Report on the Deliberation Results

December 4, 2018

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Evenity Subcutaneous Injection 105 mg Syringe
Non-proprietary Name	Romosozumab (Genetical Recombination) (JAN*)
Applicant	Amgen Astellas BioPharma K.K.
Date of Application	December 19, 2016

Results of Deliberation

In its meeting held on December 3, 2018, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, and the re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

November 15, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Evenity Subcutaneous Injection 105 mg Syringe
Non-proprietary Name	Romosozumab (Genetical Recombination)
Applicant	Amgen Astellas BioPharma K.K.
Date of Application	December 19, 2016
Dosage Form/Strength	Aqueous injection: each syringe contains 105 mg of romosozumab (genetical recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Definition

Romosozumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human sclerostin monoclonal antibody and framework regions and constant regions derived from human IgG2. Romosozumab is produced in Chinese hamster ovary cells. Romosozumab is a glycoprotein (molecular weight, approximately 149,000) composed of 2 heavy (H)-chains (γ2-chains) consisting of 449 amino acid residues each and 2 light (L)-chains (κ-chains) consisting of 214 amino acid residues each.

Structure

Amino acid sequence and major disulfide bonds:

L-chains

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DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKP GKAPKLLIYY
TSRLLSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GDTLPYTFGG
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC
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H-chains

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EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
INPNSGGAGY NQKFKGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARLG
YDDIYDDWYF DVWGQGTTVT VSSASTKGPS VFPLAPCSRS TSESTAALGC
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSNFG
TQTYTCNVDH KPSNTKVDKT VERKCCVECP PCPAPPVAGP SVFLFPPKPK
DTLMISRTPE VTCVVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS
TFRVVSVLTV VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGQPREPQV
YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPML
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK
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Pyroglutamic acid (partial): H-chain E1

Glycosylation: H-chain N299

Processing (partial): H-chain K449

Intrachain disulfide bonds: intra L, C23-C88 and C134-C194; intra H, C22-C96, C150-C206, C263-C323, and C369-C427

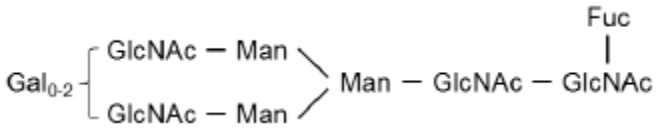
Interchain disulfide bonds: inter L-H, C214-C225; inter H-H, C137-C226, C229-C229, and C232-C232

Or

Intrachain disulfide bonds: intra L, C23-C88, C134-C194; intra H, C22-C96, C150-C206, C229-C232, C263-C323, and C369-C427

Interchain disulfide bonds: inter L-H, C214-C225; inter H-H, C137-C226

Deduced structure of major glycan:



Gal, galactose; GlcNAC, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6452}H_{9926}N_{1714}O_{2040}S_{54}$ (protein moiety)

Molecular weight: approximately 149,000

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of osteoporosis with a high risk of fracture, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication	Osteoporosis with a high risk of fracture
Dosage and Administration	The usual adult dosage is 210 mg of romosozumab (genetical recombination) administered as a subcutaneous injection once a month for 12 months.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

October 15, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval	
Brand Name	Evenity Subcutaneous Injection 105 mg Syringe
Non-proprietary Name	Romosozumab (Genetical Recombination)
Applicant	Amgen Astellas BioPharma K.K.
Date of Application	December 19, 2016
Dosage Form/Strength	Aqueous injection: each syringe contains 105 mg of romosozumab (genetical recombination)
Proposed Indication	Osteoporosis with a high risk of fracture
Proposed Dosage and Administration	The usual adult dosage is 210 mg of romosozumab (genetical recombination) administered as a subcutaneous injection once a month for 12 times.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Romosozumab (Genetical Recombination) (hereinafter referred to as "romosozumab") is a humanized IgG2 monoclonal antibody against sclerostin developed by a US-based company, Amgen. Sclerostin, a glycoprotein produced by osteocytes, is a negative regulator of the canonical Wingless-related integration (Wnt) signaling pathway, which mediates degradation inhibition of β-catenin. Inhibition of canonical Wnt signaling in osteoblast-lineage cells by sclerostin inhibits osteoblastic bone formation and promotes osteoclastic bone absorption. Romosozumab binds to sclerostin, preventing inhibition of canonical Wnt signaling in osteoblast-lineage cells, thereby promoting bone formation and inhibiting bone absorption. It is by this mechanism that the volume of cancellous bone and cortical bone is thought to increase, leading to enhanced bone strength.

Recently, an application for marketing approval has been filed based on data that demonstrated the efficacy and safety of romosozumab for the treatment of osteoporosis with a high risk of fracture.

Outside Japan, applications for approval of romosozumab were filed in the US in July 2016, [redacted] in [redacted], and [redacted] and [redacted] in [redacted] 20[redacted]. In a foreign active-controlled study (Study 20110142), which was ongoing when the application was filed in Japan, there was an imbalance in the incidence of serious cardiovascular adverse events between the romosozumab group and the control group treated with alendronate. In July 2017, the US authority therefore released a Complete Response Letter. Subsequently, results of 3 phase III studies including Foreign Study 20110142 were analyzed again, and a re-application was filed in July 2018 in response to the Complete Response Letter. As of October 2018, romosozumab has not been approved in any country or region.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Preparation and control of cell substrate

Sclerostin gene knockout mice were immunized with recombinant full-length mature human sclerostin, and their splenocytes were fused with mouse myeloma cells to create hybridomas, from which optimal clones were selected on the basis of indicators such as [redacted] and [redacted]. The gene arrangements encoding the heavy chain variable region and light chain variable region obtained from the clones were humanized, and were fused with the gene arrangements of human hybridoma-derived [redacted] and [redacted], respectively, thereby creating gene fragments encoding the heavy chain and light chain. The gene expression construct for the heavy chain and light chain was produced respectively by inserting these gene fragments into the expression vectors. The expression construct for both genes was introduced into the Chinese hamster ovary (CHO) cell line. The master cell bank (MCB) and working cell bank (WCB) were prepared from the clones optimal for the production of romosozumab.

