers;

PASS activities and risk minimisation measures are described in the section below.

PASS

Additional PV activities are already included in the EU RMP in the form of European multi-national multi-database PASS during the initial review.

The first PASS aims to evaluate the adherence to the RMMs among romosozumab users in real-world conditions.

The second PASS aims to assess the incidence of serious CV events in a cohort of users of romosozumab in line with the proposed target population and in cohorts of comparable patients treated with currently available drugs for OP.

PASS enhancements

To further enhance the ability of the previously proposed PASS to assess the potential CV risk, the applicant proposed during the re-examination to expand the PASS through 2 additional approaches.

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

These populations will be analysed separately within the PASS and will facilitate the implementation of the planned subgroup analyses providing a more complete population-based monitoring of the potential CV risk.

In the second approach, the Applicant plans 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 OP and thus minimize channelling bias. Furthermore, the quality of the assessment of CV outcomes will be enhanced by the registry validation procedures. The Applicant is currently evaluating CV

registries in Sweden and in other European countries. This will be dependent on the willingness of the relevant registries to participate.

In designing the above described enhancements of the PASS, the Applicant aims to cover large enough study periods to provide a sufficient sample size to estimate the study parameters with adequate power and thus precision. These additional subgroup analyses will be provided as a separate report.

Information from other regions

In addition to the above, the Applicant will also submit the protocol-defined outputs from PASS performed in US and Japan, where romosozumab has been approved.

The first PASS aims to evaluate the adherence to the RMMs among romosozumab users in real-world conditions. In the view of the CHMP, this study will optimize adherence to the agreed label and is considered useful. Based on this assessment, a comparison of the populations in which romozosumab is actually used and the studies in the dossier should be an important objective of this PASS.

The proposed PASS to assess the risk of MACE will aim to exclude an absolute increase in CV risk attributable to romosozumab of more than 1%. More detailed objectives are probably not feasible. In a real world setting, it is impossible to account for the effect of channelling and confounding by indication, through RMM that were implemented and knowledge and opinions in the medical community. Methods like propensity score matching will not completely solve such uncertainties and their effectiveness cannot be estimated.

For the PASS, subgroup analyses are pre-specified; this is acceptable (and is in contrast to study 142 where such analyses were done 'ad hoc').

The additional activities in the PASS appear acceptable but are subject to further review and advice by PRAC once study protocols become available.

RMM summary

The Applicant proposes a comprehensive EU RMP following a thorough review of the most recent EMA RMP guidance and the 2014 Council for International Organizations of Medical Sciences (CIOMS) Working Group IX Report "Practical Approaches to Risk Minimisation for Medicinal Products". In addition, recommendations from CHMP and PRAC during the initial review have been addressed. The proposed EU RMP measures for romosozumab are comparable to other products with identified or potential ischemic CV risks. The Applicant considers these proposed RMMs to be proportionate with the magnitude and the associated uncertainty of the potential risk of MI and stroke.

In patients who are treated with romosozumab, the potential risk of MACE can be adequately managed by restricting the initiation of treatment to OP specialists who can appropriately evaluate patients for their expected benefit, their baseline CV risk and keep the absolute CV risk low by applying the proposed RMMs in the SmPC and educational materials. In addition, the measures will also encourage patients and physicians to react quickly to a MACE and thus optimize outcome.

The proposed PASS will provide appropriate assessment of the potential risk of MI and stroke. Routine PV activities in addition to the regular output from the PASS will enable early detection of an emerging signal.

5.1.2. Overall conclusion on the applicants grounds for re-examination - Safety

CHMP agreed with the Applicant that there is considerable uncertainty around the associations of romosozumab with all-cause mortality and MACE. Taking into account that there was a trial with favourable and a trial with unfavourable results, it is, however, not agreed with the Applicant that the average of the two is a 'conservative' approach to estimate the risk.

There is much uncertainty as to why subjects exposed to romosozumab in study 142 apparently displayed more cardiovascular risk than those exposed to alendronate-only or those subjects in study 337. In this respect, trial 142 with the older and frailer population shows most adverse events. The adverse event rate in the control group changes (increases) over the course of the trial, which is unexpected. Furthermore, trial 142 was ALN controlled, but there is no evidence for a beneficial effect (or any other effect) of ALN on MACE. As there is considerable overlap between the trial populations in terms of severity of OP more consistent results would have been expected.

Trial 142 is most representative for the currently proposed target population, as the intended indication for romosozumab has been restricted to 'severe osteoporosis' during the procedure.

Over the first 12 months of study subjects exposed to romosozumab in study 142 apparently displayed more cardiovascular risk than those exposed to alendronate-only or those subjects in study 337. The increased risk of approx. 1% is considered to be small and appears to decrease over 36 months of follow-up.

It was not possible to identify a subgroup in which MACE risk was increased or decreased. Romosozumab seems to add a constant relative risk and the additional absolute risk depends on the baseline risk. The apparent increased cardiovascular risk in study 142 for those exposed to romosozumab is considered to be a general effect rather than a subgroup effect.

An exact (patho)physiologic involvement of sclerostin in vasculature and atherosclerosis, suggested by tissue receptor expression, has not (yet) been elucidated. Non-clinical studies did not identify a mechanism for an adverse effect on MACE.

There was a small difference in all cause mortality that is not entirely explained by the MACE findings. These differences were observed in both trials in patients over 75 years of age. The analysis of those over 75yrs was a mix of pre-specified and post hoc subgroup analyses; for this reason and because subgroup analyses ought not to be the basis for substantive clinical decisions, a specific risk for those over 75yrs cannot be concluded (it may be a chance finding).

5.2. Grounds for re-examination - Efficacy

The grounds for refusal were as follows:

The efficacy of Evenity (romosozumab) for the treatment of osteoporosis appears to be of clinically relevant magnitude in the proposed target population of postmenopausal women with severe osteoporosis. In subjects with less severe osteoporosis, where there might be a lower absolute risk of MACE, the efficacy of romosozumab is less convincing, e.g., a statistically significant benefit on non-vertebral fractures and hip fractures could not be shown.

In particular:

- "the efficacy of romosozumab for the treatment of osteoporosis was acknowledged to be of clinically relevant magnitude in the proposed target population of postmenopausal women with severe osteoporosis", yet "in subjects with less severe osteoporosis, the efficacy of romosozumab" is considered less convincing, eg, a statistically significant benefit on nonvertebral fractures and hip fractures could not be shown.
- "the primary endpoints of both pivotal studies had been met", and "the effect of romosozumab was superior to alendronate for reducing the risk of non-vertebral fractures and hip fractures at the time of primary analysis at 33 months". However, it was also pointed out that "there is no direct comparison of the effect size with other potent antiresorptive treatments available".

Choice of Comparator and Demonstration of Fracture Risk Reduction

With regard to the appropriateness of the design of the 2 pivotal studies (20110142 and 20070337), the Applicant considered and implemented the recommendations of the CHMP's osteoporosis guideline (CPMP/EWP/552/95 Rev.2, Nov 2006); endpoints include the efficacy for different fracture types (vertebral and nonvertebral including hip) and the requirement for long(er) term efficacy data on fracture reduction is addressed. With regard to the latter, to satisfy the requirement for long(er) term data beyond the 12 months of treatment, the Applicant followed the EU Scientific Advice to compare the sequence of treatment, ie, romosozumab followed by an antiresorptive, using ALN as the appropriate standard of care in one of the studies (20110142).

The status of ALN as the standard of care in the post-fracture population is well documented. Data from observational studies from UK and Spain show that ALN alone represent up to 78% of the utilized OP medicines (Martín-Merino et al, 2017; Royal College of Physicians, 2017). In a Cochrane meta-analysis, ALN was associated with a relative risk reduction of 40% to 50% for vertebral (6% absolute risk reduction) and hip fractures (1% absolute risk reduction) in secondary fracture prevention with a similar relative risk reduction for vertebral fracture in primary prevention (Wells et al, 2008).

The CHMP acknowledged that in the pivotal studies the Applicant included populations and investigated endpoints that are consistent with CHMP's osteoporosis guideline (CPMP/EWP/552/95 Rev.2, Nov 2006). This was confirmed in the scientific advices. However, the endpoints that are defined as most important in the guideline were not systematically put high in the statistical hierarchies – this resulted in "nominal" but not formal statistically significant results. This issue was not addressed in the scientific advices. The choice of ALN as a control treatment in the trial is agreed, as it is used frequently across the EU. However, other therapies (e.g. denosumab) may have a more rapid onset of action thus responding to the unmet need brought forward by the Applicant.

