Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Romosozumab

Proprietary Product Name: Evenity

Sponsor: Amgen Australia Pty. Ltd.

January 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AESI	Adverse event of special interest
AFF	Atypical femoral fractures
AMG785	Romosozumab (drug development name)
ANCOVA	Analysis of covariance
AUC	Area under the curve
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
BMD	Bone mineral density
CHMP	Committee for Medicinal Products for Human Use (EMA/EU)
CL	Linear clearance
CL/F	Apparent clearance
C_{max}	Maximum observed concentration
CPMP/EWP	Committee for Proprietary Medicinal Products/Efficacy Working Party (EMA/EU)
CTCAE	Common terminology criteria for adverse events
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency (EU)
ESRD	End stage renal disease
EU	European Union
FDA	Food and Drug Administration (USA)
FEA	Finite element analysis
FRAX	Fracture risk assessment tool
ICH	International Council for Harmonisation

Abbreviation	Meaning
IgG2	Immunoglobulin G2
IV	Intravenous
LRP5	Low density lipoprotein related receptor 5
LRP6	Low density lipoprotein related receptor 6
MedDRA	Medical Dictionary for Regulatory Activities
NOF	National Osteoporosis Foundation (USA)
OSG	Office of the Surgeon General (USA)
P1NP	Serum type 1 aminoterminal propeptide or procollagen type 1 N-telopeptide
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PMSB/ELD	Evaluating and Licensing Division of the Pharmaceutical and Medical Safety Bureau (Japan)
PopPK	Population pharmacokinetics
PTH	Parathyroid hormone
Q6M	Every 6 months
QM	Once monthly
RRR	Relative risk reduction
SAE	Serious adverse event
SC	Subcutaneous(ly)
sCTx	Serum C-telopeptide
SE	Standard error
SMQ	Standardised MedDRA query
SOST	Sclerostin gene
TNF	Tumour necrosis factor
US(A)	United States (of America)
WHO	World Health Organization

Abbreviation	Meaning
Wnt	Wingless-related integration site

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	21 June 2019
Date of entry onto ARTG:	1 July 2019
ARTG numbers:	296830, 296831
▼ *Black Triangle Scheme*	Yes
Active ingredient:	Romosozumab
Product name:	Evenity
Sponsor's name and address:	Amgen Australia Pty. Ltd. Mezzanine Level, 115 Cotham Road KEW VIC 3101
Dose form:	Solution for injection
Strength:	105 mg in 1.17 mL
Container:	Syringe or syringe with pen injector
Pack size:	2
Approved therapeutic use:	*Evenity is indicated for:* • *The treatment of osteoporosis in postmenopausal women at high risk of fracture (see Section 5.1 Pharmacodynamic properties, Clinical trials).* • *Treatment to increase bone mass in men with osteoporosis at high risk of fracture.*
Route of administration:	Subcutaneous injection
Dosage:	The recommended dose of Evenity is 210 mg administered subcutaneously. To administer the 210 mg dose, give 2 subcutaneous injections of Evenity. Administer Evenity once every month for 12 doses

Product background

This AusPAR describes the application by Amgen Australia Pty Ltd (the sponsor) to register Evenity romosozumab for the following indication:

> *Evenity is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Evenity reduces the risk of vertebral, clinical, and non-vertebral fractures.*
>
> *Evenity is indicated for the treatment of osteoporosis in men at increased risk of fracture. Evenity increases bone mass*

Romosozumab is a humanised immunoglobulin G2 (IgG2) monoclonal antibody that binds and inhibits sclerostin. Romosozumab increases bone formation due to the activation of bone lining cells, increased bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells. Additionally, romosozumab results in changes to expression of osteoclast mediators, thereby decreasing bone resorption. Together, this dual effect of increasing bone formation and decreasing bone resorption results in rapid increases in trabecular and cortical bone mass, improvements in bone structure and strength, and fracture risk reduction.

Osteoporosis is a major public health problem that affects 15% to 38% of women age 50 years or older. While osteoporosis and osteoporotic fractures are most commonly associated with postmenopausal women, osteoporosis in men is also an important clinical and public health issue.

The current treatment guidelines for the management of post-menopausal osteoporosis by the Royal Australian College of General Practitioners (RACGP) and osteoporosis Australia recommend bisphosphonates or denosumab as first line therapy. Denosumab has advantages over bisphosphonates in terms of greater efficacy, and better compliance. Teriparatide is used when patients sustain fractures despite treatment with other anti-resorptive treatments. In men, alendronate and denosumab are considered to be a treatment option for osteoporosis.

There are concurrent applications under review in the United States of America (USA), Europe, Canada and Japan.

Regulatory status

At the time the TGA considered this application, a similar application was under consideration in the countries specified below.

Table 1: International regulatory status

Country /region; regulatory agency	Date of submission	Status
USA (FDA)	19 July 2016 (original application) 9 July 2018 (CRL resubmission)	Approved 9 April 2019
Canada (Health Canada)	17 August 2016 (original NDA) 8 August 2018 (NOD response)	Approved 17 June 2019
Japan (PMDA)	19 December 2016 (original JNDA)	Approved 8 January 2019

Country /region; regulatory agency	Date of submission	Status
European Union (EU) via the Centralised procedure (EMA)	20 November 2017	CHMP positive opinion 17 October 2019. EC decision anticipated December 2019.
Switzerland (SwissMedic)	25 January 2018	Outcome pending

FDA = (United States) Food and Drug Administration; CRL = Complete Response Letter (FDA); NDA = New Drug Application (FDA; Health Canada); NOD = Notice of deficiency (Health Canada); PMDA = Pharmaceuticals and Medical Devices Agency (Japan); JNDA = Japanese New Drug Application (PMDA); EMA = European Medicines Agency; CHMP = Committee for Medicinal Products for Human Use (EU);

The marketing application has not been deferred, withdrawn or rejected by any of the countries in which a marketing application has been submitted.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2. Time line for Submission PM-2017-04339-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	5 January 2018
First round evaluation completed	31 May 2018
Sponsor provides responses on questions raised in first round evaluation	2 July 2018
Second round evaluation completed	13 August 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	3 September 2018
Sponsor's pre-Advisory Committee response	17 September 2018

Description	Date
Advisory Committee meeting	4 October 2018
Registration decision (Outcome)	21 June 2019
Completion of administrative activities and registration on ARTG	1 July 2019
Number of working days from submission dossier acceptance to registration decision*	239

*Statutory timeframe for standard applications is 255 working days

III. Quality findings

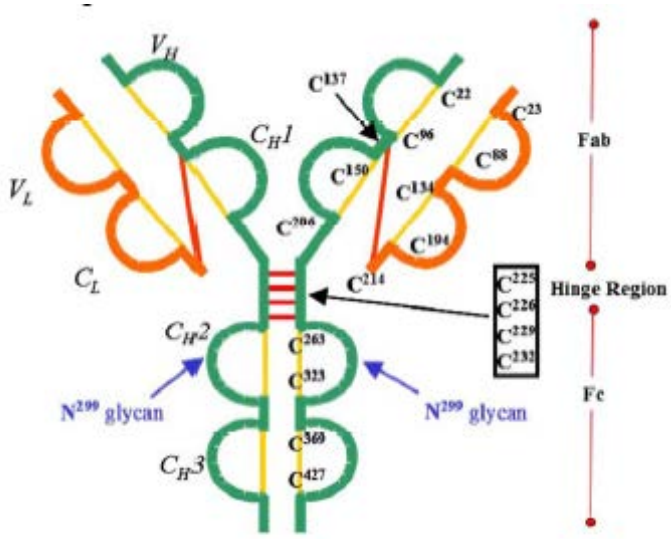
Drug substance (active ingredient)

Romosozumab is a humanised immunoglobulin G2 (IgG2) monoclonal antibody that is produced in Chinese hamster ovary cells. It consists of two heavy chains of the lgG2 subclass and two light chains of the human kappa subclass. Each heavy chain contains 449 amino acids with 4 intrachain disulfides.

The theoretical mass of fully assembled, glycosylated (containing 2 N-linked glycans (1 per heavy chain)) and disulphide bonded with heavy chain C-terminal glycine romosozumab antibody is 148,511 Da. The theoretical mass is in agreement with experimentally determined predominant romosozumab mass.

Asn299 is a consensus glycosylation site. Lys449 is removed during cell culture process. Schematic of romosozumab antibody is given below:

Figure 1: Schematic structure of romosozumab



Heavy chains are shown in green and light chains are shown in orange

V_H is the variable domain of the heavy chain

C_H1, C_H2, and C_H3 are the constant domains of the heavy chain

V_L is the variable domain of the light chain

C_L is the constant domain of the light chain

After production by cell culture and harvesting the antibody is purified using a series of chromatography and filtration steps including viral inactivation.

The characterisation and testing of the master and working cell banks, comply with International Council for Harmonisation (ICH) guidelines CPMP/ICH139/95 ICHQ5B;[1] and 3AB1a;[2]. Both cell banks were confirmed to be of Chinese hamster origin by isoenzyme analysis and the expression of the expected complementary DNA (cDNA) sequence was also confirmed. No animal derived material is used in the growth medium for master cell bank or working cell bank.

Critical process parameters and In-process controls for the manufacturing of romosozumab drug substance are defined and appeared to be well-controlled.

Process validation studies demonstrated both cleaning effectiveness as well as performance over the lifetime of the chromatography resin and ultrafiltration/diafiltration (UF/DF) membrane. Reproducibility of the manufacturing process and consistency of romosozumab drug substance is demonstrated to meet predetermined acceptance criteria.

Taken together the results of characterisation studies, forced degradation studies and studies of specific impurities indicated that process-related and product-related impurities have been well characterised, can be detected by various methods employed, controlled and cleared via the manufacturing process. Testing results have shown that the romosozumab drug substance manufacturing process could effectively reduce process-related impurities to satisfactory levels.

The specifications used are in accordance or more stringent than those applied in the process validation studies. These specifications are consistent with ICH Q6B.[3]

Analytical procedures were validated in accordance with the ICH guideline.[4] Compendial methods are appropriately qualified for their intended use. The method validation, specificity, accuracy, linearity and precision of all non-compendial methods is provided and found acceptable.

Drug product

The finished product is formulated to control viscosity and pH.

The recommended shelf-life of the drug product is 36 months at 2 to 8°C and a short term room temperature exposure (controlled, 25°C or less) for up to 30 days within the 36 months shelf life, protected from light for both romosozumab prefilled syringe and autoinjector pen. Following short term storage at room temperature (below 25°C) for not more than 30 days, Evenity (romosozumab) should be discarded.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Evenity.

Proposed conditions of registration

- Batch release testing and compliance with Certified Product Details (CPD)

[1] CPMP/ICH/139/95 ICH Q5B Analysis of the expression construct in cell lines used for production of rDNA-derived protein products
[2] 3AB1a Production and quality control of medicinal products derived by recombinant DNA technology
[3] ICH Q6B; Note for guidance on specifications: test procedures and acceptance criteria for biotechnological/biological products (CPMP/ICH/365/96)
[4] ICH Harmonized Tripartite Guide Validation of Analytical Procedures: Text and Methodology (Q2(R1)

The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

IV. Nonclinical findings

Introduction

The sponsor has applied to register a new biological entity, romosozumab, a monoclonal antibody against sclerostin. Evenity is proposed to be used for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. The proposed dose is 210 mg, given as two subcutaneous (SC) injections, once per month. Treatment is for a maximum of 12 months.

The nonclinical dossier was of good overall good quality, and in general accordance with relevant TGA-adopted guidelines, including ICH S6 (R1) (Preclinical safety evaluation of biotechnology-derived pharmaceuticals);[5] and CPMP/EWP/552/95 Rev. 2 (Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis).[6] All pivotal safety-related studies were conducted according to Good Laboratory Practices (GLP).

Pharmacology

Primary pharmacology

Sclerostin is a negative regulator of bone formation predominantly secreted by mature osteocytes. By binding to sclerostin, romosozumab is intended to increase bone formation and decrease bone resorption.

In vitro studies showed that romosozumab binds to human sclerostin with picomolar (pM) affinity (equilibrium dissociation constant (K_D) 11 pM). The affinity of the antibody for the cynomolgus monkey and rat forms of sclerostin was similarly high cf. human (respective K_D values, 23 and 3 pM), consistent with sclerostin being well conserved across species (98% and 92% amino acid identity with human for the two animal species).

[5] ICH guideline S6 (R1); preclinical safety evaluation of biotechnology-derived pharmaceuticals. EMA/CHMP/ICH/731268/1998

[6] Committee for Medicinal Products for Human Use (CHMP) 2006 Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis (EU: CPMP/EWP/552/95 rev. 2)

Sclerostin binds to LRP5 and LRP6 (low density lipoprotein receptor-related proteins 5 and 6) to antagonise the canonical Wingless-related integration site (Wnt) signalling pathway; it also interacts with LRP4 (required for the inhibitory action of sclerostin)[7]. Immunoprecipitation assays showed that romosozumab inhibits the binding of sclerostin to LRP5 and LRP6, but not to LRP4. Romosozumab was demonstrated to antagonise the inhibitory effects of sclerostin (mouse, rat, cynomolgus monkey and human forms) on mineralisation in vitro in assays using a mouse osteoblast cell line.

In vivo, once weekly treatment with romosozumab dose-dependently increased bone mineral content, bone mineral density (BMD), bone mass, bone thickness and bone strength (long bones and vertebrae) in ovariectomised rats and cynomolgus monkeys (well established models of postmenopausal bone loss), with efficacy seen at all doses tested (≥ 3 mg/kg/week SC for 12 to 52 weeks). This was accompanied by increases in bone formation biomarkers (osteocalcin, pro-collagen type 1 N terminal propeptide (P1NP), and bone specific alkaline phosphatase (ALP)). Partial reversal of the increases in bone parameters was seen after withdrawal of treatment. Efficacy was also evident in studies on fibular fracture healing in male cynomolgus monkeys, with the fracture gap area significantly reduced in animals treated with romosozumab (30 mg/kg SC twice weekly for 10 to 28 weeks), and bone formation rate, BMD and bone strength increased. Positive effects on bone were also evident in the repeat-dose toxicity studies conducted in intact male and female rats and cynomolgus monkeys.

Romosozumab is a humanised IgG2 antibody. Studies conducted with rodent surrogate antibodies (containing mouse or rat Fc regions (to reduce or avoid immunogenicity) and displaying similar affinity for sclerostin as romosozumab) also showed increases in BMD, bone mineral content, bone formation parameters and bone strength in treated ovariectomised rats.

Secondary pharmacodynamics and cross-reactivity

Treatment with the rat surrogate antibody (or its Fab fragment) was shown to produce positive effects on bone in various other rodent models of osteoporosis (androgen ablation, inflammatory bone loss, and reduced mechanical loading), but did not affect the progression of osteoarthritis.

The expression profile of sclerostin was investigated in human and laboratory animal tissues in studies submitted by the sponsor. Expression of the sclerostin gene was detected in the pulmonary artery, left atria and kidney (human), aorta (human, mouse, monkey), heart (mouse), bone (mouse, rat, monkey (human not analysed)) and male reproductive tract (mouse and rat). Sclerostin gene and/or protein expression has been reported in non-mineralised human tissues including heart, aorta, liver, lung and kidney in the literature.[8,9,10]

Immunohistochemical assays examining cross-reactivity, involving a suitably comprehensive panel of tissues, revealed no off-target binding for romosozumab, with staining limited to osteocytes (human, monkey, rabbit) and aorta or pulmonary artery (monkey), consistent with known or expected sclerostin expression; no staining was

[7] Delgado-Calle J., Sato A.Y. and Bellido T. (2017) Role and mechanism of action of sclerostin in bone. *Bone*. 96: 29–37

[8] Balemans W. et al. (2001) Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum. Mol. Genet*. 10: 537–543

[9] Brunkow M.E. et al. (2001) Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am. J. Hum. Genet*. 68: 577–589

[10] Hernandez P. et al. (2014) New insights into the location and form of sclerostin. *Biochem. Biophys. Res. Commun.* 446: 1108–1113.

observed in rats. It is noted that binding to human aorta and pulmonary artery was not examined in the experiments.

Safety pharmacology

Specialised safety pharmacology studies with romosozumab covered the core battery of systems. Central nervous system function was unaffected in rats and electrocardiogram (ECG) parameters were unaffected in cynomolgus monkeys (tested up to 300 mg/kg intravenously (IV) in each species). Notable increases in heart rate, blood pressure and respiratory rate (each by around 20 to30% at multiple time points) were observed in monkeys at 300 mg/kg IV, but only during the light-on phases of the post dose period rather than continuously. There was no treatment-related effect at 100 mg/kg IV in the study, and monitoring incorporated into the general repeat dose toxicity studies in monkeys revealed no treatment-related effects on cardiovascular function (≤ 300 mg/kg/week SC for 4 weeks and ≤ 100 mg/kg/week SC for 26 weeks).

Pharmacokinetics

Romosozumab showed a pharmacokinetic profile typical of an IgG antibody, and similar in laboratory animal species and humans. Absorption after SC administration was slow, with peak serum levels were typically reached 2 or 3 days post dose in rats and cynomolgus monkeys (compared with 5 days post dose in patients). Peak and overall exposure were approximately dose-proportional in animals and humans except at the lowest doses tested, where greater than dose-proportional exposure was seen; this is consistent with the involvement of target-specific binding and clearance. Bioavailability of romosozumab was moderate in rats (50% at 35 mg/kg), high in monkeys (around 75% at 300 mg/kg) and moderate to high in humans (around 50 to 80% at various doses). The half-life was very long in all species (for example, around 40 to70 hours in monkeys). As expected, a low volume of distribution was evident for the mouse surrogate antibody in rats and for romosozumab in humans, consistent with limited extravascular distribution.

No specific studies on tissue distribution, metabolism, excretion or pharmacokinetic interactions were conducted. This is acceptable given the protein nature of the drug, in accordance with ICH S6 (R1).[11] It is expected that romosozumab will be eliminated by normal protein degradation pathways for IgG molecules.

Toxicology

Acute toxicity

No dedicated single-dose toxicity studies were performed. This is acceptable, with relevant information on acute toxicity available from repeat-dose toxicity studies instead. No acute toxic effects were apparent in rats and monkeys in those studies up to the highest dose tested (300 mg/kg SC and IV).

Repeat dose toxicity

Repeat dose toxicity studies were conducted in rats (2, 4, 6 and 26 weeks), rabbits (4 weeks) and cynomolgus monkeys (2, 4 and 26 weeks). Administration was once weekly in all studies (that is, given more frequently than the once a month regimen in patients) and by the clinical route (SC); additional IV treatment groups were included in some of the

[11] ICH Guideline S6 (R1); preclinical safety evaluation of biotechnology-derived pharmaceuticals. EMA/CHMP/ICH/731268/1998

shorter studies (2 week rat; 2 and 4 week monkey). The pivotal studies were appropriately designed and conducted in terms of the species used (rat and cynomolgus monkeys), duration (6 months), group size and range of endpoints examined.

Exposure ratios

Animal: human exposure multiples achieved in the key toxicity studies are calculated below based on comparison of serum area under the curve (AUC) for romosozumab, adjusted for differences in dosing frequency (that is, animal values are multiplied by 4 to account for weekly compared to monthly dosing). Very high multiples of the human exposure were obtained at the highest doses tested.

Table 3: Relative exposure in key repeat-dose toxicity studies

Species	Study duration (Study no.)	Dose (mg/kg/week); route		AUC_{0-t}^ (µg·h/mL)	Exposure ratio#
Rat (SD)	2 weeks (105909)	30	SC	41100	13
		100		106500	35
		300		253500	83
		300	IV	607000	199
	4 weeks (105908)	10	SC	5895	1.9
		100		146500	48
		300		174500	57
	6 months (pivotal; 107425)	3	SC	1840	0.6
		10		12900	4.2
		100		124000	41
Monkey (cynomolgus)	4 weeks (105776)	10	SC	23800	8
		30		77200	25
		300		645000	211
		300	IV	588000	193
	6 months (pivotal; 107426)	3	SC	3490	1.1
		10		17100	6
		100		301000	99
Human (patients)	Population PK analysis (119384A)	210 mg SC once monthly		12216	–

^ = animal data are for the sexes combined, measured at the last sampling occasion; # = animal:human serum AUC0–t × animal:human dosing frequency PK = pharmacokinetics

Anti-drug antibodies developed in some rats and monkeys, and a great many rabbits, resulting in reduced systemic exposure. Toxicokinetic data from animals positive for anti-drug antibodies have been excluded from the calculations above. Immunogenicity in rats and monkeys was not so prevalent as to affect the validity of the studies, but was in rabbits. The rabbit is therefore seen to be an unsuitable species for examining romosozumab toxicity, and findings from the rabbit study are not discussed below. Immunogenicity in animals (to this humanised protein) is not predictive of the development of anti-drug antibodies in humans.

Major findings

Romosozumab produced treatment-related microscopic changes in bone, liver and spleen.

Hyperostosis, pharmacologically mediated -was evident in rats and monkeys from the lowest dose level tested, that is, 3 mg/kg/week. This was increased in incidence and severity with dose, and more prominent in female compared with male rats, but comparable between sexes in monkeys. The hyperostosis was characterised by an increased thickness of the trabeculae that resulted in a relative reduction in bone marrow space. Partial reversibility following a 14 week treatment-free period was demonstrated in the pivotal studies.

In rats, extramedullary haematopoiesis was observed in the liver and increased in the spleen from the lowest dose level tested (≥ 3 mg/kg/week). Similar findings were not observed in monkeys, but both species showed slight reductions in red blood cell indices (at ≥ 10 mg/kg/week). These findings are considered to be secondary to the reduction in bone marrow space, and were reversible.

No target organ toxicity by romosozumab was identified. This includes toxicity to the various tissues known to express sclerostin.

Genotoxicity

No genotoxicity studies were performed. This is acceptable in accordance with ICH S6 (R1);[11] with a large protein like romosozumab not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

The carcinogenic potential of romosozumab was investigated in a 2 year study in rats. The study was appropriately designed and conducted, and involved SC administration at doses up to 50 mg/kg/week. Dose selection was appropriate, with relative exposure at the high-dose level estimated to be 20 (based on interpolation of the serum AUC for the 100 mg/kg/week dose in the 26-week general repeat dose toxicity study in rats).

No treatment-related increase in tumour incidence was observed. Of note, osteosarcomas were observed in 2 of 56 high-dose males, present in tibia and frontal bone of the skull. The incidence marginally exceeded the upper historical control range for the test facility (2 of 60), but was not statistically significant by either trend test or pairwise comparison. The examination of potential bone neoplasms was more extensive in this study than in the historical control data set, promoting their detection. Osteosarcoma was not accompanied by findings of osteoblast hyperplasia (as seen with teriparatide, known to produce osteosarcoma in rats), and not seen in females despite drug-induced hyperostosis being more prominent in that sex. Accordingly, the tumour finding is not considered to be treatment-related.

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages (fertility, early embryonic development, embryofetal development, and pre and postnatal development). All studies were conducted in rats by the SC route, administered once weekly. The absence of an embryofetal development study in a second non rodent species is considered to be acceptable; the use of the rabbit is not appropriate given that romosozumab is highly immunogenic in the species. The pivotal studies were appropriately designed and conducted in terms of dose selection, group size, the timing and duration of treatment, and the endpoints examined.

Table 4: Relative exposure in reproductive toxicity studies

Species	Study type (Study no.)	Dose (mg/kg/ week); SC	AUC_{0-t} (µg·h/mL)	Exposure ratio[#]
Rat (SD)	Fertility and embryofetal development; Pre-/postnatal development (108061; 108062)	10	4752	1.6
		60	60480	20
		300	179760	59
	Embryofoetal development (108059)	30	17000[a]	6
		100	53300[a]	17
		300	115000[a]	38
Human (patients)	Population PK analysis (119384A)	210 mg SC once monthly	12216	–

[a] = predicted based on highest AUC values from Study 108057 (which used the same dosing regimen as Study 108059); [#] = animal:human serum AUC_{0-t} × animal:human dosing frequency

Placental transfer of romosozumab was demonstrated in rats, and found to be high. Excretion in milk was not examined.

No adverse effects on male or female fertility were observed with romosozumab in rats up to the highest dose tested (300 mg/kg/week; relative exposure, 59).

Foetuses of rats treated at 300 mg/kg/week showed an increased incidence of various external and skeletal malformations (extra digits, fused digits, extra phalanx, absence of ossified metacarpals and bent tibia; predicted relative exposure, 38). While these occurred in only a single litter (of 22) in the definitive study, the fetal and litter incidences exceeded the historical control range. It cannot be ruled out that the observed malformations are treatment-related given a role for sclerostin in digit formation is recognised in humans and animals;[12] although it is noted that such malformations are not seen in heterozygous carriers of a loss of function mutant sclerostin gene.[13] The malformations observed in the embryofetal development study occurred in the absence of maternotoxicity. The no

[12] Collette N.M. et al.(2013) Sost and its paralog Sostdc1 coordinate digit number in a Gli3-dependent manner. *Dev. Biol.* 383: 90–105

[13] Sebastian A. and Loots G.G. (2018) Genetics of Sost/SOST in sclerosteosis and van Buchem disease animal models. *Metab. Clin. Exp.* 80: 38–47.

observed adverse effect level for adverse effects on embryofetal development in the rat is considered to be 100 mg/kg/week (predicted relative exposure, 17), with findings at this dose limited to an increase in the incidence of a minor skeletal variation (reduced ventral processes of the 6th cervical vertebra, representing a developmental delay of an anatomic structure not present in humans).

No adverse effects on pup development were observed with maternal treatment with romosozumab throughout gestation and lactation (≤ 300 mg/kg/week; relative exposure, 59).

Pregnancy classification

The sponsor proposes Pregnancy Category B3 for romosozumab [14]. This is considered appropriate based on the findings in the animal studies. While teratogenicity was observed in the study with romosozumab in rats (being consistent with the known biological role of the target), the low incidence of malformations and the high exposure margin at the no observed effect level mean that concern for foetal harm in humans is not so high as to warrant assignment to a stricter category; that is, Category D.[15] Although a pharmacological mechanism is seen to be involved, Category Cis not appropriate given the nature of the adverse effects (malformations).[16]

Local tolerance

Romosozumab was well tolerated locally in rats and monkeys. The maximum tested strength in the general toxicity studies (80 mg/mL) was below that proposed clinically (90 mg/mL), but higher strengths (up to 120 mg/mL) were used in specialised studies, conducted in rats. Examination of SC injection sites revealed minimal to mild oedema, increased incidence and severity of granulomatous inflammation, and increased severity of inflammatory cell infiltrates, considered to be non-adverse reactions to the injection of foreign protein.

Immunotoxicity

Signs of immunotoxicity were not observed in general repeat dose studies and no specialised immunotoxicity studies were performed.

Phototoxicity

Phototoxicity studies were not conducted using romosozumab. This is acceptable in accordance with the ICH S10 guideline.[17]

Paediatric use

Romosozumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted. Effects on skeletal development would be expected.

[14] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.
[15] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[16] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
[17] ICH guideline S10 Guidance on photosafety evaluation of pharmaceuticals Step 3 EMA/CHMP/ICH/752211/2012

Comments on the nonclinical safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for romosozumab detailed in the sponsor's draft risk management plan (RMP) are in general concordance with those of the nonclinical evaluator except for the following:

- Despite their low incidence, foetal skeletal malformations (including syndactyly and polydactyly) observed in rats with maternal dosing at 300 mg/kg/week may be related to treatment based on a weight of evidence approach, with biological plausibility downplayed by the sponsor.
- Minor discrepancies in animal: human exposure ratios are noted. Exposure ratios calculated in this report are based on a serum AUC value of 509 µg.d/mL (= 12,216 µg.h/mL) as given in the Population pharmacokinetics report provided with the submission (Study 119384A), while those cited by the sponsor appear to be based on an earlier value of 537 µg.d/mL (= 12,888 µg.h/mL).

Nonclinical summary and conclusions

- Sclerostin is a negative regulator of bone formation predominantly secreted by mature osteocytes. It is also expressed in various non mineralised human tissues, including heart, aorta, liver, lung and kidney.
- *In vitro* studies established that romosozumab binds to human sclerostin with high affinity (K_D, 11 pM), inhibits the binding of sclerostin to LRP5 and LRP6 receptors through which it signals, and antagonises the action of sclerostin to reduce mineralisation in a mouse osteoblast cell line. *In vivo*, romosozumab increased bone mineral content, BMD, bone mass, bone thickness and bone strength in rat and monkey models of postmenopausal bone loss. Positive effects on bone were also observed in a variety of other models of bone loss (including androgen ablation), and in repeat-dose toxicity studies conducted in normal male and female rats and monkeys. These studies offer support for efficacy for the proposed indication.
- Sclerostin is highly conserved in rats, cynomolgus monkeys and humans. Romosozumab showed comparable affinity for the animal forms of sclerostin compared with the human form.
- High specificity for binding was evident in immunohistochemistry assays examining cross-reactivity. Safety pharmacology studies (covering the central nervous, cardiovascular and respiratory systems) identified no relevant concerns.
- Pharmacokinetic studies with romosozumab and a mouse surrogate antibody (of comparable potency) revealed a typical profile for an IgG antibody; nonlinear pharmacokinetics (consistent with target-specific binding and clearance), slow absorption after SC administration, a long serum half-life, and a low volume of distribution (consistent with limited extravascular distribution).
- Repeat dose toxicity studies of up to 6 months duration were conducted in rats and cynomolgus monkeys. These species are seen to be appropriate models for the investigation of romosozumab toxicity on pharmacodynamic and pharmacokinetic grounds, and with immunogenicity (to the humanised protein) in the species not so prevalent as to affect study validity. Weekly SC administration of romosozumab at doses producing very high multiples of the clinical systemic exposure was well tolerated, with no target organs for toxicity identified. Histological changes were observed in bone, liver and spleen, but represent pharmacological effects (hyperostosis in bone; and extramedullary haematopoiesis in liver and spleen, occurring secondary to a reduction in bone marrow space).

- Genotoxicity studies were not conducted, in line with the ICH S6 (R1) guideline.[5] Romosozumab was not carcinogenic in rats.
- Weak teratogenicity was observed in fetuses of rats given romosozumab, with skeletal malformations (including syndactyly and polydactyly). This was observed at low incidence and at a high animal: human exposure margin (38 fold). This finding is consistent with a role for sclerostin in digit formation recognised in humans and animals. A relationship between treatment and effects on embryofetal development cannot be excluded, but the risk in patients is considered to be low. No adverse effects on male and female fertility, or on postnatal development, were observed. Pregnancy Category B3, as the sponsor proposes, is considered appropriate.[14]
- Romosozumab was well tolerated locally in rats and monkeys.
- There are no nonclinical objections to the registration of Evenity for the proposed indication.

V. Clinical findings

Introduction

Osteoporosis is characterised by low bone mass and compromised bone strength predisposing individuals to an increased risk of fracture[18,19] The WHO defines osteoporosis as a BMD (bone mineral density) less than or equal to 2.5 standard deviations below the mean BMD of a young-adult population. Women age ≥ 50 years have a 40% to 50% lifetime risk of suffering an osteoporosis-related fracture (National Osteoporosis Foundation (NOF), 2014).[20] Osteoporosis is a major public health problem that affects 15% to 38% of women age 50 years or older. Across the US, Europe (EU), Canada, Australia and Japan, an estimated 44 million women age 50 years and over have postmenopausal osteoporosis and approximately 4.5 million suffer osteoporotic fractures annually.[21],[22],[23],[24],[25]

Osteoporotic fractures result in significant disability and economic burden to individuals and to society. Factors associated with an increased fracture risk include low BMD, a prior osteoporotic fracture, long term glucocorticoid treatment, age and other factors.[18,19,20]Prior fracture is among the strongest risk factors for subsequent fracture with risk for subsequent fractures increased 2.5 fold, 5 fold and 2 to 3 fold following hip fracture, vertebral fractures and fractures at other sites, respectively. A 10% loss of bone

[18] World Health OrganizationL WHO scientific group on the assessment of osteoporosis at primary health care level. WHO Press, World Health Organization. Geneva, Switzerland; 2007.
[19] Office of the Surgeon General (US). Bone Health and Osteoporosis: A Report of the Surgeon General; Rockville (MD) USA: Office of the Surgeon General (US); 2004.
[20] Cosman F et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014; 25(10): 2359–2381
[21] Wade SW, Strader C, Fitzpatrick LA, et al. Estimating prevalence of osteoporosis: examples from industrialized countries. *Arch Osteoporos*. 2014; 9: 182
[22] Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014; 29: 2520-2526
[23] Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*. 2013; 8: 136
[24] Wade SW, Strader C, Fitzpatrick LA, Anthony MS. Sex- and age-specific incidence of non-traumatic fractures in selected industrialized countries. *Arch Osteoporos*. 2012;7: 219-227
[25] Burge R, Dawson-Hughes B, Solomon DH, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res.* 2007;22: 465-475

mass in the vertebrae can double the risk of vertebral fractures, and similarly, a 10% loss of bone mass in the hip can result in a 2.5 times greater risk of hip fracture. Overall, a prior fracture is associated with an 86% increased risk of any fracture.

Minimal trauma fractures are relatively common in people aged 50 and over. It is estimated that, for Australians aged 50 and over, 1 in 4 men and 2 in 5 women will experience a minimal trauma fracture in the future. Minimal trauma fracture of the hip is one of the most serious outcomes of osteoporosis. In 2011 to 2012, 19,000 people aged 50 and over were hospitalised due to a minimal trauma hip fracture, of which 71% were aged 80 and over and 72% were women. Although the rate of minimal trauma hip fracture for people aged 50 and over has decreased over time (age-adjusted), the actual number of hip fractures continues to increase due to the increasing number of older adults in Australia. Nearly 75% of hip, spine and distal forearm fractures occur among patients 65 years old or over.

Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds. Osteoporosis is estimated to affect 200 million women worldwide with increased incidence with age (affecting one-tenth of women aged 60 to almost two-thirds of women aged 90 years). Worldwide, 1 in 3 women over the age of 50 will experience osteoporotic fractures, as will 1 in 5 men aged over 50. While osteoporosis and osteoporotic fractures are most commonly associated with postmenopausal women, osteoporosis in men is an important clinical and public health issue. In 2011 to 2012 the estimated prevalence of self-reported diagnosed osteoporosis among those aged 50 and over living in the community was 15% of women and 3% of men, according to the Australian Health Survey. Based on a recent study measuring bone density in a population sample, the prevalence of osteoporosis among those aged 50 and over was estimated to be 23% of women and 6% of men. This estimate includes both diagnosed and undiagnosed cases of osteoporosis. With the aging of the overall population and the increasing longevity, fractures as the primary consequence of osteoporosis and the ensuing health care burdens are expected to greatly increase in coming years.