Characterization and purity testing were conducted for the MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) in accordance with the "Viral Safety Evaluation of Biotechnology Products

Derived from Cell Lines of Human or Animal Origin" (ICH Q5A (R1) Guidelines, PMSB/ELD Notification No.329 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare, dated February 22, 2000), "Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products" (ICH Q5B Guidelines, PMSB/ELD Notification No.3, dated January 6, 1998), and "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (ICH Q5D Guidelines, PMSB/ELD Notification No.873, dated July 14, 2000). The results of the characterization and purity testing demonstrated genetic stability during production. Within the range tested, no viruses or nonviral infectious substances were detected other than general endogenous retrovirus-like particles from rodent-derived cell lines.

Both the MCB and WCB are stored at [redacted]°C [redacted]. While no renewal of the MCB is planned, the WCB will be renewed as necessary.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: expansion culture, production culture, harvesting, [redacted] chromatography, low-pH viral inactivation, [redacted], [redacted], virus filtration, ultrafiltration/diafiltration, [redacted], and filtration/filling/storage/testing.

Critical steps are [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

Process validation is performed in [redacted] for the manufacturing process of the drug substance.

2.1.3 Safety evaluation of adventitious agents

With the exception of CHO cell lines, the host cells, no biologically derived materials are used in the manufacturing process of the drug substance.

Purity was tested on the MCB, WCB, and CAL [see Section "2.1.1. Preparation and control of cell substrate"]. Bioburden testing, mycoplasma testing, *in vitro* adventitious virus testing, and transmission electron microscopy were performed on pre-harvest unprocessed bulk manufactured on a commercial scale. Within the range studied, the tests detected no contamination caused by viral or nonviral adventitious infectious substances.

The bioburden testing, mycoplasma testing, and *in vitro* adventitious virus testing on pre-harvest unprocessed bulk are selected as in-process control tests.

A viral clearance study was performed with model viruses for the purification process. The results showed that the purification process has a sufficient viral clearance capacity (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Viral clearance factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Low pH viral inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus filtration[a)]	[redacted]	[redacted]	[redacted]	[redacted]
Total viral clearance factor	≥18.29[a)]	≥19.32[a)]	≥11.15[a)]	≥7.88

a) Only the minute virus of mice detection assay was performed for the virus filtration process. According to the applicant's explanation, the total viral clearance factors calculated by adding the clearance factor for minute virus of mice as an estimated value are ≥23.44 for xenotropic murine leukemia virus, ≥24.47 for pseudorabies virus, and ≥16.30 for reovirus type 3.

2.1.4 Manufacturing process development

The major changes made to the manufacturing process during the drug substance development process are shown below (the manufacturing processes are referred to as Process A, Process B, and the proposed manufacturing process). The formulation manufactured with the drug substance manufactured by Process B was used in the phase III study of romosozumab conducted in and outside Japan.

- From Process A to Process B: Changes including [redacted] (from [redacted] to [redacted]), [redacted] condition and [redacted] component in the [redacted] and [redacted], [redacted], [redacted], and [redacted] in each [redacted] step in [redacted].
- From Process B to the proposed manufacturing process: Changes including addition of [redacted] to [redacted], [redacted], and [redacted] components.

When the manufacturing processes were changed, comparability was evaluated in terms of the quality attributes, and the results demonstrated comparability of the drug substance before and after the change. A bioequivalence study was performed using formulations produced from the drug substances manufactured by Process B or the proposed manufacturing process, and the results demonstrated the bioequivalence of the formulations [see Section "6.1.1 Bioequivalence study of formulations produced from drug substances at different manufacturing sites and/or by different manufacturing processes"].

The manufacturing process was developed using a quality-by-design (QbD) approach [see Section "2.3 QbD"].

2.1.5 Characterization

2.1.5.1 Structure and properties

The characterization was performed as summarized in Table 2.

Table 2. Evaluation items for characterization

Primary structure	Amino acid sequence, N- and C- terminal amino acid sequences, oxidation, deamidation of asparagine, [redacted], glycation, and N-glycosylation sites
Higher order structure	Secondary structure, tertiary structure, disulfide bonds, disulfide isoforms, trisulfide bonds, thioether group, free thiol group, thermal stability
Physicochemical properties	Molecular weight, charge variants, size variants, non-glycosylated heavy chain
Glycan structure	N-linked glycans, non-consensus N-linked glycosylation, sialylation, non-human glycans, O-linked glycans
Biological activity	Sclerostin binding activity, sclerostin inhibitory activity, neonatal Fc receptor binding activity

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization in Section "2.1.5.1 Structure and properties," Product-related Substances A, B, C, D, E, F, G, H, I, J, K, and L were specified. Also, Product-related Impurities A, B, C, D, and E were specified. The Product-related Impurities are adequately controlled by the specifications for the drug substance and drug product except for Product-related Impurities C and E. Product-related Impurities C and E are regarded as controllable at a sufficiently low level by the manufacturing process, and are therefore not controlled by the specifications.

2.1.5.3 Process-related impurities

Process-related impurities were defined as host cell protein (HCP), host cell deoxyribonucleic acid (DNA), and Process-related Impurity A. All the process-related impurities were confirmed to be adequately removed during the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include strength, identification (ELISA), purity ([redacted]), bacterial endotoxins, microbial limits, potency ([redacted] inhibitory activity), and assay (ultraviolet-visible spectrophotometry). The strength and assay were specified during the review process after the application for approval was filed.

2.1.7 Stability of drug substance

Main stability studies for the drug substance are shown in Table 3.

Table 3. Summary of main stability studies for the drug substance

	Manufacturing process	No. of batches	Storage condition	Study period	Storage form
Long-term testing	Process B	3	−30 ± [redacted]°C	60 months	[redacted] container
	Proposed process	3		[redacted] months[a)]	
Accelerated testing	Process B	3	5 ± [redacted]°C	6 months	
	Proposed process	3			
Stress testing	Process B	3	25 ± [redacted]°C	6 months	
	Proposed process	3			
	Process B	3	40 ± [redacted]°C	3 months	
	Proposed process	3			

a) The study for [redacted] batches will be conducted for up to [redacted] months; the stability studies are ongoing up to Month 60

The long-term testing showed no clear changes in quality attributes throughout the test period.

The accelerated testing showed that high molecular weight molecular species tended to increase in [redacted] or [redacted].

In the stress testing (at 25°C), high molecular weight molecular species increased in [redacted] or [redacted], [redacted] and [redacted] peaks tended to increase in [redacted], and [redacted] tended to decrease in [redacted] ([redacted]).