Study Outcomes

Study 20110142

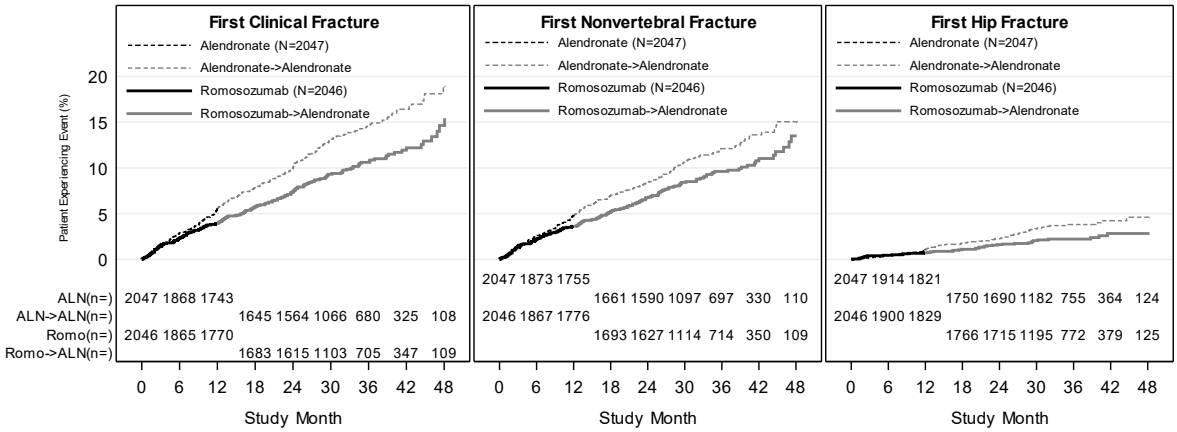
Study 20110142 enrolled a population of postmenopausal women with severe OP and who, as a consequence of their prior fracture(s), were at high risk of subsequent fracture. The CHMP acknowledged that the efficacy of romosozumab for the treatment of OP in the proposed target population of postmenopausal women with severe OP was of clinically relevant magnitude.

,The sequential treatment with romosozumab 210mg administered subcutaneously by a healthcare professional (HCP) every month (QM) for a year followed by ALN reduced the incidence of new vertebral

fracture at Month 24 from 8.0% in the ALN alone group to 4.1%, with an absolute risk reduction of 4.0% (95% confidence interval [CI]: 2.5, 5.6) and a relative risk reduction of 50% (95% CI: 34, 62).

For nonvertebral fractures, the CHMP also acknowledged that the effect of romosozumab was superior to ALN for reducing the risk of non-vertebral fractures (10.6% vs 8.7%) and hip fractures (3.2% vs 2.0%) at the time of primary analysis at 33 months. The superiority of romosozumab is further illustrated in Figure 37, which provides the broader perspective of the cumulative incidence of clinical, nonvertebral, and hip fractures through Primary Analysis.

Figure 37: Cumulative incidence of clinical fracture, nonvertebral fracture, and hip fracture through the Primary Analysis in 20110142



ALN=alendronate; ISE=integrated summary of efficacy; N=number of subjects randomized; n=number of subjects at risk for event at time point of interest; Romo=romosozumab

At the time of the Primary Analysis, 464 subjects had experienced a clinical fracture and 395 subjects had experienced a nonvertebral fracture and the median follow-up time was 33 months. The incidence of clinical fracture was 13.0% in the ALN group and 9.7% in the romosozumab group, yielding a hazard ratio (HR) of 0.73 (95% CI: 0.61, 0.88). The incidence of nonvertebral fracture was 10.6% in the ALN group and 8.7% in the romosozumab group, yielding a HR of 0.81 (95% CI: 0.66, 0.99). Although significance was not yet achieved at 12 and/or 24 months, Figure 37 illustrates that these reductions in fracture risk began as early as 12 months (when the arms start to separate) and reached statistical significance at the time of the prespecified Primary Analysis timepoint, when the study was sufficiently powered to detect differences in fracture risk with statistical significance.

Study 20070337

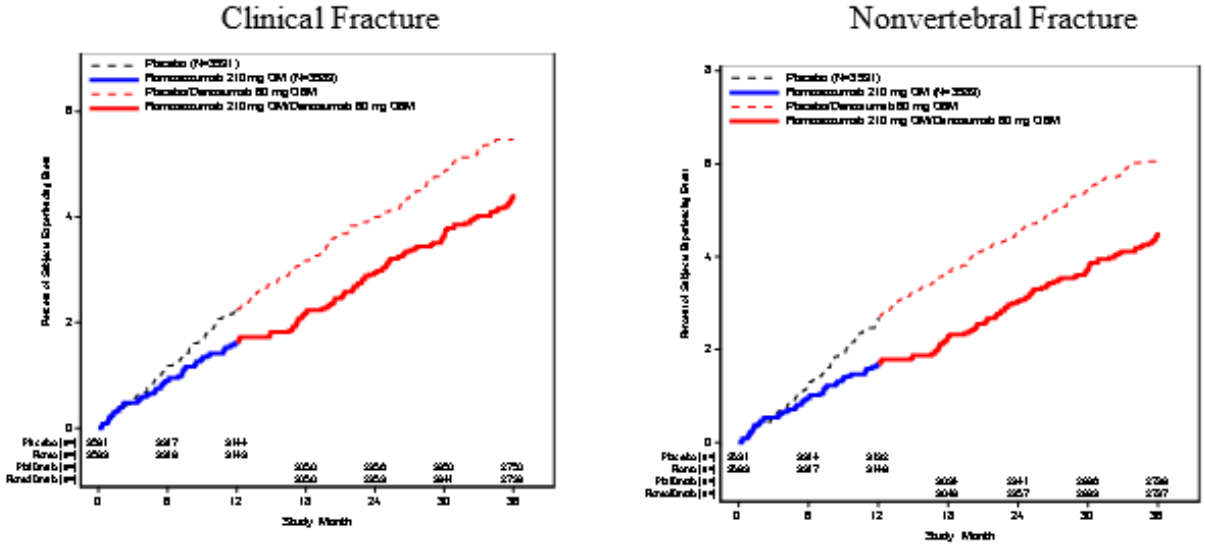
The CHMP has acknowledged that study 20070337 demonstrated that "romosozumab reduced the risk of new radiological vertebral fractures at 12 and 24 months and the risk of clinical fractures (vertebral and nonvertebral) compared to placebo at 12 months" and that, thereby, the predefined primary endpoints of comparing romosozumab vs placebo were met. However, it was also pointed out that the effect on nonvertebral fractures (secondary endpoint) did not reach statistical significance, and, therefore, the efficacy of romosozumab was considered less convincing in subjects with less severe osteoporosis.

Iin 20070337, romosozumab reduced morphometric vertebral fractures compared to placebo ($p < 0.001$). At 12 months, the new morphometric vertebral fracture absolute risk reduction was 1.3% (95% CI: 0.8, 1.8) and the relative risk reduction was 73% (95% CI: 53, 84) with romosozumab compared to placebo. At 24

months, the new morphometric vertebral fracture incidence was 2.5% in the placebo-denosumab group and 0.6% in the romosozumab-denosumab group with an absolute risk reduction of 1.9% (95% CI: 1.3, 2.5) and a relative risk reduction of 75% (95% CI: 60, 84). For clinical fractures (defined as a composite of nonvertebral fractures and symptomatic vertebral fractures), the study showed significant reduction at Month 12 with romosozumab compared to placebo (with an absolute risk reduction of 1.2% and a relative risk reduction of 36% [p=0.008]).

With regard to nonvertebral fractures, as illustrated in Figure 38, there was clear separation between treatment arms in favor of romosozumab, but the 25% relative risk reduction in nonvertebral fractures at both 12 and 24 months did not achieve statistical significance. This observation was influenced by a low background fracture rate in the highest enrolling region of Central/Latin America. A significant treatment-by-region interaction for the nonvertebral fracture endpoint was detected when comparing the Central/Latin America population with the remaining Rest-of-World (ROW) population, with no treatment effect observed in Central/Latin America, where the background nonvertebral fracture rate (1.2%) was low. In fact, a (nominally) significant nonvertebral fracture risk reduction (42%) was observed in ROW (p=0.012).