Current treatment options

Although the impact of osteoporosis is widely recognised, studies show that a fragility fracture is often not acknowledged as a symptom of underlying osteoporosis and only about 20% of these patients initiate osteoporosis treatment within the year following fracture.[26],[27] Pharmacologic therapies for osteoporosis and the prevention of osteoporotic fractures consist of several types of anti-resorptive therapies (including bisphosphonates and selective oestrogen receptor modulators), and active vitamin D3 preparations. Calcitonin (salmon) is also available in some EU countries for the indication of pain in osteoporosis. Of the drugs commonly used to treat osteoporosis, bisphosphonates have been shown to be effective agents against osteoporosis and have been used as the established standard for treatment.[27] For some anti-resorptive therapies (alendronate, ibandronate and bazedoxifene), it took 3 years or longer to demonstrate a significant reduction in the risk of vertebral, non-vertebral, or clinical fracture. Furthermore, drugs of this class have to be administered with an adequate volume of water at the time of waking up every morning when taken orally, and patients receiving this therapy are not permitted to lie down, to ingest anything else but water, nor to take other oral medication drugs for at least 30 minutes after each dose. Due to these limitations, there are patients who cannot begin or continue to use these kinds of drugs or who cannot comply with the instructions for dosing, despite an increased risk of fracture.

[26] Balasubramanian A, Tosi LL, Lane JM, et al. Declining rates of osteoporosis management following fragility fractures in the U.S., 2000 through 2009. *J Bone Joint Surg Am.* 2014; 96: e52
[27] Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 2013; 24: 23-57

Although other anti-resorptive therapies such as risedronate, raloxifene and denosumab demonstrated significant reductions of 60% to 68% in the risk of vertebral fractures in their respective pivotal clinical studies within 1 year;[28,29,30] bone-forming therapies can provide larger improvements in bone structure and strength; however, only one class of bone forming therapies is available; parathyroid hormone analogs. The parathyroid hormone fragment teriparatide (rhPTH (1-34)) (20 µg/day subcutaneously) is the only widely available bone forming agent. Teriparatide significantly reduced the risk of new vertebral fractures by 65% relative to placebo within an average of 19 months, yet the time to onset of effect with teriparatide for daily use may leave patients relatively unprotected early in treatment. Other limitations of teriparatide are a relatively small BMD increase at the hip (2.6 to 3.7%);[31,32] and treatment duration is limited to a maximum of 24 months over the patient's lifetime due to the potential risk of osteosarcoma. In the US, a parathyroid hormone analogue (a modified variant of teriparatide) was approved in 2017, abaloparatide (Tymlos PI, 2017), for postmenopausal women with osteoporosis at high risk for fracture due to a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have not responded to or are intolerant to other available osteoporosis therapy. Like teriparatide, abaloparatide is administered by daily SC injection. However, abaloparatide is not available in Australia.

Clinical rationale

Romosozumab represents a new class of bone-forming agents that can address this unmet need. It is a humanised immunoglobulin G2 (IgG2) monoclonal antibody that binds and inhibits sclerostin. Sclerostin was identified as a target of interest by genetic analysis of two rare bone disorders, which are associated with thick bones, increased density and resistance to fracture: sclerosteosis and Van Buchem disease. It was found that both diseases are caused by different mutations in the sclerostin (SOST) gene; a mutation within the coding region affecting the protein;[33] and a regulatory element control expression of the SOST gene, respectively.[34] Both mutations indicate that an absence or reduced expression of sclerostin is involved in the increase of bone density and strength. Homozygous carriers with sclerosteosis, who completely lack sclerostin, can also experience negative effects, such as facial palsy, hearing impairment and syndactyly.[35,36,37] However, when sclerostin expression is merely reduced, such as in heterozygous carriers of a SOST gene mutation, there is still increased BMD but without the associated negative effects. Based on these observations, sclerostin was identified as a potential therapeutic

[28] Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis (FREEDOM Trial). *N Engl J Med.* 2009; 361: 756-765
[29] Maricic M et al. Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis, *Arch Intern Med*. 2002; 162: 1140-1143.
[30] Harris KB et al., The Clinical Use of Denosumab for the Management of Low Bone Mineral Density in Postmenopausal Women*, J.Pharmacy Practice* 2012; 25: 310-318
[31] Neer RM, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001; 344: 1434-1441
[32] Miyauchi A, et al. Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-Month, randomized, placebo-controlled, double-blind and 12-month open-label phases. *Bone*. 2010; 47: 493–502
[33] Brunkow ME, et al. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am J Hum Genet*. 2001; 68: 577-589
[34] Balemans W, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet*. 2001; 10: 537-543
[35] van Lierop AH, et al. Patients with sclerosteosis and disease carriers: human models of the effect of sclerostin on bone turnover. *J Bone Miner Res*. 2011; 26: 2804-2811
[36] van Lierop AH, et al. Van Buchem disease: clinical, biochemical, and densitometric features of patients and disease carriers*. J Bone Miner Res*. 2013; 28: 848-854.
[37] Gardner JC, et al. Bone mineral density in sclerosteosis; affected individuals and gene carriers. *J Clin Endocrinol Metab*. 2005; 90: 6392-6395

target for treatment of disorders that are associated with low bone mass and reduced bone strength.

By inhibiting sclerostin, romosozumab demonstrates a dual effect on bone, increasing bone formation and decreasing bone resorption, leading to rapid and substantial gains in BMD and improved bone strength. Romosozumab is administered monthly as two SC injections of 105 mg each for 12 months and has a rapid onset of effect, thus offering an important additional treatment option for osteoporosis in patients at increased risk of fractures.

There is an unmet need for a therapy that rapidly increases bone mass and bone strength and delivers fracture efficacy in the near-term, which is particularly important in patients who have already suffered a fracture or are otherwise at increased risk of fracture in the near-term. Potential benefits of romosozumab include rapid fracture risk reduction, significant BMD gains, and improved underlying skeletal strength for ongoing fracture risk reduction that is maintained with follow-on anti-resorptive therapy.

Guidance

The development program has been informed by regulatory interactions with EU National Competent Authorities and the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), Health Canada and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

EU regulatory interactions led to key agreements on the nonclinical program and major design aspects of the placebo controlled pivotal fracture study (Study 20070337), including the requirement for 3 years of data for approval. Key aspects of the study design and statistical analysis plan for Study 20070337 were also agreed with input from the US FDA. In addition to the placebo controlled study, EU regulatory feedback reflected interest in a head-to-head study assessing the safety and efficacy of romosozumab versus standard of care, which was addressed in the second pivotal fracture Study 20110142, which used alendronate as a comparator. Regulatory interactions with PMDA in Japan secured agreement on the participation of Japanese subjects in the pivotal Study 20070337 in parallel with the conduct of a dose-finding Phase II study in Japanese women (Study 20101291). For the evaluation of osteoporosis in men, PMDA indicated that the conduct of Study 20110174 would be acceptable for this purpose in conjunction with positive results for romosozumab 210 mg administered monthly in Study 20070337.

Regulatory feedback confirming the plan for the proposed Phase III studies was obtained from Health Canada in the context of a clinical trial application (pre-Phase III) meeting held on 21 July 2011. Health Canada noted that due to romosozumab's new mechanism of action and the clinical dosing duration, Health Canada expected a 2 year carcinogenicity study to be conducted. The relevant nonclinical study has been completed and submitted.

Contents of the clinical dossier

The clinical dossier contained the following:

- Clinical pharmacology
  - seven pharmacokinetic studies
  - five pharmacodynamics studies
  - three population pharmacokinetic/pharmacodynamic studies.

- Efficacy and Safety
  - Three pivotal studies:
    - Study 20070337 (FRAME trial): A Phase III pivotal, placebo controlled study in postmenopausal women with osteoporosis
    - Study 20110142 (ARCH trial): A Phase III active controlled (alendronate) study in postmenopausal women with osteoporosis.
    - Study 20110174 (BRIDGE trial): A Phase III placebo controlled study in men with osteoporosis.
  - Four supportive studies:
    - Study 20120156: A Phase III study in postmenopausal women with osteoporosis (90 mg/mL versus 70 mg/mL).
    - Study 20080289: A Phase IIIb active controlled (teripratide) study in postmenopausal women with osteoporosis previously treated with bisphosphonates.
    - Study 20060326: A Phase IIb study in postmenopausal women with low BMD.
    - Study 20101291: A Phase IIb in postmenopausal Japanese women with osteoporosis.

The submission also included an Integrated Summary of Efficacy and Integrated summary of Safety. An Integrated Cardiovascular Report (dated October 2017) was also included in the submitted dossier.

Paediatric data

No paediatric data was submitted as the proposed usage is not likely to be prevalent in paediatric subjects.

Good clinical practice

Clinical studies were conducted under Good Clinical Practice (GCP) as described in ICH guideline E6 (ICH, 1996)[38], under the principles of the Declaration of Helsinki, and in accordance with local and regional regulations and guidance.

Guidance

Formal regulatory guidance for development of osteoporosis products includes:

- Committee for Medicinal Products for Human Use (CHMP) 2006 Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis (EU: CPMP/EWP/552/95 rev. 2); and
- Japanese Guidelines for Clinical Evaluation Methods of Drugs for Osteoporosis (PMSB/ELD no. 742 1999).

The dossier was well presented. Romosozumab was investigated in a comprehensive development program which included 19 clinical studies conducted between 2006 and 2017 that enrolled approximately 14,000 subjects to support the proposed indications for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. Studies included healthy volunteers, postmenopausal women with osteoporosis or low BMD and men with osteoporosis.

[38] EMA/CHMP/ICH/135/1995 Guideline for good clinical practice E6(R2)

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5: Submitted pharmacokinetic studies

Pharmacokinetics topic	Subtopic	Study ID
Pharmacokinetics in healthy adults	General pharmacokinetics (single dose)	20060220
	General pharmacokinetics (multi-dose)	20060221
	Bioequivalence† (single dose)	20101180
		20120277
		20150197
		20090418
	Relative bioavailability	20120274
	Food effect	None.
Pharmacokinetics in special populations	Target population§ (single dose)	20060223
	Target population§ (multi-dose)	20090153
	Renal impairment	20110227
Genetic/gender related pharmacokinetics	Males versus females	None
	Japanese women	20090378
Population pharmacokinetics analyses	Healthy subjects/target population	119384A

† Bioequivalence of different formulations; § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

All pharmacokinetics studies used a validated assay methodology based on enzyme linked immune sorbent (ELISA) technology with a quantitation range of 50 to 2492 ng/mL to quantify serum romosozumab concentrations. pharmacokinetics parameters were estimated using non-compartmental methods and were conducted satisfactorily.

Romosozumab is slowly absorbed from the SC injection sites reaching maximum plasma concentration in about 5 days. When administered to healthy subjects at single SC doses ranging from 0.1 mg/kg to 10 mg/kg, romosozumab exhibited nonlinear pharmacokinetics. Mean apparent clearance (CL/F) was approximately 4 fold higher at a dose of 0.1 mg/kg than at 3 mg/kg. At doses between 3 mg/kg and 10 mg/kg, the pharmacokinetics appeared to be linear, based on relatively similar clearance and

dose-normalised maximum serum concentration (C_{max}) and area under the concentration-time curve from time 0 to infinity (AUC_{inf}). Serum romosozumab concentrations declined with a mean half-life ($T_{1/2}$) of approximately 11 to 18 days during the beta (plateau) phase and 6 to 7 days during the gamma (terminal) phase. The bioavailability of romosozumab was estimated to be 50% to 70% after SC administration of 1 to 5 mg/kg.

Following administration of SC doses every 4 weeks at 3 mg/kg for 3 months, accumulation based on mean C_{max} and AUC values following 3 doses was approximately 20% to 36% more than exposure after the first dose. The mean effective $T_{1/2}$ was 12.8 days after 3 doses of 3 mg/kg. Approximately linear pharmacokinetics was observed when comparing C_{max} and AUC values following 2 mg/kg and 3 mg/kg every 4 weeks. When multiple SC doses of romosozumab 70 mg, 140 mg, or 210 mg monthly were administered to postmenopausal women with osteoporosis or low BMD, steady state was generally reached by Month 3 with minimal accumulation (< 2 fold). Trough concentrations were approximately dose proportional from 140 mg to 210 mg, however a more than dose-proportional increase was observed from 70 mg to 140 mg. Although renal clearance is not expected to play a role in the total clearance of romosozumab, there were some differences in pharmacokinetics between healthy controls and patients with stage 4 renal disease (AUC approximately 44% higher in renal disease subjects). Based on population pharmacokinetic (PopPK) modelling, no dose adjustment is required for subjects with renal impairment. Romosozumab is not eliminated via hepatic metabolism.

Results from the clinical pharmacology program, including population pharmacokinetics and pharmacokinetics/pharmacodynamics analyses, support the clinical use of the proposed 210 mg SC monthly dosing regimen.

Population pharmacokinetics and pharmacokinetics/pharmacodynamics analyses in healthy subjects and postmenopausal women with low BMD or osteoporosis suggested that after SC administration of 210 mg, bioavailability was high (81%) and absorption was complete in approximately 14 days. There were no differences in romosozumab pharmacokinetics between healthy subjects or postmenopausal women with low BMD or osteoporosis. pharmacokinetics/pharmacodynamics modelling demonstrated body weight and estimated glomerular filtration rate (eGFR) had minimal impact on BMD gain at 12 months. Dose adjustment on the basis of these covariates is not warranted.

The proposed product information adequately reflects the findings of the pharmacokinetics studies presented by the sponsor.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 6: Submitted pharmacodynamic studies

Pharmacodynamics Topic	Subtopic	Study ID
Primary pharmacology	Effect on BMD	20090153
	Effect on BMD	20110253
Secondary pharmacology	Effect on serum type 1 aminoterminal propeptide (P1NP)	20060223
	Effect on serum type 1	20090153,

Pharmacodynamics Topic	Subtopic	Study ID
	aminoterminal propeptide (P1NP)	20110253
	Effect on serum C-telopeptide	20060223, 20090153, 20110253
Gender, other genetic and age related differences in pharmacodynamic response	Effect of gender	None
	Effect of age	None
Pharmacodynamics; interactions		None
Population pharmacodynamics and pharmacokinetics-pharmacodynamics analyses	Target population	119384B
	Target population	119384C

Evaluator's conclusions on pharmacodynamics

Administration of single or multiple doses of romosozumab > 1 mg/kg resulted in a dual effect on bone with increased bone formation markers (serum type 1 aminoterminal propeptide (P1NP), osteocalcin, bone specific alkaline phosphatase) and decreased bone resorption markers (serum C-telopeptide, tartrate-resistant acid phosphatase 5b (TRAP 5b)). The concentration-response model adequately described the relationship between romosozumab concentration, bone turnover makers (P1NP and serum C-telopeptide) and BMD gains at the lumbar spine. Of the dosing regimens studied, the highest BMD gains at 12 months were observed for 210 mg SC monthly. The greatest increase in the bone formation marker P1NP, and the longest duration of P1NP increase above baseline were also obtained with the 210 mg SC monthly dosing regimen.

Romosozumab was without effect on the QTc interval;[39] in Phase I and II single and repeated dose studies.

The pharmacodynamic section of the proposed PI adequately reflects the findings of the studies presented by the sponsor in the application.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

Pharmacokinetics/pharmacodynamics modelling and simulations using the dose-BMD and concentration, bone turnover marker and BMD (lumbar spine) models demonstrated that a romosozumab dose of 210 mg SC monthly provided greater BMD gains at Month 12 compared to the other dosing regimens tested.

Following a single SC dose of romosozumab at 0.1 to 10 mg/kg, increases in P1NP levels were observed as doses increased greater than 1 mg/kg. Following doses of 3 mg/kg or 210 mg, the maximum effect was generally 100% to 150% above the baseline and occurred between 2 and 4 weeks post-dose. Thereafter, P1NP levels returned to baseline

[39] QTc interval; cardiac QT-interval corrected for heart rate

by 8 to 12 weeks (Studies 20060220, 20090378). Serum C-telopeptide levels decreased following administration of doses greater than 1 mg/kg with the nadir occurring between 1 and 2 weeks post-dose and a return to near baseline at approximately 8 to 12 weeks post-dose. Following multiple SC doses of romosozumab of 1 to 3 mg/kg for 3 months, temporal changes in increases in P1NP levels and decreases in serum C-telopeptide (sCTX) levels were observed in once two weekly, four weekly and monthly regimens (Studies 20060221, 20090153 and 20110253). The magnitude of increases in P1NP levels and decreases in sCTX levels attenuated following multiple doses of romosozumab. The levels of P1NP and sCTX returned to near baseline by the end of the study. The profiles of the other bone formation markers, osteocalcin and bone specific alkaline phosphatase, in Phase I studies were dose dependent and similar to the P1NP profiles following single or multiple doses.

Phase II dose finding studies

The main dose-ranging Phase II studies are Studies 20060326 and 20101291. Integrated analyses of BMD data for the monthly dose groups in Studies 20060326 and 20101291 demonstrated that the 210 mg monthly dosing regimen resulted in the greatest increase in BMD (Month 12) at the lumbar spine, total hip and femoral neck compared with the other romosozumab dosing regimens tested (70 and 140 mg monthly). Furthermore, 210 mg monthly and 140 mg monthly consistently increased BMD at the lumbar spine, total hip and femoral neck at Months 6 and 12 ($p < 0.001$); whereas, results for the romosozumab 70 mg monthly group were less robust, in particular early in treatment when the percent change from baseline in BMD was similar to placebo at Month 6 for the total hip and femoral neck. The 210 mg monthly dose was also associated with greater increases in BMD at the lumbar spine and total hip than the two active controls, alendronate (Study 20060326) and teriparatide (Study 20060326 and Study 20080289). The 210 mg SC monthly dosing regimen produced the largest and most prolonged increase in markers of bone formation, with median P1NP, bone specific alkaline phosphatase and osteocalcin levels remaining above baseline for 6 to 12 months compared to 3 to 6 months for 140 mg SC monthly. In contrast to the bone formation markers which exhibit increases in a dose dependent manner, the reduction in markers of bone resorption appeared to be less dose-dependent. This suggests that compared with 140 mg monthly, the 210 mg monthly dose of romosozumab has a greater impact on promoting bone formation without a corresponding further reduction of bone resorption.

Efficacy, as measured by BMD and bone turnover marker, was significantly lower when romosozumab was given in 3 month intervals for both of the doses tested. For example, at Month 12, the 210 mg every 3 month BMD efficacy was closer to the BMD efficacy achieved with 70 mg monthly dosing.

A dose-ranging study in subjects previously treated with bisphosphonates has not been conducted, however BMD gains at the lumbar spine, total hip and femoral neck appeared to be greater for bisphosphonate-treated subjects who transitioned to romosozumab 210 mg monthly in Study 20080289 than for subjects in Study 20060326 who transitioned from alendronate to romosozumab 140 mg monthly. Furthermore, the romosozumab 210 mg monthly dose does not appear to have a different safety or immunogenicity profile compared with the other regimens tested in the dose-ranging studies.

A longitudinal dose-BMD response model using a nonlinear mixed effects modelling approach was developed that jointly describes the time courses of BMD change from baseline at lumbar spine and total hip as a function of romosozumab dose. The dose-BMD response model demonstrated that treatment with romosozumab lead to dose-dependent BMD gains at both lumbar spine and total hip for all data including 210 mg SC monthly dose in postmenopausal osteoporosis subjects. Subjects who were on prior denosumab

treatment had a slower rate of onset for romosozumab treatment effect at lumbar spine (6.2 months) but showed no total hip gain when transitioned to romosozumab.

The dose-BMD model demonstrated a significant relationship between romosozumab dose and frequency with BMD gains at lumbar spine and hip. For a given dose, monthly administration provided significantly greater BMD gains at lumbar spine and total hip than with every 3 months administration, while BMD gains were similar for monthly and every 3 months dosing of the same cumulative dose (for example, 70 mg monthly versus 210 mg every 3 months). Model predicted time courses for the monthly dose regimens indicated that the 210 mg dose provided the most rapid and extensive gains in BMD over the course of 12 month treatment.

Phase III pivotal studies investigating more than one dose regimen

Only the proposed dose of 210 mg SC administered monthly was evaluated in all three Phase III studies (Studies 20070337, 20110142 and 20110174).

Evaluator's conclusions on dose finding for the pivotal studies

The Phase II Studies 20060326 and 20101291, evaluated a range of doses, durations and intervals to allow identification of the most efficacious dosing regimen without incurring additional adverse events. As recommended in the CHMP guidelines;[40] on the evaluation of medicinal products in the treatment of primary osteoporosis (adopted 2007), a parallel group, fixed dose, double blind, placebo controlled study design was used in these dose-finding Phase II studies; the efficacy variables included BMD measured at the spine and/or the hip and appropriate biochemical markers of bone turnover and the studies were powered to detect significant effects on each variable. Results from the Phase II studies showed that romosozumab exhibits robust dose-exposure-response relationships and supported the 210 mg monthly dose regimen tested in the Phase III clinical program.

Overall, the proposed dosing of 210 mg SC monthly for the pivotal Phase III studies was supported by the efficacy and safety data from the Phase II studies (Studies 20060326 and 20101291) and was later confirmed by the pharmacokinetics/pharmacodynamics based exposure-response analyses which also used data from the pivotal Phase III studies.

Efficacy

Studies providing efficacy data

- Two pivotal Phase III efficacy studies:
  - Study 20070337 (FRAME trial): a multicentre, international, randomised, double blind, placebo controlled, parallel group study to assess the efficacy and safety of romosozumab treatment in postmenopausal women with osteoporosis.
  - Study 20110142 (ARCH trial): a multicentre, international, randomised, double blind, alendronate controlled study to determine the efficacy and safety of romosozumab in the treatment of postmenopausal women with osteoporosis.

[40] Committee for Medicinal Products for Human Use (CHMP) 2006 Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis (EU: CPMP/EWP/552/95 rev. 2)

- Four supportive studies:
  - Study 20120156: A Phase III study in postmenopausal women with osteoporosis (90 mg/mL versus 70 mg/mL).
  - Study 20080289: A Phase IIIb active-controlled (teripratide) study in postmenopausal women with osteoporosis previously treated with bisphosphonates.
  - Study 20060326: A Phase IIb study in postmenopausal women with low BMD.
  - Study 20101291: A Phase IIb in postmenopausal Japanese women with osteoporosis.

Evaluator's conclusions on efficacy

Indication 1:

> *Evenity is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Evenity reduces the risk of vertebral, clinical and non-vertebral fractures.*

The efficacy of romosozumab was evaluated in two pivotal Phase III multicentre, international, randomised, double blind studies in 11,273 women with postmenopausal osteoporosis at increased risk of fracture: Study 20070337 (FRAME trial) was a placebo controlled study in 7180 women and Study 20110142 (ARCH trial) was an active controlled (alendronate) study in 4093 women. Majority of the subjects were white (57% to 70%) with mean age of 71 to74 years. Mean years since menopause was longer for women in Study 20110142 than in Study 20070337 (27 versus 23 years), which is consistent with the somewhat older population in Study 20110142 (52.4% of subjects were aged over 75 years compared to 31.2% in Study 20070337). BMI was similar between the two pivotal Phase III Studies 20070337 and 20110142. 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 Study 20110142 (99.0% and 96.1%, respectively) than in Study 20070337 (35.2% and 18.3%, respectively). In Study 20110142, baseline radiographs indicated the presence of one or more severe vertebral fracture for more than 60% of subjects in each treatment group. The 10 year probabilities of a major osteoporotic fracture or hip fracture, calculated with BMD according to the fracture risk assessment tool (FRAX);[41] were also higher for subjects in Study 20110142 (20.1% and 9.8%) than in Study 20070337 (13.4% and 5.9%), suggesting a population at higher risk for fracture in the alendronate-controlled study. Other baseline characteristics that contribute to the FRAX determination of fracture risk (for example, body mass index, smoking history, glucocorticoid use) were generally consistent between the two studies.

Supplementation with calcium and/or vitamin D was consistent in all patient groups and clearly documented. However, dietary and relevant life style factors were not summarised. Overall, the study population was representative of the target patient population in Australia with similar baseline demographics and disease characteristics between treatment groups in both pivotal studies. However, only 6 to 9% of patients in both pivotal studies had received prior treatments for osteoporosis (mainly bisphosphonates).

[41] The FRAX tool was developed to evaluate fracture risk in patients and was developed based on individual patient models that integrate the risks associated with clinical risk factors as well as BMD) at the femoral neck. The FRAX algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).

The proposed dosing of 210 mg SC monthly for the pivotal Phase III studies was supported by the efficacy and safety data from the Phase II studies (Studies 20060326 and 20101291) and was later confirmed by the pharmacokinetics/pharmacodynamics based exposure-response analyses which also used data from the pivotal Phase III studies. Although the 70 mg/mL prefilled syringe used in both the pivotal Phase III studies was not the proposed marketing formulation, bioequivalence between the clinical trial formulation and the proposed 90 mg/mL formulation was established in Study 20120277 and bioequivalence of 90 mg/mL romosozumab delivered SC using a prefilled syringe versus an auto-injector/pen was also demonstrated in an open label, randomised, single dose, parallel group Study 20090418. Furthermore, the results of the Phase III placebo controlled, non-inferiority Study 20120156 demonstrated that romosozumab 210 mg SC monthly for 6 months administered as the proposed 90 mg/mL concentration was non-inferior to the 70 mg/mL concentration based on comparison of the percent changes from baseline in BMD (by dual energy x-ray absorptiometry (DXA)) at the lumbar spine in 294 postmenopausal women with osteoporosis.

The co-primary efficacy endpoint in the alendronate controlled study was incidence of new vertebral fracture and clinical fracture (non-vertebral fracture and clinical vertebral fracture) through Month 24. However, clinical fracture and non-vertebral fractures were only secondary endpoints in the placebo controlled study (co-primary efficacy endpoints were subject incidence of new vertebral fracture at 12 and 24 months). It is difficult to determine relative contribution of 'non-vertebral fractures' and 'clinical vertebral fractures' in the 'clinical fracture' endpoint. Other secondary endpoints were assessment of changes in BMD (by DXA) at lumbar spine, total hip and femoral neck. Effect of romosozumab on quality of life was assessed by the patient reported outcome/clinical reported outcome endpoints. Vertebral fractures were assessed by the central imaging vendor based on lateral spine x-rays (T4 to L4).[42] Fractures were validated according to pre-defined criteria and assessment was done by central blinded investigators using a visual semi quantitative grading scale.[43] Serial x-rays performed once a year were used to assess vertebral fractures. Bone density measurements were performed by DXA (only Lunar or Hologic bone densitometers were allowed for the study) with same DXA machine used for all study procedures and all DXA scans were submitted to and analysed by the central imaging vendor. For all subjects, bone density was measured at the lumbar spine and the proximal femur; lumbar spine scans must include L1 to through L4. Overall, assessment of fractures and BMD complied with the CHMP guidelines for evaluation of medicinal treatments for treatment of postmenopausal women with osteoporosis at increased risk of fracture.

Study 20070337 assessed whether the BMD gains observed in Phase I and II studies translated into fracture risk reduction after 1 year of romosozumab treatment, and whether there was continued benefit with follow-on treatment with denosumab. Study 20110142 assessed the efficacy of 1 year of romosozumab treatment in relation to alendronate alone, both during romosozumab treatment and afterwards when all subjects received alendronate. Alendronate (70 mg orally every week) is considered standard of Care and was the appropriate choice for the pivotal active controlled Phase III study. Denosumab (60 mg SC every 6 months) is approved in Australia for treatment of osteoporosis in postmenopausal women (it significantly reduces risk of vertebral, non-vertebral and hip fractures).

The subject incidence of new vertebral fracture through Month 24 was a primary endpoint in both pivotal fracture studies. Vertebral fracture risk reduction persisted through Month 24 for subjects initially randomised to romosozumab, independent of the follow-on

[42] From T4 (thoracic (T) vertebrae 4) to L4 (lumbar (L) vertebrae 4).
[43] Genant HK, et-al. Vertebral fracture assessment using a semi quantitative technique. J. *Bone Miner. Res*. 1993; 8: 1137-1148

anti-resorptive therapy. Romosozumab for 12 months followed by denosumab for 12 months significantly reduced the risk of new vertebral fractures through Month 24 compared with placebo followed by denosumab (0.6% versus 2.5%, odds ratio = 0.24, $p < 0.001$) and romosozumab for 12 months followed by alendronate for 12 months significantly reduced the risk of new vertebral fractures through month 24 compared with alendronate alone (4.1% versus 8.0%, odds ratio = 0.48, $p < 0.001$). The relative risk reductions for new vertebral fracture through month 24 were 75% (95% CI: 60% to 84%) in Study 20070337 and 50% (95% CI: 34% to 62%) in Study 20110142. A consistent treatment effect for romosozumab over placebo and alendronate was observed in all subgroups of baseline characteristics examined (age, prevalent vertebral fracture status, race, geographic region, baseline lumbar spine BMD T-score;[44] baseline total hip/femoral neck BMD T-score, baseline body mass index, FRAX score, history of non-vertebral fracture at or after age 55 and history of fragility fracture).

Evidence of efficacy of romosozumab for reducing incidence of non-vertebral and clinical fractures was not consistent and unequivocal. In the placebo controlled Study 20070337, romosozumab treatment for 12 months failed to show statistically significant reduction in the incidence of non-vertebral fracture at month 12 (1.6% versus 2.1%, odds ratio = 0.75, adjusted $p = 0.096$) or 24 (romosozumab/ denosumab versus romosozumab/placebo: 2.7% versus 3.6%, odds ratio = 0.75, adjusted $p = 0.057$). The incidence of clinical fracture did not show statistically significant reduction in the romosozumab/denosumab versus placebo/denosumab group at month 24 (2.8% versus 4.1%, odds ratio = 0.67, adjusted $p = 0.096$) although the difference between romosozumab and placebo was statistically significant at Month 12. In the alendronate controlled Study 20110142, romosozumab 210 mg monthly for 12 months followed by alendronate 70 mg weekly through the primary analysis significantly reduced the risk of non-vertebral fractures by 19% (romosozumab/alendronate: 178 of 2046, 8.7% versus alendronate/alendronate: 217 of 2047, 10.6%; hazard ratio = 0.81, 95% CI: 0.66 to 0.99; 2-sided adjusted p value = 0.040). However, the difference for non-vertebral fractures just statistically significant (as upper limit 95% CI was 0.99) and furthermore, romosozumab/ alendronate failed to show statistically significant reduction in non-vertebral fractures at the end of the double blind treatment period at Month 12 ($p = 0.057$) or at Month 24 ($p = 0.074$). The risk of clinical fractures (non-vertebral fracture and clinical vertebral fracture) was significantly reduced by 27% compared with alendronate alone (romosozumab/ alendronate versus alendronate/ alendronate: 9.7% versus 13%; hazard ratio = 0.73; 95% CI: 0.61 to 0.88, adjusted $p < 0.001$).

Other fracture endpoints such as hip, major non-vertebral, major osteoporotic, all osteoporotic and new or worsening vertebral fractures showed numerically lower incidence in the romosozumab group compared to both placebo (in Study 20070337, Table 7) and alendronate (in Study 20110142, Table 8).

[44] BMD T-score; A BMD T-score compares the measured bone mineral density to that typical of a healthy 30 year old subject.

Table 7: Subject incidence rates of new vertebral fracture at Month 12; and Month 24 (Primary efficacy analysis set, LOCF imputation)

	New Vertebral Fracture Through Month 12		New Vertebral Fracture Through Month 24	
Statistic	Placebo (N = 3591)	Romosozumab 210 mg QM (N = 3589)	Placebo/ Denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589)
Incidence, n/N1 (%)	59/3322 (1.8)	16/3321 (0.5)	84/3327 (2.5)	21/3325 (0.6)
Risk Comparison Estimates				
Absolute risk reduction (%)[a]				
Point est (SE); (95% CI)	1.30 (0.26); (0.79, 1.80)		1.89 (0.30); (1.30, 2.49)	
Risk ratio[a]				
Point est (SE)[b]; (95% CI)	0.27 (0.28); (0.16, 0.47)		0.25 (0.24); (0.16, 0.40)	
RRR (95% CI)[c]	73% (53, 84)		75% (60, 84)	
Odds ratio[d]				
Point est (SE)[e]; (95% CI)	0.27 (0.28); (0.15, 0.47)		0.24 (0.25); (0.15, 0.39)	
p-value	< 0.001		< 0.001	

LOCF = last observation carried forward; Point est = point estimate; Q6M = every 6 months; QM = every; month; RRR = relative risk reduction; N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures; Positive values for absolute risk reduction and values < 1 for risk ratio and odds ratio favour romosozumab.; a Based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification; variables; b SE represents the standard error of log(risk ratio).; c Calculated from risk ratio as 100 x (1 – risk ratio); d Based on logistic regression model adjusted for age and prevalent vertebral fracture stratification variables;; p-value based on score test; e SE represents the standard error of log(odds ratio)

Table 8: Subject incidence of non-vertebral fracture through primary analysis (Study 20110142 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

Hazard ratio < 1 favours 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

In Study 20070337, romosozumab 210 mg SC monthly for 12 months increased BMD compared with placebo at the lumbar spine, total hip and femoral neck, with mean differences of 12.7%, 5.8% and 5.2%, respectively. Similar increases were observed in Study 20110142, in which romosozumab increased BMD compared with alendronate at Month 12, with mean differences of 8.7% at the lumbar spine, 3.3% at the total hip and 3.2% at the femoral neck (multiplicity adjusted $p < 0.001$ for all three sites) (see Table 9).

Table 9: BMD of 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

ANCOVA = analysis of covariance; BMD = bone mineral density; LOCF = last-observation-carried-forward; LS = least squares; N = Number of subjects randomized; n = Number of subjects with evaluable data at the time point of interest; NA = not applicable (BMD endpoints were not part of sequential testing procedure in Study 20070337); QM = every month; QW = every week

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.

A *post hoc* responder analysis in Study 20070337 demonstrated that among subjects randomised to romosozumab, 96.2%, 92.4% and 68.4% had an increase from baseline in lumbar spine BMD at Month 12 of > 3%, > 5% and > 10%, respectively. For total hip and femoral neck, 77.7% and 71.2% of subjects achieved at least a 3% BMD increase from Baseline at Month 12, with 58.0% and 51.7% of subjects achieving a ≥ 5% BMD increase, respectively. Similar results were observed for the post hoc responder analysis in Study 20110142: Among subjects randomised to romosozumab, 95.1%, 91.2% and 68.2% had and had an increase from Baseline in lumbar spine BMD at Month 12 of > 3%, > 5% and > 10%, respectively. For total hip and femoral neck, 74.1% and 65.6% of subjects achieved at least a 3% BMD increase from baseline at Month 12, with 55.9% and 49.6% of subjects achieving a ≥ 5% BMD increase, respectively. In both Phase III pivotal studies, the statistically and clinically relevant improvements in BMD (at lumbar spine and total hip) with romosozumab compared with placebo/ denosumab or alendronate were observed in all subgroups by baseline T-score, age and geographic region.