In the stress testing (at 40°C), high molecular weight molecular species increased in [redacted] or [redacted], [redacted] and [redacted] peaks increased in [redacted], and [redacted] tended to decrease in [redacted] ([redacted]).

Based on the above results, a shelf life of [redacted] months was proposed for the drug substance when stored [redacted] at [redacted] ± [redacted]°C in [redacted] container.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is supplied in a [redacted] syringe (1.17 mL) containing 105 mg of romosozumab. The drug product contains, as excipients, calcium acetate anhydrous, glacial acetic acid, sucrose, polysorbate 20, sodium hydroxide, and water for injection. The drug product is a combined product consisting of a needle-syringe filled with the drug solution.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of thawing/pool/mixing of the drug substance, dilution/mixing, pre-filtration, sterile filtration, filling/capping, syringe assembly/packaging/labeling, and storage/testing. [redacted] is a critical step.

Process validation was also performed for the manufacturing process of the drug product on a commercial scale.

2.2.3 Manufacturing process development

Major changes occurred during the development of the drug product in formulation (active ingredient concentration), [redacted] (from [redacted] to [redacted] or [redacted] syringe), [redacted] and [redacted]. These changes involved the evaluation of comparability in quality attributes, and the results demonstrated the comparability of the drug product before and after the change. Formulation changes required bioequivalence studies, and the results demonstrated the bioequivalence between the formulations [see Sections “6.1.1 Bioequivalence study of formulations produced from drug substances at different manufacturing sites and/or by different manufacturing processes” and “6.1.2 Bioequivalence study of formulations with different romosozumab concentrations”].

The manufacturing process was developed using a QbD approach [see Section "2.3 QbD"].

2.2.4 Control of drug product

The proposed specification for the drug product include strength, description, identification (ELISA and peptide mapping), purity (, , and [ ]), extractable volume, bacterial endotoxins, sterility, foreign insoluble matter, insoluble particulate matter, potency (inhibitory activity), and assay (ultraviolet spectrophotometry). The in-process testing ( ) of is defined as real-time release testing that substitutes specification testing for the final formulation. The peptide mapping was specified during the review after the filing of the application for approval.

2.2.5 Stability of drug product

Main stability studies for the drug product are shown in Table 4.

Table 4. Summary of main stability studies for the drug product

	Manufacturing method of drug substance[a)]	No. of batches	Storage condition	Study period	Storage form
Long-term testing	Method B	3	5 ± 3°C	months	syringe with chlorobutyl rubber plunger
	Proposed method	3		months[b)]	
Accelerated testing	Method B	3	25 ± °C	6 months	
	Proposed process	3			
	Process B	1	30 ± °C	3 months	
	Proposed method	3			
Stress testing	Method B	3	40 ± °C		
	Proposed method	3			
Photostability testing	Proposed method	1	Cumulative illumination of 1.2 million lux·h, and integrated near ultraviolet energy of ≥200 W·h/m^2		
Thermal cycling testing	Proposed method	1	After storing at −30°C , the drug product is stored at °C , and then at 40°C . Repeat the cycle times.		

a) The drug substance manufactured by the proposed method was used to prepare the drug product by the proposed method. The drug substance manufactured by Method B was used to prepare the drug product by a process different from that of the drug product in , and the like.
b) The stability studies are ongoing up to months.

The long-term testing showed no clear changes in quality attributes throughout the test period.

In the accelerated testing (at 25°C and 30°C), and peaks tended to increase in , high molecular weight molecular species (mainly) tended to increase in or , and tended to decrease in ( ).

In the stress testing, and peaks tended to increase in , high molecular weight molecular species (mainly) increased in or , and decreased in ( ).

Photostability testing showed that the drug product was not photostable.

The results of thermal cycling testing showed no clear changes in quality attributes.

Based on the above stability results, a shelf life of 36 months was proposed when the drug product is stored at 2°C to 8°C in a [redacted] syringe with chlorobutyl rubber plunger, protected from light in a cardboard box.

2.3 QbD

The QbD approach was applied to develop the drug substance and drug product. The quality control strategy has been established based on the following examinations.

- Identification of critical quality attributes (CQAs)

  Regarding the quality attributes of product-related substances, product-related impurities, process-related impurities, and general quality, the following CQAs were identified based on information obtained during the development of the drug product, relevant findings, and other.

  - [redacted], [redacted], adventitious virus or mycoplasma, [redacted], sterility or [redacted]

- Process characterization

  Steps that may have an impact on CQA were identified. In these steps, input variables (critical process parameters) and output variables (performance characteristics), both of which may have a critical impact on CQAs and process performance, were also identified.

- Development of control method

  Based on the process knowledge including the above process characterization, batch analysis data, stability data, and other relevant data, control methods for the quality attributes of romosozumab were established. The control of quality attributes comprises a combination of the control of process parameters/performance characteristics, in-process control, and specifications [see Sections "2.1.5.2 Product-related substances/Product-related impurities," and "2.1.5.3 Process-related impurities" for control of product-related impurities and process-related impurities].

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that the quality of the drug substance and drug product had been appropriately controlled.

2.R.1 Novel excipients

The drug product contains calcium acetate anhydrous, a novel excipient which has not been previously used in subcutaneous injections. Based on the submitted data, PMDA concluded that there are no problems in relation to the specification and stability of calcium acetate anhydrous, and there are no safety problems associated with clinical use of romosozumab (clinically recommended dose, 210 mg).

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Studies of primary pharmacodynamics include *in vitro* investigation of the action mechanisms of romosozumab including its binding affinity for sclerostin, and *in vivo* investigation of effects on bone volume and bone quality using rat and monkey models of osteoporosis. Studies of secondary pharmacodynamics include investigation of effects in animal models of osteoarthrosis. Studies of safety pharmacology include investigation of effects on the central nervous system, cardiovascular system, and respiratory system. Results from the main studies are presented in the following sections. No pharmacodynamic drug interaction studies were conducted.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies (CTD 4.2.1.1-1 to 3)

In the *in vitro* studies, romosozumab bound to human, monkey, and rat sclerostins, and the equilibrium dissociation constant (Kd) analyzed by kinetic exclusion assay was 11, 23, and 3 pmol/L, respectively. The Kd of r13C7, a rat anti-sclerostin antibody, against rat sclerostin was 6 pmol/L.