Figure 38: Cumulative incidence of clinical fracture and nonvertebral fracture through Month 36 in 20070337



CSR=clinical study report; D_{mab}=denosumab; N=number of subjects randomized; n=number of subjects at risk for event at time point of interest; Pla=placebo; Q6M=every 6 months; QM=every month; Romo=romosozumab

The CHMP acknowledges the results but had identified limitations of the statistical tesing as follows:
In study 142, romosozumab 210 mg QM for 12 months followed by alendronate 70 mg QW through the primary analysis significantly reduced the risk of nonvertebral fractures by 19% (p = 0.019, 1-sided nominal p-value) based on 395 subjects with nonvertebral fractures. Under the group sequential design, with an information fraction of 90% (395/440), the significance level at primary analysis (Lan-DeMets alpha spending function that approximates a Pocock boundary was determined to be 0.0233 (1-sided). This result is significant as 0.019 < 0.0223; consistent with this, the multiplicity-adjusted 2-sided p-value (adjusting for the fixed sequence and the group sequential testing) was significant at 0.040. The subject incidences of nonvertebral fracture through month 12 and through month 24 were predefined secondary endpoints, but were not included in the multiplicity adjustment (and therefore were not formally tested).

The guideline-recommended endpoints to establish efficacy in PMO are vertebral fractures and major non-vertebral fractures or hip fractures. The Applicant did not include any of the latter in the statistical sequential testing procedure, and therefore these cannot be formally tested.

About 94% of the trial population would be included in the target population as defined by the SmPC, the difference being introduced by exclusion of established cardiovascular disease. Obviously, this reduces the trial's power.

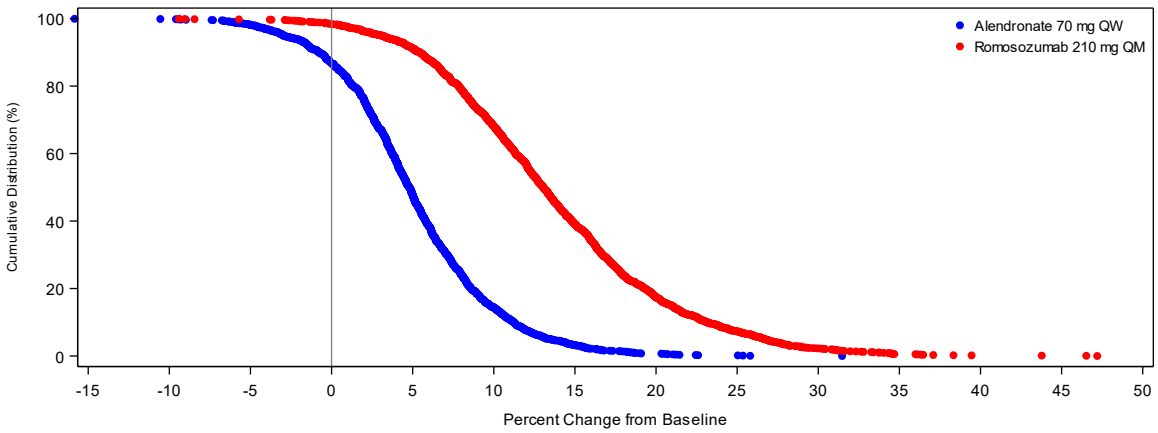
In study 337, non-vertebral fractures were included in the predefined statistical testing sequence. The simultaneous comparison of fracture incidence for the secondary endpoints of nonvertebral fracture at months 12 and 24. The 25% (95% CI: -5, 47) relative risk reduction with romosozumab for nonvertebral fracture through month 12 was not statistically significant (p = 0.096) and the p-value for nonvertebral fracture through month 24 (p = 0.029) was nominally significant, but did not meet statistical significance after applying the Hochberg procedure to adjust for multiple comparisons (p = 0.057).

Bone mineral density changes

Based on the data from 20110142 and 20070337, it has been established that romosozumab does significantly reduce the fracture incidence across vertebral and nonvertebral fractures (including hip).

In addition to these data showing the difference in average BMD increase for both study populations, the response rate to treatment at the individual patient level further illustrates the substantial benefit of romosozumab. Figure 39 shows the comparison of increase in BMD at lumbar spine with romosozumab vs ALN at Month 12 from 20110142. The "shift" between the 2 curves illustrates the improved response to romosozumab compared to ALN in terms of magnitude of BMD increase (horizontal axis), and proportion of subjects responding (vertical axis). For example, 68% of subjects treated with romosozumab gained at least a 10% increase in BMD compared with only 14.4% of subjects in the ALN group. A similar analysis for BMD gains at the total hip (figure not shown) showed 47% of romosozumab-treated subjects gained at least 6% in BMD vs 17% with ALN.

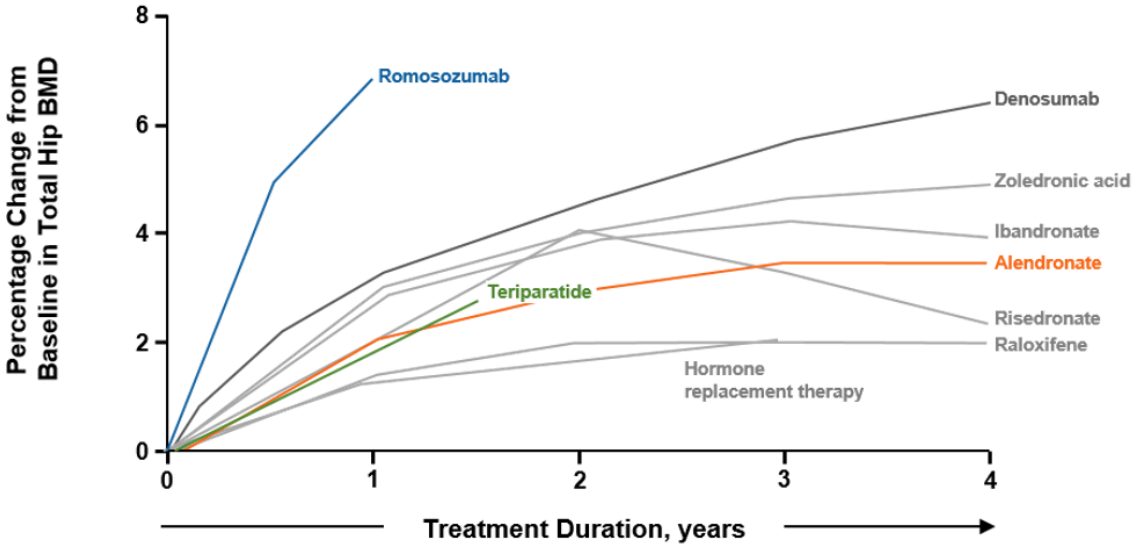
Figure 39: Cumulative distribution function for lumbar spine BMD percent change from baseline at Month 12 (20110142, Primary Efficacy Analysis Set for BMD, LOCF)



BMD=bone mineral density; ISE=integrated summary of efficacy; LOCF=last observation carried forward; PMO=postmenopausal osteoporosis; QM=every month; QW=every week
Note: Missing values were imputed by carrying forward the last nonmissing postbaseline value prior to the missing data.

With regard to the CHMP's concern that "there is no direct comparison of the effect size with other potent antiresorptive treatments available", is the Applicant acknowledged that head-to-head fracture data are only available for ALN from 20110142. However, in addition to this, BMD comparative data are available for ALN (20110142) and TPTD (20080289). Although the baseline characteristics of the study populations are slightly different, the BMD gains and superiority of romosozumab is consistently demonstrated. Given this consistency, to the applicant superimposed a romosozumab BMD gain curve on a cross-study comparison of BMD responses published by Reid (2015) (Figure 40, below). Although cross-study comparisons have limitations, this illustrates the substantial difference in BMD gains achieved with romosozumab vs other therapies, suggesting that romosozumab would improve efficacy over the OP therapies currently available in the EU.

Figure 40: Romosozumab BMD gains over 12 months superimposed on a cross-study comparison of BMD gains with selected OP therapies



BMD=bone mineral density; OP=osteoporosis

Based on inter-study comparison, the CHMP acknowledged that the effect of romosozumab on BMD seems more rapid and larger than with other agents during the first year. These data are supportive for efficacy. However, BMD is not a full surrogate for fracture reduction.

5.2.1. Overall conclusion on the applicants grounds for re-examination - Efficacy

The Applicant generally complied with the CHMP guideline on osteoporosis and scientific advice on the design, conduct and analyses of the submitted studies.