In the open label Phase IIIb Study 20080289, which enrolled subjects transitioning from bisphosphonate therapy, romosozumab led to robust gains in BMD over 12 months of treatment. However, these gains were modestly lower than in the bisphosphonate-naïve subjects enrolled in the placebo controlled studies discussed above. This apparent difference between BMD responses in pre-treated subjects is consistent with prior studies of subjects initiating bone-forming therapy after bisphosphonates that also demonstrated lower BMD increases compared to treatment-naïve subjects.[45],[46],[47]

[45] Miller PD, et al. Early Responsiveness of Women with Osteoporosis to Teriparatide After Therapy with Alendronate or Risedronate. *J Clin Endocrinol Metab*. 2008; 93: 3785-3793

The maintenance of effect after the second year (for example 3 to 5 years) was only evaluated in the placebo controlled pivotal Study 20070337. The treatment benefit on new vertebral fractures established with romosozumab for 12 months compared with placebo continued to be present when treatment was followed by denosumab for 24 months. The risk of new vertebral fractures through Month 36 was reduced by 66% for romosozumab/denosumab compared with placebo/denosumab (nominal $p < 0.001$). Other secondary fracture endpoints showed similar results to those observed in the primary 24 month analysis with a 27% reduction in risk of clinical fractures, 21% reduction in risk of non-vertebral fractures. 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. However, results of the extension study (from Month 24 to 36) were only exploratory.

In all studies among bisphosphonate-naïve and bisphosphonate pre-treated subjects, bone turnover marker levels during romosozumab treatment showed a generally similar pattern, reflecting the dual effect of romosozumab, with an increase in bone formation and a decrease in bone resorption. Across the studies, bone formation markers peaked and returned to baseline by approximately month 6 to 9 while bone resorption markers decreased within a month after the first dose and generally remained below placebo at month 12, but above the serum C-telopeptide (sCTX) levels of the anti-resorptive therapy alendronate in active-controlled Study 20110142. Despite a general trend towards baseline, transient responses in markers of bone turnover still occurred 14 days post romosozumab dose at Months 3 and 6 in Study 20070337. This same pattern was observed at the same time points in Study 20080289 and 1 week post the 12 month dose in Study 20060326. Thus across these 3 studies, bone turnover markers responded to each romosozumab administration with transient increases over the 12 month treatment period suggesting continued but lessening effect of the drug during the dosing period. The fact that P1NP, bone specific alkaline phosphatase and osteocalcin showed more dose-dependency than sCTX suggests that the selected dose of 210 mg monthly may promote the most potent bone-forming effect, without an increased anti-resorptive effect.

Assessment of bone strength by quantitative computed tomography at the total hip, lumbar spine, distal tibia and distal radius showed that the finite element analysis (FEA) percent change from baseline statistically significantly favoured romosozumab in both the cortical and trabecular compartments at the total lumbar spine (as compared to placebo), at the lumbar spine (as compared to alendronate), and the hip (as compared to teriparatide and as compared to placebo), supporting significant increases in estimated strength. At the peripheral skeletal sites, no significant increases in estimated strength were seen.

Studies 20070337, 20060326 and 20080289 included bone biopsy substudies to assess the formation of new bone and the bone quality these histologic and histomorphometric results are indicative of increased osteoblastic and decreased osteoclastic activity both leading to increased trabecular and cortical bone mass. Robust bone formation occurred early in the course of treatment with romosozumab, with inhibition of resorption present early in the course of treatment continued through to Month 12. Quantitative bone histomorphomertry on undecalcified sections were performed in a subset of patients in Phase III studies. The subset of patients evaluated in the substudies was representative of the overall patient population in the main study and also representative of target patient population. These substudies evaluated potentially negative effects of the drug on bone

[46] Obermayer-Pietsch BM, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J *Bone Miner Res*. 2008; 23: 1591-1600

[47] Ettinger B, et al. Differential Effects of Teriparatide on BMD After Treatment with Raloxifene or Alendronate. *J Bone Miner Res*. 2004; 19: 745–751

remodelling and also helped characterise its effects on bone remodelling balance, degree of mineralisation and hardness. Biopsies of patients treated with romosozumab demonstrated that bone formed during treatment is of normal lamellar structure and there was no evidence of osteomalacia or other defects.

Limitations of the submitted efficacy data

Some limitations of the submitted efficacy data were:

- Only 6 to 9% of patients in both pivotal studies had received prior treatments for osteoporosis (mainly bisphosphonates). The open label Phase IIIb Study 20080289 in 436 women with postmenopausal osteoporosis transitioning from bisphosphonate therapy demonstrated larger gains than treatment with teriparatide in total hip BMD by DXA through month 12 (primary endpoint), with a mean difference from teriparatide (romosozumab minus teriparatide) of 3.2% ($p < 0.0001$) with similar gains observed for femoral neck and lumbar spine. However, this study did not evaluate effects on incidence of fractures and so effect of romosozumab in patients with prior exposure to other treatments for osteoporosis is limited suggesting that romosozumab can only be used as first line treatment. Furthermore, efficacy of romosozumab was not evaluated in combination with other osteoporosis treatments.
- Efficacy was only demonstrated for 12 months of romosozumab treatment and effect of retreatment with romosozumab was not adequately evaluated (except in dose ranging Phase II Study 220060236).
- Follow-on treatment with denosumab (60 mg SC every 6 months) or alendronate (70 mg weekly) was required to demonstrate efficacy of romosozumab. There is no evidence for efficacy of romosozumab without other follow-on treatment.
- Efficacy of romosozumab was only evaluated in postmenopausal women and men (aged over 50 years) with primary osteoporosis. It was not evaluated in patients with glucocorticoid-induced osteoporosis (as patients on > 7.5 mg equivalent of prednisone were excluded from the studies) or other secondary osteoporosis conditions.
- The submitted efficacy data was not accurately represented in the draft PI.

Indication 2

> *Evenity is indicated for the treatment of osteoporosis in men at increased risk of fracture. Evenity increases bone mass*

No WHO definition for osteoporosis exists for men. However, in clinical practice the same cut-off for the diagnosis of osteoporosis in men, that is T-score below –2.5 of the female reference range, has been used.[44] However, the incidence of osteoporotic fractures increases with age while the predictive value of BMD becomes weaker with age. Furthermore, fracture risk is also driven by parameters including bone size and shape, bone turnover, micro-architecture, damage accumulation (micro cracks), and degree of mineralisation or collagen structure, all playing a role in bone strength, and hence in the risk of osteoporotic fractures.

The TGA adopted CHMP guidelines clearly state the following:

> 'The gold standard for being granted a marketing authorisation for the treatment of osteoporosis in men at increased risk of fracture remains the demonstration of anti-fracture efficacy (spine and/or non-spine fractures) during a 2 year minimum, placebo controlled, prospective study. However, once an initial marketing authorisation has been granted to a new chemical entity (NCE) for the treatment of postmenopausal osteoporosis in women at high risk of fracture, a separate bridging study of the same NCE, using the same formulation, dose, and route of administration in male osteoporotic patients could be sufficient for being granted a marketing authorisation with the indication 'treatment of osteoporosis in men at

> increased risk of fracture' provided that: the duration of the study is at least one year; the dosage is justified; the applicant justifies that the cut-off of BMD, age and any other risk factor chosen for the inclusion of men in the pivotal study will generate a fracture risk of a similar magnitude compared with postmenopausal women that were recruited in the studies used to obtain the indication of treatment of postmenopausal osteoporosis in women at increased risk of fracture. The increase in BMD observed in men should also be similar to that observed in the studies in postmenopausal women.'

The pivotal Phase III Study 20110174 in 245 men with osteoporosis showed that treatment with romosozumab 210 mg SC monthly increases BMD at the lumbar spine, total hip and femoral neck compared with placebo at Month 6 and Month 12. Consistency of effects on BMD was shown in per protocol analysis set or using a linear mixed effects model for repeated measures.

Compared to the improvement in BMD observed in the pivotal study in postmenopausal women, similar increase in BMD in lumbar spine was observed in this pivotal study in men with osteoporosis; however, the increases in BMD at the femoral neck and hip were lower than those observed in the pivotal study in postmenopausal women.

The baseline demographics and disease characteristics were generally representative of the target population of Australian men with osteoporosis. However, there were some imbalances between the treatment groups especially with respect to the baseline characteristics relevant to determination of the 10 year probability of a major osteoporotic fracture, according to the WHO Fracture Risk Assessment tool (FRAX) score for major osteoporotic fracture;[41] differed between treatment groups with respect to secondary osteoporosis (romosozumab versus placebo: 11.7%; versus 2.4%) and alcohol use (< 3 drinks per day; 47.9% versus 56.1%). For the total subject population, the mean 10 year probabilities of major osteoporotic fractures and of hip fractures, respectively, (calculated with BMD) was slightly higher in the romosozumab (8.9%; range: 1.5% to 33.0%) compared to the placebo group (3.9%; range: 0.1% to 22.6%). Furthermore, interpretation of efficacy results may have been confounded by slightly higher incidence of protocol deviations in the romosozumab compared with the placebo group (11.7% versus 3.7%).

The bone formation marker P1NP showed a significant increase from baseline to Month 1 in the romosozumab group when compared to the placebo group, and returned to approximately baseline level by Month 6. The bone resorption marker sCTX decreased in the romosozumab group early in treatment, reaching a nadir at Month 1 which was statistically significant when compared to placebo, and remained below the placebo level through Month 12.

All evaluable biopsies at Month 12 showed normal lamellar bone and normal mineralisation, and all evaluable biopsies showed normal osteoid. There was no evidence of osteomalacia, marrow fibrosis, woven bone or clinically significant marrow abnormality in any subject.

Romosozumab is not yet approved for treatment of postmenopausal osteoporosis in women at increased risk of fracture. Hence, the evidence to support proposed indication of treatment of osteoporosis in men at increased risk of fracture is inadequate at this stage.

Safety

Studies providing safety data

The romosozumab clinical program consists of 19 clinical studies in healthy volunteers, postmenopausal women, and men with osteoporosis or low BMD conducted between 2006 and 2017.

The main studies providing safety data for romosozumab were the pivotal Phase III studies for the treatment of osteoporosis in postmenopausal women (Studies 20070337 and 20110142) and in men (Study 20110174) at increased risk of fractures.

Data are also included from the following studies:

- Study 20080289: a Phase IIIb active controlled study with teriparatide)
- Study 20060326: a Phase IIa dose ranging placebo and active controlled study (teriparatide or alendronate)
- Study 20101291: a Phase IIb dose ranging placebo controlled study in Japanese women; and
- Study 20120156: a Phase III placebo controlled non-inferiority study.

The clinical trials supporting this submission were conducted in North America, Europe, the Middle East, Central and Latin America, Australia, New Zealand, Asia (including Japan) and South Africa.

The safety profile of romosozumab for the treatment of osteoporosis was based on data from studies in the following integrated safety populations:

- 12 month placebo controlled osteoporosis safety analysis set:
  - subjects who were randomised and received at least 1 dose of romosozumab 210 mg monthly or placebo in the 12 month placebo controlled osteoporosis randomised analysis set.
- Osteoporosis safety analysis set:
  - subjects who were randomised and received at least 1 dose of romosozumab (any dose or frequency) or control (placebo, alendronate, teriparatide) in the seven Phase II and Phase III osteoporosis studies. For this analysis set, 24 month data from Study 20060326, 12 month data from Study 20070337, 12 month data from Study 20080289, 12 month data from Study 20101291, 12 month data from Study 20110142, 12 month data from Study 20110174 and 6 month data from Study 20120156 were used to summarise safety endpoints.
- Overall safety analysis set:
  - subjects who were randomised and received at least 1 dose of romosozumab (any dose or frequency) or control (placebo, alendronate, teriparatide). This analysis set includes all data from the Phase I, II and III studies and was used to summarise exposure to romosozumab and placebo and to produce an integrated death listing.

Data from Study 20110142 were not integrated with Study 20070337 to evaluate safety because of the difference in target study population (population was older and more likely to have comorbid conditions) and the difference in the comparator arm (alendronate versus placebo).

Phase I studies were not included in pooled integrated analyses other than the overall exposure analysis and death listing due to differences in study design and/or study populations.

Only treatment emergent adverse events were included in the safety analyses. The Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 was used to code all adverse events to a system organ class, preferred term, and high level group term for all studies.

Unless otherwise specified, the data presentation using the osteoporosis safety analysis set will present:

- integrated data across all studies excluding Study 20110142 for placebo and romosozumab 210 mg monthly;
- data from Study 20110142 for alendronate and romosozumab 210 mg monthly; and
- integrated data across all studies for: the integrated control (including placebo, alendronate and teriparatide), romosozumab 210 mg monthly, total romosozumab groups (any dosing and frequency including 3 monthly).

For the overall summary of adverse events (AE) and summary of adverse events of special interest (AESI) using the osteoporosis safety analysis set, the data were also presented by placebo, romosozumab 70 mg monthly, romosozumab 140 mg monthly, romosozumab 210 mg monthly, and total romosozumab groups (any dosing or frequency (monthly or three monthly)) groups to evaluate a potential dose response.

Investigator assessed relationship to treatment, subject incidence of treatment related AEs and treatment related serious adverse events (SAE) were tabulated by Preferred Term (PT) and System Organ Class (SOC) in descending order of frequency using the 12 month placebo controlled osteoporosis safety analysis set. Exposure-adjusted incidence rates were also provided.

AEs of special interest

The subject incidence rates of AEs corresponding to preferred terms for hypocalcaemia , injection site reactions, adverse events potentially related to hypersensitivity, malignancy (malignant or unspecified tumour Standardised MedDRA Query (SMQ)), hyperostosis, osteoarthritis, adjudicated positive osteonecrosis of the jaw, and adjudicated positive atypical femoral fracture (AFF) were provided using the 12 month placebo controlled osteoporosis safety analysis set. Exposure-adjusted incidence rates of AEs corresponding to preferred terms for events of interest were also summarised using the osteoporosis safety analysis set. Osteonecrosis of the jaw and atypical femoral fracture were adjudicated in Studies 20070337, 20110142, 20060326, 20080289 and 20110174, but not in Studies 20101291 and 20120156.

Patient exposure

The safety database includes 11,553 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, safety evaluation is mainly focussed on data from 7157 postmenopausal women with osteoporosis in Study 2007337; 4054 postmenopausal women with osteoporosis in Study 20110142; 218 subjects with osteoporosis who were transitioning from bisphosphonate therapy Study 20080289; 353 subjects with low bone mass Study 20060326; 252 Japanese subjects with osteoporosis in a dedicated study in Japan Study 20101291; 244 subjects from the male osteoporosis Study 20110174, and 294 subjects with osteoporosis enrolled in a non-inferiority Study 20120156.

Overall, 7681 subjects (6573 women and 163 men) received at least 1 dose of romosozumab, 6338 subjects (6177 women and 158 men) received romosozumab for at least 6 months and 5863 subjects (5712 women and 151 men) received romosozumab for at least 12 months (see Table 10).

Table 10: 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]	3578	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.

Demographics were generally similar between treatment groups in the 12 month placebo controlled osteoporosis population and were generally similar between the total romosozumab, romosozumab 210 mg monthly and integrated control groups in the osteoporosis safety analysis set. In the 12 month placebo controlled osteoporosis population, baseline characteristics were consistent between the total romosozumab and placebo groups. Prior use of osteoporosis medication was reported for only 7.1% of subjects in both treatment groups, and was higher in the Phase II dose ranging Study 20060326 (romosozumab: 17.6%; placebo: 14.0%). Approximately 99% of all subjects reported baseline use of calcium and vitamin D, and approximately 41% of subjects had a history of fractures. Height, weight and mean creatinine results were lower in Study 20101291 (Japanese women) and higher in Study 20110174 (men with osteoporosis) compared with the total population, but this was not unexpected. Baseline laboratory values were consistent across studies and between treatment groups within studies.

In the osteoporosis safety analysis set, baseline characteristics were generally similar between the total romosozumab, romosozumab 210 mg monthly and integrated control groups. Prior use of osteoporosis medication was reported for about 11% of subjects, 99% of all subjects reported baseline use of calcium and vitamin D, and 60 to 62% had a history of fractures.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

12 month placebo controlled osteoporosis safety analysis set

The occurrence of elevated baseline aspartate transaminase (AST) of > 3 x upper limit of normal (ULN) and > 5 x ULN was slightly lower in the romosozumab group (< 0.1% and 0.0%, respectively) than the placebo group (0.2% and < 0.1%, respectively) with no baseline elevations > 10 x ULN and > 20 x ULN in both treatment groups. Elevations to 3 x ULN, 5 x ULN and 10 x ULN during the 12 month double blind period were reported for ≤ 0.4% in the romosozumab group and ≤ 0.8% in the placebo group. No subject in either treatment group had an elevation to 20 x ULN. At baseline no subject met the criteria for Hy's Law (defined as alanine transaminase (ALT) or AST > 3 x ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN) in either treatment group. One (< 0.1%) subject in the romosozumab group of Study 20070337 met all of these criteria while on study with all results occurring within a 7 day window. The subject was diagnosed with cholelithiasis and fatty liver deposit that were considered by the investigator as not related to treatment.

Osteoporosis safety analysis set

The subject incidences of elevated ALT and AST at Baseline and while on study for the osteoporosis safety analysis set were similar to those observed in the 12 month placebo controlled osteoporosis safety analysis set. In Study 20110142, at Baseline, ALT or AST > 3 x the ULN was reported in 7 (0.3%) and 5 (0.2%) subjects in the romosozumab and alendronate groups, respectively; 19 (1.0%) and 17 (0.9%) subjects in the romosozumab and alendronate groups, respectively had these values during the 12 month double blind period. At baseline, total bilirubin > 2 x the ULN was reported for 1 (< 0.1%) subject in the romosozumab group and no subjects in the alendronate group. During the 12 month double blind period, these results were reported for 3 (0.2%) subjects in the romosozumab group and 2 (0.1%) subjects in the alendronate group. No subject met all of the laboratory criteria for potential Hy's Law at any time.

Renal function and renal toxicity

No meaningful differences between treatment groups were observed for renal function parameters in any of the individual studies or integrated analyses.

Other clinical chemistry

12 month placebo-controlled osteoporosis safety analysis set

Laboratory test results with grade ≥ 2 were reported for 19.1% in the romosozumab group and 18.4% in the placebo group with no clinically important trends were noted (see Table 11). Laboratory test results with common terminology criteria for adverse events (CTCAE) grade ≥ 3 were reported for 4.2% in the romosozumab group and 3.8% in the placebo group. All grade 3 and 4 laboratory results were reported for < 1% of subjects in both treatment groups, with the exception of grade 3 increase in glucose, which was reported for 1.5% of subjects in the romosozumab group and 1.9% in the placebo group; grade 4 glucose results were reported for < 0.1% and 0.0%, respectively. No clinically important trends were noted (Table 11).

Table 11: Subject incidence of 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 (%)
Sodium										
Decrease	25 (0.7)	33 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	25 (0.7)	34 (0.9)
Increase	3 (<0.1)	3 (<0.1)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	3 (<0.1)	5 (0.1)
Potassium										
Decrease	3 (<0.1)	9 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	9 (0.2)
Increase	85 (2.4)	110 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.7)	2 (1.2)	88 (2.3)	112 (2.9)
Bicarbonate										
Decrease	41 (1.1)	51 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	3 (1.8)	43 (1.1)	54 (1.4)
Magnesium										
Decrease	5 (0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	5 (0.1)	2 (<0.1)
Increase	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)
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)
Creatinine										
Increase	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	0 (0.0)
AST										
Increase	24 (0.7)	10 (0.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	26 (0.7)	10 (0.3)
ALT										
Increase	31 (0.9)	19 (0.5)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	32 (0.8)	19 (0.5)

	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 (%)
Alkaline Phosphatase										
Increase	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)
Total Bilirubin										
Increase	1 (<0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	3 (<0.1)	6 (0.2)
Albumin										
Decrease	13 (0.4)	10 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	13 (0.3)	11 (0.3)
Glucose										
Decrease	10 (0.3)	18 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	11 (0.3)	18 (0.5)
Increase	65 (1.8)	61 (1.7)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	66 (1.8)	62 (1.6)

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = Number of subjects in the analysis set; QM = every month; SC = subcutaneously

The incidence of discontinuation of study treatment with > 2 grade laboratory value shifts from Baseline was low and similar in the romosozumab (< 0.1%, n = 2) and placebo treated subjects (0.1%, n = 5). In the romosozumab group, the laboratory shifts included: grade 3 increases in ALT and AST in a subject with pancreatic malignancy in Study 20070337 and increase in intact parathyroid hormone without any associated AE in Study 20101291. Neither discontinuation was due to the abnormal laboratory values. In the placebo group, the laboratory shifts included the following: increase in intact parathyroid hormone, grade 2 decrease in magnesium, 1 grade 2 and 1 grade 3 increase in ALT and AST, and a grade 2 increase in creatinine. No new concomitant medications were reported to be taken by these 7 subjects within 30 days of investigational product discontinuation.

Osteoporosis safety analysis set

The percentages of subjects with grade of 2, 3 or 4 laboratory abnormalities, shifts of ≥ 2 severity grades from Baseline for selected laboratory parameters were not integrated for the osteoporosis safety analysis set.

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. Laboratory test results with grade ≥ 2 during the 12 month double blind period were reported for 22.2% of subjects in the romosozumab group and 23.3% of subjects in the alendronate group. Results for the entire study period (through

the end of the study) were similar to those for the primary analysis and generally balanced between the treatment groups.

In Study 20110142, 155 of 2040 (7.6%) subjects in the romosozumab group had grade 3 and 4 laboratory results. Four (0.2%) subjects in the romosozumab group had grade 4 laboratory results including 2 (< 0.1%) subjects with below-normal sodium; 1 (< 0.1%) subject with below-normal bicarbonate; 2 (< 0.1%) subjects with below-normal haemoglobin; and 1 (<0.1%) subject with below-normal platelet count. In the alendronate group 152 of 2014 (7.5%), group had grade 3 and 4 laboratory results. Subjects with grade 4 laboratory results included 1 (< 0.1%) subject with above-normal glucose and 1 (< 0.1%) subject with below-normal neutrophil count.

For the male osteoporosis Study 20110174, laboratory test results with grade ≥ 2 were reported for 19.0% in the romosozumab group and 19.8% in the placebo group. No clinically important trends were noted and few grade 3 or 4 results were observed; 11 of163 (6.7%) subjects in the romosozumab group had grade 3 or 4 laboratory results including 1 (0.6%) subject with grade 3 below-normal sodium; 1 (0.6%) subject with grade 4 below-normal magnesium; 5 (3.1%) subjects with grade 3 below-normal phosphorous; 3 (1.8%) subjects with grade 3 above-normal glucose and 1 (0.6%) subject with grade 3 below-normal total neutrophil count. These results were similar to those observed in the placebo group of Study 20110174 and in the postmenopausal osteoporosis Study 20070337.

Lipid parameters were not evaluated in the three pivotal Phase III studies.

Haematology and haematological toxicity

Overall, clinical laboratory evaluations for haematology demonstrated no meaningful differences between treatment groups in the individual studies.

Other laboratory tests

Serum calcium

For the 12 month placebo controlled osteoporosis safety analysis set, slightly higher proportion of subjects in the romosozumab group reported albumin-corrected serum calcium with a maximum decrease of ≥1 grade (romosozumab versus placebo: 0.4% versus 0.1%) with similar results for grade 2 decreases in serum calcium (0.2% versus < 0.1%). The median nadir of corrected serum calcium from Baseline was observed by month 1. No subject in the romosozumab group had a grade 3 or 4 decrease in serum calcium.

In the osteoporosis safety analysis set, the exposure-adjusted incidence of albumin-adjusted serum calcium maximum decrease of ≥1 grade shift from baseline per 100 subject-years was 0.5 in the total romosozumab and romosozumab 210 mg groups and 0.2 in the integrated control group. No subject in the romosozumab groups and 1 subject in the placebo group had an increase of grade ≥ 3 in albumin-corrected serum calcium.

Similar to the postmenopausal osteoporosis Study 20070337, romosozumab administration was associated with mild, transient decreases in serum calcium in the male osteoporosis Study 20110174. There was a slight decrease in corrected serum calcium levels at Month 1; calcium levels returned toward near-baseline levels over time, such that at Month 12, the median percent change from baseline was -1.3% for the romosozumab group and -0.9% for the placebo group. One (0.6%) subject in the romosozumab group had a grade 2 below-normal serum corrected calcium result. No grade 3 or 4 serum corrected calcium results were reported in the romosozumab or placebo groups.

Serum intact parathyroid hormone and urinary calcium

Because romosozumab increases bone formation, there may be compensatory responses in intact parathyroid hormone as a result of calcium demands from bone matrix mineralisation. In the Phase I Study 20110227, the administration of romosozumab resulted in a greater increase in intact parathyroid hormone in subjects with stage 4 renal impairment and stage 5 chronic kidney disease requiring haemodialysis than in healthy subjects.

Study 20070337 included an intact parathyroid hormone and urinary calcium sub study comprising 656 subjects to characterise serum intact parathyroid hormone concentration and urinary calcium excretion through Month 12. The median percentage change from baseline in intact parathyroid hormone was statistically significantly higher in the romosozumab versus placebo group (nominal p-value < 0.001 from Wilcoxon rank-sum test without multiplicity adjustment) at both month 6 (29% versus 4%) and Month 12 (27% versus 8%) time points. Corresponding median percentage change from baseline in estimated 24 hour urinary calcium excretion values were also statistically significantly greater in the romosozumab group at Month 6 (-16.8% versus 3.0%) and Month 12 (-15.9% versus -7.6%). Differences between romosozumab and placebo for urinary calcium excretion were statistically significant at 6 months (nominal p-value < 0.001) but not at 12 months (nominal p-value = 0.10).

In the bone turnover marker and biomarker sub study of Study 20110142, intact parathyroid hormone was analysed for 67 subjects in the romosozumab/alendronate group and 64 subjects in the alendronate/alendronate group. At baseline, the median intact parathyroid hormone value was 4.83 pmol/L (45.60 pg/mL) and 4.80 pmol/L (45.25 pg/mL) in the romosozumab and alendronate groups, respectively. There was a statistically significantly greater median percent change in intact parathyroid hormone at Month 1 (60.1% and 34.7% in the romosozumab and alendronate groups, respectively, nominal p-value < 0.006 using the Wilcoxon rank-sum test) and remained statistically significantly higher in the romosozumab through Month 6. After subjects began to receive alendronate at Month 12, serum intact parathyroid hormone was increased relative to baseline in both the romosozumab/alendronate and alendronate/ alendronate groups at Month 15 (median percent changes from Baseline of 33.9% and 29.3%, respectively), then stabilised and remained above baseline thereafter. The difference between the romosozumab/alendronate and alendronate/alendronate groups in median percent change in serum intact parathyroid hormone level was not statistically significant at Month 15 or any point thereafter.

In the male osteoporosis Study 20110174, the levels of intact parathyroid hormone increased at Month 6; the median percent change from baseline was 39.4% and 3.6% for subjects who received romosozumab and placebo, respectively. Levels of intact parathyroid hormone 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 and 5.7%, respectively.

Phosphorus

As romosozumab increases bone formation, there is an increased demand for phosphorus, in addition to calcium, to support bone matrix mineralisation. For the 12 month placebo controlled osteoporosis safety analysis set, mild decreases in phosphorus levels with romosozumab treatment were observed. The median percent change from baseline at Month 12 was -5.6% and -1.9% in the romosozumab and placebo groups, respectively; grade 3 below-normal phosphorus was reported for 0.3% and 0.2%, respectively.

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. Phosphorus 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 phosphorus values remained within the normal range. With the exception of Month 1, no differences in the phosphorus levels between treatment groups were statistically significant.

In the male osteoporosis Study 20110174, 5 (3.1%) subjects in the romosozumab group and 2 (2.5%) subjects in the placebo group had a grade 3 below-normal phosphorus result; no grade 4 results were reported in either group; these results were higher than those observed in the postmenopausal osteoporosis Study 20070337 (0.1% in each treatment group). There was a decrease in phosphorus levels at month 1 for subjects who received romosozumab; the median percent change from Baseline was -6.5% (0.0% for subjects who received placebo). Phosphorus levels remained below baseline levels for subjects in the romosozumab group and decreased slightly for subjects in the placebo group over time. At month 12, the median percent change from Baseline was -7.8% for the romosozumab group and -2.4% for the placebo group.

Magnesium

There may be an increased demand for magnesium, in addition to calcium and phosphorus, to support bone matrix mineralisation. For the 12 month placebo controlled safety analysis set, no change in magnesium was observed in either treatment group. One subject in the romosozumab treatment group had a grade 4 below-normal magnesium result. Four subjects (0.1%) in the total romosozumab group and 3 subjects (< 0.1%) in the placebo group had grade 3 above-normal magnesium results.

In Study 20110142, during the 12 month double blind period, 2 (< 0.1%) subjects in the romosozumab group and 1 (< 0.1%) subject in the alendronate group had a grade 3 below-normal result for magnesium. No grade 4 results were reported and no grade > 2 above-normal magnesium results were reported in either group. One (< 0.1%) subject in the romosozumab group and no subjects in the alendronate group had a decrease in magnesium of 2 CTCAE toxicity grades from grade 0 at Baseline.

In the male osteoporosis study, 1 (0.6%) subject in the romosozumab group had a decrease in magnesium of 4 toxicity grades from grade 0 at Baseline. No other grade 3 or grade 4 results were reported in either treatment group.

Electrocardiograph findings and cardiovascular safety

Electrocardiogram (ECG) data collected in Study 20060326 and some Phase I studies are also provided in individual clinical study reports. Electrocardiograms were not performed in Studies 20070337, 20080289, 20110142 and 20110174. Analysis of ECG results in individual studies in which they were analysed demonstrated no clinically important effect of romosozumab.

During the development program, an imbalance in positively adjudicated cardiovascular SAEs were observed between treatment groups in Study 20110142. This imbalance was due specifically to serious cardiac ischemic and cerebrovascular events; however, these findings were not observed in the larger, placebo controlled Study 20070337. In the smaller placebo controlled study of men with osteoporosis, an imbalance in positively adjudicated cardiovascular events was observed between treatment groups. However, due to the limited number of subjects, meaningful conclusions could not be drawn.

In order to address the concerns associated with higher incidence of serious cardiovascular events, the sponsors have provided a detailed integrated cardiovascular safety report in the submitted dossier. This report included an analysis of adjudicated cardiovascular SAEs across the three pivotal Phase III studies; analyses of baseline factors (cardiovascular related medical history, medications, impact of age and other cardiovascular risk factors on results); Other known cardiovascular risks; literature review and epidemiology assessment.

The romosozumab clinical study program revealed an imbalance in positively-adjudicated cardiovascular SAEs between treatment groups in Study 20110142, which was not observed in the larger, placebo controlled Study 20070337. While subjects enrolled in Study 20110142 were on average 4 years older than in Study 20070337, there was no evidence to suggest that increased age was associated with the observed difference in cardiovascular risk between the two studies. Furthermore, analysis of baseline characteristics within each study and across studies, including baseline cardiovascular risk factors, cardiovascular-related medical history, baseline cardiovascular medications, and vital signs (blood pressure) did not explain the imbalance in cardiovascular events with romosozumab treatment. The differences in Study 20110142 were driven by a small number of events in a population with a high cardiovascular comorbidity and incidence rates were within those expected from the epidemiology in similar populations. The Kaplan-Meier curves for positively adjudicated serious cardiovascular AEs, cardiac ischemic event and cerebrovascular event indicate early separation between romosozumab/alendronate and alendronate/alendronate groups which is maintained up to 48 months (that is, 36 months after discontinuation of romosozumab treatment. An assessment of clinical and preclinical studies in animals and humans, early cardiovascular events (that is, within 3 to 6 months of dosing) were observed with romosozumab, while the literature would suggest any cardioprotective effects of alendronate would be seen after longer term observations. Thus, the available evidence does not suggest a consistent cardioprotective effect of alendronate. 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. However, interpretation was limited as the reviewed literature mainly consisted of two types of publications, those that described clinical and radiographic features of a group of patients with sclerosteosis or van Buchem disease, or case studies of a single individual with one of these disorders.

Overall a causal relationship between romosozumab and positively-adjudicated cardiovascular SAEs was not established although a relationship to romosozumab could not be excluded. However, the sponsors hope to address the important potential risk of cardiovascular SAEs with ongoing monitoring and evaluation in pharmacovigilance activities (risk management plan).

Vital signs and clinical examination findings

Absolute values and changes from Baseline in vital signs are provided in individual study reports with no integration of data. Analysis of vital signs (mean values of systolic and diastolic blood pressures, pulse rate, body temperature, body weight, and body mass index) in individual studies demonstrated no clinically important effect of romosozumab.

Immunogenicity and immunological events

The pharmacokinetic exposure, safety (for example, hypersensitivity, injection site reactions, or autoimmune disorder) and efficacy (changes in BMD) profiles of the subjects who tested positive for binding anti romosozumab antibodies were found to be consistent with the profiles of anti romosozumab antibody-negative subjects.

In Phase II and III clinical studies of osteoporosis in postmenopausal women, the incidence of developing anti romosozumab antibodies was 18.6% (1162 of 6244) across all doses studied. Neutralising antibodies developed in 0.9% (58 of 6244) of subjects. The incidence of developing binding and neutralising anti romosozumab antibodies in women who received 210 mg once monthly (QM) was similar to the overall studies at 18.1% (1068 of 5914) and 0.7% (43 of 5914), respectively.

In men with osteoporosis who received romosozumab 210 mg monthly, the incidence of anti-romosozumab antibodies through Month 15 was consistent for binding antibodies

(17.3% (28 of 162 subjects)) and neutralising antibodies (0.6% (1 of 161 subjects) with that observed for postmenopausal women with osteoporosis.

The effect of anti romosozumab antibodies on the subject incidence of treatment emergent AEs of injection site reactions, hypersensitivity and autoimmune disorders was evaluated for the 12 month placebo controlled safety analysis set and the osteoporosis safety analysis set.

Injection site reaction AEs were reported for 6.9%, 5.0% and 2.9% of subjects who were binding antibody positive, binding antibody negative and placebo groups, respectively. The most frequently reported AEs were injection site erythema (2.1%, 1.4% and 0.2%, respectively), injection site pain (1.9%, 1.8% and 1.2%), injection site pruritus (1.5%, 0.5% and 0.2%) and injection site bruising (1.0%, 0.8% and 0.6%). Similar results were observed for neutralising antibodies: injection site reaction AEs were reported for 7.1%, 6.8% and 2.9% of subjects who were neutralising antibody positive, antibody negative and placebo groups, respectively; the most frequently reported AEs were injection site erythema (3.6%, 2.1% and 0.2%, respectively) and injection site haemorrhage (3.6%, 0.4% and 0.4%, respectively).

AEs potentially related to hypersensitivity were reported for 7.0%, 6.9% and 6.9% of subjects who were binding antibody positive, binding antibody negative and placebo groups, respectively. The only AE reported for ≥ 1.0% of subjects was rash (1.1%, 1.1% and 0.9%, respectively). For neutralising antibodies, there was no relation between AEs potentially related to hypersensitivity (3.6%, 7.2% and 6.9% of subjects who were neutralising antibody positive, negative and placebo groups, respectively); the most frequently reported AE was conjunctivitis allergic (3.6%, 0.4% and 0.5%, respectively).