Sclerostin is considered to bind to low-density lipoprotein receptor-related protein (LRP) 4, LRP5, and LRP6, thereby inhibiting canonical Wnt signaling (*FASEB J.* 2005;19:1842-4, and *J Exp Med.* 2004;199:805-14). The effects of romosozumab against binding of human sclerostin to extracellular domains of LRP4, LRP5, or LRP6 were studied by immunoprecipitation. Romosozumab inhibited the binding of sclerostin to LRP5 or LRP6, but did not inhibit binding to LRP4.

In mouse calvaria-derived osteoblast-lineage cell lines (MC3T3-E1-BF) in which differentiation was induced by ascorbic acid and β-glycerophosphate, human, monkey, rat, and mouse sclerostins suppressed calcification in a concentration-dependent manner. Romosozumab (0, 10, 20, and 40 μg/mL) inhibited the calcification suppressing effect of sclerostin derived from the above species in a concentration-dependent manner.

3.1.2 Investigation using animal models for osteoporosis

3.1.2.1 52-week repeated administration study in ovariectomized rats (CTD 4.2.1.1-5)

Female rats (6 months of age; n = 20-50/group) were ovariectomized (OVX), and romosozumab (3, 10, or 50 mg/kg) or vehicle[1)] was subcutaneously administered to the rats from 2 months after the ovariectomy once weekly for 52 weeks. The vehicle was administered to the sham surgery group (6 months of age; n = 20) in a similar manner. Serum drug concentrations and anti-drug antibodies were measured over time, and antibody-positive animals were excluded from all the analyses.[2)]

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1) 55 mmol/L acetate, 13 mmol/L calcium, 6% sucrose, and 0.006% polysorbate 20 (pH5.2)

2) Anti-drug antibody-positive rats at Week 12 and later were to be excluded from the study. However, in order to secure an adequate number of rats for the analysis, anti-drug antibody-positive rats that received romosozumab were included in the analysis in descending order of increase in lumbar vertebral BMD at Week 12, and 20 rats (sham surgery group), 20 (OVX control), 18 (romosozumab 3 mg/kg), 18 (romosozumab 10 mg/kg), and 20 (romosozumab 50 mg/kg) were continuously treated up to Week 52. Further, rats with a high S/N ratio (ratio to the negative control) and a low serum drug concentration at Week 52 and the like were excluded. Consequently, the number of rats analyzed at Week 52 were 10 (sham surgery group), 15 (OVX control), 15 (romosozumab 3 mg/kg), 10 (romosozumab 10 mg/kg), and 15 (romosozumab 50 mg/kg).

Bone volume was measured over time,[3] using dual-energy X-ray absorptiometry (DXA) for the lumbar vertebrae and femur, and peripheral quantitative computed tomography (pQCT) for the tibia. The results showed that the percentage change from baseline[4] in bone mineral density (BMD) at the lumbar vertebrae and femur, as well as that of cancellous BMD at the tibial metaphysis increased over time. Bone mineral density increased in a dose-dependent manner in the romosozumab ≥3 mg/kg groups, and was higher than in the OVX control group at Week 12/13 and later. Bone mineral density in the romosozumab ≥3 mg/kg groups also tended to be higher at Week 12/13 and later than sham surgery controls. The percentage change from baseline in cortical BMD at the tibial diaphysis increased over time. Bone mineral density increased at Week 51/52 in the romosozumab 3 mg/kg group, and at Week 12/13 and later in the romosozumab ≥10 mg/kg groups, relative to the OVX control group.

Bone turnover markers were measured over time.[5] Serum osteocalcin (OC), and serum type I collagen cross-linked C-telopeptide (CTX) tended to be higher in the romosozumab group than in the OVX control group at Week 11 and later. No effects of romosozumab on urinary deoxypyridinoline (DPD) were noted.

Bone histomorphometry was performed on the tibiae and lumbar vertebrae removed at Week 52. Bone formation rates at the lumbar vertebrae and tibial metaphysis were higher in the romosozumab ≥3 mg/kg groups than in the OVX control group, while no effects of romosozumab therapy on osteoclast surface, osteoid volume, or osteoid surface were noted. The trabecular thickness at the lumbar vertebrae and tibial metaphysis, and the osteonal wall width of the lumbar vertebrae increased in a dose-dependent manner in the romosozumab ≥3 mg/kg groups, and were higher than those of the OVX control group. The bone formation rates on the endocortical and periosteal surfaces at the tibial diaphysis tended to increase more in the romosozumab group than in the OVX group, while romosozumab did not affect the eroded surface of the endocortical bone. The results showed a significant dose-dependent increase in cortical bone thickness and decrease in bone marrow cavity size in the romosozumab ≥3 mg/kg groups relative to the OVX control group, indicating that the trends were in agreement with the decreased endocortical perimeter and increased periosteal perimeter. The bone architecture of the lumbar vertebrae and femoral neck removed at Week 52 was evaluated by micro-computed tomography (micro-CT), and the results indicated the same trends.

Bone strength using the bones removed at Week 52 was measured by the following method: the lumbar vertebrae by the compression test, the femoral diaphysis by the 3-point bending test, and the femoral neck by the shearing test. The results showed that the maximum load for the lumbar vertebrae increased in a dose-dependent manner. The maximum load at the femoral neck and femoral diaphysis increased roughly in a dose-dependent manner in the romosozumab group relative to the OVX control group. At Week 52, the maximum load at the lumbar vertebrae and femoral neck was positively correlated with the bone mineral content (BMC) (lumbar vertebrae by pQCT; femoral neck by DXA), and the maximum load at the femoral diaphysis was positively correlated with the cortical BMC (pQCT).

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[3] Measurements were taken at Weeks 0, 12/13, 25/26, and 51/52.

[4] Percentage change from baseline when the administration of the investigational drug or vehicle began

[5] Measurements were taken at Weeks 0, 11, 24, 39, and 50.

3.1.2.2 26-week administration study in OVX rats (CTD 4.2.1.1-4)

Female rats (4 months of age; n = 10-12/time point/group) were ovariectomized, and from 2 months after the ovariectomy, rat-anti-sclerostin antibody (r13C7, 25 mg/kg) was subcutaneously administered once weekly for 26 weeks, or vehicle[6)] was subcutaneously administered once or twice weekly for 26 weeks. Vehicle was subcutaneously administered to the rats in the sham surgery group (4 months of age; n = 10-12/time point) once or twice weekly for 26 weeks.