It is acknowledged that alendronate represents standard of care and is an appropriate comparator; use of alendronate as a comparator is acceptable. Published data describe and confirm the efficacy of alendronate in the management of primary osteoporosis and illustrate that alendronate sets a high standard against which

to compare romosozumab. The efficacy results over alendronate confirm the importance of the beneficial effects of romosozumab.

There are many other agents available to manage osteoporosis, mostly anti-resorptives such as alendronate. There is no requirement to compare romosozumab against these other treatments.

The primary endpoints in the pivotal studies (Study 2007337 and Study 20110142) had been met. In particular, the level of evidence for the primary endpoint Study 2007337 is considered compelling from a statistical perspective. The secondary endpoints were generally supportive in both studies.

In Study 20110142 the cumulative incidence of clinical fracture, nonvertebral fracture and hip fracture up to 48 months post treatment, was consistently lower in the romosozumab group compared to alendronate group.

In Study 2007337, the cumulative incidence of clinical and non-vertebral fracture up to 36 months post treatment was lower in the romosozumab group compared to the placebo group.

Although the cross-study comparison of BMD gains showed a trend in favour of romosozumab, supporting a superior effect, methodological limitations associated with cross-study comparisons mean the observed patterns should be interpreted with caution.

A clinically relevant and superior efficacy over alendronate (in terms of reducing both vertebral and non-vertebral fractures in patients with severe osteoporosis) has been demonstrated. Although the treatment duration is limited to 12 months, the benefits in terms of reducing fractures seen in the first 12 months continues to be accrued for the subsequent two years when treatment with romosozumab is stopped and treatment is continued with an anti-resorptive agent (denosuzumab or alendronate).

Additional expert consultation

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc Expert group inviting the experts in the field of osteoporosis, cardiology and patient representatives to provide their views on the CHMP grounds for refusal, taking into account the applicant's response. The corresponding answers are presented below:

1. Efficacy in the proposed target population

Do you consider that, based on the available data from study 20070337 (less severe OP) and study 20110142 (severe OP), clinical relevant efficacy is established in the proposed target population?

AHEG discussion: Efficacy has been convincingly demonstrated in the view of the experts. The reduction of vertebral fractures was demonstrated in both trials 20070337 (FRAME study; romosozumab vs. placebo) and 20110142 (ARCH study; romosozumab vs. alendronate). Also, in the view of the experts, clinical significant efficacy was clearly shown regarding non-vertebral fractures in the intended target population, even though statistical significance in formal testing may not have been achieved at various time points. The experts also highlighted the exceptional superior efficacy shown in comparison to a commonly used established standard treatment as comparator, alendronate. The recalculation of event rates in a subset of patients from study 337, defined by a CV risk profile comparable to participants of study 142, was considered to be problematic to be relied on due to the limitations as a post-hoc analysis. No rebound or increase of fracture risk after

completion of the romosozumab treatment phase was apparent, and the experts were further reassured by the long-term (i.e. including the subsequent time of exposure to antiresorptive therapy) efficacy of treatment with romosozumab. The patient representatives (including a patient) participating in the meeting highly welcomed the possible future availability of such a treatment.

2. Cardiovascular (CV) risk in OP

In order to gain insight in the current practices with regard to identification and management of CV risk/disease in osteoporosis patients please discuss:

a. the frequency of CV disease in osteoporosis patients and how this currently influences your treatment choice for these patients

AHEG discussion: The experts acknowledged that there is an association between the presence of osteoporosis and risk of CV events / manifest CV disease; however, they considered the association as relatively weak and of limited practical relevance in guiding patient treatment.

b. how would you interpret the MACE findings in the romosozumab studies

AHEG discussion: The experts noted the difference in CV event rates between the 2 arms in study 142. While this could be due to an effect of romosozumab, the experts also noted the unexpected low rate of CV events in the control (i.e. alendronate) arm during the first year (taking into account expected event rates considering the CV risk profile of the population of this study) and the resulting non-linearity of the Kaplan-Meyer curve of the event rate in the patients continuously treated with alendronate. Although any interpretation of these curves has severe limitations , the experts agreed that a linear increase would have been expected, opening the possibility that the observed difference in event rate to be a chance finding originating from a lower than expected event rate in the control arm. It was also discussed whether this could be due to a protective effect of alendronate. Notwithstanding that there has been so far no support for alendronate having a protective CV effect, including an analysis done by the FDA, some of the experts suggested this should nevertheless not be dismissed entirely as a hypothesis (observations of a reduction of CV events in one study with zoledronate and an acute phase response as a speculative hypothesis for a temporary beneficial effect were mentioned). It was also pointed out that early interim analyses in dedicated CV outcome trials have led sometimes to aberrant results in the past which were not confirmed by the eventual outcome of these trials. It was also noted that the two curves in trial 142 eventually merge, suggesting that there might be no difference in the long-term effect, although it was acknowledged that the data at the very end of such curves needs cautious interpretation (i.e. patient selection, number of events – subjects).

Also, the study was neither designed nor powered as a CV outcome trial, and usual limitations of post hoc analyses apply. In all, it was agreed with the applicant, that there might have been an overestimation of the CV event rate in trial 142, but a real effect cannot be excluded. However, in any case the estimated excess rate of MACE events based on the results from the studies in patients without a history of MI or stroke of ca. 0.3% per year in a post hoc analysis was considered to be considerably smaller than the rate of prevented (vertebral) fractures. With regard to the clinical impact of fractures, the patient representatives participating

in the meeting made a very strong case that even vertebral fractures can have a profound impact on pain-free living, mobility, independence, and life quality.

The experts agreed that a contraindication in patients with a history of MI or stroke would reduce the absolute risk of CV events and would constitute a meaningful way to mitigate the risk.

Findings in post-hoc subgroup analyses with small patient numbers where seen critically in general. This applies also to the post-hoc subgroup analysis in patients over the age of 75 years; for the latter, they also reminded of the very high biological variability of age-related risks in general, including CV risk.

c. In clinical practice, how do you currently assess CV risk in OP patients (e.g. standardized tools, imaging, referral) and do you envisage a change in assessing CV risk if romosozumab becomes available

AHEG discussion: The osteoporosis experts stated that prescribers of osteoporosis medicines have already some experience with prescribing medicines for the treatment of osteoporosis associated with CV risk, such as strontium ranelate or hormone replacement therapy, in the past. It was considered that following contraindications based on patients history of MI or stroke would be very straight-forward. Beyond that, any concerns of a patient being at an increased CV risk would and should be followed up independently by physicians. To mandate the use of other indicators of CV risk, or of a risk score, was considered to be impractical, and also not rationally based on data, as such data is not available from the studies, which was seen as one of the weaknesses of the studies by one of the cardiology experts. The experts stated that in general the highest risk for MI and stroke is in the 3 months after these events and up to one year. However they acknowledged that an analysis as to time of MI or stroke after a prior event has not been presented in study 142. The proposed contraindication based on a history of MI or stroke was questioned by a cardiology expert, as a contraindication for recent MI or stroke during the last year and a warning only regarding events further in the past could be considered more adequate and justified.

3. Medical need

In the context of available treatment options for osteoporosis and given the available data on efficacy and safety for romosozumab, is there an identifiable subgroup of patients who would derive a greater relevant benefit with romosozumab that could not be fulfilled by other existing treatments and if so, how would you characterise this subgroup? What aspects of the submitted evidence and clinical context could be used to reliably identify such a subgroup?

AHEG discussion: The osteoporosis experts outlined various scenarios where romosozumab would fill a need for treatment, such as insufficient effectiveness or intolerance of past treatment, high risk menopausal patients using long-term high dose corticosteroids, but also in general patients with a very high risk of fracture. Actual eventual use in practice, if the product should be approved, is envisioned to be potentially depending on country-dependent health care system, and might be primary therapy, or as second-line therapy only. However, even in the latter scenario, experts pointed to data from applicant's smaller studies, showing usefulness even following antiresorptive therapy. They pointed out that the only osteoanabolic therapy currently available is teriparatide, which constitutes a limitation of the treatment options. The patient representatives very much emphasized the need for romosozumab as treatment option, in particular in advanced cases, and where other treatments either have failed or are not suitable. They both emphasized

the high burden of the disease, both for the patients and their families, and found that in their view the benefits would far outweigh the associated CV risk in appropriate patients.