The incidence of autoimmune disorders AEs was low and similar across groups based on presence of binding antibody (0.7%, 0.9% and 0.9% of subjects who were binding antibody positive, binding antibody negative and placebo groups, respectively) or neutralising antibody (0.0%, 0.7% and 0.9% of subjects who were neutralising antibody positive, negative and placebo groups, respectively), chronic gastritis (neutralising antibody positive: 0.7%; neutralising antibody negative: 0.6%; placebo: 0.4%).

Results for the osteoporosis safety analysis set were similar to those for the 12 month placebo controlled safety analysis set.

Serious skin reactions

None listed.

AEs of special interest (AESIs) and adjudicated AEs

Events of interest included hypocalcaemia, injection site reactions, adverse events potentially related to hypersensitivity, malignancy (malignant or unspecified tumour SMQ), hyperostosis and osteoarthritis. Adjudicated AEs included positive osteonecrosis of the jaw and adjudicated positive atypical femoral fracture.

Summary of AESI and adjudicated AEs in the 12 month placebo controlled osteoporosis safety set and Osteoporosis safety set are summarised in Tables 12 and 13, respectively.

Table 12: Summary of treatment-emergent AEs of interest and adjudicated AEs (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.

Table 13: Summary of exposure-adjusted incidence rate of treatment-emergent AEs 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 mineralisation.

In the 12 month placebo controlled osteoporosis population, a non-serious AE of hypocalcaemia (grade 2) was reported for 1 (< 0.1%) subject in the total romosozumab 210 mg monthly treatment group (Study 20070337); no hypocalcaemia events were reported in the placebo group. No SAEs of hypocalcaemia were reported. No subject had both a ≥ 1 grade decrease from Baseline and a hypocalcaemia AE. Results for the osteoporosis safety analysis set were similar to the 12 month placebo controlled osteoporosis population.

In the alendronate controlled Study 20110142, during the 12 month double blind period, 1 (< 0.1%) AE of hypocalcaemia (PT) was reported in each treatment group. No hypocalcaemia event was serious. All AEs of hypocalcaemia were grade 1 or grade 2 in severity, considered not related to investigational product, and did not result in discontinuation of investigational product or discontinuation from the study. No subject who received romosozumab had a decrease in serum albumin-corrected calcium from grade 0 at baseline during the 12 month double blind period. In the alendronate group, 3 (0.1%) subjects had a decrease in serum corrected calcium to grade 1 and 2 (< 0.1%) subjects had a decrease to grade 2 from grade 0 at Baseline. No hypocalcaemia AEs were reported in the male osteoporosis Study 20110174.

Hypersensitivity

Overall, review of the hypersensitivity cases across the 12 month placebo controlled osteoporosis safety analysis set showed that there were no anaphylactic reactions reported that were attributable to romosozumab.

In the 12 month placebo controlled osteoporosis population, AEs potentially related to hypersensitivity were reported for 6.7% of subjects in the total romosozumab group and 6.9% of subjects in the placebo group. The most frequently reported (> 0.5%) AEs were rash (romosozumab versus placebo: 1.1% versus 0.9%), dermatitis allergic (0.7% versus 0.8%), eczema (0.6% versus 0.8%), rhinitis allergic (0.6%versus 0.7%), urticaria (0.5% versus 0.6%) and dermatitis (0.4%, 0.8%). SAEs 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). AEs 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 (all AEs were reported in Study 20070337). All events were reported for single subjects with the exceptions of dermatitis allergic (romosozumab: 3 subjects; placebo: 1 subject) and rash (2 subjects; 0 subjects). AEs potentially related to hypersensitivity led to discontinuation from the study for 3 (< 0.1%) subjects in the romosozumab group and 2 (< 0.1%) subjects in the placebo group (Table 14). All events were reported in Study 20070337 and included 1 event each of alveolitis allergic, drug eruption and rash maculo-papular in the romosozumab group and 1 event each of eczema and rhinitis allergic in the placebo group.

AEs potentially related to hypersensitivity leading to discontinuation from the study were not collected in Study 20110174.

Table 14: Treatment-emergent AEs potentially related to hypersensitivity by PT reported (> 0.2% of subjects in the total romosozumab or placebo groups (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 adverse events potentially related to hypersensitivity	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)
Rash	31 (0.9)	38 (1.1)	1 (2.0)	1 (2.0)	0 (0.0)	1 (1.6)	1 (1.2)	1 (0.6)	33 (0.9)	41 (1.1)
Dermatitis allergic	31 (0.9)	25 (0.7)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	1 (0.6)	32 (0.8)	27 (0.7)
Eczema	27 (0.8)	23 (0.6)	0 (0.0)	1 (2.0)	1 (1.6)	1 (1.6)	2 (2.5)	0 (0.0)	30 (0.8)	25 (0.6)
Rhinitis allergic	26 (0.7)	23 (0.6)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	27 (0.7)	24 (0.6)
Urticaria	22 (0.6)	18 (0.5)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	1 (0.6)	23 (0.6)	20 (0.5)
Conjunctivitis allergic	17 (0.5)	15 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	17 (0.5)	16 (0.4)
Dermatitis	30 (0.8)	15 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (0.8)	15 (0.4)
Injection site rash	2 (<0.1)	13 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	13 (0.3)
Dermatitis contact	15 (0.4)	10 (0.3)	0 (0.0)	1 (2.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	16 (0.4)	11 (0.3)
Rash pruritic	15 (0.4)	11 (0.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (0.4)	11 (0.3)
Hypersensitivity	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)

N = Number of subjects in the analysis set; n = Number of subjects reporting ≥ 1 event; QM = every month; SC = subcutaneously
Hypersensitivity includes only treatment-emergent adverse events as a result of a narrow search/scope in standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ).
Preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using MedDRA version 19.1.

AEs potentially related to hypersensitivity that occurred ≤ 2 days after administration of investigational product were reported for 48 (1.2%) subjects in the total romosozumab group and 32 (0.8%) subjects in the placebo group; injection site rash (romosozumab versus placebo: 0.3% versus < 0.1%) and rash (0.2%versus 0.1%). AEs potentially related to hypersensitivity that occurred from > 2 days to ≤ 7 days after administration of investigational product were reported for 54 (1.4%) subjects in the romosozumab group and 39 (1.0%) subjects in the placebo group. The most frequently reported AEs (≥ 0.2% in either treatment group) were dermatitis allergic (romosozumab versus placebo: 0.3% versus 0.2%), rash (0.2% in each group) and eczema (0.2% versus 0.0%).
Recurrent events reported for more than 1 subject in either group, were rash (romosozumab: 5 subjects; placebo: 6 subjects), urticaria (4 subjects; 1 subject), dermatitis allergic (3 subjects; 1 subject), injection site hypersensitivity (2 subjects; 0 subjects), injection site rash (2 subjects; 1 subject), dermatitis (1 subject; 2 subjects) and dermatitis contact (0 subjects; 2 subjects).

Fatal or life-threatening AEs

Events potentially related to hypersensitivity were reported for 2 subjects, both in Study 20070337:

- one fatal event of circulatory collapse was reported on Day 365 in a subject who received romosozumab 210 mg monthly. This 78 year old subject with a medical history of tobacco use developed unspecified cardiovascular disease and was hospitalised on Day 345, 8 days after receiving her twelfth dose of romosozumab. She was hospitalised in the intensive care unit and died from cardiovascular collapse on Day 365. The investigator considered the event to be unrelated to treatment.
- the life–threatening event occurred in a 74 year old subject with a relevant medical history of allergic respiratory disease, allergies to roxithromycin and codeine, aspergillosis, asthma, bronchiectasis, gastroesophageal reflux disease, hypercholesterolaemia, osteoporosis and nephrolithiasis (all of which were ongoing at Baseline) who had dyspnoea, cough and wheezing approximately 24 hours after receiving the first dose of romosozumab. On Day 3, she presented with a rash on her chest and back. A serious, grade 4 adverse event of acute allergic reaction with unknown aetiology (on chest and back) was reported. The rash resolved after treatment with hydrocortisone, and the event was reported as resolved on Day 7. The investigator considered the event to be related to treatment, as he was unaware of exposure to any other antigens, and investigational product was withdrawn.

Hypersensitivity

Three subjects had SAEs potentially related to hypersensitivity that were considered related to romosozumab, all of which occurred in Study 20070337:

- A 64 year old subject with a medical history of chronic obstructive pulmonary disease and eczema had a grade 3 adverse event of eczema 9 days after first dose, and was hospitalised for a serious adverse event of dermatitis on Day 166; the subject received IV steroids and IV antihistamines, and the event resolved.
- A 65 year old subject with a medical history of allergic rhinitis and a milk allergy, had nonserious adverse events of skin tingling for 2 days after the first 3 doses of romosozumab. Approximately 3 weeks after the fifth dose, the subject developed facial eczema and generalised rash. The subject was hospitalised with a serious adverse event of dermatitis allergic and received IV corticosteroids and topical steroids, IV fluids and oral antihistamine. Study drug was withdrawn; the event resolved.
- A 75 year old subject with a medical history of childhood asthma developed nausea, ill being, chills, and burning sternal pressure 8 hours after the initial romosozumab dose. On Day 3, a serious adverse event of macular rash on trunk was reported and a skin biopsy revealed '*unspecific superficial dermatitis with urticarial components, drug reaction cannot be excluded*'. Study drug was withdrawn, and the event resolved on Day 10. On Day 28, the subject was hospitalised with a serious adverse event of dermatitis exfoliative and angioedema (considered by the investigator as not related to study drug). A skin biopsy showed discrete superficial perivascular dermatitis. The subject was treated with topical steroids and creams, and the events resolved on Day 31. On Day 135, the subject was hospitalised for a macular rash and treated with topical steroid creams and oral antihistamines; the event resolved on Day 148.

In Study 20070337, potential anaphylactic events were identified using the World Allergy Organization Guidelines (2012);[48] to further assess the anaphylactic reactions using the 'Anaphylaxis Reaction' SMQ algorithm. The subject incidence of potential anaphylactic reactions was generally similar between both treatment groups and both study periods. Based on a review of the cases, none of the anaphylactic reactions were associated with romosozumab use.

In the osteoporosis safety analysis set, exposure-adjusted incidence rates per 100 subject-years of AEs potentially related to hypersensitivity were 7.3 in the total romosozumab group, 7.1 in the romosozumab 210 mg group, and 7.1 in the integrated control group with similar profile to that observed in the 12 month placebo controlled osteoporosis safety set (see Table 15).

[48] Simons F, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis*. Curr Opin AllergyClin Immunol*. 2012; 12: 389-399

Table 15: Exposure-adjusted incidence of treatment-emergent concomitant or recurrent AEs potentially associated with hypersensitivity by preferred term: exposure-adjusted incidence rate of > 0.5 per 100 subject years in total romosozumab or integrated control groups (osteoporosis safety analysis set)

	All Studies Excluding 20110142		20110142		All Studies Including 20110142		
Adverse Event of Interest 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 = 5836) n (r)	Romosozumab 210 mg QM[d] (N = 6358) n (r)	Romosozumab Total* (N = 6688) n (r)
Recurrent hypersensitivity event[f]	266 (7.6)	284 (7.4)	118 (6.3)	122 (6.5)	384 (7.2)	406 (7.1)	450 (7.3)
Rash	33 (0.9)	46 (1.1)	22 (1.1)	22 (1.1)	55 (1.0)	68 (1.1)	73 (1.1)
Eczema	30 (0.8)	27 (0.7)	13 (0.7)	8 (0.4)	43 (0.8)	35 (0.6)	49 (0.8)
Dermatitis allergic	33 (0.9)	33 (0.8)	15 (0.8)	12 (0.6)	48 (0.9)	45 (0.8)	47 (0.7)
Dermatitis	30 (0.8)	16 (0.4)	12 (0.6)	17 (0.9)	42 (0.8)	33 (0.6)	36 (0.6)
Rhinitis allergic	29 (0.8)	26 (0.6)	7 (0.4)	5 (0.3)	36 (0.6)	31 (0.5)	33 (0.5)
Urticaria	24 (0.7)	20 (0.5)	5 (0.3)	5 (0.3)	29 (0.5)	25 (0.4)	31 (0.5)

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; SC = subcutaneously

Hypersensitivity includes only treatment-emergent adverse events as a result of a narrow search/scope in standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ). Preferred terms are sorted by descending order of the exposure-adjusted incidence rate in the total romosozumab group and control group, and 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), and alendronate from Study 20110142 (12 months). Events for the alendronate arm are identified based on the date of the placebo SC injection.

[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).

* 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] When subject reports the same hypersensitivity event preferred term at 2 or more different investigational product administration dates.

During the 12 month double blind period of the alendronate controlled Study 20110142, AEs potentially related to hypersensitivity were reported for 122 (6.0%) subjects in the romosozumab group and 118 (5.9%) subjects in the alendronate group. AEs potentially related to hypersensitivity reported for ≥ 0.5% of subjects in either treatment group were rash (romosozumab versus alendronate: 1.1% versus 1.1%), dermatitis (0.8% versus 0.6%), rash pruritic (0.6% versus 0.3%), dermatitis allergic (0.6% versus 0.7%) and eczema (0.4% versus 0.6%). SAEs potentially related to hypersensitivity were reported for 3 (0.1%) subjects in the romosozumab group and 2 (< 0.1%) subjects in the alendronate group. AEs potentially related to hypersensitivity led to discontinuation from investigational product and from the study for 4 (0.2%) and 1 (< 0.1%) subjects, respectively, in the romosozumab group and 3 (0.1%) and 0 (0.0%) subject in the alendronate group. All events leading to discontinuation from investigational product were reported for single subjects (angioedema, dermatitis allergic, injection site rash, pruritus allergic, urticarial, rash pruritic), with the exception of rash, which was reported for 2 subjects in the alendronate treatment group.

In the male osteoporosis Study 20110174, AEs potentially related to hypersensitivity were reported for 4.9% of subjects in each treatment group, which was lower than the rates observed in Study 20070337 (romosozumab: 6.8%; placebo: 6.9%). No SAEs potentially related to hypersensitivity were reported in Study 20110174 and AEs potentially related to hypersensitivity leading to discontinuation from the study were not collected in Study 20110174.

Injection site reactions

In the 12 month placebo controlled osteoporosis safety analysis set, AEs of injection site reactions were reported for 5.2% and 2.9% of subjects in the total romosozumab and placebo groups, respectively; common AEs were injection site pain (1.8%, 1.2%) and injection site erythema (1.5%, 0.2%). Most AEs were mild or moderate; the only severe events reported were injection site pain (1 event each in the total romosozumab and placebo groups) and no SAEs of injection site reactions were reported. The incidence of AEs injection site reactions leading to discontinuation of investigational product or from study was low (< 0.1% in both groups) all of which were reported in Study 20070337. The median time to onset of the first injection site reaction adverse event was 88.0 days (range: 1 to 338 days) for the total romosozumab group and 62.0 days (range: 1 to 338 days) for the total placebo group, and varied across studies.

In the osteoporosis safety analysis set, the exposure-adjusted incidence rate per 100 subject-years of adverse events of injection site reactions was 6.1 in the total romosozumab group, 5.8 in the romosozumab 210 mg group and 2.9 in the integrated control group. No serious adverse events of injection site reactions were reported.

During the 12 month double blind period of the alendronate controlled Study 20110142, AEs of injection site reactions were reported for 90 (4.4%) subjects in the romosozumab group and 53 (2.6%) subjects in the alendronate group; none were considered serious. In both the romosozumab and alendronate groups, all events were considered mild to moderate in severity with the exception of 1 severe event of administration site pain in the alendronate group.

In the male osteoporosis Study 20110174, injection site reactions occurred at similar rates (romosozumab versus. placebo: 5.5% versus 3.7%) as in Study 20070337 (5.2% versus 2.9%).

Malignancy (malignant or unspecified tumour)

In the 12 month placebo controlled osteoporosis safety analysis set, AEs of malignant or unspecified tumours were reported for 1.4% of subjects in the total romosozumab treatment group and 1.6% of subjects in the placebo group; SAEs 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 leukaemia were low and balanced between the romosozumab and placebo groups.

In the osteoporosis safety analysis set, the exposure-adjusted incidence rate per 100 subject-years of AEs of malignant or unspecified tumours was 1.5 in the total romosozumab and romosozumab 210 mg groups and 1.6 in the integrated control group; SAEs occurred at an exposure-adjusted incidence rate per 100 subject-years of 1.1 across all treatment groups. The only preferred term reported at an exposure-adjusted incidence rate per 100 subject-years of ≥ 0.2 in either treatment group was basal cell carcinoma (0.3 for both romosozumab groups; 0.4 for the control group).

During the 12 month double blind period of the alendronate controlled Study 20110142, 31 (1.5%) subjects in the romosozumab group and 28 (1.4%) subjects in the alendronate group were reported to have adverse events of malignancies or unspecified tumours. Serious adverse events of malignancy were reported for 25 (1.2%) subjects in the romosozumab group and 20 (1.0%) subjects in the alendronate group.

In the male osteoporosis Study 20110174, malignancies occurred at similar rates (romosozumab: 1.8%; placebo: 2.5%) as in Study 20070337 (romosozumab: 1.4%; placebo: 1.5%). In the romosozumab group of Study 20110174, events included 2 (1.2%) subjects with basal cell carcinoma and 1 (0.6%) subject with oropharyngeal cancer. In the male osteoporosis Study 20110174, malignancies occurred at a similar rate in placebo and romosozumab treatment groups with no evidence of treatment-related effects on prostatic tumours.

Hyperostosis

Based on nonclinical and clinical studies, hyperostosis is not considered a potential risk in skeletally mature patients (that is, adults). In the 12 month placebo controlled osteoporosis safety analysis set, AEs suggestive of hyperostosis were reported for 0.5% of subjects in the total romosozumab treatment group and 0.8% of subjects in the placebo group; SAEs were reported for < 0.1% and 0.1%, respectively. All events occurred in Study 20070337 with the exception of 2 events of exostosis in the placebo group of Study 20060326. AEs preferred terms for hyperostosis in Study 20070337 were lumbar spinal stenosis (0.2% in each group), exostosis (romosozumab: 0.2%; placebo: 0.3%), spinal column stenosis (< 0.1%; 0.2%) and cervical spinal stenosis (< 0.1% in each group).

A potential consequence of hyperostosis is nerve compression which may include facial drooping, numbness, or changes in hearing or vision. Neurological sequelae due to early signs of hyperostosis, such as changes in hearing, were not observed in the substudy involving 498 subjects conducted in pivotal Phase III Study 20070337. No significant difference in average change in hearing threshold, nor in incidence of protocol defined hearing loss was observed between treatment groups at Month 12, although the follow-up was not long enough to detect any problems.

Results for the osteoporosis safety analysis set were generally similar to the 12 month placebo controlled osteoporosis safety analysis set.

During the 12 month double blind period of the alendronate controlled Study 20110142, 2 (< 0.1%) subjects in the romosozumab group and 12 (0.6%) subjects in the alendronate group were reported to have AEs of hyperostosis; main AEs were heel and calcaneal spurs. Serious hyperostosis events were reported for 2 (< 0.1%) subjects in the alendronate group and no subjects in the romosozumab group. No hyperostosis AEs were reported in the male osteoporosis Study 20110174.

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 monthly on a mg/kg basis increased bone mass as anticipated, with no effects on cartilage thickness or area.

In the 12 month placebo controlled osteoporosis safety analysis set, AEs of osteoarthritis were reported for 7.9% of subjects in the total romosozumab treatment group and 8.6% of subjects in the placebo group; SAEs were reported for 0.2% and 0.5%, respectively Results for the osteoporosis safety analysis set were generally similar to the 12 month placebo controlled osteoporosis safety analysis set.

In the Phase II dose ranging Study 20101291 in Japanese subjects, there was a higher incidence of osteoarthritis AEs in the total romosozumab groups (13 (6.9%)) compared with placebo (0.0%), with more events occurring in the higher dose groups (1 (1.6%) in the 70 mg group, 2 (3.2%) in the 140 mg group and 10 (15.9%) in the 210 mg group). These numerical differences in osteoarthritis were not observed across doses in Study 20060326. In addition, among Japanese subjects in the Phase III Study 20070337, the incidence of osteoarthritis was similar between the placebo and romosozumab groups.

In an osteoarthritis substudy of pivotal Study 20070337, osteoarthritis AEs were reported for 7.7% (13 of168) of subjects in the romosozumab group and 12.0% (21 of175) of subjects in the placebo group. The most frequently reported AE (preferred term) was osteoarthritis (6.0% (10 subjects), 9.1% (16 subjects)).

During the 12 month double blind period of the alendronate controlled Study 20110142, 138 (6.8%) subjects in the romosozumab group and 146 (7.2%) subjects in the alendronate group were reported to have AEs of osteoarthritis; most common AEs were osteoarthritis (romosozumab versus alendronate: 5.7%, versus 5.6%), spinal osteoarthritis (1.2% versus 1.3%) and exostosis (< 0.1% versus 0.3%). Serious osteoarthritis events were reported for 8 (0.4%) subjects in the romosozumab group and 6 (0.3%) subjects in the alendronate group.

AEs of osteoarthritis were reported for 4.9% of subjects in each treatment group of the male osteoporosis Study 20110174, and 8.0% in the romosozumab group and 8.8% in the placebo group of the postmenopausal osteoporosis Study 20070337.

TNF-mediated inflammatory AEs

Sclerostin has been proposed as having a role as a negative regulator of tumour necrosis factor (TNF) TNF alpha (TNFα) production in synovium, and expression of sclerostin has been shown in synoviocytes from patients with rheumatoid arthritis.[49] 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.[50,51]

For the 12 month placebo controlled osteoporosis safety analysis set, the subject incidence of treatment emergent TNF-mediated inflammatory AEs was 0.3% in the romosozumab group and 0.4% the placebo group. AE preferred terms reported for ≥ 0.1% in either treatment group were psoriasis (0.2% in each group) and rheumatoid arthritis (< 0.1% in the romosozumab group and 0.1% in the placebo group). The subject incidence rate was lower in the romosozumab than placebo group for subjects with a prior history of a TNF-mediated inflammatory disease (8.1% and 12.5%, respectively) and subjects with no prior history of TNF-mediated inflammatory disease (0.1% and 0.2%, respectively. Results for the osteoporosis safety analysis set were generally similar to the 12 month placebo controlled osteoporosis safety analysis set.

During the 12 month double blind treatment period of the alendronate controlled Study 20110142, TNF-mediated inflammatory events were reported for 0.5% of subjects in the romosozumab group and 0.7% in the alendronate group. The most frequently reported event (preferred terms) was rheumatoid arthritis (romosozumab: 0.3%; alendronate: 0.4%). The incidence of TNF-mediated inflammatory events was consistent between treatment groups for subjects with a prior history of these events (romosozumab: 9.3%; alendronate: 8.7%) and those with no prior history (0.3% and 0.4%, respectively). The incidence of TNF-mediated inflammatory events was consistent between treatment groups for subjects with a prior history of rheumatoid arthritis (romosozumab: 11.1%; alendronate: 10.0%); all preferred terms were rheumatoid arthritis.

In other studies, the following 2 events of palindromic rheumatism were reported in subjects who received romosozumab: 1 subject in the Phase I1 Study 20150197 had a SAE of palindromic rheumatism reported on day 10; and 1 subject in Study 20070337 with a medical history of palindromic rheumatism had a non-serious AE of worsening palindromic rheumatism on Days 76 to 128.

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 (psoriasis and rheumatoid arthritis in 1 subject each).

Sarcopaenia

Theoretically, sarcopaenia (reduced muscle weight) may be associated with sclerostin inhibition. In the 12 month placebo controlled osteoporosis safety analysis set, the incidence of AEs of sarcopaenia (narrow and broad scope) was 5.8% (in both romosozumab and placebo groups); common AEs were asthenia (romosozumab versus placebo: 2.2% versus 2.2%), fatigue (1.3% versus 1.5%), weight decreased (0.6% versus 0.3%), muscle contracture (0.6% versus 0.5%), muscular weakness (0.5% each) and musculoskeletal stiffness (0.5% each). Results for the osteoporosis safety analysis set were generally similar to the 12 month placebo controlled osteoporosis safety analysis set. In the male osteoporosis Study 20110174, AEs of sarcopaenia (narrow and broad scope)

[49] Wehmeyer C, et al. Sclerostin inhibition promotes TNF-dependent inflammatory joint destruction. *Sci Transl Med*. 2016; 8: 330-335.
[50] Chen XX, et al. Sclerostin inhibition reverses systemic, periarticular and local bone loss in arthritis. *Ann Rheum Dis*. 2013; 72: 1732-1736
[51] Marenzana M, et al. Effect of sclerostin-neutralising antibody on periarticular and systemic bone in a murine model of rheumatoid arthritis: a microCT study. *Arthritis Res Ther.* 2013; 15: R125

were reported for 1.8% of subjects in the romosozumab group and 7.4% of subjects in the placebo group compared with 5.9% of subjects in the romosozumab group and 5.8% of subjects in the placebo group of the postmenopausal osteoporosis Study 20070337.

Adjudicated positive atypical femoral fracture

Atypical femoral fracture has been observed with the use of anti-resorptive agents. Because inhibition of bone resorption is a component of the dual effect of romosozumab, there is a potential concern for increased risk of atypical femoral fracture. In the 12 month placebo controlled osteoporosis safety analysis set, 1 subject in the romosozumab group and no subjects in the placebo group had a positively adjudicated SAE of atypical femoral fracture. The occurrence after 3.5 months of romosozumab treatment and a history of prodromal pain in the fracture area before starting the study suggests an idiopathic event in this subject who also had a low screening vitamin D level. In the osteoporosis safety analysis set, in addition to the event described above, in Study 20110142, no positively adjudicated adverse events of atypical femoral fracture were reported during the 12 month double blind period. Positively adjudicated 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. All were considered serious adverse events and all occurred while subjects were receiving alendronate. One additional positively adjudicated adverse event of atypical femoral fracture was noted for Study 20110142 after the snapshot date of 27 February 2017. In the male osteoporosis Study 20110174, no AEs of atypical femoral fracture were positively adjudicated.

Adjudicated positive osteonecrosis of the jaw

Osteonecrosis of the jaw has been observed with the use of anti-resorptive agents. 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 osteonecrosis of the jaw. This case was confounded by continuous use of a maladaptive fitting denture. One additional positively adjudicated case 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 osteonecrosis of the jaw 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. In the male osteoporosis Study 20110174, there were no positively adjudicated AEs of osteonecrosis of the jaw.

Other safety issues

Safety in special populations

No safety analyses were performed for subgroups by race, body mass index or renal impairment in Study 20110142 or in the male osteoporosis Study 20110174.

Age

In the 12 Month placebo controlled osteoporosis safety analysis set, there were no notable differences in the subjects incidences of AEs among age groups, or between the romosozumab and placebo groups within each age group, and these percentages were similar to those seen in the overall population for each treatment group. The incidence of AEs was < 65 years of age: romosozumab versus placebo: 78.0% versus 77.0%; 65 to 74 years of age: 77.8% versus 81.0%; ≥ 75 to 84 years of age: 79.4% versus 80.5%; ≥ 85 years of age: 81.6% versus 81.1%. The most frequently reported AEs in each age

subgroup were the same events that were most frequently reported in the overall population, that is, nasopharyngitis, arthralgia and back pain. In general, AEs by preferred term were reported with similar frequency in the romosozumab and placebo groups within each age subgroup, and these incidences were similar to those seen in the overall population. In Study 20110142, the subject incidences of AEs between age groups were generally comparable within each treatment group and study period. No safety analyses were performed for subgroups in the male osteoporosis Study 20110174.

Race

There was no notable difference in the incidence of AEs in White and Non-White subgroups. The most frequently reported AEs in each race subgroup were the same events that were most frequently reported in the overall population, that is, nasopharyngitis, arthralgia and back pain. No safety analyses were performed for subgroups by race in Study 20110142 or in the male osteoporosis Study 20110174.

Body mass index

There were no notable differences between treatment groups in the incidence of AEs within any body mass index subgroup, and this was similar to results seen in the overall population for each treatment group. In general, AEs by preferred term were reported with similar frequency in the romosozumab and placebo groups within each body mass index subgroup, and these incidences were similar to those seen in the overall population.

Safety in renal/hepatic impairment

The pharmacokinetics, pharmacodynamics and safety of romosozumab in subjects with renal impairment was evaluated in the Phase I Study 20110227. The administration of romosozumab resulted in a greater decrease in serum calcium level and a greater compensatory physiological increase in intact parathyroid hormone in subjects with stage 4 and stage 5 chronic kidney disease receiving haemodialysis than in healthy subjects. Most of these changes were transient and returned to Baseline by end of the study. AEs were presented by each of the following subgroups using the 12 month placebo controlled osteoporosis safety analysis set and osteoporosis safety analysis set: Estimated glomerular filtration rate (eGFR; < 15; 15 to < 30; 30 to < 60; 60 to < 90; ≥ 90 mL/min/1.73 m^2). 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 m^2. Overall, the types of AEs reported were consistent across eGFR subgroups. No safety analyses were performed for subgroups by renal impairment in Study 20110142.

Monoclonal antibodies are not eliminated via hepatic metabolic mechanisms; therefore, no studies have been conducted in subjects with hepatic impairment.

Safety in subjects who transitioned from bisphosphonate therapy

Study 20080289 was a multicentre, randomised, open label, 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 AEs was slightly higher in the romosozumab group (164 of 218 subjects (75.2%)) compared with teriparatide group (148 of 214 subjects (69.2%)). The incidences and types of events reported were those that would be expected in the population studied and were generally similar between the teriparatide and romosozumab groups. Injection site reactions were observed more frequently with romosozumab (7.8%) compared with teriparatide (2.8%) and led to study drug discontinuation for 1 subject in the romosozumab group. Of the subjects who reported injection site reactions, the median time to the first AE was 92.0 days in the romosozumab group and 36.5 days in the teriparatide group. The median duration of injection site reaction AEs was 2.0 days in the

romosozumab group and 5.5 days in the teriparatide group. The safety findings in this study of subjects transitioning from at least 3 years of oral bisphosphonate therapy and alendronate in the year immediately prior were consistent with the overall safety profile of romosozumab.

Study 20060223 was a multicentre, randomised, open label, single dose study in 40 postmenopausal women with low bone mass who had been receiving alendronate for at least 1 year and in postmenopausal women with low bone mass who were treatment naive (that is, had not received alendronate, other bisphosphonates, or other treatments for osteoporosis/bone loss). Subjects who had been receiving alendronate were randomised to continue alendronate treatment or transition to romosozumab; treatment naive subjects received romosozumab.

Overall, AEs were reported for 5 of 10 subjects (50%) who received alendronate only; 10 of 24 subjects (42%) who received romosozumab after previous alendronate treatment; and 5 of 6 subjects (83%) who received romosozumab and were previously treatment naive. These differences may be attributed to the small number of subjects in each group. AEs were reported as treatment related for 1 subject (4%) who received romosozumab after previous alendronate treatment (injection site reaction) and for 3 subjects (50%) who received romosozumab and were previously treatment naive (injection site erythema, injection site reaction and nausea); all of these events were reported as mild in severity.

Use in pregnancy and lactation

All studies were conducted in men and postmenopausal women, and no pregnancy has been reported across the romosozumab development program. Also, no studies have been conducted to determine whether romosozumab is present in breast milk or to assess the effects of romosozumab in breast-fed infants.

Overdose, drug abuse effects on ability to drive or operate machinery or impairment of mental ability

Neither the effects of overdose of romosozumab nor an antidote to overdose are known. Data from completed Phase I clinical studies demonstrate that romosozumab has an acceptable safety profile up to the highest dose tested (doses up to 10 mg/kg SC and 5 mg/kg IV). There is no evidence that romosozumab is habit forming or could lead to dependence. There is no pharmacological basis or clinical evidence that romosozumab would affect the ability to operate machinery or cause impairment of mental ability.

Withdrawal and rebound

There was no evidence of withdrawal or rebound effects with romosozumab. Reduction in incidence of vertebral and clinical fractures was sustained after 12 months of treatment although it is very important to stress that follow-on treatment with other medications for osteoporosis such as denosumab and alendronate is essential for maintenance of efficacy. Rebound or withdrawal effects without any other osteoporosis treatment following end of the 12 months of romosozumab treatment was not evaluated.

Long-term safety

Safety data after stopping romosozumab treatment (off-treatment) and following re-exposure to romosozumab:

- There was no integration of studies for off-treatment and re-exposure to romosozumab. Safety data for post- or re-exposure of romosozumab was only provided in the Phase II dose ranging Study 20060326.
- Events occurring during the 24 month treatment period were included in the osteoporosis safety analysis set results. The proportion of subjects reporting AEs,

SAEs, fatal AEs and AEs leading to discontinuation from study or investigational product over the 24 month treatment period were similar between the romosozumab and placebo groups (Table 16).

Table 16: Summary of AEs (events starting during the initial 24 month treatment period) (safety analysis set for subjects enrolled in the initial treatment period) (Study 20060326, Month 72 final analysis)

	Placebo	Alendronate/ Romosozumab	Romosozumab					
Adverse Event	Total (N = 50)	70 mg QW/ 140 mg QM (N = 51)	70 mg QM (N = 50)	140 mg Q3M (N = 52)	140 mg QM (N = 49)	210 mg Q3M (N = 53)	210 mg QM (N = 51)	Total (N = 255)
All	48 (96.0)	50 (98.0)	50 (100.0)	48 (92.3)	46 (93.9)	53 (100.0)	48 (94.1)	245 (96.1)
Serious	9 (18.0)	8 (15.7)	9 (18.0)	8 (15.4)	8 (16.3)	6 (11.3)	7 (13.7)	38 (14.9)
Fatal	1 (2.0)	0 (0.0)	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 (3.9)	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)	4 (7.8)	3 (6.0)	3 (5.8)	3 (6.1)	1 (1.9)	3 (5.9)	13 (5.1)

IP = investigational product; N = subjects who received at least one dose of investigational product; QM = every month; Q3M = every 3 months; QW = every week
Includes only adverse events started on or before the end of the first 24-month period.
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 events occurring through the 24-month study period are also included in the osteoporosis population pooled results.
Source: Modified from Study 20060326 FA Table 14t-6.200.1.1

There was no dose-dependent trend seen in the overall incidence of AEs across the romosozumab groups. SAEs (preferred terms) reported in more than 1 subject across all romosozumab treatment groups were osteoarthritis, pneumonia, appendicitis and breast cancer. All of these events were reported in < 2% of subjects in any treatment group. Two fatal AEs occurred during the first 12 months (1 romosozumab subject (post-operative ileus) and 1 placebo subject (colon cancer)); no fatal AEs occurred during Months 12 to 24 (Table 17).