Bone volume was measured over time,[7)] using DXA in the lumbar vertebrae and hindlimb. BMD increased in the r13C7 group over time up to Week 26. Bone mineral density was higher in the treatment group at Week 3 and later relative to the OVX control group, and at Week 6 and later than the sham surgery group.

The results of bone turnover marker levels over time[7)] showed that serum OC, and serum type I procollagen-N-propeptide (P1NP) remained higher in the r13C7 group than the OVX control group, up to Week 12 and Week 26, respectively. Although serum tartrate-resistant acid phosphatase 5b (TRACP5b) was lower than the OVX control group at Weeks 6 and 9, the levels remained similar to OVX control levels at the remaining time points.

Bone histomorphometry of the lumbar vertebrae and tibiae removed at Weeks 0, 6, 12, and 26 indicated that bone formation rates on the trabecular surface of the lumbar vertebrae and tibial metaphysis, and on the endocortical and periosteal surfaces at the tibial diaphysis peaked at Week 6 in the r13C7 group. The bone formation rates were higher than the OVX control group, and then decreased. Bone formation rates on the trabecular surface of the lumbar vertebrae and tibial metaphysis, and the eroded surface and osteoclast surface of the endocortical bone at the tibial diaphysis decreased in the r13C7 group compared to the OVX control group over most of the treatment period. It was found that the osteoid thickness of the vertebral trabecular surface was not affected by r13C7 treatment. Osteoclast formation was investigated by tartrate-resistant acid phosphatase (TRAP) staining using femoral bone marrow sampled at Weeks 6, 12, and 26. While the increase in osteoclasts by OVX was suppressed in the r13C7 group at Week 6, no effects of r13C7 treatment were noted at Week 12 or at Week 26.

The bone architecture of the lumbar vertebrae and femurs removed at Weeks 0, 6, and 26 was evaluated by micro-CT. The trabecular thickness of lumbar vertebral cancellous bone, and the cortical bone thickness at the femoral diaphysis increased significantly in the r13C7 group compared to the OVX control and sham surgery groups at Weeks 6 and 26. The trabecular number of the lumbar vertebral cancellous bone decreased significantly compared to the OVX control and sham surgery groups.

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6) 10 mmol/L sodium acetate, 9% sucrose, and 0.004% polysorbate 20 (pH5.0)

7) Measurements were taken at Weeks 0, 3, 6, 9, 12, 15, 18, 22, and 26.

Bone strength using the bones removed at Weeks 0, 6, and 26 was measured by the following method: the lumbar vertebrae by the compression test, the femoral diaphysis by the 3-point bending test, and the femoral neck by the shearing test. Compared with the OVX control and sham surgery groups, the maximum load at the lumbar vertebrae and femoral neck increased at Weeks 6 and 26, and the maximum load at the femoral diaphysis increased at Week 26. At Week 26, the maximum load at the lumbar vertebrae and femoral neck was positively correlated with the BMC (micro-CT), and the maximum load at the femoral diaphysis was positively correlated with the cortical BMC (micro-CT).

3.1.2.3 52-week repeated administration study in OVX monkeys (CTD 4.2.1.1-6)

Female monkeys (≥8.5 years of age; n = 16/group) were ovariectomized, and romosozumab (3, and 30 mg/kg) or vehicle[1)] was subcutaneously administered to the monkeys from 4 months after the ovariectomy once weekly for 52 weeks. Also, romosozumab (30 mg/kg) was subcutaneously administered to female monkeys (≥8.5 years of age; n = 16) from 4 months after the ovariectomy once weekly for 26 weeks, which was followed by subcutaneous administration of vehicle once weekly for 26 weeks (romosozumab 30 mg/kg-vehicle group). Furthermore, vehicle was subcutaneously administered to the sham surgery group (≥8.5 years of age; n = 16) once weekly for 52 weeks. Serum drug concentrations and anti-drug antibodies were measured over time, and antibody-positive animals were excluded from all the analyses.[8)]

Bone volume was measured over time,[9)] using DXA for the lumbar vertebrae, femur, etc., and pQCT for the tibia and radius. The result showed that the percentage change from baseline[4)] in lumbar vertebral BMD increased in the romosozumab 3 and 30 mg/kg groups up to Week 52. Bone mineral density increased relative to the OVX control group at Week 9/10 and later, and tended to increase more than that of the sham surgery group. The percentage change from baseline in femoral BMD, and the percentage change from baseline in cancellous BMD at the tibial and radial metaphyses showed similar trends. The percentage change from baseline in cortical BMD at the radial diaphysis tended to be lower in the romosozumab 3 and 30 mg/kg group than in the OVX control group at Weeks 11/12 and 24/25, and then returned to the similar levels to the OVX control group at Week 51/52. The percentage change from baseline in the cortical bone thickness at the radial diaphysis increased in a dose-dependent manner in the romosozumab 3 and 30 mg/kg groups throughout the treatment period, and the trends were in agreement with the increased periosteal perimeter and decreased endocortical perimeter.

The results of bone turnover markers measured over time[10)] showed that the percentage change from baseline[4)] in serum bone alkaline phosphatase (BAP), OC, P1NP, and CTX increased in a dose-dependent manner in the romosozumab 3 and 30 mg/kg groups, and peaked at around Week 9/10 before decreasing. The percentage change from baseline in serum type I collagen cross-linked N-telopeptide (NTX) tended to be

8) The following animals were excluded from the analysis: (1) positive for anti-drug antibody, and S/N ratio of >1000; (2) positive for neutralizing antibody; and (3) serum romosozumab concentration below the limit of quantitation, up to Week 52 (for the romosozumab 3 mg/kg and 30 mg/kg groups), or up to Week 26 (for the romosozumab 30/0 mg/kg group). The number of animals analyzed were 6 (romosozumab 3 mg/kg group), 15 (romosozumab 30 mg/kg group), and 14 (romosozumab 30/0 mg/kg group).

9) Measurements were taken at Weeks 0, 11/12, 24/25, and 51/52.