Although some experts were inclined to consider the use of the product in patients at very high risk of fracture (e.g. based on FRAX score), even without a prior fracture, they were suggesting that use in secondary osteoporosis, such as glucocorticoid-induced osteoporosis, should be based on dedicated studies. It was mentioned that the indication wording "severe osteoporosis in postmenopausal women" without "at high risk of fracture" might be considered, depending on precedent with other labelling.

4. Generation of additional data

Current proposals for risk management include an observational study in the US and EU to further characterize CV effects of romosozumab. Please describe if and how already existing datasets or other studies (e.g. prospective studies) could inform about effectiveness and safety of romosozumab in case it is introduced in the EU.

AHEG discussion: The possibility of a randomized controlled cardiovascular outcome trial was mentioned but the feasibility of such a trial was questioned due to lack of enrichment of CV risk and the consequent required sample size. Use of existing/ongoing observational studies of CV events were considered not suitable. The possibility of the use of a register to answer this question would result in a large size and additionally the problem of the lack of a comparator would arise.

With regard to the currently proposed observational post authorisation study, there were divergent views whether it is possible to satisfactorily adjust for the expected strong channelling bias of higher CV risk patients away from romosozumab treatment, and whether such a study could contribute significantly to further characterise the possibly small increase in CV risk, beyond what is available from the available RCTs.

The experts also mentioned, should there be further RCTs in secondary forms of osteoporosis, this would be an additional opportunity to prospectively generate additional data for the better characterization of the CV safety profile.

5.3. Risk Management Plan

Safety concerns

Table 1: 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 Serious infections
Missing information	Osteoporosis rebound effects

Pharmacovigilance plan

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 EU-ADR Alliance ***Planned***	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 analysing the utilization patterns	Serious cardiovascular events of myocardial infarction and stroke	Final PASS protocol Monthly interim descriptive reports Annual descriptive reports until study completion	Planned submission date of the final PASS protocol: Feb 2020. Monthly descriptive reports will be submitted every six months during the first two years of the study. Annual descriptive reports will be submitted starting in year 3 (2022/2023) after marketing authorization.

European non-interventional PASS related to serious cardiovascular adverse events of Myocardial infarction and stroke for romosozumab by the EU-ADR Alliance. ***Planned***	The main objective is to evaluate potential differences in terms of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions.	Serious cardiovascular events of myocardial infarction and stroke	Final PASS protocol Monthly interim descriptive reports Annual descriptive reports Interim comparative report Final study report	Planned submission date of the final PASS protocol: Feb 2020. Monthly descriptive reports will be submitted every six months during the first two years of the study. Annual descriptive reports will be submitted starting in year 3 (2022/2023) after marketing authorization. Interim comparative report is estimated in year 5 (2024/2025) after marketing authorization. Final study report is estimated in year 6 (2025/2026) after marketing authorization.

European non-interventional PASS related to serious infections risk for romosozumab by the EU-ADR Alliance ***Planned***	The main objective is to evaluate potential differences in terms of serious infection between romosozumab and currently available therapies used in comparable patients in real-world conditions.	Serious infections	Final PASS protocol Annual descriptive reports Interim comparative report Final study report	Planned submission date of the final PASS protocol: Feb 2020 Annual descriptive reports will be submitted Starting in year 1 (2020) after marketing authorization Interim comparative report is estimated in year 3 (2022/2023) after marketing authorization. Final study report is estimated in year 4 (2023/2024) after marketing authorization.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance (PhV) activities
Important identified risks		
Hypersensitivity	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: None

	(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	
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
Hypocalcaemia	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.	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: None

	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	
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) and 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. A targeted follow-up questionnaire will be utilized in the post-marketing setting. Additional PhV activities: - European non-interventional PASS related to the adherence to the risk minimization measures by the EU-ADR Alliance (effectiveness on behavior). - European non-interventional PASS related to serious cardiovascular events of myocardial infarction and stroke for romosozumab by the EUADR Alliance.
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	Routine PhV activities beyond adverse reactions reporting and signal detection: ongoing adjudication of potential serious adverse events reported in clinical studies as appropriate.

	(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	Additional PhV activities: None
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
Serious infections	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). Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None. Additional PhV activities: - European non-interventional PASS related to serious infections for romosozumab by the EU-ADR Alliance.
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.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

5.4. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 08.01.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

5.5. Product information

5.5.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

5.5.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Evenity (romosozumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

See section 3.3.1

6.1.2. Available therapies and unmet medical need

See section 3.3.2.
In addition, and in further support of the unmet medical need, experts at the second ad hoc expert group (AHEG) meeting outlined various scenarios where romosozumab would fill a need for treatment, such as insufficient effectiveness or intolerance of past treatment, high risk menopausal patients using long-term high dose corticosteroids, but also in general patients with a very high risk of fracture.

6.1.3. Main clinical studies

See section 3.3.3.
In addition, a study in male osteoporosis (20110174; placebo controlled bridging study in men with osteoporosis (N=245), considered as pivotal initially during the assessment, was subsequently considered only as supportive, as the Applicant withdrew the request for an indication in that populatation, but was still considered, e.g. within safety assessements.

6.2. Favourable effects

Study 337

Romosozumab reduced the risk of new vertebral fractures compared with placebo up to month 12 (risk ratio = 0.27 [95% CI: 0.16, 0.47]). Vertebral fracture risk reduction persisted over the 24-month study period for subjects initially randomized to romosozumab, (with patients receiving romosozumab for 12 months followed by denosumab for 12 months) reduced the risk of new vertebral fractures compared with patients receiving placebo for 12 months followed by denosumab for 12 months (risk ratio = 0.25 [95% CI: 0.16, 0.40], $p < 0.001$). The co-primary endpoints of study 337 were met; secondary endpoints were generally supportive towards the primary endpoints.

Study 142

Romosozumab 210 mg QM for 12 months followed by alendronate 70 mg QW for 12 months reduced the risk of new vertebral fracture through month 24 compared with alendronate alone (relative risk = 0.50; adjusted $p < 0.001$). It also reduced the risk of clinical fractures (nonvertebral fracture and clinical vertebral fracture) compared with alendronate alone, based on 464 subjects with clinical fractures (hazard ratio = 0.73 [95% CI: 0.61, 0.88], $p<0.001$). The primary endpoints of study 142 were met; secondary endpoints were generally supportive. A clinically relevant and superior efficacy over alendronate (current standard of care treatment) in terms of reducing both vertebral and non-vertebral fractures in patients with severe osteoporosis has been demonstrated.

For presentation of additional quantitative outcomes from these two studies see section 3.2.

6.3. Uncertainties and limitations about favourable effects

Despite the study size, the absolute numbers of non-vertebral fractures were moderate resulting in modest absolute risk reductions. In study 20070337 at month 12, hip fractures had occurred in 7/3589 (0.2%) romosozumab patients vs 13/3591(0.4%) on placebo. In study 20110142 at month 12, hip fractures had occurred in 14/2046 (0.7%) romosozumab patients vs 22/2047 (1.1%) on alendronate.

A by-region subgroup analysis showed lack of efficacy in Central/Latin America (43% of the randomised subjects) and North America (2.7%, very few fractures in total) (see also section 3.3).

In the pivotal studies, not all results reached formal statistical significance according to the predefined testing strategies. However, in the view of the experts of the second AHEG meeting, clinical relevant efficacy was clearly shown in the intended target population, including specifically non-vertebral fractures, which was also acknowledged by CHMP.

6.4. Unfavourable effects

The safety profile was characterised in a large safety database which included more than 11000 subjects.

Adverse events following exposure to romosozumab included hypersensitivity reactions (mainly skin), injection site reactions, headache and musculoskeletal aches and pains and infections of the upper respiratory tract. Instances of hypocalcaemia, osteonecrosis of the jaw and cataract have been reported.

In general, romosozumab displayed a risk profile that is expected for biological medicinal products.

All-cause mortality was 30/2040 (romosozumab 1.5%) versus 22/2014 (placebo 1.1%) in trial 142 and 29/3581 (romosozumab 0.8%) versus 24/3576 (placebo 0.7%) in trial 337 during the 1-year treatment period.

Cardiovascular events: Independent adjudication of serious cardiovascular events was pre-specified in the two pivotal studies. An imbalance in positively-adjudicated cardiovascular serious adverse events was observed between romosozumab (2.5%) and alendronate (1.9%) in Study 20110142. This imbalance was due specifically to serious cardiac ischaemic (0.8% vs 0.3%) and serious cerebrovascular (0.8% vs 0.3%) events. Death, serious MI or serious stroke (MACE) occurred in 53/2040 (2.6%) patients treated with romosozumab compared to 32/2014 (1.6%) patients treated with alendronate, HR 1.7 (95%CI 1.1-2.6). In the larger, placebo-controlled study (Study 20070337) the adjudicated MACE HR was 1.1 (95%CI 0.7-1.7).