Table 17: Subject incidence of AEs of interest during the initial 24 month treatment period (events starting during the initial 24 month treatment period) (safety analysis set for subjects enrolled in the initial treatment period (Study 20060326, Month 72 final analysis)

	Placebo	Alendronate/ Romosozumab	Romosozumab					
Adverse Event of Interest	Total (N = 50)	70 mg QW/ 140 mg QM (N = 51)	70 mg QM (N = 50)	140 mg Q3M (N = 52)	140 mg QM (N = 49)	210 mg Q3M (N = 53)	210 mg QM (N = 51)	Total (N = 255)
Injection site reactions								
Adverse events	2 (4.0)	3 (5.9)	12 (24.0)	6 (11.5)	12 (24.5)	6 (11.3)	3 (5.9)	39 (15.3)
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)
Hypersensitivity								
Adverse events	8 (16.0)	3 (5.9)	10 (20.0)	8 (15.4)	7 (14.3)	4 (7.5)	6 (11.8)	35 (13.7)
Serious adverse events	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypocalcemia								
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)
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)
Hyperostosis								
Adverse events	2 (4.0)	0 (0.0)	3 (6.0)	0 (0.0)	1 (2.0)	1 (1.9)	0 (0.0)	5 (2.0)
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)
Malignant or unspecified tumours								
Adverse events	3 (6.0)	3 (5.9)	0 (0.0)	0 (0.0)	2 (4.1)	1 (1.9)	2 (3.9)	5 (2.0)
Serious adverse events	2 (4.0)	3 (5.9)	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.9)	1 (2.0)	3 (1.2)
Osteoarthritis								
Adverse events	6 (12.0)	7 (13.7)	6 (12.0)	8 (15.4)	5 (10.2)	8 (15.1)	2 (3.9)	29 (11.4)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.0)	1 (1.9)	0 (0.0)	3 (1.2)

N = subjects who received at least one dose of investigational product; Q3M = every 3 months; QM = every month; QW = every week.
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 events occurring through the 24-month study period are also included in the osteoporosis population pooled results.

Overall, during the 24 to 36 month extension phase of the study, the subject incidence of AEs was similar between the denosumab group (99 (79%) subjects) and the placebo group (95 (75%) subjects). The incidence of SAEs was 9 (7.2%) subjects in the denosumab group and 7 (5.5%) subjects in the placebo group. No additional fatal AEs occurred by Month 36.

During the romosozumab retreatment phase (Month 35 to 48), the overall subject incidence of AEs in the re-exposed group compared with the treatment-naive group was generally similar (84.3% for the romosozumab group and 85.0% in the all treatment group). No additional fatal AEs were reported in the romosozumab retreatment period. Incidence of discontinuations due to AEs was reported for 5 subjects (3%) but 8 subjects (4.8%) had SAEs: 5 subjects with neoplasms, 1 subject with myocardial infarction, 1 subject with inguinal hernia and 1 subject with osteoarthritis (none of these SAEs were considered treatment-related). Reasons for discontinuation of both investigational product and study were malignant lung neoplasm; thyroid cancer; Meniere's disease; allergic dermatitis and injection site rash; and injection site rash in 1 subject each. There were no AEs of hypocalcaemia. One subject had a grade 1 decrease in albumin-adjusted serum calcium that resolved. There were no AEs potentially associated with hyperostosis. The subject incidence of osteoarthritis or arthritis was 3.6% (6 subjects); 3 of these subjects had a history of osteoarthritis. Of the 3 subjects with new onset of osteoarthritis, 2 subjects had received placebo in all previous periods, and one had received romosozumab up to 24 months and placebo in the extension phase. There were no cases of adjudicated positive osteonecrosis of the jaw or atypical femoral fracture.

During the 24 month follow-on phase (Months 48 to 72) of Study 20060326, subjects received zoledronic acid or no intervention. AEs and SAEs were reported for 72.5% and 15.7%, respectively of subjects assigned to no intervention; 83.9% and 13.8% of subjects who received zoledronic acid. No subject discontinued investigational product or the study due to AEs. One (2.0%) fatal AE was reported in the group of subjects assigned to no intervention. The event of cardiorespiratory arrest was not considered related to study treatment. For subjects who received zoledronic acid, treatment related AEs and SAEs were reported for 37.9% and 1.1% of subjects, respectively, but none of these were fatal or led to discontinuation from study. AEs reported for ≥ 10% of subjects who received zoledronic acid were influenza-like illness (16.1%), myalgia (13.8%), arthralgia (12.6%), influenza (12.6%) and nasopharyngitis (11.5%). Treatment related AEs (preferred terms) reported for > 3% of all subjects who received zoledronic acid were influenza-like illness (13.8%), myalgia (10.3%), arthralgia (3.4%) and influenza (5.7%). SAEs reported by more than 1 subject were pneumonia (no intervention, 0 subjects; zoledronic acid, 3 subjects) and osteoarthritis (2; 0). AEs potentially associated with hypersensitivity (no intervention, 5.9%; zoledronic acid, 3.4%); hypocalcaemia (both 0%); hyperostosis (both 0%); malignancies (0%; 2.3%); osteoarthritis (9.8%; 8.0%) with no adjudicated osteonecrosis of the jaw or atypical femoral fracture.

In the pivotal Phase III Study 20070337 the proportion of subjects reporting AEs, SAEs, fatal AEs and AEs leading to discontinuation from study or investigational product over the 24-month study period were similar between the treatment groups (Table 18). During the 36 month study period (that is, 24 month primary analysis study period followed by the 12 month extension period), subjects who received romosozumab/ denosumab and subjects who received placebo/denosumab showed similar incidence of AEs (88.1% versus 89%), SAEs (20.3% versus 20.5%), deaths (2.0% (72) versus 2.4% (85)), AEs leading to discontinuation (1.8% versus 1.8%). During the 36 month study period, treatment related AEs were reported for 18.8% of subjects in the romosozumab/denosumab group and 16.0% of subjects in the placebo/denosumab group. During the 36 month study period, 72 deaths (2.0%); 3 (< 0.1%) and 1 (< 0.1%), respectively, were considered by the investigator to be related to treatment.

Table 18: Subject incidence of AEs (Safety analysis set) (Study 20070337, 24 month primary analysis period)

	Double-blind Period		24-Month Study Period	
	Placebo (N = 3576)	Romosozumab 210 mg QM (N = 3581)	Placebo/ Denosumab 60 mg Q6M (N = 3576)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3581)
All TEAEs – n (%)	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)	57 (1.6)	52 (1.5)
Fatal adverse events	23 (0.6)	29 (0.8)	47 (1.3)	52 (1.5)
Treatment-related TEAEs[a] - n (%)	494 (13.8)	596 (16.6)	557 (15.6)	653 (18.2)
Serious adverse events	13 (0.4)	16 (0.4)	20 (0.6)	31 (0.9)
Leading to discontinuation of IP	46 (1.3)	54 (1.5)	50 (1.4)	60 (1.7)
Leading to discontinuation from study	17 (0.5)	18 (0.5)	17 (0.5)	19 (0.5)
Fatal adverse events	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)

IP = investigational product; N= Number of subjects who received at least 1 dose of investigational product in the double-blind period; Q6M = every 6 months; QM = every month; TEAE = treatment-emergent adverse event

[a] Includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product.

The subject incidence rates for the 24-month study period includes all events that occurred in the double-blind period and all events that occurred in the open-label period for those subjects who received at least 1 dose of denosumab.

Safety related to drug-drug interactions and other interactions

No studies on potential drug-drug interactions were conducted with romosozumab. Romosozumab is a monoclonal antibody that binds specifically to sclerostin, and there are no known mechanisms or previous pharmacokinetics or pharmacodynamic experience whereby romosozumab may precipitate pharmacokinetics drug-drug interactions.

Post marketing data

Romosozumab has not yet received marketing approval in any country.

Evaluator's conclusions on safety

The romosozumab clinical program consisted of an extensive database that included around 14,000 subjects who received at least 1 dose of romosozumab (n = 7681), placebo (n = 3872) or active comparator (n = around 2400) in 19 romosozumab clinical studies. This was adequate to evaluate safety of the new chemical entity in the target population for proposed usage.

The overall subject incidence of AEs, SAEs, fatal AEs, and AEs leading to withdrawal of investigational product or study were similar between the romosozumab and placebo groups across the phase 2 and 3 placebo controlled studies. Of the 7628 subjects in the placebo controlled osteoporosis safety analysis set, the proportion of subjects who had at least 1 treatment emergent AE during the study period was similar in the romosozumab and placebo groups (78.4% versus 80%); nasopharyngitis (13.6% versus 12.6%), arthralgia (12.4% versus 11.8%) and back pain (10.2% versus 10.4%) were most common and no AE was reported at a ≥ 2% difference in the total romosozumab group than in the placebo group. Treatment-related AEs were reported in slightly more subjects in the romosozumab compared with the placebo group (16.1% versus 13.5%). Adverse reactions

for romosozumab were determined by evaluating AEs that occurred with a ≥ 2% incidence rate in the total romosozumab group and more frequently in the romosozumab group than the placebo group for the 12 month placebo controlled population; common adverse drug reactions included nasopharyngitis, arthralgia, headache, muscle spasms, cough, peripheral oedema and neck pain. Based on review of all clinical data, injection site reactions, hypersensitivity and hypocalcaemia were also considered adverse reactions. The incidence of fatal AEs was similar in the romosozumab and placebo groups (0.8% versus 0.7%); fatal AEs reported for more than 1 subject were death (6 (0.2%) subjects in each group), lung neoplasm malignant (4 (0.1%) versus 0), cardiorespiratory arrest (3 (< 0.1%) versus 0), myocardial infarction (2 (< 0.1%) subjects in each group), angina pectoris (0 versus 2 (< 0.1%)) and cerebrovascular accident (0 versus 2 (<0.1%)). Only 1 death in the romosozumab groups was considered treatment related (deep vein thrombosis). Incidence of SAEs (9.7% versus 8.9%) was similar in both treatment groups. The only SAE occurring in ≥ 0.5% of subjects in the total romosozumab or placebo groups was pneumonia (0.5% romosozumab, 0.3% placebo) and no SAEs (preferred terms) were reported at a ≥ 2% higher incidence in the total romosozumab group compared to the placebo group. The incidence of treatment-related SAE was 0.4% in each treatment group. The incidence of AEs leading to permanent discontinuation was similar in both treatment groups (romosozumab versus placebo: 3% versus 2.6%) with most common AEs leading to discontinuation being pain in extremity, arthralgia, dizziness, lung neoplasm malignant and nausea.

The subject incidence of AEs of interest was similar between treatment groups in the 12 month placebo controlled osteoporosis safety analysis set except for injection site reactions (5.2% for romosozumab and 2.9% for placebo). Similar results were obtained for exposure-adjusted incidence rates in the osteoporosis safety analysis set.

The overall subject incidences of AEs, SAEs, fatal AEs and AEs leading to withdrawal of investigational product or study were similar between the romosozumab and alendronate groups in Study 20110142. The subject incidence of AEs of interest was similar between treatment groups except for injection site reactions (romosozumab versus alendronate: 4.4% versus 2.6%) and positively adjudicated serious cardiovascular AEs (2.5% versus 1.9).

The subject incidences of AEs and SAEs were generally balanced between the romosozumab and teriparatide groups in Study 20080289 that enrolled subjects previously treated with bisphosphonates. The types of events reported were those that would be expected in the population studied. Injection site reactions were observed more frequently with romosozumab compared with teriparatide (7.8% and 2.8%, respectively), which led to study drug discontinuation for 1 subject in the romosozumab group. Most AEs related to injection site reactions were reported as mild in severity and none was considered serious.

The overall safety profile in men with osteoporosis (based on subject incidences of AEs, SAEs, fatal AEs and AEs leading to withdrawal of investigational product or study) was similar to that observed for women in the pivotal Phase III placebo controlled fracture Study 20070337.

There were no clinically relevant differences between romosozumab and placebo (or control groups) on liver, renal function parameters, clinical chemistry, haematology and vital signs among the individual studies. ECG data were collected in Study 20060326 and some Phase I studies are also provided in individual clinical study reports. However, ECGs were not performed in pivotal Phase III Studies 20070337, 20110142 and 20110174 and the Phase IIIb Study 20080289. Analysis of ECG results in individual studies in which they were analysed demonstrated no clinically important effect of romosozumab.

The romosozumab clinical study program revealed an imbalance in positively-adjudicated cardiovascular SAEs between treatment groups in Study 20110142, which was not observed in the larger, placebo controlled Study 20070337. The external, independent adjudication of cardiovascular SAEs in the three pivotal Phase III Studies (Studies 20070337, 20110142 and 20110174) in the romosozumab clinical program was pre specified in the respective protocols. Based on the totality of the evidence including nonclinical, clinical, and epidemiologic data, a causal relationship between romosozumab and positively-adjudicated cardiovascular SAEs has not been established. A true relationship to romosozumab has not been excluded; therefore, cardiovascular SAEs remain an important potential risk and will require ongoing monitoring and evaluation in pharmacovigilance activities.

In Phase II and III clinical studies of osteoporosis in postmenopausal women, the incidence of developing anti romosozumab binding and neutralising antibodies was 18.6% (1162 of 6244) and 0.9% (58 of 6244), respectively across all doses studied. The incidence of developing binding and neutralising anti romosozumab antibodies in women who received 210 mg monthly was similar to the overall studies at 18.1% (1068 of 5914) and 0.7% (43 of 5914), respectively. Similar results were observed in men with osteoporosis who received romosozumab 210 mg monthly; the incidence of anti romosozumab binding and neutralising antibodies through Month 15 was 17.3% (28 of 162) and 0.6% (1 of 161), respectively which was consistent with that observed for postmenopausal women with osteoporosis. The pharmacokinetic exposure, safety (for example, hypersensitivity, injection site reactions, or autoimmune disorder) and efficacy (changes in BMD) profiles of the subjects who tested positive for binding anti romosozumab antibodies were found to be consistent with the profiles of anti romosozumab antibody-negative subjects.

In the 12 month placebo controlled osteoporosis population, AEs potentially related to hypersensitivity were reported for 6.7% of subjects in the total romosozumab group and 6.9% of subjects in the placebo group. Fatal or life-threatening AEs potentially related to hypersensitivity were reported for 2 subjects receiving romosozumab (both in Study 20070337: circulatory collapse after 1 year of romosozumab treatment and severe allergic reaction after first dose of romosozumab) and 3 subjects had SAEs potentially related to hypersensitivity that were considered related to romosozumab (all of which occurred in Study 20070337). The incidence of hypersensitivity reactions was also similar in the romosozumab and alendronate groups in pivotal Study 20110142 (6% versus 5.9%). The incidence of hypersensitivity reactions in Study 20110174 in men with osteoporosis was slightly lower (4.9%) than that reported in the Study 20070337 in PM women with osteoporosis (6.8%). Atypical low-energy or low trauma fractures of the femoral shaft have been reported in patients receiving romosozumab. However, the number of osteonecrosis of the jaw and atypical femoral fracture cases observed in the clinical trials was low and causality has not been established.

There was no evidence of withdrawal or rebound effects with romosozumab. Reduction in incidence of vertebral and clinical fractures was sustained after 12 months of treatment although it is very important to stress that follow-on treatment with other medications for osteoporosis such as denosumab and alendronate is essential for maintenance of efficacy. Rebound or withdrawal effects without any other osteoporosis treatment following end of the 12 months of romosozumab treatment was not evaluated.

Overall the safety profile of romosozumab was generally comparable to that of placebo and the active comparators (alendronate and teriparatide) with the exception of higher incidence of injection site reactions and cardiovascular SAEs in the romosozumab treated patients.

First round benefit-risk assessment

First round assessment of benefits

Table 19: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Rapid onset of action. Following 12 months treatment with romosozumab (210 mg SC monthly), fracture risk reduction (for vertebral and clinical fracture) observed within 12 months in women with postmenopausal osteoporosis and increased risk of fractures.	Fracture reduction effects of romosozumab require follow up treatment with another osteoporosis treatment; only follow-on treatment with alendronate and denosumab was evaluated in the submitted studies.
Romosozumab for 12 months followed by denosumab for 12 months significantly reduced the risk of new vertebral fractures through Month 24 compared with placebo followed by denosumab by 75% (0.6% versus 2.5%, odds ratio = 0.25, p < 0.001) and clinical fracture by 33% (2.8% versus 4.1%, odds ratio = 0.67, p = 0.096).	Reduction in clinical fracture was not statistically significant due to non-significant result for non-vertebral fracture. Exploratory analysis up to Month 36 showed persistent risk reduction across fracture types through 36 months after subjects in both treatment groups transitioned to denosumab (new vertebral fracture: 1% versus 2.8%; hazard ratio = 0.34).
In Study 20110142, 12 months of romosozumab followed by 12 months of alendronate significantly reduced the risk of new vertebral fracture by 50% (4.1% versus 8.0%) and clinical fracture by 27% (9.7% versus 13%) compared with alendronate alone.	Reduction in vertebral and clinical fractures demonstrated against alendronate which is considered a standard-of-care treatment for osteoporosis.
A consistent treatment effect for romosozumab over placebo and alendronate was observed in all subgroups of baseline characteristics examined (age, prevalent vertebral fracture status, race, geographic region, baseline lumbar spine BMD T-score, baseline total hip/femoral neck BMD T-score, baseline body mass index, FRAX score, history of non-vertebral fracture at or after age 55 and history of fragility fracture).	
Patients evaluated in the Phase II and III studies were representative of the target	Only 6 to 9% of patients had prior history of treatment with other

Indication	
patient population of Australian women with postmenopausal osteoporosis at increased risk of fractures.	treatments for osteoporosis. This is despite fact that almost all (99%) of subjects in the alendronate-controlled study had history of osteoporotic fracture. Only subjects with primary osteoporosis were evaluated.
Robust improvement in BMD at the spine and the hip (including in subjects previously treated with anti-resorptive therapy). Consistent effects on BMD observed regardless of baseline age, baseline BMD and geographic region.	The effect of romosozumab on BMD was consistent with significant BMD gains in a direct comparison with alendronate (Study 20110142) and teriparatide (Study 20080289).
The monthly dose of romosozumab 210 mg (consisting of 2 injections per dose in a prefilled syringe or prefilled AI/pen) provides convenience.	Romosozumab treatment for 12 months has to be followed up with another treatment for osteoporosis such as alendronate or denosumab.
Safety of romosozumab was generally comparable to that of placebo and active comparators (alendronate and teriparatide).	However romosozumab was associated with a higher incidence of injection site reactions and cardiovascular SAEs.

First round assessment of risks

Table 20: First round assessment of risks

Risks	Strengths and Uncertainties
Evidence for reduction in risk of non-vertebral fractures was not consistent in both pivotal Phase III studies in women with postmenopausal osteoporosis. In the placebo controlled Study 20070337, romosozumab treatment for 12 months failed to show statistically significant reduction in the incidence of non-vertebral fracture at Month 12 (1.6% versus 2.1%, odds ratio = 0.75, adjusted p = 0.096) or 24 (romosozumab/ denosumab versus romosozumab/placebo: 2.7% versus 3.6%, odds ratio = 0.75, adjusted p = 0.057).	In the alendronate controlled Study 20110142, romosozumab 210 mg monthly for 12 months followed by alendronate 70 mg weekly through the primary analysis significantly reduced the risk of non-vertebral fractures by 19% (romosozumab/alendronate: 178 of 2046, 8.7% versus alendronate/ alendronate: 217 of 2047, 10.6%; hazard ratio = 0.81, 95% CI: 0.66 to 0.99; 2-sided adjusted p value = 0.040). However, upper limit 95% CI was 0.99 and romosozumab/ alendronate failed to show statistically significant reduction in non-vertebral fractures at the end of the double blind treatment period at Month 12 (p = 0.057) or at Month 24 (p = 0.074).

Risks	Strengths and Uncertainties
Increased risk of hypersensitivity reactions.	Clinically significant hypersensitivity reactions, including dermatitis, rash, angioedema, erythema multiforme and urticaria, occurred in the romosozumab group.
Increased risk of hypocalcaemia. Inhibition of sclerostin by romosozumab leads to rapid bone mass accrual at initiation of treatment and an increased demand for bone-building substrates such as calcium.	Mild and transitory decreases in albumin-corrected calcium and a compensatory increase in intact parathyroid hormone were observed after initiation of romosozumab.
During the 12 month, double blind, alendronate controlled portion of Study 20110142 (n = 4054), there was a numerical imbalance observed between the romosozumab and alendronate groups in the incidence of positively adjudicated cardiovascular SAEs (2.5% and 1.9%, respectively), mainly cardiac ischemic events (0.8% versus 0.3%) and cerebrovascular events (0.8% versus 0.3%).	This imbalance was not observed in the placebo controlled fracture Study 20070337 (n = 7157), where the subject incidence of positively adjudicated serious cardiovascular adverse events was 1.3% in the romosozumab and placebo groups. In both trials, most participants had common risk factors for cardiovascular disease, and within each trial, cardiovascular risk factors were balanced between treatment arms. A comprehensive pharmacovigilance program and additional pharmacovigilance activities will be used to monitor this potential risk in the post marketing setting.
Osteonecrosis of the jaw and atypical femoral fracture are considered important potential risks for romosozumab and have been reported in patients receiving romosozumab.	The number of osteonecrosis of the jaw and atypical femoral fracture cases observed in the clinical trials was low and causality has not been established
Efficacy of romosozumab was only evaluated in postmenopausal women and men (aged over 50 years) with primary osteoporosis.	It was not evaluated in patients with glucocorticoid-induced osteoporosis (as patients on >7.5 mg equivalent of prednisone were excluded from the studies) or other secondary osteoporosis conditions.
Rebound or withdrawal effects without any other osteoporosis treatment following end of the 12 months of romosozumab treatment was not evaluated.	

First round assessment of benefit-risk balance

Romosozumab is a high-affinity humanised immunoglobulin G2 (IgG2) monoclonal antibody directed against sclerostin that inhibits its interaction with LRP5/LRP6 and activates Wnt signalling in the osteoblast lineage. Sclerostin-mediated decreases in Wnt signalling in osteoblast-lineage cells result in inhibition of osteoblast-mediated bone formation and stimulation of osteoclast-mediated bone resorption. By blocking sclerostin, romosozumab increases bone formation due to the activation of bone lining cells, increased bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells. Additionally, romosozumab results in changes in expression of osteoclast mediators, thereby decreasing bone resorption. Together, the dual effect of increasing bone formation and decreasing bone resorption results in improvements in bone mass, structure and strength.

Romosozumab was investigated in a comprehensive development program comprised of 19 clinical studies conducted between 2006 and 2017 that enrolled approximately 14,000 subjects to support the proposed indications for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. Studies included healthy volunteers, postmenopausal women with osteoporosis or low BMD, and men with osteoporosis. Endpoints (primary/secondary/exploratory) to assess the effect of romosozumab include the subject incidence of various fracture categories for romosozumab and comparator groups, percent change from baseline in BMD, and percent change from baseline in bone turnover markers (bone turnover markers). The efficacy and safety of romosozumab was compared against placebo as well against active comparators. Study 20070337 (FRAME trial) assessed whether the BMD gains observed in Phase I and II studies translated into fracture risk reduction after 1 year of romosozumab treatment, and whether there was continued benefit with follow-on treatment with denosumab. Study 20110142 (ARCH trial) assessed the efficacy of 1 year of romosozumab treatment in relation to alendronate alone, both during romosozumab treatment and afterwards when all subjects received alendronate. Alendronate (70 mg orally every week) is considered standard of care and was the appropriate choice for the pivotal active controlled Phase III study. Denosumab (60 mg SC every 6 months) is approved in Australia for treatment of osteoporosis in postmenopausal women (it significantly reduces risk of vertebral, non-vertebral and hip fractures). Overall, study design, efficacy endpoints, study population complied with the CHMP guidelines for evaluation of medicinal treatments for treatment of postmenopausal women with osteoporosis at increased risk of fracture.

The key efficacy results support the benefits of fracture risk reduction and improvement in BMD. Compared with placebo, romosozumab for 12 months followed by denosumab for 12 months significantly reduced the risk of new vertebral fractures by 75% and clinical fracture by 33%; 12 months of romosozumab followed by 12 months of alendronate significantly reduced the risk of new vertebral fracture by 50% and clinical fracture by 27% compared with alendronate alone, which is considered a standard of care treatment for osteoporosis. A consistent treatment effect for romosozumab over placebo and alendronate was observed in all subgroups of baseline characteristics examined (age, prevalent vertebral fracture status, race, geographic region, baseline lumbar spine BMD T-score, baseline total hip/femoral neck BMD T-score, baseline body mass index, FRAX score, history of non-vertebral fracture at or after age 55 and history of fragility fracture).

However, evidence for reduction of non-vertebral fractures was not consistent and robust across pivotal Phase III studies. According to the recommended guidelines, evidence of fracture reduction should be provided for both spinal and non-spinal fractures. Although romosozumab treatment led to reduction in 'clinical fractures', it is difficult to determine relative contribution of 'non-vertebral fractures' and 'clinical vertebral fractures' in the 'clinical fracture' endpoint.

Other fracture endpoints such as hip, major non-vertebral, major osteoporotic, all osteoporotic and new or worsening vertebral fractures showed numerically lower incidence in the romosozumab group compared to both placebo and alendronate.

In both Phase III pivotal studies, the statistically and clinically relevant improvements in BMD (at lumbar spine and total hip) with romosozumab compared with placebo/denosumab or alendronate were observed in all subgroups by baseline T-score, age and geographic region. In the open label Phase IIIb Study 20080289, which enrolled subjects transitioning from bisphosphonate therapy, romosozumab led to robust gains in BMD over 12 months of treatment. However, these gains were modestly lower than in the bisphosphonate-naïve subjects enrolled in the placebo controlled studies.

The efficacy and safety results of the pivotal Phase III fracture studies (Studies 20070337 and 20110142), in combination with the clinical pharmacology program, supported the dosing regimen of 210 mg SC monthly for a duration of 12 months for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. The monthly dose of romosozumab 210 mg (consisting of 2 injections per dose in a prefilled syringe or prefilled autoinjector/pen) provides convenience over current products and is supported by dose and exposure-response models, placebo controlled studies that explored combinations of dose and dose interval, a comprehensive biopharmaceutics program, including a bioequivalence study comparing the prefilled syringe and a prefilled autoinjector/pen presentation, and a noninferiority study of romosozumab administered at two different concentrations.

The maintenance of effect after the second year (for example 3 to 5 years) was only evaluated in the placebo controlled pivotal Study 20070337. The treatment benefit on new vertebral fractures established with romosozumab for 12 months compared with placebo continued to be present when treatment was followed by denosumab for 24 months. The risk of new vertebral fractures through Month 36 was reduced by 66% for romosozumab/denosumab compared with placebo/denosumab (nominal $p < 0.001$) with similar results for other secondary fracture endpoints. 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. However, results of the extension study (from Month 24 to 36) were only exploratory.

Studies 20070337, 20060326 and 20080289 included bone biopsy substudies to assess the formation of new bone and the bone quality these histologic and histomorphometric results are indicative of increased osteoblastic and decreased osteoclastic activity both leading to increased trabecular and cortical bone mass. Robust bone formation occurred early in the course of treatment with romosozumab, with inhibition of resorption present early in the course of treatment continued through Month 12. Quantitative bone histomorphomertry on undecalcified sections were performed in a subset of patients in Phase III studies. The subset of patients evaluated in the substudies was representative of the overall patient population in the main study and also representative of target patient population. Biopsies of patients treated with romosozumab demonstrated that bone formed during treatment is of normal lamellar structure and there was no evidence of osteomalacia or other defects.

The overall subject incidence of AEs, SAEs, fatal AEs, and AEs leading to withdrawal of investigational product or study were similar between the romosozumab and placebo groups across the Phase II and III placebo controlled studies. Common adverse drug reactions included nasopharyngitis, arthralgia, headache, muscle spasms, cough, peripheral oedema and neck pain. Based on review of all clinical data, injection site reactions, hypersensitivity and hypocalcaemia were also considered adverse reactions. The incidence of fatal AEs was low and similar in the romosozumab and placebo groups (0.8% versus 0.7%). Romosozumab did not show a dose-related increase in incidence of AEs. The overall subject incidences of AEs, SAEs, fatal AEs and AEs leading to withdrawal

of investigational product or study were similar between the romosozumab and alendronate groups in the pivotal Phase III active controlled study. The subject incidences of AEs and SAEs were generally balanced between the romosozumab and teriparatide groups in the Phase IIIb Study 20080289 that enrolled subjects previously treated with bisphosphonates. Injection site reactions were observed more frequently with romosozumab compared with teriparatide (7.8% and 2.8%, respectively), which led to study drug discontinuation for 1 subject in the romosozumab group.

Most AEs related to injection site reactions were reported as mild in severity and none was considered serious. The overall safety profile in men with osteoporosis (based on subject incidences of AEs, SAEs, fatal AEs and AEs leading to withdrawal of investigational product or study) was similar to that observed for women in the pivotal Phase III placebo controlled fracture Study 20070337. The number of cases of osteonecrosis of the jaw and atypical femoral fracture observed in the clinical trials was low and causality was not established.

Romosozumab was associated with an increased risk of cardiovascular SAEs although the sponsor did try to address this in an integrated cardiovascular safety report. Based on nonclinical, clinical and epidemiologic data, a causal relationship between romosozumab and positively-adjudicated cardiovascular SAEs was not established, although a causal relationship between romosozumab and increased risk of cardiovascular SAEs could not be excluded. The sponsor plans to address this important potential risk by ongoing monitoring and pharmacovigilance activities.

In Phase II and III clinical studies of osteoporosis in postmenopausal women, the incidence of developing anti romosozumab binding and neutralising antibodies was 18.6% (1162 of 6244) and 0.9% (58 of 6244), respectively across all doses studied. Similar results were observed in the study in men with osteoporosis. The pharmacokinetic exposure, safety (for example, hypersensitivity, injection site reactions, or autoimmune disorder) and efficacy (changes in BMD) profiles of the subjects who tested positive for binding anti romosozumab antibodies were found to be consistent with the profiles of anti romosozumab antibody-negative subjects.

Efficacy is based on seven adequately powered, placebo controlled, and active comparator controlled studies (including standard of care treatment) in a representative population. The data across the Phase II and III studies in the clinical development program were consistent and can be generalised to the target patient population of postmenopausal women with osteoporosis and men at increased risk of fracture despite variations across studies in specific inclusion and exclusion criteria (for example, age, fracture history, BMD T-scores). However, romosozumab was only evaluated in subjects with primary osteoporosis which has not been specified in the proposed indication.

Only 6 to 9% of patients had prior history of treatment with other treatments for osteoporosis. This is despite fact that almost all (99%) of subjects in the alendronate controlled study had history of osteoporotic fracture. In Phase IIIb Study 20080289 involving 498 postmenopausal women transitioning from bisphosphonate therapy, treatment with romosozumab resulted in larger gains of 3.2% than treatment with teriparatide in total hip BMD by DXA through Month 12 and statistically significant gains in the other secondary endpoints of femoral neck and lumbar spine BMD by DXA and total hip BMD by quantitative computed tomography, compared to teriparatide at Months 6 and 12. However, effect of romosozumab on risk of fractures was not evaluated in patients transitioning from bisphosphonate therapy. Overall, evidence for efficacy/ safety in patients who have received prior treatments for osteoporosis was not adequate. Based on data provided, romosozumab could be used as first line of treatment with follow-up treatment required with denosumab or alendronate in order to sustain the fracture reduction benefits observed following 12 months of romosozumab treatment.

Furthermore, efficacy/safety of romosozumab was not evaluated in combination with other osteoporosis treatments.

Efficacy was only demonstrated for 12 months of romosozumab treatment and effect of retreatment with romosozumab was not adequately evaluated (except in dose ranging Phase II Study 220060236). Follow-on treatment with denosumab (60 mg SC every 6 months) or alendronate (70 mg weekly) was required to demonstrate efficacy of romosozumab. There is no evidence for efficacy of romosozumab without other follow-on treatment. Rebound or withdrawal effects without any other osteoporosis treatment following end of the 12 months of romosozumab treatment was not evaluated.

Overall, the benefit risk profile for romosozumab in treatment of women with postmenopausal osteoporosis at increased risk of fractures was not favourable. As approval of romosozumab for proposed indication in women with postmenopausal osteoporosis has not yet been approved, the fracture benefits observed in women cannot be extended to men based on the comparable BMD efficacy that was observed in the bridging study in only 292 men with osteoporosis at increased risk of fracture. Hence, the benefit risk profile for romosozumab in treatment of men with osteoporosis at increased risk of fractures was also not favourable.

First round recommendation regarding authorisation

It is recommended that the application for marketing authorisation of romosozumab be rejected for the following proposed indications:

> *Evenity is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Evenity reduces the risk of vertebral, clinical and non-vertebral fractures.*
>
> *Evenity is indicated for the treatment of osteoporosis in men at increased risk of fracture. Evenity increases bone mass*.

The main reasons for rejection at this stage are:

- lack of adequate evidence for reduction of 'non-vertebral fractures' which is included in the proposed wording of the indications.
- efficacy/safety was only evaluated in subjects with primary osteoporosis although this is not clearly stated in the wording of the proposed indication.
- place of romosozumab in treatment for the proposed indication not clearly stated-evidence was only provided for use as initial treatment in patients with not much prior exposure to other treatments for osteoporosis. Efficacy/safety of romosozumab was not evaluated in combination with other osteoporosis treatments.
- approval for the indication in women with postmenopausal osteoporosis at increased risk of fractures has not yet been granted. Hence, evidence from the bridging study in 292 men based on comparable effects on BMD is not adequate for the proposed indication in men with osteoporosis in men at increased risk of fracture.

Clinical questions and second round evaluation

Efficacy

Question 1

Supplementation with calcium and/or vitamin D was consistent in all patient groups and clearly documented in all pivotal Phase III studies. However, dietary and relevant

life style factors were not summarised. Could the sponsors clarify if this information was collected and evaluated as recommended in the CHMP recommended guidelines for evaluation of medicinal products in the treatment of primary osteoporosis?

Sponsor's response

Data regarding dietary and relevant lifestyle factors were not systematically collected or evaluated as part of the study protocol. However, to determine the level of calcium and vitamin D supplementation as part of standard of care for an individual subject, principal investigators at each site were required to take relevant dietary and lifestyle factors into account.

Notably, calcium and vitamin D supplementation has been a precedent for clinical trials conducted in the osteoporosis field;[52] as part of the standard of care for these patients. Trial specific requirements varied based on contemporary recommendations at the time for calcium and vitamin D supplementation. As part of protocol required therapy in the romosozumab clinical trial program, calcium 500 to 1000 mg daily and vitamin D 600 to 800 IU daily at a minimum were required as well as a vitamin D loading dose if a subject were deemed vitamin D deficient as part of the standard of care in the management of patients with osteoporosis. To account for individual differences in dietary intake and lifestyle factors, these dose requirements for calcium and vitamin D were aligned with the daily recommended requirements by several clinical osteoporosis organizations including Osteoporosis Australia, which recommend a daily calcium intake in the range of 1000 to 1300 mg per day (requiring supplementation upwards of 500 mg daily, aligned with the protocol specified requirements) and vitamin D intake of 600 to 800 IU per day.

Evaluation of response

The sponsor's response is satisfactory. Data regarding dietary and relevant lifestyle factors were not systematically collected or evaluated as part of the study protocols. However, the dose requirements for calcium and vitamin D were aligned with the daily recommended requirements accounting for individual differences in dietary and lifestyle factors.