10) Measurements were taken at OVX, Week 0, 9/10, 23/24, 37, and 49/50.

higher in the romosozumab 3 and 30 mg/kg groups relative to the OVX control group throughout the treatment period. The percentage change from baseline in serum calcium level showed a transient decrease in the romosozumab 30 mg/kg group at Weeks 9/10 and 23/24, and the percentage change from baseline[4)] in serum parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D, or $1,25(OH)_2$ vitamin D level tended to be higher in the romosozumab 3 and 30 mg/kg groups than in the OVX control group throughout the treatment period.

Bone histomorphometry was performed on the ribs and ilia obtained by biopsy at Weeks 13 and 27, and lumbar vertebrae, femurs, and ribs removed at Week 52. The results showed increases in bone volume and trabecular thickness, and a decrease in trabecular spacing in cancellous bone of the ilium in the romosozumab 3 and 30 mg/kg groups relative to the OVX control group at Weeks 13 and 27. The bone formation rate increased in the romosozumab 3 and 30 mg/kg groups relative to the OVX control group at Week 13 then slightly decreased at Week 27. While a dose-dependent decrease in the eroded surface and increase in osteonal activation frequency were noted at Week 13, effects of romosozumab therapy were not found at Week 27. The bone formation surface increased, and resting bone surface decreased in the romosozumab 3 and 30 mg/kg groups relative to the OVX control group at Weeks 13 and 27. In the cancellous bone at the lumbar vertebrae and femoral neck, bone volume and trabecular thickness increased significantly in the romosozumab 30 mg/kg group relative to the OVX control group at Week 52; however, romosozumab did not affect bone formation rates. Throughout the treatment period, romosozumab did not affect osteoid thickness or mineralization lag time. In the rib cortical bone, the cortical thickness increased and the marrow region decreased in the romosozumab 30 mg/kg group relative to the OVX control group at Weeks 13, 27, and 52. Similar trends were noted in the romosozumab 3 mg/kg group. Bone formation rates increased in the endocortical and periosteal surfaces in the romosozumab 30 mg/kg group relative to the OVX control group at Week 13, and then decreased over time. Endocortical eroded surface decreased at Week 13 in the romosozumab 3 and 30 mg/kg groups, and at Week 27 in the romosozumab 30 mg/kg group relative to the OVX control group; however, no effects of romosozumab were noted at Week 52. Haversian bone formation rates tended to increase in the romosozumab 3 and 30 mg/kg groups at Weeks 13 and 27 relative to the OVX control group; however, no effects of romosozumab were noted at Week 52.

The bone architecture of the lumbar vertebrae and other bones was evaluated by micro-CT. The trabecular thickness of lumbar vertebral cancellous bone increased relative to the OVX control group in a dose-dependent manner. However, no effects on trabecular number were found. Structure model index (SMI), an index of trabecular structure, decreased in a dose-dependent manner, and relative to the OVX control group.

Bone strength using the bones removed at Week 52 was measured by the following method: the lumbar vertebrae and the vertebral core by the compression test, the femoral diaphysis by the 3-point bending test, and the femoral neck by the shearing test. Compared with the OVX control group, the maximum load was higher at the lumbar vertebrae and vertebral core in the romosozumab 3 and 30 mg/kg groups, and at the

femoral diaphysis and femoral neck in the romosozumab 30 mg/kg group. Furthermore, the maximum load at the femoral diaphysis was positively correlated with the cortical BMC (pQCT). With the exception of the romosozumab 3 mg/kg group, the maximum load at the lumbar vertebrae was positively correlated with the BMC (pQCT), and the maximum load at the femoral neck was positively correlated with the BMC (DXA).

In the romosozumab 30 mg/kg-vehicle group, effects on bone volume and bone strength (maximum load) were reduced by switching to vehicle, and were the similar levels to those of the romosozumab 3 mg/kg group or the sham surgery group at Week 52. Bone turnover markers decreased to the similar levels to the OVX control group by Week 52. Overall, effects on bone histomorphometry indices decreased to OVX control levels, and the trabecular thickness and the bone formation rate of the cancellous bone at the lumbar vertebrae and femoral neck were similar to OVX control levels. Cortical thickness of the rib and femoral diaphysis, and the bone formation rates at the periosteal surface, endocortical surface and Haversian bone were similar to OVX control levels. While the eroded surface in the cancellous bone at the femoral neck and the rib endocortical surface tended to be greater relative to the OVX control group, it tended to be smaller on the endocortical surface at the femoral diaphysis.

3.1.2.4 26-week repeated administration study in OVX monkeys (CTD 4.2.1.1-7)

OVX Female monkeys (9-16 years of age; 12-32 animals/group) received romosozumab (3 mg/kg) or vehicle[1)] subcutaneously from 4 months post-surgery once weekly for 26 weeks. Anti-drug antibodies were measured at Weeks 12 and 26, and antibody-positive animals were excluded from any of the analyses.[11)]

Bone volume was measured over time,[12)] using DXA for the lumbar vertebrae, etc., pQCT and high-resolution peripheral quantitative computed tomography (HRpQCT) for the radius, etc. The percentage change from baseline in the lumbar vertebral BMD[4)] at Week 25/26 (DXA), and the percentage change from baseline in cancellous BMD at the radial metaphysis (pQCT) at Weeks 12/13 and 25/26 were higher relative to the OVX control group. The trabecular thickness of cancellous bone at the radial metaphysis at Week 25/26 was higher than the OVX control group (HRpQCT). While the percentage change from baseline in cortical tissue BMD at the radial diaphysis remained lower than the OVX control group (HRpQCT), the percentage change from baseline in cortical thickness at the radial diaphysis at Weeks 12/13 and 25/26 were higher than the OVX control group (pQCT).

Bone turnover markers were measured over time,[13)] and percentage change from baseline[4)] in serum P1NP, OC, and BAP increased in the romosozumab group relative to the OVX control group from Week 1 or 4 up to Week 24, peaked at Weeks 4 to 7. The percentage change from baseline in serum CTX increased in the romosozumab group relative to the OVX control group from Weeks 7 to 24, and peaked at Week 10. The

11) Based on data including anti-drug antibody levels, S/N ratio, neutral antibody levels, serum romosozumab concentrations, of the anti-drug antibody-positive animals at Week 12, 9 animals were excluded from the study, and 23 animals continued treatment up to Week 26. More animals, including 2 animals positive for anti-drug antibody at Week 26, were excluded from the analysis. The number of animals analyzed at Week 26 was 19.