For further information on adverse events in general and for other events of interest see section 3.4.

6.5. Uncertainties and limitations about unfavourable effects

A cardiovascular risk signal has been noted in study 142 yet not in study 337. Within the 12 month controlled period, 2% subjects in study 142 experienced a positively-adjudicated cardiovascular event leading to death, serious myocardial infarction or stroke versus 1.1% exposed to alendronate. This is in contrast to the 0.8% of subjects in both arms of study 337 who experienced stated adverse event in the first 12 months. The cardiovascular risk in study 142 is considered to be a general effect rather than a subgroup effect. A meta-analysis based on data from the 2 studies provided by the applicant during re-examination was considered not to resolve the uncertainties regarding the issue on the grounds that the designs of studies 337 and 142 are too different.

There are many uncertainties with regard to the interpretation of the cardiovascular risk as ascertained in study 142:

- The non-clinical studies have not shown any strong evidence to suggest a biological plausibility for Evenity to increase the risk of MACE
- The study 142 was not designed to evaluate the cardiovascular risk and the total number of cardiovascular events observed in the study is small as compared to dedicated cardiovascular outcome studies. Moreover the analyses of MACE used a conservative approach i.e. the undetermined deaths where a non-cardiovascular cause could not be confirmed were treated as 'cardiovascular deaths'.
- Whilst the observation could suggest an increased risk for romosozumab in the first year, this could also be due to a temporary cardioprotective effect of alendronate
- The study population had a background risk of cardiovascular disease and this in context of the overall small number of events may also suggest that this is a spurious imbalance especially when compared over a 12 month study period which is short for such comparisons
- When treatment with romosozumab was stopped after 12 months and patients were switched to alendronate, there was no marked decrease in the rate of MACE events as would be expected if it was the cause of MACE and contrary to expectations, the rate of MACE events increased in the alendronate arm in the subsequent two years although there was no change in treatment in that arm

The major uncertainties in this application caused by inconsistent results in the two large trials that were submitted could not be resolved by further analyses duing the re-examination. Study 20110142 in severe OP included women that were on average older and had more comorbidities than those in study 20070337, which included women with a broader OP-severity range from less severe to severe OP. The first trial was actively controlled with alendronate, which is agreed to represent the standard of care. In the course of the procedure, the Applicant presented post-hoc analyses representing respectively 94% and 38% of the trial populations of the 2 studies, respectively, aiming to match the treatment population foreseen in the proposed SmPC (see also section 6.6). As that definition is data-driven, it is difficult to value these analyses and the results of the post-hoc analyses between the two trials remained discrepant.

Given the above uncertainties, an increased risk of MACE associated with the use of romosozumab can neither be confirmed nor excluded. Interpreting the above results in the context of the placebo controlled study which showed no increased risk (albeit in a study population of varying osteoporosis severities), it is

likely the observed small increase in absolute risk (absolute risk difference of 0.92% for 12 months for MACE in study 142) is over-estimated, particularly when the overall risk after three years in study 142 seems more comparable between the two treatment groups.

For further information regarding uncertainties regarding neoplasms, hypocalcaemia, and the use in patients with severe renal impairment see section 3.5.

6.6. Effects Table

The Effects Tables below present data from the pivotal trials as well as estimates of effect sizes in the proposed target population (see also tables' legend).

Table 83*: Effects Table (1 year)*

Event	romo	ALN	placebo	Treatment effect	p-value	reference
Patients with events	**n/N (%)**	**n/N (%)**	**n/N (%)**	**risk ratio (95% ci)**		
Favourable effects						
Clinical vertebral and non-vertebral fractures	79/2046 (3.9%)	110/2047 (5.4%)		0.72 (0.54; 0.95)	ns2	study 142
	75/1923 (3.9%)	105/1920 (5.5%)		0.71 (0.53; 0.96)	ns3	target population
	58/3589 (1.6%)		90/3591 (2.5%)	0.64 (0.46; 0.89)	p=0.008	study 337
	30/1353 (2.2%)		43/1383 (3.1%)	0.71 (0.44; 1.13)	ns1, ns3	target population
Components						
Radiological vertebral	55/1696 (3.2%)	85/1703 (5.0%)		0.63 (0.44; 0.89)	ns2	study 142
	50/1592 (3.1%)	78/1598 (4.8%)		0.62 (0.44; 0.88)	ns3	target population
	16/3321 (0.5%)		59/3322 (1.8%)	0.27 (0.15; 0.47)	p<0.001	study 337
	11/1242 (0.9%)		28/1262 (2.2%)	0.40 (0.20; 0.79)	ns3	target population
Major non-vertebral	59/2046 (2.9%)	88/2047 (4.3%)		0.67 (0.48; 0.94)	ns2	study 142
	37/3589 (1.0%)		55/3591 (1.5%)	0.67 (0.44; 1.02	ns1	study 337
All non-vertebral	70/2046 (3.4%)	95/2047 (4.6%)		0.74 (0.54; 1.01)	2	study 142
	67/1923 (3.5%)	91/1920 (4.7%)		0.74 (0.54; 1.00)	ns1, ns3	target population
	56/3589 (1.6%)		75/3591 (2.1%)	0.75 (0.53; 1.05)	ns1	study 337
	29/1353 (2.1%)		37/1383 (2.7%)	0.80 (0.49; 1.29)	ns1, ns3	target population
Hip	14/2046 (0.7%)	22/2047 (1.1%)		0.64 (0.33; 1.26)	2	study 142
	14/1923 (0.7%)	22/1920 (1.1%)		0.63 (0.32; 1.24)	ns1, ns3	target population
	7/3589 (0.2%)		13/3591 (0.4%)	0.54 (0.22; 1.35)	ns1	study 337
	3/1353 (0.2%)		9/1383 (0.7%)	0.34 (0.09; 1.25)	ns1, ns3	target population

Event	romo	ALN	placebo	Treatment effect	p-value	reference
Patients with events	**n/N (%)**	**n/N (%)**	**n/N (%)**	**risk ratio (95% ci)**		
Unfavourable effects						
All-cause mortality	30/2040 (1.5%)	22/2014 (1.1%)		1.37 (0.798; 2.37)		study 142
	27/1916 (1.4%)	20/1890 (1.1%)		1.35 (0.76; 2.41)		target population
	29/3581 (0.8%)		24/3576 (0.7%)	1.20 (0.70; 2.07)		study 337
	10/1352 (0.7%)		8/1376 (0.6%)	1.26 (0.50. 3.20)		target population
Adjudicated MACE	41/2040 (2.0%)	22/2014 (1.1%)		1.87 (1.11; 3.14)		study 142
	37/1916 (1.9%)	17/1890 (0.9%)		2.19 (1.23. 3.88)		target population
	30/3581 (0.8%)		29/3576 (0.8%)	1.03 (0.62. 1.72)		study 337
	9/1352 (0.7%)		13/1376 (0.9%)	0.70 (0.30; 1.63)		target population
Components						
CV mortality	10/2040 (0.5%)	5/2014 (0.2%)		1.97 (0.68; 5.77)		study 142
	6/3581 (0.2%)		9/3576 (0.3%)	0.67 (0.24; 1.87)		study 337
'undetermined' Mortality	7/2040 (0.3%)	7/2014 (0.3%)		0.99 (0.35; 2.81)		study 142
	11/3581 (0.3%)		6/3576 (0.2%)	1.83 (0.68; 4.95)		study 337
Non CV Mortality	12/2040 (0.6%)	10/2014 (0.5%)		1.18 (0.51; 2.74)		study 142
	12/3581 (0.3%)		9/3576 (0.3%)	1.33 (0.56; 3.16)		study 337
All-cause mortality in elderly ≥75 years	25/1070 (2.3%)	17/1049 (1.6%)		1.47 (0.79; 2.72)		study 142
	19/1117 (1.7%)		8/1115 (0.7%)	2.36 (1.03; 5.40)		study 337

Table 84: Effects Table (Entire study period)