Question 2

In pivotal Phase III Study 20110142, it is important to note that the difference for non-vertebral fractures was just statistically significant (as upper limit 95% CI was 0.99). Furthermore, romosozumab/ alendronate failed to show statistically significant reduction in non-vertebral fractures at the end of the double blind treatment period at month 12 (p = 0.057) or at month 24 (p = 0.074). Hence, results for reduction in non-vertebral fracture were not robust, could the sponsors comment on this?

Sponsor's response

Study 20110142, the active comparator fracture trial, was designed and powered to demonstrate a reduction in new vertebral, clinical, and non-vertebral fractures at the time of the primary analysis, consistent with international regulatory advice, after all subjects had the opportunity to complete the Month 24 visit and at least 330 clinical fractures had been confirmed. While the study was not designed with adequate statistical power to detect differences in non-vertebral fracture between treatment groups at earlier time points, anti-fracture efficacy was pre-specified as a secondary endpoint at Months 12 and 24.

Separation in the Kaplan-Meier curves between the two treatment groups for non-vertebral fracture occurred as early as Month 6 with continued divergence (with near constant slopes) over the follow-up period, suggesting the effect of 12 months of

[52] Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis (FREEDOM Trial). N Engl J Med. 2009;361(8):756-765.

romosozumab treatment in reducing the incidence of non-vertebral fractures is maintained after subjects transitioned to alendronate. Importantly, a trend in risk reduction in the subject incidence of non-vertebral fractures favouring romosozumab was observed through Month 12 (romosozumab: 3.4%, alendronate: 4.6%; relative risk reduction 26%; p = 0.057) and continued through Month 24 (romosozumab/alendronate: 6.3%, alendronate/alendronate: 7.8%; relative risk reduction 19%; p = 0.074). This risk reduction in favour of romosozumab reached statistical significance at the time of the primary analysis (conducted after a median follow-up of 33 months), the time at which the study was powered to demonstrate statistically significant efficacy for this endpoint. Specifically, based on 395 subjects with non-vertebral fractures, the incidence of non-vertebral fractures was significantly lower in the romosozumab/alendronate group compared with alendronate alone (romosozumab/alendronate: 8.7%, alendronate/alendronate: 10.6%; relative risk reduction 19%; p = 0.040, 2-sided adjusted p-value).

In historical clinical trials for other agents used for the treatment of osteoporosis including alendronate, extended therapy versus placebo was required to demonstrate clinically relevant and statistically significant reductions in the risk of non-vertebral fracture. Study 20110142 demonstrated not only a statistically significant reduction in the risk of non-vertebral fractures at the time of the primary analysis (median follow-up of 33 months) for romosozumab versus alendronate, an active comparator, but also a trend in romosozumab reducing the risk of non-vertebral fractures compared with alendronate at pre specified earlier time points of Months 12 and 24. Thus, these findings are robust and of clinical importance to prescribing physicians, as they consider romosozumab within the current treatment armamentarium to make individualized treatment decisions for patients.

Evaluation of response

Romosozumab failed to show statistically significant reduction in incidence of secondary endpoint of non-vertebral fracture in the pivotal placebo controlled Study 20070337. As mentioned by the sponsors, extended therapy versus placebo was required to demonstrate clinically relevant and statistically significant reductions in the risk of non-vertebral fracture in clinical trials for other agents used for the treatment of osteoporosis including alendronate. However, the proposed romosozumab treatment is for 12 months only and requires follow-up treatment with other treatments for osteoporosis (alendronate and denosumab) to demonstrate its anti-fracture efficacy. This limits interpretation of efficacy of romosozumab for reducing risk of non-vertebral fractures.

A significant reduction in the risk of non-vertebral fractures at the time of the primary analysis (median follow-up of 33 months) was observed for romosozumab versus alendronate (romosozumab/alendronate: 8.7%, alendronate/alendronate: 10.6%; relative risk reduction 19%; p = 0.040, 2-sided adjusted p-value) in the other pivotal alendronate controlled Study 20110142.

However, as results were not consistent across the two pivotal Phase III studies, the evaluators recommend that the reduction in non-vertebral fractures in the alendronate controlled study should only be included in the 'Clinical trials' section of the proposed PI and not in the wording of the proposed indication.

Question 3

In the Phase IIIb Study 20080289, the incidence of important protocol deviations was higher in the teriparatide group (17.4%) compared with romosozumab (5.0%). Majority of deviations in the teriparatide group included wrong treatment or incorrect dose. Could the sponsors provide details regarding these deviations and its impact on interpretation of results?

Sponsor's response

The incidence of important protocol deviations was higher in the teriparatide group compared to the romosozumab group with the majority due to dosing deviations; there were 26 (11.9%) important dosing deviations in the teriparatide arm (defined as < 75% or > 125% adherence) compared to 19 (8.7%) dosing deviations in the romosozumab arm (defined as subjects having missed more than 3 doses of romosozumab over the life of the study). No subjects received more than 12 doses of romosozumab.

Table 21: Important protocol deviations other than eligibility criteria deviations (all randomised subjects) (Study 20080289 Month 12 final analysis)

	Teriparatide 20 µg SC QD (N = 218) n (%)	Romosozumab 210 mg SC QM (N = 218) n (%)	All (N = 436) n (%)
Number of subjects with at least one important protocol deviation other than eligibility criteria deviations	38 (17.4)	11 (5.0)	49 (11.2)
Missing data (other than TA or TC)	7 (3.2)	11 (5.0)	18 (4.1)
Missing data required for primary endpoint analysis	7 (3.2)	11 (5.0)	18 (4.1)
Received the wrong treatment or incorrect dose	29 (13.3)	0 (0.0)	29 (6.7)
Less than 75% or more than 125% of planned TPTD doses	26 (11.9)	0 (0.0)	26 (6.0)
Temperature excursion for TPTD	3 (1.4)	0 (0.0)	3 (0.7)
Received an excluded concomitant treatment	3 (1.4)	0 (0.0)	3 (0.7)
IV Bisphosphonates use as specified	1 (0.5)	0 (0.0)	1 (0.2)
Oral Bisphophonates use as specified	1 (0.5)	0 (0.0)	1 (0.2)
SERMs use as specified	1 (0.5)	0 (0.0)	1 (0.2)

IV = intravenous; N = Number of subjects randomized; QD = each day; QM = each month; SC = subcutaneously; SERM = selective estrogen receptor modulator; TA = test article; TC = treatment compliance; TPTD = teriparatide
Subjects can have more than one deviation. Therefore, incidences for individual deviations may not sum to the total for a given category.

The primary analysis of efficacy followed the intent to treat principle and included all randomised patients regardless of protocol adherence or dosing deviations in either the romosozumab or teriparatide arm. The impact of the protocol deviations, including dosing deviations, on the interpretation of the results was explored in a sensitivity analysis of the primary efficacy endpoint was conducted using the per protocol analysis set, excluding subjects with dosing deviations or other important protocol deviations. The results for the primary efficacy endpoint of percent change from baseline in BMD at the total hip based on both the primary efficacy analysis set and per protocol analysis set were similar (Table 22), thus the per protocol sensitivity analysis demonstrates no impact on the interpretation of the efficacy results from dosing and other important protocol deviations.

Table 22: Total hip BMD by DXA percent change from Baseline through Month 12 (Repeated Measures Model) (Study 20080289 Month 12 Final Analysis)

	Teriparatide 20 µg SC QD LS mean (95% CI)	Romosozumab 210 mg SC QM LS mean (95% CI)	Difference from Teriparatide	p-value
Primary Efficacy Analysis Set, Observed Data	-0.6 (-1.0, -0.2)	2.6 (2.2, 3.0)	3.2 (2.7, 3.8)	<0.0001
Per-Protocol Set	-0.8 (-1.2, -0.3)	2.5 (2.1, 2.9)	3.3 (2.7, 3.9)[b]	<0.0001

Evaluation of response

The sponsor's response is satisfactory.

Question 4

In the Phase III male osteoporosis Study 20110174, the number of subjects excluded from PP analysis was greater in the romosozumab compared with the placebo group (11.7% versus 3.7%). Could the sponsors clarify if this had any effect on interpretation of the efficacy results?

Sponsor's response

The number of subjects who were excluded from the per protocol analysis set was greater in the romosozumab group compared to the placebo group (11.7% versus 3.7%). The majority of subjects who were excluded from the *per protocol* analysis was due to not having received ≥ 9 doses of investigational product (10.4% romosozumab versus 3.7% placebo) (Table 23).

Table 23: Reasons for exclusion from the per protocol analysis set (All randomised subjects) (Study 20110174 Month 12 primary analysis)

	Placebo (N = 82) n (%)	Romosozumab 210 mg SC QM (N = 163) n (%)	All (N = 245) n (%)
Number of subjects completely excluded from the per protocol analysis set[a]	3 (3.7)	19 (11.7)	22 (9.0)
Number of subjects partially excluded from the per protocol analysis set[b]	0 (0.0)	1 (0.6)	1 (0.4)
Reasons for complete exclusion			
Subjects enrolled but not meeting the following inclusion criteria	0 (0.0)	1 (0.6)	1 (0.4)
Increased risk of fracture at the lumbar spine, total hip, or femoral neck, as assessed at the time of screening, based on DXA scans defined as: BMD T-score <= -2.50 or BMD T-score <= -1.50 fracture	0 (0.0)	1 (0.6)	1 (0.4)
Subjects enrolled but meeting the following exclusion criteria	0 (0.0)	2 (1.2)	2 (0.8)
History of metabolic or bone disease that may interfere with the intp results, such as sclerosteosis, Paget disease, rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, osteopetrosis, etc.	0 (0.0)	1 (0.6)	1 (0.4)
Vitamin D insufficiency (defined as 25 (OH) vitamin D levels < 20 ng/ml as determined by the central laboratory). Vitamin D repletion will be permitted and subjects may be rescreened	0 (0.0)	1 (0.6)	1 (0.4)
Did not receive ≥ 9 complete doses of investigational product	3 (3.7)	17 (10.4)	20 (8.2)
Reason for partial exclusion			
Received the investigational product not matching the subject's randomized treatment group	0 (0.0)	0 (0.0)	0 (0.0)
Received a proscribed therapy on study	0 (0.0)	1 (0.6)	1 (0.4)

N = Number of subjects randomized, QM = each month; SC = subcutaneously
Percentages based on number of subjects randomized.
Subjects can have more than one reason for exclusion. Therefore, incidences for individual deviations may not sum to the total for a given category.
[a] Complete exclusion is defined as excluding the subject from the analysis.
[b] Partial exclusion is defined as excluding subject data after the first event leading to exclusion.

The results from the intent to treat and per protocol analysis sets demonstrated a consistent treatment effect of romosozumab over placebo for the primary BMD endpoint (lumbar spine BMD by DXA percent change from baseline at Month 12 (Table 24).

Table 24: Lumbar spine BMD by DXA percent change from Baseline at Month 12 (ANCOVA): LOCF (Study 20110174 Month 12 primary analysis)

	Placebo LS Mean (95% CI)	Romosozumab 210 mg SC QM LS Mean (95% CI)	Difference from Placebo[a] LS Mean (95% CI)	p-value	Source
Lumbar spine bone mineral density percent change from baseline at month 12					
Primary Efficacy Analysis Set	1.2 (0.2, 2.2)	12.1 (11.2, 13.0)	10.9 (9.6, 12.2)	<0.0001	Table 14-4.2.1
Per-Protocol Set	1.2 (0.2, 2.2)	12.6 (11.7, 13.5)	11.4 (10.1, 12.7)	<0.0001	Table 14-4.2.3

ANCOVA = analysis of covariance; BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; LOCF = last observation carried forward; LS = least squares; QM = every month; SC = subcutaneously
[a] Based on ANCOVA model adjusting for treatment, baseline DXA BMD value, machine type, machine type-by-baseline DXA BMD value, baseline testosterone level, geographic region (stratification factor), and using a variance structure allowing for heterogeneity between treatment groups.
Source: *Clinical Study Report 20110174*

Therefore, the exclusion of more subjects from the romosozumab group compared to the placebo group did not change the interpretation of the efficacy results, which was that romosozumab significantly increased BMD compared to placebo.

Evaluation of response

The sponsor's response is satisfactory.

Safety

Question 5

Definition of AEs to detect 'hyperostosis' were not clearly specified in the submission. Could the sponsors provide this information?

Sponsor's response

The sponsor agrees that the definition of adverse events to detect hyperostosis was not clearly defined in the submission. Since the medical concept of hyperostosis is not part of the Standard MedDRA (SMQ) in MedDRA, Amgen used the Amgen MedDRA (AMQ) of hyperostosis as defined by the following MedDRA (Version 19.1) preferred terms: acquired foramen magnum stenosis; acral overgrowth; bone formation increased; cervical spinal stenosis; enostosis; exostosis; exostosis of external ear canal; exostosis of jaw; extra-skeletal ossification; foramen magnum stenosis; high turnover osteopathy; intracranial pressure increased; lumbar spinal stenosis; macrogenia; melorheostosis; periostosis; senile ankylosing vertebral hyperostosis; spinal column stenosis; vertebral foraminal stenosis; vertebral osteophyte.

Evaluation of response

The sponsor's response is satisfactory.

Question 6

Was the incidence of all fractures including fragility fractures monitored as a safety endpoint in the following studies (where it was not the primary efficacy endpoint): Phase III b Study 20080289: Phase III Study 20110174: Phase IIb Studies 20060326 and 20101291. Could the sponsors please provide this data if available?

Sponsor's response

The treatment emergent fracture adverse events were collected as part of adverse event reporting as these studies were not fracture endpoint studies. The subject incidences of adverse events of all fracture types for Studies 20080289, 20110174, 20101291 and 20060326 were provided.

Evaluation of response

In the Phase IIIb teriparatide controlled study, the incidence of treatment emergent fracture AEs was similar in the teriparatide (8 of 214, 3.7%) and the romosozumab (8 of 218, 3.7%) groups. In the Phase III Study 20110174, the incidence of treatment emergent fracture AEs was numerically lower in the romosozumab (3 of 163, 1.8%) compared to the placebo (3 of 81, 3.7%) group at the Month 15 final analysis. The Phase II Study 20101291 showed similar incidence of treatment emergent fracture AEs across the placebo, romosozumab 140 mg SC monthly and 210 mg SC monthly and 70 mg SC monthly groups (3.2%, 3.2%, 3.2% and 1.6%, respectively). In Phase II Study 20060326, slight numerical imbalances were observed in the subject incidence of treatment emergent fracture AEs between the placebo (0%), alendronate (5.9%), teriparatide (3.7%) and various romosozumab dose regimen groups (6%, 3.8%, 2%, 3.8% and 3.9% in the 70 mg monthly, 140 mg three monthly, 140 mg monthly, 210 mg three monthly and 210 mg monthly

groups, respectively). No trends were observed with respect to types of fractures with upper limb fractures being most common across all treatment groups in all above studies.

Second round benefit-risk assessment

After consideration of the responses to clinical questions, the benefits of Evenity in the proposed usage are unchanged from those identified above.

After consideration of the responses to clinical questions, the risks of Evenity in the proposed usage are as shown in Table 25, below.

Table 25: Second round assessment of risks

Risks	Strengths and Uncertainties
Evidence for reduction in risk of non-vertebral fractures was not consistent in both pivotal Phase III studies in women with postmenopausal osteoporosis. In the placebo controlled Study 20070337, romosozumab treatment for 12 months failed to show statistically significant reduction in the incidence of non-vertebral fracture at Month 12 (romosozumab versus placebo: 1.6% versus 2.1%, odds ratio = 0.75, adjusted p = 0.096) or 24 (romosozumab/ denosumab versus placebo/ denosumab: 2.7% versus 3.6%, odds ratio = 0.75, adjusted p = 0.057).	In the alendronate controlled Study 20110142, romosozumab 210 mg monthly for 12 months followed by alendronate 70 mg weekly through the primary analysis significantly reduced the risk of non-vertebral fractures by 19% (romosozumab/alendronate: 178 of 2046, 8.7% versus alendronate/ alendronate: 217 of 2047, 10.6%; hazard ratio = 0.81, 95% CI: 0.66 to 0.99; 2-sided adjusted p = 0.040).
Increased risk of hypersensitivity reactions	Clinically significant hypersensitivity reactions, including dermatitis, rash, angioedema, erythema multiforme and urticaria, occurred in the romosozumab group.
Increased risk of hypocalcaemia. Inhibition of sclerostin by romosozumab leads to rapid bone mass accrual at initiation of treatment and an increased demand for bone-building substrates such as calcium.	Mild and transitory decreases in albumin-corrected calcium and a compensatory increase in intact parathyroid hormone were observed after initiation of romosozumab.
During the 12 month, double blind, alendronate controlled portion of Study 20110142 (n = 4054), there was a numerical imbalance observed between the romosozumab and alendronate groups in the incidence of positively adjudicated cardiovascular SAEs (2.5% and 1.9%, respectively), mainly cardiac	This imbalance was not observed in the placebo controlled fracture Study (20070337, n = 7157), where the subject incidence of positively adjudicated serious cardiovascular adverse events was 1.3% in the romosozumab and placebo groups. In both trials, most participants had

Risks	Strengths and Uncertainties
ischemic events (0.8% versus 0.3%) and cerebrovascular events (0.8% versus 0.3%).	common risk factors for cardiovascular disease, and within each trial, cardiovascular risk factors were balanced between treatment arms. A comprehensive pharmacovigilance program and additional pharmacovigilance activities will be used to monitor this potential risk in the post marketing setting.
Osteonecrosis of the jaw and atypical femoral fracture are considered important potential risks for romosozumab and have been reported in patients receiving romosozumab.	The number of osteonecrosis of the jaw and atypical femoral fracture cases observed in the clinical trials was low and causality has not been established. Appropriate warnings/ precautions included in the proposed PI.
Efficacy of romosozumab was only evaluated in postmenopausal women and men (aged over 50 years) with primary osteoporosis.	It was not evaluated in patients with glucocorticoid-induced osteoporosis (as patients on > 7.5 mg equivalent of prednisone were excluded from the studies) or other secondary osteoporosis conditions. This has been addressed by specifying 'primary osteoporosis' in wording of proposed indications.
Rebound or withdrawal effects without any other osteoporosis treatment following end of the 12 months of romosozumab treatment was not evaluated.	

It is recommended that marketing approval for Evenity be granted subject to incorporation of the following modified wording for the proposed indication and other minor changes suggested below:

> *Evenity is indicated for the treatment of primary osteoporosis in postmenopausal women and in men at increased risk of fracture.*

The approval for the proposed indication in men with primary osteoporosis at increased risk of fracture is subject to final TGA approval of Evenity for proposed indication in postmenopausal women with primary osteoporosis at increased risk of fracture.

VI. Pharmacovigilance findings

Risk management plan[53]

The sponsor has submitted EU-RMP version 0.1 (dated 10 November 2017; data lock point (DLP) 30 June 2017) and Australian Specific Annex (ASA) version 1.0 (dated 22 November 2017) in support of this application. An updated ASA version 2.0 (dated 26 June 2018) has been submitted with the sponsor's response to questions.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 26.

Table 26: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity	✓	–	✓	–
	Immunogenicity (development of antibodies to romosozumab)	✓	–	✓	–
	Hypocalcaemia	✓	–	✓	–
Important potential risks	Serious cardiovascular adverse events	✓	✓[1]	✓	–
	Osteonecrosis of the jaw	✓	–	✓	–
	Atypical femoral fracture	✓	–	✓	–
	Foetal risk	✓	–	✓	–
Missing information	Pregnant or breastfeeding women	✓	–	✓	–
	Patients with hepatic impairment	✓	–	✓	–

[1]Post-authorisaation Safety Study in the EU

The only additional pharmacovigilance activity is the planned post authorisation safety study conducted in the EU. Although considered applicable to Australian context, the

[53] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and upharmacodynamicsating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

implementation of the activity depends on dependent on the market authorisation in the EU. The sponsor has indicated that a similar study is planned in the US, which could also provide further information on the risk of serious cardiovascular adverse events.

Routine risk minimisation is considered sufficient to manage the safety concerns for this product as they are consistent with those for similar medicines.

New and outstanding recommendations from second round evaluation

There are two outstanding issues from the first round evaluation (recommendation 1), as described below:

Recommendation 1.

The non-clinical evaluation report noted the following discrepancies in the RMP:

> 'Despite their low incidence, foetal skeletal malformations (including syndactyly and polydactyly) observed in rats with maternal dosing at 300 mg/kg/week are seen to be related to treatment based on a weight of evidence approach, with biological plausibility downplayed by the sponsor.
>
> Minor discrepancies in animal:human exposure ratios are noted. Exposure ratios calculated in this report are based on a serum AUC value of 509 µg.d/mL (= 12216 µg.h/mL) as given in the population pharmacokinetics report provided with the submission (Study 119384A), while those cited by the sponsor appear to be based on an earlier value of 537 µg.d/mL (= 12888 µg.h/mL).'

The discrepancies refer to content in the EU-RMP. The sponsor should rectify the discrepancies in the EU-RMP document in the next RMP update. It is noted that the fetal malformations are of limited relevance to the indicated population.

Post second round RMP update

As requested by the TGA Delegate, the sponsor has submitted another updated EU-RMP version 0.2; dated 13 July 2018, DLP 22 May 2018 with ASA version 4.0; dated 13 May 2019. These RMP documents have been reviewed with the consideration of recommendations from the Advisory Committee on Medicines (ACM) and TGA Delegate. No further recommendations to update the RMP documents are made at this stage.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- The Evenity EU-Risk Management Plan (RMP) version 0.2 (dated 13 July 2018; DLP 22 May 2018), with Australian Specific Annex version 4.0 (dated 13 May 2019), included with submission PM-2017-04339-1-5 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  The following wording is recommended for the PSUR requirement: (this does not include the TGA delegate's request for the submission of annual reports on overseas PASS to avoid repetition):

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Evenity is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

- Evenity (romosozumab) is to be included in the Black Triangle Scheme. The PI and CMI for Evenity must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Background

Romosozumab is a high-affinity humanised immunoglobulin G2 (IgG2) monoclonal antibody directed against sclerostin that inhibits its interaction with LRP-5/LRP-6 and activates Wingless-related integration site signalling in the osteoblast lineage. Sclerostin-mediated decreases in Wingless-related integration site signalling in osteoblast lineage cells result in inhibition of osteoblast mediated bone formation and stimulation of osteoclast mediated bone resorption. By blocking sclerostin, romosozumab increases bone formation due to the activation of bone lining cells, increased bone matrix production by osteoblasts, and recruitment of osteo-progenitor cells. Additionally, romosozumab results in changes in expression of osteoclast mediators, thereby decreasing bone resorption. Together, the dual effect of increasing bone formation and decreasing bone resorption results in improvements in bone mass, structure and strength.

Sclerostin was identified as a target of interest by genetic analysis of two rare bone disorders (sclerosteosis and Van Buchem disease) that are associated with thick bones, increased density and resistance to fracture. Homozygous patients also experience facial palsy, hearing impairment and syndactyly.

Romosozumab is a large protein, theoretical mass 145,622 daltons.

Table 27 (shown below) describes the currently available options for the treatment of osteoporosis.

The current treatment guidelines for the management of post-menopausal osteoporosis by the RACGP and osteoporosis Australia recommend bisphosphonates or denosumab as first line therapy. Denosumab has advantages over bisphosphonates in terms of greater

efficacy, and better compliance. Teriparatide is used when patients sustain fractures despite treatment with other anti-resorptive treatments. In men, alendronate and denosumab are considered to be a treatment option for osteoporosis.

Table 27: Currently approved options for the treatment of osteoporosis

Drug	Indications	Physiology	Notes
Risedronate		Decrease bone resorption	Needs to take with water and not lie down Gastrointestinal side effects Uveitis Osteonecrosis of the jaw
Alendronate	Fosamax is indicated for the treatment of: • Osteoporosis, including glucocorticoid-induced osteoporosis • Paget's disease of bone • Fosamax is also indicated for the prevention of: • Osteoporosis in postmenopausal women with low bone mass (at least 1 standard deviation below the mean for young adults) • Glucocorticoid-induced osteoporosis in those patients on long term corticosteroid therapy		
Zoledronic acid	• Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures. • Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fractures. • To increase BMD in men with osteoporosis. • To increase BMD in patients with osteoporosis associated with long term glucocorticoid use. • To prevent glucocorticoid-induced BMD loss. • Treatment of Paget's disease of bone.		Only if Vitamin D > 50, calcium normal, eGFR > 35 mL/min Renal impairment Osteonecrosis of the jaw
Denosumab	• Treatment of osteoporosis in postmenopausal women. Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures. • Treatment to increase bone mass	Decrease bone resorption Increase bone formation can be used renal	Osteonecrosis of the jaw Musculoskeletal pain Hypercholesterol-

Drug	Indications	Physiology	Notes
	in men with osteopenia receiving androgen deprivation therapy for non-metastatic prostate cancer • Treatment to increase bone mass in men with osteoporosis at increased risk of fracture. • Treatment to increase bone mass in women and men at increased risk of fracture due to long-term systemic glucocorticoid therapy.	impairment	emia Eczema
Teriparatide	• Forteo is indicated for the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures. • Forteo is indicated for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture.	synthetic form of parathyroid hormone increases bone formation	caused bone sarcoma in rats, lifelong therapy limited to 2 years contra-indicated < 25 years, Paget's disease, previous radiotherapy, hypercalcaemia, malignancy, kidney disease, malignancy
Strontium	Discontinued 2017		
Raloxifene	Evista is indicated for the prevention and treatment of osteoporosis in post-menopausal women.	Oestrogen receptor modulator	Reduces vertebral fracture risk in women > 3 years post menopause. Avoid in women at risk of venous thrombo-embolism -hot flushes

International registration status

There are concurrent applications in the USA, Europe (EU), Canada and Japan.

The USA submitted a complete response letter in July asking for data from a clinical study (Study 20110174) that had been submitted to Japan including men with osteoporosis that showed an imbalance in cardiovascular events. A resubmission of the data is planned for Q4 2018.[54]

The drug development program was informed by regulatory interactions between the EU, US FDA, Health Canada and Japanese PMDA.

[54] Clarification: The submission with the FDA was approved 9 April 2019

Quality

There were no objections of quality grounds for the approval of romosozumab.

Nonclinical

There are no nonclinical objections to the registration of Evenity for the proposed indication.

Sclerostin is predominantly secreted by mature osteocytes. It is also expressed in various non-mineralised human tissues, including heart, aorta, liver, lung and kidney.

In vitro studies established that romosozumab binds to human sclerostin with high affinity (K_D, 11 pM), inhibits the binding of sclerostin to LRP5 and LRP6 receptors through which it signals, and antagonises the action of sclerostin to reduce mineralisation in a mouse osteoblast cell line. *In vivo*, romosozumab increased bone mineral content, BMD, bone mass, bone thickness and bone strength in rat and monkey models of post-menopausal bone loss. Positive effects on bone were also observed in a variety of other models of bone loss (including androgen ablation), and in repeat-dose toxicity studies conducted in normal male and female rats and monkeys.

Romosozumab showed comparable affinity for the animal and human forms of sclerostin.

High specificity for binding was evident in immunohistochemistry assays examining cross-reactivity. Safety pharmacology studies (covering the central nervous, cardiovascular and respiratory systems) identified no relevant concerns.

Pharmacokinetic studies with romosozumab and a mouse surrogate antibody (of comparable potency) revealed a typical profile for an IgG antibody; non-linear pharmacokinetics (consistent with target-specific binding and clearance), slow absorption after subcutaneous administration, a long serum half-life, and a low volume of distribution (consistent with limited extravascular distribution).

Repeat dose toxicity studies of up to 6 months duration were conducted in rats and cynomolgus monkeys. These species are seen to be appropriate models for the investigation of romosozumab toxicity on pharmacodynamic and pharmacokinetic grounds, and with immunogenicity (to the humanised protein) in the species not so prevalent as to affect study validity. Weekly SC administration of romosozumab at doses producing very high multiples of the clinical systemic exposure was well tolerated, with no target organs for toxicity identified. Histological changes were observed in bone, liver and spleen, but represent pharmacological effects (hyperostosis in bone; and extramedullary haematopoiesis in liver and spleen, occurring secondary to a reduction in bone marrow space).

Genotoxicity studies were not conducted, in line with ICH guideline S6 (R1).[5] Romosozumab was not carcinogenic in rats.

Weak teratogenicity was evident with romosozumab in rats, with skeletal malformations (including syndactyly and polydactyly) observed at low incidence and at a high animal: human exposure margin (59 fold). This finding is consistent with a role for sclerostin in digit formation recognised in humans and animals. No adverse effects on male and female fertility, or on postnatal development, were observed. Pregnancy Category B3;[14] as the sponsor proposes, was considered appropriate.

Clinical

Clinical evaluator's recommendation

At the end of the second round evaluation, the clinical evaluator recommended approval of the following revised indication:

> *Evenity is indicated for the treatment of primary osteoporosis in postmenopausal women and in men at increased risk of fracture.*

The evaluator did not agree with inclusion of the following statement in the *indication:*

> *Evenity reduces the risk of vertebral, clinical and non-vertebral fractures*.

as the reduction in non-vertebral fractures was not statistically significant in a number of studies as either a primary or secondary outcome.

Pharmacology

Pharmacokinetics

- Given as a subcutaneous injection via syringe or pen twice a month
- time to maximum concentration 3 to 5 days
- relative bioavailability 50 to 70%
- lower bioavailability with higher strength solutions. Clearance decreases with increasing dose. Biphasic elimination. The way in which romosozumab is metabolised is not entirely clear. Renal clearance is unlikely due to the large size.
- Population pharmacokinetic studies were performed to explain the pharmacokinetic characteristics of romosozumab. Results from the model suggested that following SC administration of romosozumab 210 mg, bioavailability was high (81%) and absorption was complete in around 14 days. The rate of absorption was similar across the range of doses evaluated. Romosozumab was eliminated through a slow nonspecific elimination pathway mediated by the hepatic reticuloendothelial system (that is, linear clearance (CL)), and a rapid saturable elimination pathway (that is, target-mediated nonlinear clearance) mediated by degradation of romosozumab and 12.2 mL/h at high concentrations of romosozumab). Body weight and eGFR had a small impact on pharmacokinetic characteristics but did not alter the changes in BMD.

Pharmacodynamics

- Study 20090153 evaluated the effects of romosozumab on bone quality of the ultra-distal radius and distal radius with in patients with low BMD using quantitative computed tomography. Patients were randomised 1:1 to receive romosozumab or placebo. At Day 57, decreases in the mean polar of inertia of 1% from Baseline was observed in both groups, however by Day 85 there was an increase of 1.5% above baseline in the romosozumab group. There was also an increase in total BMD, total bone area, trabecular bone area, trabecular bone mineral content, and trabecular BMD.
- Study 20110253 examined the impact of 140 mg or 210 mg of romosozumab given monthly to postmenopausal women with osteoporosis (BMD -2 to -4) who had received alendronate. Romosozumab increased BMD at the lumbar spine, femoral neck and hip for both doses.
- Studies 20060220, 20090378 and 20060221 evaluated the impact of romosozumab on markers of bone formation. There was a dose dependent increase in markers of bone formation; P1NP, osteocalcin and bone specific alkaline phosphatase. The maximum

increase in P1NP occurred in the first 2 months of dosing, and returned to baseline 4 to 8 weeks after the final dose.

- Studies 20060220, 20090378 and 20060221 also evaluated the impact of romosozumab on markers of bone resorption. There was a decrease in bone resorption markers sCTX which reached a nadir within 1 to 2 months and returned to Baseline 3 to 6 weeks post treatment.

Pharmacokinetic/pharmacodynamics modelling and simulations using the dose-BMD and concentration; bone turnover marker; BMD (lumbar spine) models demonstrated that a romosozumab dose of 210 mg SC monthly provided greater BMD gains at Month 12 compared to the other dosing regimens tested.

Efficacy

Post-menopausal women

Studies providing efficacy data

- Two pivotal Phase III efficacy studies:
  - Study 20070337 (FRAME trial): a multicentre, international, randomised, double blind, placebo controlled, parallel group study to assess the efficacy and safety of romosozumab treatment in postmenopausal women with osteoporosis.
  - Study 20110142 (ARCH trial): a multicentre, international, randomised, double blind, alendronate controlled study to determine the efficacy and safety of romosozumab in the treatment of postmenopausal women with osteoporosis.
- Four supportive studies:
  - Study 20080289: a Phase IIIb active controlled (teriparatide) study in postmenopausal women with osteoporosis previously treated with bisphosphonates (important study as examined use *after* bisphosphonates)
  - Study 20060326: a Phase IIb study in postmenopausal women with low BMD.
  - Study 220120156: a Phase III study in postmenopausal women with osteoporosis (90 mg/mL versus 70 mg/mL).
  - Study 20101291: a Phase IIb in postmenopausal Japanese women with osteoporosis.

Table 28: Summary of Study 20070337 (FRAME)

Study 20070337 (FRAME trial)	
Design	Phase III global randomised controlled trial. 2012 to 2016
Population	Postmenopausal women. Age 55 to 90 years with a BMD T-score at the total hip or femoral neck of less than or equal to -2.50 and at least 2 vertebrae in the L1 through L4 region and at least one hip evaluable by DXA. excluded if BMD < -3.5 or hip fracture or > 2 vertebral fractures.
Treatment	210 mg SC monthly romosozumab versus placebo for 12 months (blinded 12 months then open label 12 months with denosumab in both groups)
Outcome	Primary outcome was new vertebral fracture at 12 months and 24 months

Study 20070337 (FRAME trial)	
Baseline	7180 randomised. 89 % completed 12 month follow up, 84% 24 month follow up. Mean age 70.9 years (31% were > 75 years). 40% had a history of fracture. Mean 10 year probability of fracture based on FRAX score was 13.4%. Only 6.8% had received previous treatment with osteoporotic medication at baseline, of these 4.9% were bisphosphonates
Results	Romosozumab significantly reduced the risk of new vertebral fractures compared with placebo through Month 12 (romosozumab versus placebo: 0.5% versus 1.8%; odds ratio = 0.27, p < 0.001), with an absolute risk reduction of 1.30% (95% CI: 0.79 to1.80) and a relative risk reduction of 73% (risk ratio = 0.27; 95% CI: 0.16 to 0.47). Vertebral fracture risk reduction was maintained over the 24 month study period for subjects in the romosozumab/ denosumab compared with placebo/ denosumab (0.6% versus 2.5%; odds ratio = 0.24, p < 0.001), with an absolute risk reduction of 1.89% (1.30 to 2.49) and a relative risk reduction of 75% (risk ratio = 0.25 (95% CI: 0.16 to 0.40)). The fracture risk reduction was observed using all fracture descriptors (clinical, non-vertebral, major non vertebral, hip, major osteoporotic), but this was only statistically significant when corrected for multiplicity for clinical fracture at 12 months. There was a significant improvement in BMD (up to 14.4% at the lumbar spine and 6.6% at the hip at Month 12). No changes to symptoms or quality of life. At Month 36, after 2 years of denosumab, the group previously treated with romosozumab had a reduced risk of vertebral fracture (relative risk 0.34). There were no significant changes at the radius when assessed by DXA, high resolution quantitative computed tomography or finite element analysis (strength).