12) Measurements were taken at Weeks 0, 12/13 (pQCT and HRpQCT), and 25/26.

13) Measurements were taken at Weeks 0, 1, 4, 7, 10, 17, and 24.

percentage change from baseline in serum calcium level was transiently lower relative to the OVX control group at Week 10. The percentage change from baseline in serum PTH and $1,25(OH)_2$ vitamin D levels remained significantly higher in the romosozumab group than in the OVX control group for most of the treatment period.

Bone histomorphometry was performed on the radii and other bones removed at Week 26. Haversian bone formation rates were higher in the romosozumab group than the OVX control group at Week 26. While the eroded surface on the endocortical surface at the radial diaphysis tended to decrease compared with the OVX control group, romosozumab did not affect architectural parameters including cortical porosity at the radial diaphysis. Mineralization rates, measured approximately every 4 weeks, on the periosteal and endocortical surfaces at the radial diaphysis tended to be higher in the romosozumab group than in the OVX control group throughout the treatment period. The osteon number in radial cortical bone at Week 26 increased in the romosozumab group compared with the OVX control group.

Bone strength using the bones removed at Week 26 was measured by the following method: the radial diaphysis by the 3-point bending test, and the radial metaphysis by the compression test. The peak load at the radial diaphysis decreased in the romosozumab group relative to the OVX control group. However, no intergroup difference was found based on the covariate analysis with the cortical BMC at the end of the bone depletion period as the covariate. The peak load at the radial diaphysis was positively correlated with the cortical BMC at the radial diaphysis (HRpQCT). While romosozumab did not affect the peak load at the radial metaphysis, an increase in peak load was found in the covariate analysis with the total BMC at the end of the bone depletion period as the covariate, and the peak load at the radial metaphysis was positively correlated with the BMC at the radial metaphysis (HRpQCT).

3.1.2.5 Retreatment study in OVX rats (CTD 4.2.1.1-10)

Female rats (4.5 months of age; n = 8/time point/group) were ovariectomized. Rat anti-sclerostin antibody (r13C7, 5 mg/kg) or vehicle[14)] was subcutaneously administered to the rats from 11 weeks after the ovariectomy twice weekly for 12 weeks, and then the rats were left untreated for 12 weeks. After the OVX female rats (4.5 months of age; n = 8/group) were treated with subcutaneous r13C7 (5 mg/kg) twice weekly for 12 weeks (initial treatment period) 11 weeks post-OVX, and left untreated for 12 weeks (withdrawal period), r13C7 (5 mg/kg) or vehicle was subcutaneously administered twice weekly for 6 weeks (retreatment period). Additionally, female rats (4.5 months of age; n = 8) of the sham surgery group were subcutaneously administered vehicle twice weekly for 12 weeks, followed by no treatment for 12 weeks, and then vehicle was subcutaneously administered twice weekly for 6 weeks.

The time course measurement[15)] of bone volume in the lumbar vertebrae and limb by DXA showed that BMD increased over time in the r13C7 group, peaking at Week 14 (Week 2 of the withdrawal period), and

14) 10 mmol/L sodium acetate, 9% sucrose, 0.004% polysorbate 20 (pH5.2)

15) Measured every 2 weeks up to Week 30.

then decreased over time. At Week 24 (Week 12 of the withdrawal period), BMD at the lumbar vertebrae was similar to that of the sham surgery group, while BMD at the limb tended to be higher than that of the sham surgery group.

The time course measurement[15)] of bone turnover markers showed that serum OC and P1NP in the r13C7 group peaked at Week 2 or 4, decreased up to Week 12 over time, and remained similar to the OVX control levels up to Week 24 (Week 12 of the withdrawal period). Serum TRACP-5b levels remained lower in the r13C7 group than the OVX control group up to Week 6, and then remained higher relative to the OVX control group during most of the withdrawal period.

Bone histomorphometry was performed on the lumbar vertebrae and tibiae removed at Weeks 6, 12, 24, and 26. The bone formation rates at the trabecular surface of the lumbar vertebrae, and at the endocortical and periosteal surfaces at the tibial diaphysis in the r13C7 group peaked at Week 6, decreased in the withdrawal period, and tended to be the similar to or lower than those of the OVX control group at Week 24 (Week 12 of the withdrawal period). The eroded surface on the trabecular surface of the lumbar vertebrae and endocortical surface of the tibial diaphysis decreased in the r13C7 group relative to the OVX control group at Weeks 6 and 12, and increased in the withdrawal period. The eroded surface at the lumbar vertebrae remained higher at Week 24 than the OVX control group. The bone volume and trabecular thickness at the lumbar vertebrae, and cortical bone volume and cortical thickness at the tibial diaphysis were higher at Weeks 6 and 12 than the OVX control group, and even though these parameters decreased during the withdrawal period, remained higher at Week 24 than the OVX control group.

Bone mineral density, bone turnover markers, and bone histomorphometry indices in the retreatment period changed in a similar manner as in the initial treatment period.

3.1.3 Other effects

3.1.3.1 Effects on bone modeling/remodeling in male monkeys (CTD 4.2.1.1-12)

Bone histomorphometry was performed using bones including the lumbar vertebrae and femur removed at Week 10 from male monkeys that underwent fibular osteotomy [see Section “3.1.4.1 Effects on bone healing in male monkeys following fibular osteotomy”]. Romosozumab increased the modeling-based bone formation (MBF) surface, and decreased the resting bone surface and the bone resorption surface on the trabecular surface of the lumbar vertebrae and endocortical surface at the femoral diaphysis. However, romosozumab did not affect remodeling-based bone formation (RBF) surface at any sites. At all sites, the bone mineralizing surface and bone formation rate on MBF surface increased greater in the romosozumab group, romosozumab did not affect RBF surface. Furthermore, the results suggested an extended bone formation period at all sites.