Event	romo	ALN	placebo	Treatment effect	p-value	reference
Patients with events	**n/N (%)**	**n/N (%)**	**n/N (%)**	**risk ratio (95% ci)**		
Favourable effects						
Clinical vertebral and non-vertebral fractures	198/2046 (9.7%)	266/2047 (13.0%)		0.73 (0.61; 0.88)	p<0.001	study 142
	190/1923 (9.9%)	252/1920 (13.1%)		0.73 (0.61; 0.89)	ns3	target population
	99/3589 (2.8%)		147/3591 (4.1%)	0.67 (0.52; 0.87)	ns1	study 337
	50/1353 (3.7%)		73/1383 (5.3%)	0.70 (0.49; 1.00)	ns1, ns3	target population
Components						
Radiological vertebral (24 months)	74/1825 (4.1%)	147/1834 (8.0%)		0.48 (0.36; 0.64)	p<0.001	study 142
	69/1715 (4.0%)	133/1724 (7.7%)		0.51 (0.39; 0.68)	ns3	target population
	21/3325 (0.6%)		84/3327 (2.5%)	0.24 (0.15; 0.39)	p<0.001	study 337
	12/1243 (1.0%)		42/1264 (3.3%)	0.29 (0.15; 0.54)	ns3	target population
Major non-vertebral	146/2046 (7.1%)	196/2047 (9.6%)		0.73 (0.59; 0.90)	4	study 142
	67/3589 (1.9%)		101/3591 (2.8%)	0.67 (0.49; 0.91)	1	study 337
All non-vertebral	178/2046 (8.7%)	217/2047 (10.6%)		0.81 (0.66; 0.99)	0.040	study 142
	171/1923 (8.9%)	207/1920 (10.8%)		0.81 (0.66; 0.99)	ns3	target population
	96/3589 (2.7%)		129/3591 (3.6%)	0.75 (0.53; 1.05)	ns1	study 337 (24 months)
	49/1353 (3.6%)		65/1383 (4.7%)	0.77 (0.53; 1.12)	ns1, ns3	target population
Hip	41/2046 (2.0%)	66/2047 (3.2%)		0.62 (0.42; 0.92)	ns2	study 142
	40/1923 (2.1%)	64/1920 (3.3%)		0.62 (0.42; 0.92)	ns1, ns3	target population
	11/3589 (0.3%)		22/3591 (0.6%)	0.50 (0.24; 1.04)	ns1	study 337
	5/1353 (0.4%)		13/1383 (0.9%)	0.40 (0.14; 1.11)	ns1, ns3	target population

Event	romo	ALN	placebo	Treatment effect	p-value	reference
Patients with events	**n/N (%)**	**n/N (%)**	**n/N (%)**	**risk ratio (95% ci)**		
Unfavourable effects						
All-cause mortality	101/2040 (5.0%)	103/2014 (5.1%)		0.98 (0.74; 1.29)		study 142
	95/1916 (5.0%)	92/1890 (4.9%)		1.03 (0.77; 1.37)		target population
	72/3581 (2.0%)		85/3576 (2.4%)	0.86 (0.63; 1.17)		study 337
	15/1352 (1.1%)		16/1376 (1.2%)	0.95 (0.47; 1.93)		target population
Adjudicated MACE	117/2040 (5.7%)	102/2014 (5.1%)		1.15 (0.88. 1.50)		study 142
	107/1916 (5.6%)	91/1890 (4.8%)		1.18 (0.89; 1.56)		target population
	95/3581 (2.7%)		86/3576 (2.4%)	1.12 (0.83; 1.49)		study 337
	17/1352 (1.3%)		19/1376 (1.4%)	0.91 (0.47; 1.75)		target population
Components						
CV or 'undetermined' Mortality	67/2040 (3.3%)	68/2014 (3.4%)		0.94 (0.65; 1.35)		study 142
	43/3581 (1.2%)		50/3576 (1.4%)	0.86 (0.57; 1.29)		study 337

Both "all-cause mortality" and Adjudicated MACE" include "CV or undetermined mortality"

Romo romosozumab
ALN : alendronate
study 337 (romosozumab or placebo) followed by denosumab. Endpoints presented after 2 years
study 142 (romosozumab or alendronate) followed by alendronate. Efficacy endpoints presented through primary analysis (through Month 24 for radiological vertebral fractures). Safety endpoints presented at end of study (after median 33 months).
ns1 not significant. $p > 0.05$
ns2 not significant, not included in testing strategy
ns3 post-hoc analysis
ns4 not tested according to testing strategy
target population refers to posthoc subgroup analysis in the proposed target population (history of fracture after 45 years, no history of myocardial infarction or stroke)

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

The aim of treatment of osteoporosis is prevention of fractures. Patients with new clinical fractures, defined as symptomatic vertebral fractures and nonvertebral fractures encompass all major fracture categories. This endpoint was assessed as one of the key endpoints in the main trials submitted by the applicant. In the context of this benefit-risk assessment, these symptomatic fractures are considered most relevant for the patient and reflect disease burden.

With regard to fracture reduction, clinical fractures were statistically significantly reduced in trial 142, which is especially relevant considering that this was over active treatment/standard of care and not placebo. The effect size of around 25% fracture reduction is considered clinically relevant. The result was not statistically significant in trial 337 based on Applicant statistical analysis strategy at some of the time points. The result on clinical fractures is supported by statistically highly significant results on vertebral fractures in both trials. The results on major non-vertebral fractures did not reach statistical significance creating an uncertainty although the estimate for the relative risk reduction is between 25 and 50%. It was acknowledged that these studies were not designed to demonstrate a significant effect on non-vertebral fractures. The result is supported by results for change in BMD that suggest a rapid and large increase in interstudy comparisons. Further, from a clinical perspective, romosozumab demonstrated better effects on both vertebral and non-vertebral fractures than alendronate in study 142, an effect which was maintained over the subsequent two years. Moreover, in both AHEG meetings, the experts endorsed the view that the results from both studies taken together were supportive of an inference of a clinically relevant effect on both vertebral and non-vertebral fractures, which was also acknowledged by CHMP. The effect is considered to be superior to alendronate (representing commonly used standard of care) and so would be able to address an unmet clinical need. The inputs from patient representatives suggested that prevention of both vertebral and non-vertebral fractures were important as even vertebral fractures can result in pain and disabilities which severely affect their daily life.

During the initial assessment, major concerns arose over increased all-cause mortality and increased serious adverse cardiovascular events, especially during the first year of trial 142. This safety issue seemed to concern the most frail patients more, notably those over 75 years. The discussion provided by the Applicant in this re-examination supports that chance events may have led to over-estimation of the risk in the first year. Further the review showed that the initially perceived risks in those over 75 years were based on a post-hoc sub-group analyses and not a robust observation. Taking into account the follow-up period, during which both treatment groups were actively treated (in trial 142 with alendronate, in trial 337 with denosumab), the mortality differences disappear and magnitude of the unfavourable effects on MACE decreases relevantly. It is considered that the cause of the cardiovascular risk signal is uncertain. Although the risk of MACE events in the target population is considered to be small, it cannot be excluded, and has therefore been now addressed as an identified risk in the risk management of the product.

To mitigate the risk several risk minimisation measures are foreseen, such as a contraindication for use in patients with history of MI or stroke, warnings in the PI text, prescriber guide for careful evaluation of

individual benefit-risk when patients have increased baseline cardiovascular risk and patient alert card with key messages; these measures are considered adequate by CHMP and the exclusion of patients with history of MI and stroke was shown in the post-hoc analyses to considerably reduce the increase in absolute risk of MACE. The experts at the second AHEG meeting also considered these risk minimization measures appropriate.
The management of the risk will include two PASSs to further address uncertainties in risk, in particular cardiovascular risk. The first PASS will follow the use of romosozumab in practice by studying adherence to the risk minimization measures in the product information incuding adherence to contraindications. The second PASS intends to assess potential differences in the incidence of serious cardiovascular adverse events between romosozumab and currently available therapies used in comparable patients in real-world conditions in a cohort of users of romosozumab using national healthcare databases.

6.7.2. Balance of benefits and risks

A clinically relevant and superior efficacy over alendronate (current standard of care treatment) in terms of reducing both vertebral and non-vertebral fractures in patients with severe osteoporosis has been demonstrated. Romosozumab rapidly increases BMD and although the treatment duration is limited to 12 months, the benefits in terms of reducing fractures seen in the first 12 months continues to be accrued for the subsequent two years when treatment with romosozumab is stopped and treatment is continued with an anti-resorptive agent like denosumab or alendronate. Both vertebral and non-vertebral fractures can be debilitating and adversely affect the quality of life. As romosozumab can offer better protection than the current standard of care, it can address an unmet clinical need.