Table 29: Summary pivotal Phase III Study 20110142 (ARCH trial)

Study 20110142 (ARCH trial)	
Design	Phase III global randomised controlled trial
Population	Post-menopausal osteoporosis.
Treatment	Romosozumab 210 mg monthly for 12 months, followed by open label alendronate 70 mg weekly for 12 months. Compared to alendronate 70 mg weekly All patients also received calcium and vitamin D
Outcome	Clinical fracture at 12 and 24 months
Baseline	4093 were randomised, 89.3% completed 12 months and 77% completed 24 months. Mean age was 74.3 years, 52.4% were > 75 years. 99% had a prior osteoporotic fracture. The mean 10 year probability of major

Study 20110142 (ARCH trial)	
	osteoporotic fracture was 20.1%. The use of prior osteoporotic medication was reported by 9%.
Results	Romosozumab 210 mg monthly for 12 months followed by alendronate 70 mg once weekly for 12 months significantly reduced the risk of new vertebral fracture by 50% compared with alendronate alone (romosozumab/ alendronate versus alendronate/alendronate: 74 of 1825, 4.1% versus 147 of 1834, 8%; odds ratio = 0.48; 95% CI: 0.36 to 0.64; adjusted p < 0.001). There was also a significant reduction in the risk of clinical fractures (non-vertebral fracture and clinical vertebral fracture) by 27% compared with alendronate alone (romosozumab/ alendronate versus alendronate/alendronate: 198 of 2046, 9.7% versus 266 of 2047, 13%; Hazard ratio = 0.73; 95% CI: 0.61 to 0.88, adjusted p < 0.001). Romosozumab 210 mg monthly for 12 months followed by alendronate 70 mg once weekly through the primary analysis significantly reduced the risk of non-vertebral fractures by 19% (romosozumab/alendronate: 178 of 2046, 8.7% versus alendronate/alendronate: 217 of 2047, 10.6%; Hazard ratio = 0.81, 95% CI: 0.66 to 0.99; 2-sided adjusted p = 0.040)

Other efficacy studies

Study 20060326: This was a Phase II randomised controlled trial of romosozumab in the treatment of 419 postmenopausal women with low BMD.

Table 30: Study design for Phase II Study 20060326

<table>
<tr><th>month</th><th colspan="2">0-12</th><th>13-24</th><th>25-36</th><th>37-47</th><th>48</th></tr>
<tr><td rowspan="4">DRUGS</td><td colspan="2">Romosozumab (3 or 4W, 120 or 140mg)</td><td rowspan="3">Randomised to denosumab or placebo</td><td rowspan="3">romosozumab</td><td rowspan="3">Zoledronic acid if not in the R-D-R group</td></tr>
<tr><td colspan="2">Placebo</td></tr>
<tr><td>Alendronate</td><td>romosozumab</td></tr>
<tr><td>Teriparatide</td><td></td><td></td><td></td><td></td></tr>
</table>

There was a high number of protocol deviations. The sample size was calculated at 400. Only 141 continued the follow up stage at Month 48.

At Month 12, the mean percent change from baseline in BMD at the lumbar spine for subjects who received romosozumab increased for both dose frequencies (monthly: 8.6%, three monthly: 5.5%) and both dose levels (140 mg: 7.3%, 210 mg: 8.4%) versus placebo (-0.1%). Compared with placebo, there was a statistically significant ($p < 0.0001$) difference in BMD at Month 12 at the lumbar spine at both dose frequencies and dose levels. The romosozumab 140 mg monthly and 210 mg monthly dose groups also demonstrated statistically significant increases in bone density when compared with alendronate ($p < 0.0001$) and teriparatide ($p \leq 0.0276$).

Treatment with romosozumab between 12 and 24 months resulted in less gains in BMD than in the first 12 months. Bone formation markers increased in the first 1 to 9 months of treatment, then decreased to baseline or below. Bone resorption markers decreased and remained low. In patients who continued denosumab when romosozumab was ceased, BMD continued to increase. However, in those that received placebo, BMD decreased.

Retreatment with romosozumab during Months 36 to 48 following placebo from Months 24 to 36 resulted in BMD increases at the spine and hip comparable to those seen in the group that received initial treatment with romosozumab 210 mg monthly during the first 12 months. Retreatment with romosozumab in those transitioning from denosumab yielded a more modest increase in BMD at the spine and femoral neck and maintenance of BMD at the total hip.

Study 20080289

This was a Phase IIIb randomised, teriparatide controlled, open label study of 436 postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy to romosozumab or teriparatide. Subjects must have taken oral bisphosphonates at the dose approved for post-menopausal osteoporosis for at least 3 years before study entry. This study used hip rather than spine as the primary efficacy endpoint. 436 subjects were randomised into the study. The mean duration of prior bisphosphonate use was 6.2 years (range: 3 to 27 years). Through 12 months of treatment, the mean percent change from baseline in BMD for the total hip was 2.6% (2.2% to 3.0%) in the romosozumab group and -0.6% (95% CI: -1.0 to -0.2%) in the teriparatide group. All secondary endpoints including femoral neck (romosozumab versus teriparatide 3.2% versus -0.2%) and lumbar spine (9.8% versus 5.4%) BMD by DXA demonstrated statistically significant increases in the romosozumab treatment group compared with teriparatide.

Study 201011291

This was a Phase IIb, multicentre, parallel group dose ranging study in 252 postmenopausal Japanese women with osteoporosis. Patients were randomised 1:1:1:1 to receive romosozumab 70, 140 or 210 mg or placebo.

After 12 months of treatment, romosozumab administration resulted in a dose dependent increase in lumbar spine BMD compared with placebo, with the largest increase in the romosozumab 210 mg group. The differences between each of the romosozumab groups versus placebo and within the romosozumab groups were also statistically significant.

Study 20120156

This was a Phase III placebo controlled study in 294 postmenopausal women with osteoporosis evaluating the non-inferiority of a fixed dose of 210 mg of romosozumab when delivered as 90 mg/mL (two SC injections with the 1.17 mL prefilled syringe) compared with 70 mg/mL (three SC injections with the 1.0 mL prefilled syringe). The mean percent increase in lumbar spine BMD was 0.8%, 9.6% and 9.2% in the placebo, romosozumab 70 mg/mL and romosozumab 90 mg/mL groups, respectively. The mean treatment difference between the romosozumab 90 mg/mL and romosozumab 70 mg/mL was -0.4% (-1.5 to 0.7%); non-inferiority between the two romosozumab groups was established as lower bound of the 1-sided 97.5% CI of the mean difference between the two romosozumab groups was -1.5%, which was greater than the pre-specified limit of -2.0%.

Studies in men

Table 31: Summary of Study 20110174 in men

Study 20110174 (BRIDGE trial)	
Design	A multicentre, randomised, double blind, placebo controlled study in men with osteoporosis.
Treatment	romosozumab 210 mg monthly for 12 months or placebo, follow up extra 3

Study 20110174 (BRIDGE trial)	
	months.
Primary outcome	BMD at lumbar spine, secondary outcomes BMD hip and femur. It was designed as a superiority study.
Inclusion criteria	ambulatory men ≥ 55 years to ≤ 90 years of age with a DXA BMD T-score at the lumbar spine, total hip, or femoral neck of ≤ -2.50 or a DXA BMD T-score at the lumbar spine, total hip or femoral neck of ≤ -1.50 and a history of fragility, non-vertebral fracture or vertebral fracture (thoracic or lumbar).
Subjects:	There were 245 randomised to the study. More patients discontinued in the romosozumab arm than the placebo arm (11% compared with 6.1%), the main reasons were subject request and adverse events (3.1 compared with 0%). The mean age was 71.4 years, body mass index 25.1kg/m^2. Mean BMD T-score was -2.26 at lumbar spine, -1.92 at the hip and -2.33 at the femoral neck. Cardiovascular risk was similar between the two groups, but less men in the romosozumab group had a history of smoking or diabetes. More patients in the placebo group had received prior osteoporosis medications. More patients in the romosozumab group had a diagnosis of secondary osteoporosis.
Results:	At Month 12, the mean percent increase in BMD at the lumbar spine from baseline was statistically significant greater in the romosozumab 210 mg monthly group compared with placebo (12.1% versus 1.2%, $p < 0.0001$). However, this data was not corrected for discrepancies at baseline such as prior use of bisphosphonates, secondary osteoporosis, smoking, and alcohol use. At Month 12, patients in the romosozumab 210 mg monthly compared with the placebo group showed statistically significant ($p < 0.0001$) greater increase the mean percent increase in BMD at the total hip (2.5% versus -0.5%) and femoral neck (2.2% versus -0.2%).

Safety

The following safety analysis comes from an integration of clinical studies comparing romosozumab to control (placebo or alendronate or teriparatide). This analysis included 24, 12 and 6 month periods of analysis. Only treatment emergent adverse events were included.

The safety database included 11,553 subjects in 19 romosozumab clinical studies who received at least 1 dose of romosozumab (n = 7681) or placebo (n = 3872). There were 5863 subjects (5712 women and 151 men) who received romosozumab for at least 12 months.

The proportion of subjects who had at least 1 treatment emergent AE during the study period was similar in the romosozumab and placebo groups. The most common AEs were nasopharyngitis, arthralgia and back pain. Of note, overall about 10% of patients fell during the study period.

There was no dose related increase in adverse events with 70, 140 and 210 mg doses.

The exposure-adjusted incidence rate of serious adverse events per 100 subject-years for the osteoporosis safety analysis set was 11.4 for the total romosozumab group, 11.7 for the romosozumab 210 mg group, and 11.7 for the integrated control group. The only SAE

with an exposure-adjusted incidence rate of ≥ 0.5 per 100 subject-years in the total romosozumab or integrated control group was pneumonia (0.6 in the total romosozumab and 210 mg romosozumab groups, 0.5 control).

It is noted that more cataracts were reported in those taking romosozumab.

Laboratory parameters

- No significant changes to haemoglobin, platelets or white blood cells to suggest marrow invasion.
- Small decrease in serum calcium and serum phosphate compared to placebo. There was a greater increase in intact parathyroid hormone in patients in the romosozumab than the placebo group. There was no significant change in serum magnesium.

Cardiac safety

Electrocardiogram (ECG) data collected in Study 20060326 and some Phase I studies are also provided in individual clinical study reports. ECGs were not performed in Studies 20070337, 20080289, 20110142 and 20110174. Analysis of ECG results in individual studies in which they were analysed demonstrated no clinically important effect of romosozumab.

During the development program, an imbalance in positively-adjudicated cardiovascular SAEs were observed between treatment groups in Study 20110142. This imbalance was due specifically to serious cardiac ischemic and cerebrovascular events. These findings were not observed in the larger, placebo controlled Study 20070337 but in the summary of serious and life threatening treatment emergent AEs from the 12 month osteoporosis safety analysis set, described in Table 32 there is an imbalance in serious cardiovascular events.

Table 32: Treatment emergent severe and life threatening SAEs by preferred term and grade (12 month placebo controlled osteoporosis safety analysis set)

	20070337		20060326		20101291		20110174		Total	
Preferred Term Severity 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 (%)
Number of subjects reporting treatment-emergent severe and life-threatening serious adverse events	181 (5.1)	178 (5.0)	3 (6.0)	1 (2.0)	2 (3.2)	2 (3.2)	6 (7.4)	14 (8.6)	192 (5.1)	195 (5.1)
Pneumonia	6 (0.2)	11 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	6 (0.2)	12 (0.3)
Life threatening	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)
Severe	5 (0.1)	10 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	5 (0.1)	11 (0.3)
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)
Life threatening	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)
Severe	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)
Angina unstable	1 (<0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (<0.1)	6 (0.2)
Life threatening	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Severe	0 (0.0)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Hypertension	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)
Life threatening	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)
Severe	2 (<0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	4 (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)
Severe	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)
Osteoarthritis	5 (0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	5 (0.1)	4 (0.1)
Severe	5 (0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	5 (0.1)	4 (0.1)
Cholelithiasis	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)
Severe	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)
Femoral neck fracture	4 (0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	3 (<0.1)
Severe	4 (0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	3 (<0.1)
Tibia fracture	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)
Severe	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)
Myocardial ischaemia	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (<0.1)	3 (<0.1)
Life threatening	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (<0.1)
Severe	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)
Cataract	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (<0.1)	3 (<0.1)
Severe	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (<0.1)	3 (<0.1)
Sepsis	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)
Severe	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)
Asthma	0 (0.0)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)
Severe	0 (0.0)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)
Atrial fibrillation	0 (0.0)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)
Life threatening	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)
Severe	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)
Coronary artery disease	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)
Life threatening	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)
Severe	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)
Urinary tract infection	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)
Severe	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)
Subdural haematoma	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (<0.1)	2 (<0.1)
Severe	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (<0.1)	2 (<0.1)
Transient ischaemic attack	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)
Severe	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)
Cardiac failure	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (<0.1)
Severe	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (<0.1)

N = Number of subjects in the analysis set
n = Number of subjects reporting ≥ 1 event
Preferred terms are sorted by descending order of frequency in the total romosozumab group and coded using MedDRA version 19.1.

Patients who suffer from sclerosteosis or van Buchem disease and have significantly reduced or absent sclerostin activity are not at increased risk of cardiovascular disease.

Immunology

The pharmacokinetic exposure, safety (for example., hypersensitivity, injection site reactions, or autoimmune disorder) and efficacy (changes in BMD) profiles of the subjects who tested positive for binding anti-romosozumab antibodies were found to be consistent with the profiles of anti-romosozumab antibody-negative subjects.

In Phase II and III clinical studies of osteoporosis in postmenopausal women, the incidence of developing anti-romosozumab antibodies was 18.6% across all doses studied. Neutralising antibodies developed in 0.9% of subjects. The incidence of developing binding and neutralising anti-romosozumab antibodies in women who received 210 mg monthly was similar to the overall studies at 18.1% and 0.7%, respectively. Similar findings occurred in men.

There were no anaphylactic reactions attributed to romosozumab.

Bone changes

There was no imbalance in the risk of hyperostosis in the clinical studies.

Osteoarthritis was included as an adverse event of special interest as sclerostin is expressed in articular cartilage and there is a possibility that blocking receptors may have a role in Wingless-related integration site signalling. However, there were no changes in articular cartilages when rats were treated with 7 times the clinical dose, and no imbalance in osteoarthritis adverse events in the clinical trials.

Atypical femoral fractures were seen in 3 patients after treatment with romosozumab, and in 4 patients who had been randomised to alendronate for 24 months.

Osteonecrosis of the jaw has been identified in 5 patients during the clinical development program.

Safety in renal/hepatic impairment: The pharmacokinetics, pharmacodynamics and safety of romosozumab in subjects with renal impairment was evaluated in the Phase I Study 20110227. The administration of romosozumab resulted in a greater decrease in serum calcium level and a greater compensatory physiological increase in intact parathyroid hormone in subjects with stage 4 chronic kidney disease and stage 5 chronic kidney disease receiving haemodialysis than in healthy subjects. Most of these changes were transient and returned to baseline by end of the study. AEs were similar across eGFR (estimated glomerular filtration rate) groups.

Risk management plan

The RMP and ASA included the following safety concerns.

A post market authorisation study to investigate the potential cardiovascular signal is proposed, however it is unclear if this would only be performed if the medicine was registered in Europe or the USA. See Table 26 above.

Risk-benefit analysis

Discussion

Efficacy

The evidence for efficacy is primarily from clinical trials in postmenopausal women. These were large randomised controlled trials, with the primary outcome being fracture. There was a clinically and statistically significant reduction in vertebral fracture. From a clinical perspective, non-vertebral fractures, in particular hip fractures, are the major cause of

morbidity and mortality in osteoporosis. There were numerically more non vertebral fractures and clinical fractures than vertebral fractures in the pivotal studies, these reduced in number with treatment but the difference was not statistically significant. This lack of effect may be due to the lumbar spine being more sensitive to changes in bone turnover than other sites as it has more trabecular bone. The clinical development program shows benefits over placebo and active treatment with alendronate and teriparatide. There were no studies in direct comparison to denosumab.

The patients in the clinical trials were representative of women with post-menopausal osteoporosis in the community. I disagree with the evaluator that the indication needs to include the word primary.

Most of the patients in the clinical trials had mild/moderate renal impairment. There is insufficient evidence to support use in patients with eGFR< 30mL/min, presumable as patients with abnormal parathyroid hormone (PTH) were excluded from clinical trials and most patients with renal failure would have renal osteodystrophy and hyper-parathyroidism. It is possible that efficacy may be different in this population group where bone disease is multifactorial due to the role of renal impairment, changes in calcium and phosphate balance, and the effects of excessive PTH. There was no subgroup analysis to determine if the efficacy in mild/moderate renal impairment was comparable to patients with eGFR > 90 mL/min.

In the pivotal clinical studies, approximately 90% of the majority of the patient population were treatment naïve. There was a supportive study of romosozumab in 436 patients whom had been treated with alendronate for over 3 years, this showed gains in BMD at the hip but was not powered for BMD at other sites or fractures.

Gains in efficacy were studies for up to 24 months after treatment. Thus, long term benefits over other treatments are unknown.

Efficacy in men was supported by clinical trials where BMD was the primary outcome. The aim of managing osteoporosis is to prevent fracture. A number of other agents in indicated in men with osteoporosis on the basis of an improvement in BMD, and an extrapolation of reduced fracture risk in other populations where improved bone mass is correlated to fracture outcome. Although not ideal, it is reasonable to do the same for romosozumab. There is no reason to believe romosozumab would be less efficacious in men than women.

Safety

The clinical development program included over 11,000 patients, of these over 7,000 were exposed to romosozumab. Of these, over 5,000 women but only 151 men were exposed for > 12 months.

No signals to suggest an increased risk of malignancy, osteoarthritis, bone marrow suppression.

The adverse event reports in the clinical trials were similar to other agents in this class. Osteonecrosis of the jaw and atypical femoral fractures were reported.

Cardiovascular events

Sclerostin is expressed in aortic vascular smooth muscle and upregulated at sites of vascular calcification. Blocking sclerostin may lead to vascular calcification, which could result in arterial stiffening and serious cardiovascular disease.

An imbalance in positively-adjudicated cardiovascular SAEs between treatment groups in Study 20110142, which was not observed in the larger, placebo controlled Study 20070337. An external, independent adjudication of cardiovascular SAEs occurred in the three pivotal Phase III studies (Studies 20070337, 20110142 and 20110174) and pre specified in the respective protocols. Based on the totality of the evidence including nonclinical, clinical, and epidemiologic data, a causal relationship between romosozumab

and positively-adjudicated cardiovascular SAEs has not been established. However, a true relationship to romosozumab has not been excluded; therefore, cardiovascular SAEs remain an important potential risk and will require ongoing monitoring and evaluation in pharmacovigilance activities. The sponsor has proposed a European post market study if romosozumab is registered in Europe.

Risk benefit analysis

Efficacy

The evidence for efficacy is primarily from clinical trials in post-menopausal women. These were large RCTs, with the primary outcome being fracture. There was a clinically and statistically significant reduction in vertebral fracture. From a clinical perspective, non-vertebral fractures-in particular hip fractures- are the major cause of morbidity and mortality in osteoporosis. There were numerically more non vertebral fractures and clinical fractures than vertebral fractures in the pivotal studies, these reduced in number with treatment but the difference was not statistically significant (see Tables 33 and 34). This lack of effect may be due to the lumbar spine being more sensitive to changes in bone turnover than other sites as it has more trabecular bone. Other bisphosphonates and teriparatide have been shown to reduce non-vertebral fractures (although these studies were generally longer in duration), denosumab appears to have less effect in a reduction in non-vertebral fractures.

Table 33: Subject incidence of new vertebral fracture 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

BMD = bone mineral density; LOCF = last-observation-carried-forward; Pt Est = point estimate; Q6M = every 6 months; QM = every month; QW = every week
Number of subjects randomized in Study 20070337: 3591 placebo and 3589 romosozumab
Number of subjects randomized in Study 20110142: 2047 alendronate and 2046 romosozumab
N1 = Number of subjects in the primary analysis set for vertebral fractures
Positive values for absolute risk reduction and values < 1 for risk ratio and odds ratio favor romosozumab.
Control = placebo/denosumab 60 mg Q6M for Study 20070337 and alendronate 70 mg QW/alendronate 70 mg QW for Study 20110142
Treatment = romosozumab 210 mg QM/denosumab 60 mg Q6M for Study 20070337 and romosozumab 210 mg QM/alendronate 70 mg QW for Study 20110142
[a] Based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables for Study 20070337, and adjusted for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline for Study 20110142
[b] Based on logistic regression model adjusted for age and prevalent vertebral fracture stratification variables for Study 20070337, and adjusted for age strata, baseline total hip BMD T-score and presence of severe vertebral fracture at baseline for Study 20110142; p-value based on score test
[c] SE represents the standard error of log(risk ratio) or log(odds ratio)
Missing values are imputed by carrying forward the last nonmissing postbaseline value prior to the missing value.

Table 34: Summary of secondary fracture endpoints through Month 12 that were common to both pivotal fracture Studies 20070337 and 20110142

	20070337			20110142		
	Placebo (N = 3591)	Romosozumab 210 mg QM (N = 3589)	Romosozumab 210 mg QM vs. Placebo	Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM (N = 2046)	Romosozumab 210 mg QM vs. Alendronate 70 mg QW
Clinical fracture through month 12						
N of subjects	3591	3589		2047	2046	
with fractures - n (%)	90 (2.5)	58 (1.6)		110 (5.4)	79 (3.9)	
Hazard ratio[a]						
Pt Est (SE)			0.64 (0.17)			0.72 (0.15)
(95% CI)			(0.46, 0.89)			(0.54, 0.96)
p-value			0.008			0.027
Nonvertebral fracture through month 12						
N of subjects	3591	3589		2047	2046	
With fractures - n (%)	75 (2.1)	56 (1.6)		95 (4.6)	70 (3.4)	
Hazard ratio[a]						
Pt Est (SE)			0.75 (0.18)			0.74 (0.16)
(95% CI)			(0.53, 1.05)			(0.54, 1.01)
p-value			0.096			0.057
Major osteoporotic fracture through month 12						
N of subjects	3591	3589		2047	2046	
With fractures - n (%)	63 (1.8)	38 (1.1)		85 (4.2)	61 (3.0)	
Hazard ratio[a]						
Pt Est (SE)			0.60 (0.21)			0.72 (0.17)
(95% CI)			(0.40, 0.90)			(0.52, 1.01)
p-value			0.012			0.053
Hip fracture through month 12						
N of subjects	3591	3589		2047	2046	
With fractures - n (%)	13 (0.4)	7 (0.2)		22 (1.1)	14 (0.7)	
Hazard ratio[a]						
Pt Est (SE)			0.54 (0.47)			0.64 (0.34)
(95% CI)			(0.22, 1.35)			(0.33, 1.26)
p-value			0.18			0.19

N = Number of subjects randomized; Pt Est = point estimate; QM = every month; QW = every week
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 and prevalent vertebral fracture stratification variables for Study 20070337, and adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline for Study 20110142.

The clinical development program shows benefits over placebo and active treatment with alendronate and teriparatide. There were no studies in direct comparison to denosumab.

The patients in the clinical trials were generally representative of women with post-menopausal osteoporosis in the community, however the participants had relatively high FRAX scores and did not include patients with high PTH. In post-menopausal women, low BMD and increased fracture risk may be due a number of contributing factors such as age, family history, low BMI, oestrogen deficiency, chronic disease, diet, medications. The Delegate disagrees with the evaluator that the indication needs to include the word primary.

Most of the patients in the clinical trials had mild/moderate renal impairment. There is insufficient evidence to support use in patients with eGFR < 30mL/min, presumable as patients with abnormal PTH were excluded from clinical trials and most patients with renal failure would have renal osteodystrophy and hyper-parathyroidism. It is possible that efficacy may be different in this population group where bone disease is multifactorial

due to the role of renal impairment, changes in calcium and phosphate balance, and the effects of excessive PTH. There was no subgroup analysis to determine if the efficacy in mild/moderate renal impairment was comparable to patients with eGFR > 90 mL/min.

In the pivotal clinical studies, approximately 90% of the majority of the patient population were treatment naïve. There was a supportive study of romosozumab in 436 patients whom had been treated with alendronate for over 3 years, this showed gains in BMD at the hip but was not powered for BMD at other sites or fractures. From my calculations it appears that approximately 30 patients in the clinical development program received denosumab prior to romosozumab. The gains in BMD and reduction in fracture risk were lower when romosozumab was used second line.

Gains in efficacy were studies for up to 24 months after treatment. Thus, long term benefits over other treatments are unknown.

Efficacy in men was supported by clinical trials where BMD was the primary outcome. The aim of managing osteoporosis is to prevent fracture. A number of other agents in indicated in men with osteoporosis on the basis of an improvement in BMD, and an extrapolation of reduced fracture risk in other populations where improved bone mass is correlated to fracture outcome. Although not ideal, it is reasonable to do the same for romosozumab. There is no reason to believe romosozumab would be less efficacious in men than women.

Safety

The clinical development program included over 11 000 patients, of these over 7000 were exposed to romosozumab. Of these, over 5000 women but only 151 men were exposed for > 12 months.

No signals to suggest an increased risk of malignancy, osteoarthritis, bone marrow suppression.

The adverse event reports in the clinical trials were similar to other agents in this class. Osteonecrosis of the jaw and atypical femoral fractures were reported.

Cardiovascular events

Sclerostin is expressed in aortic vascular smooth muscle and upregulated at sites of vascular calcification. Blocking sclerostin may lead to vascular calcification, which could result in arterial stiffening and serious cardiovascular disease.

An imbalance in positively-adjudicated cardiovascular SAEs between treatment groups in Study 20110142. An external, independent adjudication of cardiovascular SAEs occurred in the three pivotal phase 3 studies (Studies 20070337, 20110142 and 20110174) and pre specified in the respective protocols. Based on the totality of the evidence including nonclinical, clinical, and epidemiologic data, the sponsor has stated that a causal relationship between romosozumab and positively-adjudicated cardiovascular SAEs has not been established. However, a true relationship to romosozumab has not been excluded; therefore, cardiovascular SAEs remain an important potential risk and will require ongoing monitoring and evaluation in pharmacovigilance activities. The sponsor has proposed a European post market study if romosozumab is registered in Europe.

Conclusion

The Delegate considers that romosozumab has a beneficial impact on bone density and fracture. However, there are a number of important uncertainties. These include long term impact on non-vertebral fracture, efficacy relative to denosumab, cardiovascular risk and long term safety. At this point in time the Delegate is reluctant to support registration until these issues are clarified.

The clinical trials submitted are more supportive of a first line indication than a second line indication. The main concern with a second line indication is the relatively small number of patients treated with romosozumab after other agents, and the unknown efficacy and safety in this context.

In relation to the indications, the Delegate agrees with the evaluator that a reduction in non-vertebral fracture should not be included. The Delegate is of the opinion that 'treatment of osteoporosis in post-menopausal women' is acceptable alone without clarifying the type of fracture reductions seen (this is best in the clinical trials section)- however the Delegate notes other anti-osteoporosis medications include this. In relation to use in men, other anti-osteoporosis medications approved in men where there is no fracture outcome have an indication that states. '*Treatment to increase bone mass in men with osteoporosis at increased risk of fracture*', this would also be more appropriate for romosozumab at this time.

Questions for the sponsor

1. Please comment on how many patients in the clinical development program had taken alendronate, risedronate, denosumab, teriparatide or raloxifene prior to romosozumab?
2. Did renal impairment (eGRF 30 to 60, 60 to 90 or > 90 mL/min) have any impact on the efficacy of romosozumab?
3. Describe efficacy and safety in the small number of patients with eGFR < 30 mL/min in the clinical studies.
4. Is a cardiovascular safety study planned, or will this only be performed if romosozumab is registered in Europe?
5. Is there any information about whether romosozumab alters the healing of fractures?
6. Has the use of romosozumab been associated with osteonecrosis at other sites? Is this a potential risk?
7. Please summarise the results of fractures from safety analysis in the study in men.
8. Please update the TGA on the outcome of the assessment in Europe.
9. Are there further plans to perform a clinical trial with denosumab as an active comparator?

Summary of issues

- The pivotal trials were performed in postmenopausal women. Fracture was the key primary endpoint. Most of the women in this study had *not been exposed* to previous osteoporotic medications but were at high risk of fracture.
- Efficacy as second line agent is supported by the relatively small number patients (< 10%) treated with other agents in pivotal studies and a supportive study as follow on from alendronate.
- Romosozumab showed clinically and statistically significant improvements in rates of vertebral fracture and improvements in BMD, both compared to placebo and alendronate.
- There was no direct comparison between romosozumab and denosumab or zoledronic acid.
- Use in men supported by clinical study with BMD as primary endpoint.
- There was an imbalance in cardiovascular events in one of the pivotal studies.

- Data on long term safety limited to 2 years follow up after treatment for 1 year.

Pre ACM preliminary assessment

At the time, the Delegate was uncertain in romosozumab should be approved for registration. The Delegate's concerns primarily relate to use as first line therapy without a comparison to denosumab, and the risk of cardiovascular events.

Request for ACM advice

1. The sponsor's proposed indication would allow first line therapy. Is this appropriate in the context of not having a direct comparison to denosumab?
2. Is there sufficient data to support a second line indication?
3. What is the most appropriate fracture outcome measure to assess efficacy in osteoporosis (vertebral, all fractures, clinical fractures or non-vertebral fractures)?
4. Has safety been adequately established in relation to duration of follow up and the signal for cardiovascular events?

Response from sponsor

The indication proposed with the initial application was:

> *Evenity is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Evenity reduces the risk of vertebral, clinical and non-vertebral fractures. Evenity is indicated for the treatment of osteoporosis in men at increased risk of fracture. Evenity increases bone mass*."

In response to comments in the clinical evaluation report and the Delegate's Overview, Amgen proposes to amend the indication to:

> *Evenity is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture. Treatment to increase bone mass in men with osteoporosis at high risk of fracture.*

The administration text has been revised to include 'After completing Evenity therapy, transition to an anti-resorptive osteoporosis therapy is required to preserve bone mass'. In addition, text on lack of efficacy and safety for treatment for longer than 12 months and in combination with other osteoporosis treatments has been included.

Response to Delegate's questions to sponsor

1. Please comment on how many patients in the clinical development program had taken alendronate, risedronate, denosumab, teriparatide or raloxifene prior to romosozumab?

Sponsor's response

The number of subjects who had taken prior osteoporosis therapies across the clinical development program prior to initiating romosozumab therapy is summarised in Table 35.

Table 35: Prior use of osteoporosis medication (Full analysis set)

	20070337	20110142	20110174	20060326	20080289	20101291	20120156	All
	Romosozumab 210 mg QM (N = 3589) n (%)	Romosozumab 210 mg QM (N = 2046) n (%)	Romosozumab 210 mg QM (N = 163) n (%)	Romosozumab (N = 261) n (%)	Romosozumab 210 mg QM (N = 218) n (%)	Romosozumab (N = 189) n (%)	Romosozumab (N = 241) n (%)	Romosozumab (N = 6707) n (%)
Prior use of osteoporosis medication	243 (6.8)	182 (8.9)	13 (8.0)	50 (19.2)	218 (100.0)	24 (12.7)	234 (97.1)	964 (14.4)
Prior use of oral bisphosphonate	173 (4.8)	127 (6.2)	1 (0.6)	36 (13.8)	218 (100.0)	10 (5.3)	28 (11.6)	593 (8.8)
Prior use of PTH or PTH derivatives	12 (0.3)	23 (1.1)	1 (0.6)	6 (2.3)	1 (0.5)	0 (0.0)	0 (0.0)	43 (0.6)
Prior use of calcitriol	19 (0.5)	19 (0.9)	5 (3.1)	0 (0.0)	3 (1.4)	2 (1.1)	234 (97.1)	282 (4.2)
Prior use of calcitonin	17 (0.5)	13 (0.6)	2 (1.2)	0 (0.0)	1 (0.5)	7 (3.7)	1 (0.4)	41 (0.6)
Prior use of hormone replacement therapy	29 (0.8)	8 (0.4)	0 (0.0)	17 (6.5)	4 (1.8)	4 (2.1)	1 (0.4)	63 (0.9)
Prior use of denosumab	15 (0.4)	6 (0.3)	3 (1.8)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	25 (0.4)
Prior use of IV bisphosphonate	6 (0.2)	9 (0.4)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	17 (0.3)
Prior use of SERM	24 (0.7)	5 (0.2)	0 (0.0)	12 (4.6)	4 (1.8)	3 (1.6)	1 (0.4)	49 (0.7)
Prior use of strontium	0 (0.0)	4 (0.2)	1 (0.6)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	7 (0.1)

2. Did renal impairment (eGRF 30 to 60, 60 to 90 or > 90 mL/min) have any impact on the efficacy of romosozumab?

Sponsor's response

There was no impact of renal impairment on the efficacy of romosozumab.

The primary efficacy endpoints of new vertebral fracture at Months 12 and 24 in Study 20070337 and of new vertebral fracture at month 24 and clinical fracture at primary analysis in Study 20110142 and percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck for all Phase II and III studies are provided by baseline eGFR categories of 15 to < 30, 30 to < 60, 60 to < 90, and ≥ 90 mL/min/1.73 m^2 (Table 36).

Table 36: Efficacy results to eGFR group

	Study 20070337		Study 20110142			Study 20080289	Study 20120156	Study 20110174	Study 20101291	Study 20060326
	Month 12	Month 24	Month 12	Month 24	Primary Analysis					
Fractures	New Vertebral (Table 3)	New Vertebral (Table 4)	ND	New Vertebral (Table 11)	Clinical (Table 12)	ND	ND	ND	ND	ND
BMD % change from baseline										
Lumbar spine	Table 5	Table 6	Table 13	Table 14	ND	Table 19	Table 22	Table 25	Table 28	Table 31
Total hip	Table 7	Table 8	Table 15	Table 16	ND	Table 20	Table 23	Table 26	Table 29	Table 32
Femoral neck	Table 9	Table 10	Table 17	Table 18	ND	Table 21	Table 24	Table 27	Table 30	Table 33

Efficacy results suggest that baseline eGFR has no impact on the effect of romosozumab to increase BMD, with the effect being similar in all groups in all studies. Minor numeric differences between some subgroups are not considered clinically meaningful. Additionally, for Study 20070337, baseline eGFR did not seem to impact the relative risk reduction (RRR) with romosozumab compared with placebo to reduce the incidence of new vertebral fractures through 12 months (relative risk reduction range: 70% to 84% across eGFR categories (Table 37) and through 24 months (relative risk reduction range: 73% to 82%, Table 38) with no trend associated with the lower eGFR status.