The safety of romosozumab has been well characterised except for an uncertainty with regard to an increased risk of MACE (composite of myocardial infarction, stroke and cardiovascular death) which was seen in study 142 (compared to alendronate) and not seen in study 337 (compared to placebo). This risk can be neither confirmed nor excluded despite a large safety database. The estimated absolute risk difference is small. Detailed analyses suggest that this risk is likely to be over-estimated in study 142. Excluding patients with a history of MI and stroke is expected to further reduce the absolute risk. The use in patients with any other cardiovascular risk should be cautious with consideration of likely benefits and potential risks being fully discussed by the physician and the patient in each individual case. These measures are considered to adequately mitigate the risks. PASSs to follow the use of romosozumab in practice complement these measures.

The clinical benefit of the reductionof bone fracture demonstrated across various fracture outcomes is considered to outweigh the described risk of adverse cardiovascular events in patients with severe postmenopausal osteoporosis at high risk of fracture.

6.8. Conclusions

The overall B/R of Evenity is considered positive by the CHMP.

Divergent positions are appended to this report.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit-risk balance of Evenity in the following indication:

'Evenity is indicated in treatment of severe osteoporosis in postmenopausal women at high risk of fracture.'

was favourable and that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation.

Divergent positions to the majority recommendation are appended to this report.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall ensure that the educational programme is implemented for the authorised indications of treatment of severe osteoporosis in postmenopausal women at high risk of fracture.

The educational program is aimed at further minimizing the risks of serious cardiovascular events of myocardial infarction (MI) and stroke, hypocalcaemia, and of osteonecrosis of the jaw (ONJ) by reinforcing the key safety information available in the SmPC and the PIL.

The educational programme contains the following:

- Physician educational material
- Patient alert card

The **physician educational material** should contain the following key elements:

- The Summary of Product Characteristics
- Prescriber Guide:
    - Relevant information to support healthcare professionals (HCPs) in the appropriate recognition, monitoring and management of the important identified risks of serious cardiovascular (CV) events of MI and stroke and of hypocalcaemia and important potential risk of ONJ.
    - A reminder list of risk minimization actions to be performed prior to prescription of romosozumab.
    - A checklist, which reminds the prescriber to verify the contraindication and perform a careful assessment of the cardiovascular risk profile before prescribing romosozumab.
    - Instruction for 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.
    - A reminder to the healthcare professional to educate the patient and/or caregiver on the risks, especially on the CV risk, and ensure the patient is provided with a Patient Alert Card.
    - Reminding need for and how to report suspected adverse reactions.

The **patient alert card** should be provided and contain the following key messages:

- Signs and/or symptoms of the safety concerns of serious cardiovascular events of MI and stroke, hypocalcaemia, and ONJ and when to seek attention from a healthcare professional.
- 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.
- The importance of carrying the Patient Alert Card at all times and showing it to all healthcare professionals.
- Administration dates of romosozumab and contact details of the prescribing physician to be contacted for advice if needed.
- 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 hypocalcaemia and important potential risk of ONJ.

- Reminding the need to report side effects by patients, caregivers, or any other HCP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that romosozumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0066/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Appendices

1. Divergent position to the majority recommendation for the initial opinion
2. Divergent position to the majority recommendation for the re-examination.

APPENDIX 1

Divergent position dated 27 June 2019

DIVERGENT POSITION DATED 27 June 2019

Evenity EMEA/H/C/004465

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the refusal of the granting of a Marketing Authorisation for Evenity.

The reasons for the divergent opinion were as follows:

1. Superior efficacy of romosozumab over alendronate (standard of care) has been established unequivocally. In postmenopausal women with severe osteoporosis and who are at high risk of fracture, this superior efficacy represents a major clinical benefit. Osteoporotic fractures are associated with substantial pain, disability, need for long term care and ultimately early mortality.

2. An excess incidence of major adverse cardiovascular events (MACE) was observed in study 142 (41 of 2040 patients for romosozumab versus 22 of 2014 patients for alendronate). However there is no clear mechanistic explanation for this difference, either for a protective effect of alendronate or a detrimental effect of romosozumab. Furthermore, a number of inconsistencies in the data call into question whether this imbalance in MACE events is due to a true increased risk or represents a chance finding. These inconsistencies include:

    a. In the other large study (337, placebo controlled) the patient population was younger and had a generally lower cardiovascular risk, but as it was a larger study, total numbers of MACE were about the same as in study 142. In study 337 the incidence of MACE events was the same as for placebo (30 of 3581 patients for romosozumab versus 29 of 3576 patients for placebo). This result contradicts the adverse finding for MACE in study 142.

    b. In the cumulative incidence plots for MACE events for the two studies, the incidence of MACE events for the alendronate arm in study 142 closely follows the curves for the romosozumab and placebo arms in study 337. This might be considered unexpected, as the patient population in study 337 was younger and had a generally lower cardiovascular risk. After about 18 months, the incidence of MACE events for the alendronate arm in study 142 accelerates so that at the final 36 month time point there is essentially no difference in the number of MACE events between the romosozumab and alendronate arms. These observations suggest that the adverse finding for MACE in study 142 can be attributed to an unexpectedly low incidence of MACE events at 12 months in the alendronate arm, rather than a higher than expected incidence in the romosozumab arm.

    Apparently significant imbalances between treatment groups (for both efficacy and safety events) can be expected to occur from time to time in clinical data sets submitted for regulatory scrutiny. The data should be interpreted with caution.

3. Even if the observed excess MACE risk in study 142 is a true finding, the absolute risk is low. The risk will be further reduced by the contraindication, warnings and precautions proposed by the applicant.

4. Romosozumab has been shown to be a highly effective medicine, in a new class, for a chronically debilitating and sometimes life-threatening condition for which currently available treatments are of limited effectiveness. Patients, appropriately advised and supported by their treating physicians, should be allowed the possibility to decide whether the demonstrated reduction in the occurrence of

osteoporotic fractures in comparison with alendronate outweighs for them a small possible absolute risk of an adverse effect on cardiovascular risk. For many postmenopausal women with severe osteoporosis and high risk of fracture, the benefit/risk will be considered positive.

Bjorg Bolstad

John Joseph Borg

Hrefna Gudmundsdottir

Rajko Kenda

Outi Mäki-Ikola

Greg Markey

Jan Mueller-Berghaus

Koenraad Norga

Sol Ruiz

Bruno Sepodes

Bart Van der Schueren

APPENDIX 2

DIVERGENT POSITIONS DATED 17 October 2019

DIVERGENT POSITION DATED 17 October 2019

Evenity EMEA/H/C/004465/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Evenity indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.

The reason for divergent opinion was the following:

- The increased risk of MACE documented in study 20110142, which included the finally proposed target population of postmenopausal women with severe osteoporosis is a major concern. The proposed risk minimisation activities (warnings, contraindications) are not considered to satisfactorily reduce the risk considering that the mechanism is not known and no subgroup without an increased risk of MACE has been identified. Trends for increased risk of MACE with numerical imbalances were also observed in study 20110174 on male osteoporosis and in study 20080289 comparing romosozumab to teriparatide in subjects who transitioned from bisphosphonate therapy, thus supporting the observed cardiovascular safety signal. In addition, in the pooled safety data set, an increased risk of all cause mortality in patients 75 years of age and older was documented.
- The efficacy of Evenity (romosozumab) for the treatment of osteoporosis in study 20110142 appears to be of clinically relevant magnitude in the proposed target population of postmenopausal women with severe osteoporosis, however, the totality of the efficacy data of romosozumab is less convincing, as in a study including severe and less severe stages of osteoporosis (study 20070337) a statistically significant benefit on non-vertebral fractures and hip fractures could not be shown.

CHMP Member expressing a divergent position:

Alexandre Moreau
Andrea Laslop
Concepcion Prieto Yerro
Johann Lodewijk Hillege
Konstantinos Markopoulos
Loizos Panayi

DIVERGENT POSITION DATED 17 October 2019

Evenity EMEA/H/C/004465/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the granting of the marketing authorisation of Evenity indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.

The reason for divergent opinion was the following:

- The increased risk of MACE in study 20110142 representing the proposed target population of postmenopausal women with serious osteoporosis is a major concern. The proposed risk minimisation activities (warnings, contraindications) are not considered to satisfactorily reduce the risk considering that the mechanism is not known and no subgroup without an increased risk has been identified.

CHMP Member expressing a divergent position:

Christian Gartner
Kristina Dunder