Table 37: Subject incidence of new vertebral fracture through Month 12 by Baseline eGFR group (Study 20070337, Primary analysis set for vertebral fractures, LOCF imputation)

			Risk Comparison Estimates									
			Absolute Risk Reduction (%)[a]			Risk Ratio[a]			Odds Ratio[b]			
	Placebo (N = 3591) n/N1 (%)	Romosozumab 210 mg QM (N = 3589) n/N1 (%)	Pt Est	SE	(95% CI)	Pt Est	SE[c]	(95% CI)	Pt Est	SE[c]	(95% CI)	p-value
Primary analysis model	59/3315 (1.8)	16/3312 (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
Est Glomerular Filt Rate Catg at BL[d]												
30 - < 60 mL/min/1.73m²	12/581 (2.1)	4/664 (0.6)	1.50	0.65	(0.22, 2.78)	0.28	0.58	(0.09, 0.86)	0.27	0.59	(0.09, 0.85)	0.017
60 - < 90 mL/min/1.73m²	35/2337 (1.5)	10/2248 (0.4)	1.05	0.29	(0.49, 1.62)	0.30	0.36	(0.15, 0.60)	0.29	0.36	(0.15, 0.60)	<0.001
>= 90 mL/min/1.73m²	12/396 (3.0)	2/400 (0.5)	2.60	0.94	(0.76, 4.45)	0.16	0.75	(0.04, 0.70)	0.15	0.77	(0.03, 0.67)	0.005
Primary analysis model with subgroup variable added	59/3314 (1.8)	16/3312 (0.5)	1.32	0.26	(0.81, 1.83)	0.26	0.28	(0.15, 0.46)	0.26	0.28	(0.15, 0.46)	<0.001
Treatment-by-est Glomerular Filt Rate Catg at BL interaction												0.75

Table 38: Subject incidence of new vertebral fracture through Month 24 by Baseline eGFR group (Study 20070337, Primary analysis set for vertebral fractures, LOCF imputation)

			Risk Comparison Estimates									
			Absolute Risk Reduction (%)[a]			Risk Ratio[a]			Odds Ratio[b]			
	Placebo/ Denosumab 60 mg Q6M (N = 3591) n/N1 (%)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589) n/N1 (%)	Pt Est	SE	(95% CI)	Pt Est	SE[c]	(95% CI)	Pt Est	SE[c]	(95% CI)	p-value
Primary analysis model	84/3320 (2.5)	21/3316 (0.6)	1.90	0.30	(1.30, 2.50)	0.25	0.24	(0.16, 0.40)	0.24	0.25	(0.15, 0.39)	<0.001
Est Glomerular Filt Rate Catg at BL												
30 - < 60 mL/min/1.73m²	19/582 (3.3)	6/665 (0.9)	2.41	0.81	(0.82, 4.00)	0.27	0.47	(0.11, 0.66)	0.25	0.48	(0.10, 0.64)	0.002
60 - < 90 mL/min/1.73m²	49/2341 (2.1)	12/2249 (0.5)	1.56	0.33	(0.91, 2.21)	0.26	0.32	(0.14, 0.48)	0.25	0.32	(0.13, 0.47)	<0.001
>= 90 mL/min/1.73m²	16/396 (4.0)	3/402 (0.7)	3.39	1.09	(1.26, 5.53)	0.18	0.62	(0.05, 0.60)	0.16	0.64	(0.05, 0.57)	0.001
Primary analysis model with subgroup variable added	84/3319 (2.5)	21/3316 (0.6)	1.94	0.31	(1.34, 2.54)	0.24	0.24	(0.15, 0.39)	0.24	0.25	(0.15, 0.39)	<0.001

For Study 20110142, baseline eGFR did not impact the relative risk reduction with romosozumab compared with alendronate on new vertebral fractures through Month 24 (relative risk reduction range: 45% to 58% across groups) (Table 39).

Table 39: Subject incidence of new vertebral fracture through Month 24 by Baseline eGFR group (Study 20110142, Primary analysis set for vertebral fractures, LOCF imputation)

			Risk Comparison Estimates									
			Absolute Risk Reduction (%)[a]			Risk Ratio[a]			Odds Ratio[b]			
	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2047) n/N1 (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046) n/N1 (%)	Pt Est	SE	(95% CI)	Pt Est	SE[c]	(95% CI)	Pt Est	SE[c]	(95% CI)	p-value
Primary analysis model	147/1828 (8.0)	74/1823 (4.1)	4.07	0.78	(2.54, 5.61)	0.50	0.14	(0.38, 0.65)	0.47	0.15	(0.35, 0.63)	<0.001
Est Glomerular Filt Rate Catg at BL												
30 - < 60 mL/min/1.73m²	40/425 (9.4)	18/435 (4.1)	5.54	1.71	(2.18, 8.89)	0.42	0.28	(0.24, 0.73)	0.40	0.29	(0.22, 0.71)	0.001
60 - < 90 mL/min/1.73m²	74/1086 (6.8)	43/1144 (3.8)	3.09	0.95	(1.23, 4.94)	0.55	0.19	(0.38, 0.79)	0.53	0.20	(0.36, 0.78)	0.001
>= 90 mL/min/1.73m²	33/317 (10.4)	13/243 (5.3)	5.20	2.24	(0.82, 9.58)	0.51	0.31	(0.27, 0.94)	0.47	0.34	(0.24, 0.92)	0.025
Primary analysis model with subgroup variable added	147/1828 (8.0)	74/1822 (4.1)	3.98	0.78	(2.45, 5.52)	0.50	0.14	(0.38, 0.66)	0.48	0.15	(0.36, 0.64)	<0.001
Treatment-by-est Glomerular Filt Rate Catg at BL interaction												0.70

N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set
Positive values for absolute risk reduction and values < 1 for risk ratio and odds ratio favor romosozumab
[a] Based on the Mantel-Haenszel method adjusted for prevalent vertebral fracture stratification variable
[b] Based on logistic regression model adjusted for prevalent vertebral fracture stratification variable; p-value based on score test
[c] SE represents the standard error of log(risk ratio) or log(odds ratio)

For clinical fractures through the primary analysis, in subjects with baseline eGFR 15 to < 30, the numbers of fractures were too small to estimate the relative risk reduction

(2 versus 1); for subjects in the other eGFR categories, the relative risk ratio ranged from 17% to 38% and there was no treatment-by-subgroup interaction (Table 40).

Table 40: Subject incidence of clinical fracture through primary analysis by Baseline eGFR group (Full analysis set, LOCF imputation) (Study 20110142 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
Primary analysis model			
Subject status			
Number of subjects	2047	2046	
With fractures - n (%)	266 (13.0)	198 (9.7)	
Hazard ratio [b]			
Pt Est			0.73
SE			0.09
(95% CI)			(0.61, 0.88)
p-value			<0.001
15 - < 30 mL/min/1.73m²			
Subject status			
Number of subjects	7	4	
With fractures - n (%)	2 (28.6)	1 (25.0)	
Hazard ratio [b]			
Pt Est			1.40
SE			1.39
(95% CI)			(0.09, 21.51)
p-value			0.81
30 - < 60 mL/min/1.73m²			
Subject status			
Number of subjects	482	507	
With fractures - n (%)	54 (11.2)	47 (9.3)	
Hazard ratio [b]			
Pt Est			0.83
SE			0.20
(95% CI)			(0.56, 1.23)
p-value			0.35
60 - < 90 mL/min/1.73m²			
Subject status			
Number of subjects	1211	1259	
With fractures - n (%)	151 (12.5)	119 (9.5)	
Hazard ratio [b]			
Pt Est			0.75
SE			0.12
(95% CI)			(0.59, 0.95)
p-value			0.017
>= 90 mL/min/1.73m²			
Subject status			
Number of subjects	345	273	
With fractures - n (%)	59 (17.1)	31 (11.4)	
Hazard ratio [b]			
Pt Est			0.62
SE			0.22
(95% CI)			(0.40, 0.96)
p-value			0.030
Primary analysis model with subgroup variable added			
Pt Est			0.74
SE			0.09
(95% CI)			(0.62, 0.89)
p-value			0.001
Treatment-by-subgroup interaction			
p-value			0.76

B·The·hazard·ratio·estimate·is·based·on·Cox·proportional·hazards·model·adjusting·for·baseline·total·hip·BMD·T-score·and·presence·of·severe·vertebral·fracture·at·baseline¤

In addition, the population pharmacokinetics analysis included data from 463 subjects with normal renal function (eGFR < 90 mL/min/1.73 m^2), 843 with mild renal impairment (60 to < 90 mL/min/1.73 m^2), 137 with moderate renal impairment (30 to < 60 mL/min/1.73 m^2), 8 with severe renal impairment (15 to < 30 mL/min/1.73 m^2), and 8 with end stage renal disease (ESRD) requiring haemodialysis (5 to < 15 mL/min/1.73 m^2). Based on population pharmacokinetic analysis, when compared to a healthy subject with normal renal function, subjects with ESRD (eGFR < 5 to15 mL/min/1.73 m^2 and assuming no haemodialysis during romosozumab treatment) had a median fold increase of 1.58 (95% CI 1.39 to 1.84) in predicted AUC at steady state.

3. Describe efficacy and safety in the small number of patients with eGFR < 30 mL/min in the clinical studies.

Sponsor's response

A Phase I Study 20110227 evaluated the safety, tolerability, and immunogenicity profile of romosozumab after a single 210 mg subcutaneous dose in healthy subjects and subjects with stage 4 renal impairment or end-stage renal disease requiring haemodialysis. Twenty-four subjects were enrolled into three treatment groups: 8 subjects in group 1 (subjects with stage 4 renal impairment), 8 subjects in group 2 (subjects with end-stage renal disease), and 8 subjects in group 3 (healthy subjects). There were no efficacy endpoints in this study. Pharmacokinetic results showed that most of the subjects with stage 4 renal impairment and end-stage renal disease requiring haemodialysis had pharmacokinetic values that were within the range of healthy subjects.

In the Phase III studies, the BMD results for the small number of subjects with eGFR < 30 mL/min/1.73m^2 were similar to the BMD results in patients with eGFR values of 30 to < 60, 60 to < 90 and ≥ 90 mL/min/1.73m^2 (Table 41 to Table 42).

Table 41: Lumbar spine BMD percent change from Baseline at Month 12 by Baseline eGFR group (Study 20070337, Primary analysis set for BMD, observed data)

	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	
Visit	Placebo (N = 7)	Romosozumab 210 mg QM (N = 7)	Placebo (N = 555)	Romosozumab 210 mg QM (N = 624)	Placebo (N = 2213)	Romosozumab 210 mg QM (N = 2143)	Placebo (N = 372)	Romosozumab 210 mg QM (N = 377)
Month 12								
n	7	7	554	624	2211	2134	372	376
Mean	3.0	12.8	0.7	11.7	0.3	13.4	0.2	14.0
SD	3.4	5.2	3.5	5.7	3.7	6.0	3.5	6.0
Median	2.0	11.5	0.8	11.6	0.2	13.1	0.0	14.0
Q1, Q3	0.5, 6.9	8.6, 16.9	-1.4, 3.0	7.8, 15.0	-1.9, 2.5	9.3, 17.0	-2.3, 2.5	9.3, 18.0
Min, Max	-1.9, 7.8	6.2, 20.5	-13.2, 13.6	-6.1, 29.3	-20.4, 25.3	-3.9, 44.9	-9.7, 10.9	-2.7, 32.9

Table 42: Femoral neck BMD percent change from Baseline at Month 24 by Baseline eGFR Group (Study 20110142, Primary Analysis Set for BMD, Observed Data)

	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	
Visit	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 4)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 1)	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 365)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 378)	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 983)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 1031)	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 275)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 211)
Month 24								
n	4	1	364	377	983	1029	273	211
Mean	4.4	3.3	2.5	6.5	2.7	6.3	2.3	6.1
SD	1.3	-	5.0	6.0	4.9	5.9	5.3	6.4
Median	4.7	3.3	2.1	5.4	2.5	5.9	2.5	5.4
Q1, Q3	3.5, 5.2	3.3, 3.3	-0.6, 5.3	3.0, 9.2	-0.2, 5.2	2.9, 9.5	-0.9, 5.0	1.6, 9.4
Min, Max	2.5, 5.7	3.3, 3.3	-12.3, 30.1	-5.6, 28.0	-17.8, 27.3	-12.3, 52.6	-21.3, 19.9	-9.1, 24.6

Clinical fractures in Study 20110142 in subjects with eGFR < 30 mL/min/1.73m^2 were too few to make conclusions (0 to 2 fractures per group).

Safety results from Phase I Study 20110227 showed that romosozumab resulted in a greater decrease in serum calcium in subjects with stage 4 renal impairment and end stage renal disease requiring haemodialysis than in healthy subjects. 30 mL/min/1.73m^2 were

comparable between treatment groups and the types of adverse events reported were consistent with those reported in the global osteoporosis population.

4. Is a cardiovascular safety study planned, or will this only be performed if romosozumab is registered in Europe?

Sponsor's response

A post marketing cardiovascular safety study has been proposed in the EU and in the US; the nature of the planned prospective observational study is currently under review as part of the filing procedure. Details of the draft EU protocol summary are provided in EU RMP Annex 3 [not included in this document].

5. Is there any information about whether romosozumab alters the healing of fractures?

Sponsor's response

Romosozumab does not appear to alter the healing of fractures based upon review of the adverse event data. There were no reported events of fracture delayed union, mal-union, or non-union, and no reports of excessive bone callus, decreased bone formation, or delayed callus formation.

6. Has the use of romosozumab been associated with osteonecrosis at other sites? Is this a potential risk?

Sponsor's response

Based upon adverse event data review, there was not an association of osteonecrosis outside the jaw with romosozumab administration.

7. Please summarise the results of fractures from safety analysis in the study in men.

Sponsor's response

The incidence of treatment-emergent fracture adverse events by preferred term in the 12-month double blind study period of Study 20110174 is presented in Table 43. The rates of fracture adverse events were similar between the two groups.

Table 43: Subject incidence of treatment emergent fracture AEs by Preferred Term in the 12 month double blind study period (Safety analysis set) (Study 20110174 Month 15 final analysis)

Preferred Term	Placebo (N = 81) n (%)	Romosozumab 210 mg SC QM (N = 163) n (%)
Number of subjects reporting treatment-emergent adverse events	3 (3.7)	3 (1.8)
Lumbar vertebral fracture	0 (0.0)	1 (0.6)
Rib fracture	0 (0.0)	1 (0.6)
Thoracic vertebral fracture	0 (0.0)	1 (0.6)
Femur fracture	1 (1.2)	0 (0.0)
Humerus fracture	1 (1.2)	0 (0.0)
Tooth fracture	1 (1.2)	0 (0.0)
Upper limb fracture	1 (1.2)	0 (0.0)

8. Please update the TGA on the outcome of the assessment in Europe

Sponsor's response

The assessment of Evenity in Europe is ongoing. Day 180 questions are anticipated on 20 September 2018. The CHMP Opinion (Day 210) is not anticipated until 16 November 2018 at the earliest.

9. Are there further plans to perform a clinical trial with denosumab as an active comparator?

Sponsor's response

There are currently no plans to perform a romosozumab clinical trial with denosumab as an active comparator.

Response to delegate's request for advice to ACM

The Delegate posed four questions to the ACM. The sponsor's responses to these questions are provided below.

1. The sponsor's proposed indication would allow first line therapy. Is this appropriate in the context of not having a direct comparison to denosumab?

The sponsor's position is that the proposed indication of romosozumab is appropriate based on:

- the need for an agent that reduces fracture risk quickly and substantially, particularly for the patients at high risk for fracture in the next 1 to 2 years, a time frame when current therapies may be insufficiently effective including denosumab; and
- it's mechanism uniquely having dual effects on bone – increasing bone formation and decreasing bone resorption, producing a significant and clinically meaningful benefit on BMD compared with several other standard of care osteoporosis medications. romosozumab should be first line therapy followed by an anti-resorptive agent (alendronate or denosumab) to rapidly lower the likelihood of fracture in patients at high risk for fracture, where the benefit persists beyond the 12 months of initial romosozumab treatment.

Despite availability of bone-forming and anti-resorptive agents for osteoporosis; patients may remain at an unacceptably high fracture risk, especially in the near term, defined as the next 1 to 2 years.

Romosozumab was studied as a first line treatment for postmenopausal osteoporosis in the pivotal fracture trials Study 20070337 and Study 20110142, which studied treatment naïve patients. Both trials evaluated sequential therapy of romosozumab, followed by an anti-resorptive, either denosumab (Study 20070337) or alendronate (Study 20110142). The sequence of treatment of a bone forming agent followed by an anti-resorptive aligns with current perspective in the scientific community;[55] as well as Osteoporosis Australia therapeutic management guidelines.[56] The evidence suggests that denosumab is an appropriate option for follow-on therapy with romosozumab treatment.

Romosozumab led to significant gains in lumbar spine and proximal femur (total hip and femoral neck) BMD from as early as 6 months and within 12 months, resulting in rapid fracture risk reduction at 12 months. The gains achieved in the first 12 months of treatment laid the foundation for a persistent benefit on fracture risk even when both treatment groups were receiving follow-on treatment with the same anti-resorptive agent. With the completion of the alendronate-controlled

Phase III fracture Study 20110142, the benefits of romosozumab demonstrated an important therapeutic advantage over alendronate with superior anti-fracture efficacy at vertebral, non-vertebral, and hip sites.

[55] Cosman F, Nieves JW, Dempster DW. Treatment sequence matters: Anabolic and antiresorptive therapy for osteoporosis. *J Bone Miner Res*. 2017;32(2):198-202

[56] Osteoporosis Australia. Therapeutic Management. https://www.osteoporosis.org.au/therapeutic-management. Accessed 11 September 2018

First-line treatment designation is appropriate for romosozumab. These benefits were achieved in a patient population at greatest risk for fracture and in the most need of treatment.

2. Is there sufficient data to support a second line indication?

Romosozumab should be used in clinical scenarios where a rapidly acting intervention is needed to build bone in patients at high risk for fracture. The pivotal fracture trials demonstrated efficacy where romosozumab (bone building therapy) was used to achieve rapid BMD gains and was followed by denosumab or alendronate (anti-resorptive therapy) to maintain these BMD gains.

This sequence leads to long-term anti-fracture efficacy in treatment naïve patients at high risk for fracture (see Question 1 response, first-line therapy).

Another commonly encountered clinical situation where romosozumab could be used is where patients remain at increased risk for fracture despite previous treatment with bisphosphonates, a widely used class of osteoporosis therapy. There are clinical trial data to support romosozumab use after transition from bisphosphonate.

Romosozumab was studied in a Phase IIIb Study 20080289, where subjects were required to have received bisphosphonate therapy for at least 3 years prior to enrolment. In this trial, which enrolled more than 400 subjects, romosozumab demonstrated superior BMD gains compared with teriparatide, an active comparator and bone building agent, as well as superior bone strength as measured by finite element analysis. Findings on primary and key secondary endpoints are shown in Table 44. In addition to the evidence supporting a first line indication, these findings support a second line indication.

Safety in this population where subjects were previously treated with bisphosphonates was generally consistent to that seen in other clinical studies.

Table 44: Primary and key secondary endpoints for Study 20080289

Percent change from Baseline at the Total Hip	Teriparitide 20 µg SC daily (N = 209) LS Mean (95% CI)	Romosozumab 210 mg monthly (N = 206) LS Mean (95% CI)	Difference from teriparitide[a] LS mean (95% CI)
Primary endpoint	-0.6 (-1.0, -0.2)	2.6 (2.2, 3.0)	3.2 (2.7, 3.8)
BMD by DXA through Month 12			
Secondary endpoint			
BMD by DXA at Month 6	-0.8 (-1.2, -0.4)	2.3 (1.9, 2.7)	3.1 (2.5, 3.7)
BMD by DXA at Month 12	-0.5 (-0.9, -0.0)	2.9 (2.5, 3.4)	3.4 (2.8, 4.0)
Estimated strength by FEA at Month 6	-1.0 (-1.5, -0.6)	2.1 (1.6, 2.5)	3.1 (2.4, 3.8)
Estimated strength by FEA at Month 12	-0.7 (-1.5, 0.1)	2.5 (1.7, 3.2)	3.2 (2.1, 4.3)

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.

3. What is the most appropriate fracture outcome measure to assess efficacy in osteoporosis (vertebral, all fractures, clinical or non-vertebral fractures)?

The aim of a pharmacological intervention is to decrease the incidence of fractures. From the regulatory viewpoint, both the US FDA and EU CHMP have provided guidance on the types of fractures that could support approval.[57,58] In the US, efficacy on morphometric vertebral fractures[57] can support approval; in the EU, the CHMP guideline on osteoporosis states that efficacy should be demonstrated on both vertebral and non-vertebral fractures. Major non-vertebral fractures that are considered meaningful in terms of supporting a registration include combinations of pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip. Indeed, therapies approved in the last 10 years have been supported by primary endpoints that assessed the reduction in vertebral fracture.

Fracture efficacy endpoints used in osteoporosis registration trials reflect clinically meaningful outcomes and are consistent with regulatory guidance.

- Vertebral fractures are the most common osteoporosis-related fracture in postmenopausal women[59] and lead to significant morbidity, such as reduced ability to perform Activities of Daily Living (ADLs) and decreased mobility.[60,61,62,63,64,65,66,67] Therefore, vertebral fractures are key in regulatory guidance for the establishment of efficacy.
- Clinical fractures, are a composite endpoint of symptomatic clinical vertebral fractures and non-vertebral fractures. They account for much of the morbidity and mortality associated with osteoporosis and are an important endpoint that has been used as a primary or key secondary endpoint in a number of major osteoporosis clinical trial programs.[68,69]
- Hip fracture, the most devastating type of non-vertebral fracture is well recognized as a life-altering event that leads to debilitation, loss of independence and is linked to an

[57] FDA. Table of surrogate endpoints that were the basis of drug approval or licensure. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/uc m613636.htm. Accessed 2018
[58] European medicines Agency. Guideline on the Evaluation of Medicinal Products in the Treatment of Osteoporosis. Document reference: CPMP/EWP/552/95 Rev. 2. November 2016
[59] Khosla, S. Surrogates for fracture endpoints in clinical trials. *J Bone Miner Res.* 2003; 18: 1146-1149
[60] Brenneman SK, et al 3rd. Evaluation of decision rules to identify postmenopausal women for intervention related to osteoporosis. *Dis Manag*. 2003; 6: 159-160
[61] Fechtenbaum J, et al. The severity of vertebral fractures and health-related quality of life in osteoporotic postmenopausal women. *Osteoporos Int*. 2005; 16: 2175-2179
[62] Galindo-Cioconetal D, et al. Functional impairment among elderly women with osteoporotic vertebral fractures. *Rehabil Nurs*. 1995; 20: 79-83
[63] Hall SE, et al. A case-control study of quality of life and functional impairment in women with long-standing vertebral osteoporotic fracture. *Osteoporos In*t. 1999; 9: 508-515
[64] Hallberg I, et al. Health-related quality of life after vertebral or hip fracture: a seven-year follow-up study. *BMC Musculoskelet Disord*. 2009; 10: 135
[65] Hallberg I, et al. Health-related quality of life after osteoporotic fractures. *Osteoporos Int.* 2004; 15: 834-841
[66] Oglesby AK, et al. The impact of incident vertebral and non-vertebral fragility fractures on health-related quality of life in established postmenopausal osteoporosis: results from the teriparatide randomized, placebo-controlled trial in postmenopausal women. *J Rheumatol*. 2003; 30: 1579- 1583
[67] Roux C, et al. Burden of non-hip, non-vertebral fractures on quality of life in postmenopausal women: the Global Longitudinal study of Osteoporosis in Women (GLOW). *Osteoporos Int*. 2012; 23: 2863-2871
[68] Lyles KW, et al. Zoledronic acid in reducing clinical fracture and mortality after hip fracture. *N Engl J Med*. 2007; 357
[69] Black DM, et al Design of the fracture intervention trial. *Osteoporos Int*. 1993; 3 Suppl 3: S29-39

increased risk of death.[70],[71],[72] Non-vertebral and hip fractures are therefore included as endpoints in the trials.

Consistent with regulatory guidance and precedence in osteoporosis trials, pivotal Studies 20070337 and 20110142 assessed the most clinically meaningful fracture outcomes as described above in osteoporosis populations at increasing fracture risk as primary or secondary endpoints.

The co-primary endpoints of Study 20070337 were subject incidence of new vertebral fracture through Months 12 and 24; the two primary endpoints of Study 20110142 were the subject incidence of new vertebral fracture through Month 24 and the subject incidence of clinical fracture (non-vertebral and clinical vertebral fracture) through the primary analysis (occurred after a median follow-up of 33 months). Both studies have demonstrated a clinically meaningful benefit on fracture risk reduction from romosozumab.

4. Has safety been adequately established in relation to duration of follow up and the signal for cardiovascular events?

Two large, pivotal, controlled studies were conducted to establish the efficacy and safety of romosozumab for the treatment of postmenopausal osteoporosis. In Study 20070337, there was no evidence of an imbalance in cardiovascular serious adverse events. In the active controlled Study 20110142, clinically relevant and statistically significant reductions of vertebral, clinical, non-vertebral, and hip fractures were observed compared with alendronate alone, establishing a foundation of improved skeletal mass before transitioning to anti-resorptive therapy and an imbalance in positively-adjudicated cardiovascular SAEs was observed in the first year between the arms. The hazard ratio (95% CI) for MACE (composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) was 1.87 (CI 1.11 to 3.14) based on 41 (2.0%) subjects in the romosozumab group and 22 (1.1%) subjects in the alendronate group with a MACE. The risk of MACE was driven by a small number of subjects with serious myocardial infarction (16 (0.8%) romosozumab versus 5 (0.2%) alendronate) or serious stroke (13 (0.6%) romosozumab versus 7 (0.3%) alendronate) during the first year. An imbalance in MACE was not observed after the first year. A numerical imbalance in positively-adjudicated cardiovascular SAEs (8 (4.9%) romosozumab and 2 (2.5%) placebo) was observed in the small bridging study in men with osteoporosis (Study 20110174).

In addition, incidences of cardiovascular SAEs were consistent between analyses based on treatment emergent AE reporting and the adjudicated cardiovascular AEs, providing further assurance regarding the comprehensiveness of the adjudication process. Subgroup analyses did not identify a population at increased relative risk of cardiovascular SAEs of MACE with administration of romosozumab, including no difference in relative risk among subjects with and without a history of prior cardiovascular disease.

Additional exploration into plausible mechanisms were undertaken and no clear mechanistic explanation was identified:

- Genetic evidence of reduced sclerostin expression did not suggest a detrimental effect on cardiovascular health.
- Nonclinical models exploring haemostasis/coagulation, platelet activation, vasoconstriction, sclerostin expression in human atherosclerotic plaques, sclerostin

[70] Bliuc D, et al The impact of nonhip non-vertebral fractures in elderly women and men. *J Clin Endocrinol Metab*. 2014; 99: 415-423
[71] Tajeu GS, et al. Death, debility, and destitution following hip fracture. *J Gerontol A Biol Sci Med Sci.* 2014; 69: 346-353
[72] Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am J Med*. 1997; 103: S12-S17

inhibition in apolipoprotein E (ApoE)-/- mice, and unfavourable changes associated with plaque rupture, plaque erosion, or vasospasm did not identify a biologically plausible mechanism for the imbalance.

- Differences between Study 20110142 and Study 20070337 within subgroups did not suggest a common mechanism for exacerbation of underlying cardiovascular disease with romosozumab.
- Rates for myocardial infarction and stroke in Study 20110142 were similar to rates reported in population-based studies for similarly aged cohorts of women.

In the two pivotal postmenopausal osteoporosis studies, the cardiovascular imbalance was observed in the active comparator trial (Study 20110142) and not in the placebo controlled trial Study 20070337. Over the study duration, it is not expected that the rate of cardiovascular events would increase over time. This was observed in the romosozumab arm of Study 20110142 where the annual rate of events were generally constant. This linear behaviour was not observed in the alendronate group, where the rate of events the first year was lowest compared to Years 2 and 3, despite continued treatment with alendronate.

Not having been able to either rule in or rule out a causal association between romosozumab and cardiovascular SAEs at this time, the assessment by the sponsor is that there is an important potential risk of cardiovascular SAEs of myocardial infarction and stroke. The cardiovascular risk is driven by a small number of events, with the imbalance being observed in only one of the two large pivotal studies and mostly in the first 3 months. As outlined above, there is no convincing biological explanation for such findings, and given the observed early imbalance (that is, greatest within the first 3 months), it is unlikely that a chronic mechanism of vascular calcification would be a contributing factor. While sclerostin is expressed in the vasculature, current nonclinical data do not provide a mechanism to support biological plausibility for a causal relationship between romosozumab treatment and myocardial infarction or stroke.

Given the expected age and associated background of cardiovascular risk within the osteoporosis population, benefit/risk should be assessed on an individual patient basis, particularly for those patients at increased risk for MACE. The potential cardiovascular risk will be communicated through the 'Special warnings and precautions for use' section of the proposed PI, and also, the CMI, to ensure that both patients and physicians are informed when making prescribing decisions.

These analyses support that safety has been adequately established with assessment of both the romosozumab treatment period and the longer follow-up period and that the benefits are thought to outweigh the risks.

Amgen has revised the indication statement with consideration of the comments raised in both the second round clinical evaluation report and the Delegate's Overview. Amgen proposes use of 'at high risk of fracture' rather than 'at increased risk of fracture' to define the target population more clearly. The revised indication is

> *Evenity is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture. Treatment to increase bone mass in men with osteoporosis at high risk of fracture.*

The sponsor believes that the benefit-risk established for Evenity supports approval of Evenity for the proposed indication.

Advisory Committee Considerations[73]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM taking into account the submitted evidence of efficacy, safety and quality, considered Evenity solution for injection containing 105 mg in 1.17 mL of romosozumab to have an overall positive benefit-risk profile for the proposed amended indication:

> *Evenity is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture. Treatment to increase bone mass in men with osteoporosis at high risk of fracture.*

In providing this advice the ACM noted the following:

- Outcomes of the applications for registration in overseas jurisdictions, including the US and EU, were pending.
- The pivotal trials, FRAME (study 20070337) and ARCH (20110142), and BRIDGE (20110174), all demonstrated that romosozumab significantly increases BMD.
- The FRAME trial was conducted in 7180 postmenopausal women with osteoporosis. Romosozumab significantly reduced the risk of new vertebral fractures compared with placebo through month 12 (romosozumab versus placebo: 0.5% versus 1.8%; odds ratio = 0.27, $p < 0.001$), with an absolute risk reduction of 1.30% (95% CI: 0.79, 1.80) and a relative risk reduction of 73% (risk ratio = 0.27; 95% CI: 0.16, 0.47).
- The ARCH trial was conducted in 4090 post-menopausal women with osteoporosis and prevalent fractures. Romosozumab 210 mg every month for 12 months followed by alendronate once weekly for 12 months significantly reduced the risk of new vertebral fracture by 50% compared to alendronate alone.
- The BRIDGE trial was conducted in 245 men with osteoporosis. No data on fractures was captured. The mean percent increase in BMD at the lumbar spine (primary outcome) was significantly greater in the romosozumab group compared with placebo (12.1% versus 1.2%, $p < 0.0001$).

Proposed conditions of registration

The ACM was of the opinion that a long term safety study to assess cardiovascular risk be a condition of registration.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised on the inclusion of the following:

[73] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- Consideration given to including the following as part of the indication: the time restriction of 12 months of use; and mentioning the need to consolidate the effect with an anti-resorptive agent after 12 months use.
- More comprehensive information provided for patients in the CMI regarding cardiovascular safety.

Specific advice

The ACM advised the following in response to the delegate's specific questions on the submission:

1. The sponsor's proposed indication would allow first line therapy. Is this appropriate in the context of not having a direct comparison to denosumab?

The ACM considered that there was sufficient clinical data in the submission to support the use of romosozumab as a first-line therapy. The data was robust and consistent in showing a substantial increase in bone density. In the pivotal trials in post-menopausal women (FRAME and ARCH trials), romosozumab was shown to significantly reduce vertebral fractures. The Committee considered that a direct comparison with denosumab may not be clinically relevant given that the clinical effect and the onset of action are different for both drugs.

2. Is there sufficient data to support a second line indication?

The ACM noted that a relatively small number of patients have been treated with romosozumab after use of other agents. The ACM noted that based on available data, including that from a single, open-label small study (STRUCTURE trial) evaluating the effect of romosozumab (compared to teriparatide) in postmenopausal women with osteoporosis previously treated with bisphosphonate therapy, romosozumab appears to be effective and safe in the second-line context after alendronate. The ACM considered that rather than restrict romosozumab to a line of therapy, use should be allowed where fracture risk remains high after other therapies, however the committee advised that it would welcome further data to support use in the second-line setting.

3. What is the most appropriate fracture outcome measure to assess efficacy in osteoporosis (vertebral, all fractures, clinical fractures or non-vertebral fractures)?

The ACM considered that vertebral fractures were an important fracture outcome in clinical osteoporosis trials. It was noted that other fracture groups are notable for heterogeneity and regional differences in incidence. For instance, baseline risk of non-vertebral fracture in Latin America is lower compared to the rest of the world. 43% of study participants in the FRAME trial were from Latin America, and a *post-hoc* analysis shows differences in treatment effect between Latin American and rest-of-world subjects;[74] especially with respect to non-vertebral and clinical fracture.

4. Has safety been adequately established in relation to duration of follow up and the signal for cardiovascular events?

The ACM noted that long-term safety data of romosozumab beyond four years was not available, and experience with the drug is predominantly with just one year of use.

The overall safety profile of romosozumab was considered to be generally comparable to placebo and the active trial comparators (alendronate and teriparatide), apart from the higher incidence of injection site reactions and cardiovascular events in patients treated with romosozumab.

[74] Cosman, F. et al (2018), Romosozumab FRAME Study: A Post Hoc Analysis of the Role of Regional Background Fracture Risk on Nonvertebral Fracture Outcome. *J Bone Miner Res*,2018; 33: 1407-1416

The ACM was of the view that the cardiovascular signal would require further assessment, and advised that a condition of registration should include provision of long-term cardiovascular safety information when available.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Evenity romosozumab 105 mg / 1.17 mL injection solution, indicated for:

Evenity is indicated for:

- *The treatment of osteoporosis in postmenopausal women at high risk of fracture (see Section 5.1 Pharmacodynamic properties, Clinical trials).*

Treatment to increase bone mass in men with osteoporosis at high risk of fracture.

Specific conditions of registration applying to these goods

- Evenity (romosozumab) is to be included in the Black Triangle Scheme. The PI and CMI for Evenity must include the black triangle symbol and mandatory accompanying test for five years, which starts from the date the sponsor notifies the TGA of supply of the products.
- Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

  The Evenity EU-Risk Management Plan (RMP) version 0.2 (dated 13 July 2018; DLP 22 May 2018), with Australian Specific Annex version 4.0 (dated 13 May 2019), included with submission PM-2017-04339-1-5 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- You must submit to the TGA annual reports of the progress of the post market cardiovascular studies that are underway in other international jurisdictions. This may be included with the PSURs.
- You must commit to providing to the TGA the protocol and study reports for the comparative safety study, if required by the FDA, with timeframes for submission to be determined.
- Batch release testing and compliance with Certified Product Details (CPD)

  All batches of EVENITY romosozumab imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  Each batch of EVENITY romosozumab imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.

  The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the products. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

  This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Attachment 1. Product Information

The PI for Evenity approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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