3.1.3.2 Effects on bone remodeling in male monkeys (CTD 4.2.1.1-13)

Romosozumab (30 mg/kg) or vehicle[6)] was subcutaneously administered to male monkeys[16)] (10-12 years of age; n = 10-12/group) every 2 weeks for 28 weeks. Labeled materials were administered on a regular basis, and bone histomorphometry and kinetic reconstruction analysis (*Bone.* 1992;13:147-52) were performed[17)] on the lumbar vertebrae removed from 9 animals per group. The osteonal wall width in the bone multicellular unit in the romosozumab group increased by 89%, and bone resorption depth decreased by 13% relative to the control group. Furthermore, the bone resorption period and the mineralization lag time in the bone formation period were shortened. Bone remodeling balance, representing the difference between bone resorption depth and osteonal wall width, was negative in the control group and positive in the romosozumab group.

3.1.4 Effects on fracture healing

3.1.4.1 Effects on bone healing in male monkeys following fibular osteotomy (CTD 4.2.1.1-12)

Male monkeys (4-5 years of age; n =21-22/group) underwent fibular osteotomy. From the next day, the monkeys received subcutaneous romosozumab (30 mg/kg) or vehicle[14)] every 2 weeks for 10 weeks.[18)] On the basis of X-ray findings, fracture gaps were small in the romosozumab group, and the incidence of false joints was low in all treatment groups (2 of 21 animals in the control group, and 1 of 20 animals in the romosozumab group). At fracture sites, the cartilaginous portion of the callus was small in the romosozumab group. Bone mineral content and bone strength (maximum torque, absorption energy, and rigidity) tended to increase.

3.1.4.2 Effects on fracture healing in the male rat closed femur fracture model (CTD 4.2.1.2-4)

Male rats (12 weeks of age; n = 8-26/time point/group) underwent closed femoral diaphyseal fracture. From the next day, rat anti-sclerostin antibody (r13C7, 25 mg/kg) or vehicle[6)] was subcutaneously administered twice weekly for 9 weeks. Bone histomorphometry, bone volume (DXA, pQCT, or micro-CT), and torsional strength (maximum torque, rigidity) were determined over time.[19)] The bone volume and torsional strength at the fracture site increased up to Week 9 over time in all groups. The volume of external callus peaked at Weeks 3 to 5 and turned to a decreasing trend. Fibrous bone and cartilaginous bone decreased with increasing bone volume of the external callus and marrow volume. In the r13C7 group, bone volume at the fracture site was higher at Weeks 5 to 9 relative to the control group, and torsional strength was higher relative to the control group at Week 9. While significant increases in bone volume of the external callus and decreases in marrow volume were noted in the r13C7 group relative to the control group at Weeks 5 and 9, r13C7 did not affect the fibrous or cartilaginous portion. There was a transient increase in the longitudinal growth rate of

16) The study used samples that were obtained in a study on the effects on fracture healing in gap damage models at the ulnar diaphysis.

17) The following animals were excluded from the analyses: 1 animal with decreased serum drug concentration in the romosozumab group; 1 animal with an abnormal histomorphometry index in the control group.

18) The investigational product was not detected in 4 animals in the romosozumab group by Week 6, and these animals were excluded from the analysis.

19) Bone histomorphometry was performed at Weeks 1, 2, 3, 5, 7, and 9, while bone volume and torsional strength were measured at Weeks 3, 5, 7, and 9.

the distal end of the femur in the r13C7 group, which returned to a level equivalent to that in the control group at Week 9.

3.2 Secondary pharmacodynamics

3.2.1 Effects in osteoarthritis animal models (CTD 4.2.1.2-5, 4.2.1.2-6)

Male rats (n = 20/group) underwent surgery to induce a meniscus tear in the right knee joint. From the day of surgery, the rats received rat anti-sclerostin antibody (r13C7, 25 mg/kg) or vehicle subcutaneously twice weekly for 3 weeks. There were no significant differences between the groups in weight bearing or gait. The histopathology findings of the right knee joint indicated that cartilage degeneration and osteophytes were present in all animals, and the histopathology parameters including cartilage degeneration width and osteophyte size did not differ significantly between the groups. Mild decreases in total joint score[20)] and the ratio of cartilage matrix area were noted in the r13C7 group but were not significant as compared with other groups.

Male rats (n = 20/group) underwent surgery to induce a meniscus tear in the right knee joint. Antigen-binding fragment of anti-sclerostin antibody (385 μg), antigen-binding fragment of control (385 μg), or vehicle was intraarticularly administered to the animals twice weekly for 3 weeks from 3 days prior to surgery. There were no clear differences between groups in weight bearing or gait. The histopathology findings of the right knee joint showed that cartilage degeneration, osteophytes, and synovitis were present in all animals. Histopathology parameters including cartilage degeneration width and osteophyte size in animals treated with antigen-binding fragments of anti-sclerostin antibody or control were similar to vehicle controls.

3.3 Safety pharmacology

Data from the safety pharmacology studies presented in Table 5 were submitted.

Table 5. Summary of results of safety pharmacology studies

Organ system	Species/strain	Test parameter/method	Dose	Route of administration	Findings	CTD
Central nervous system	Sprague-Dawley (SD) rat (n = 5/sex/group)	Functional observational battery (FOB)	0, 30, 100, 300 mg/kg	Intravenous	No effects	4.2.1.3-1
Cardiovascular system/ respiratory system	Cynomolgus monkey (4 females/group)	Blood pressure, heart rate, electrocardiography, respiration rate, blood gas (no anesthesia)	0, 30, 100, 300 mg/kg	Intravenous	Significant increases in heart rate and blood pressure, and a trend towards increase in respiration rate in the 300 mg/kg group relative to the control group.	4.2.1.3-2

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of romosozumab

The applicant's explanation about the mechanism of action:

The canonical Wnt signaling pathways are involved in inhibition of bone formation. Wnt signaling is activated by the binding of a Wnt ligand to a coupled receptor complex comprising LRP5/6 and Frizzled receptors (*Bone Biology and Structure.* 2007;852:250-6, *J Clin Invest*. 2006;116:1202-9). Sclerostin is a

[20)] Total of cartilage degeneration score and osteophyte score in the femur and tibia. It was rated on a 5-point scale, with higher scores indicating greater severity.

glycoprotein produced/secreted from osteocytes, binding to the extracellular domains of LRP4 and 5/6 to inhibit Wnt ligand binding, thereby inhibiting canonical Wnt signaling and bone formation in osteoblast-lineage cells (e.g., *FASEB J.* 2005;19:1842-4, *EMBO J.* 2003;22:6267-76).

Romosozumab is a humanized IgG2 monoclonal antibody that binds to sclerostin. *In vitro* studies have demonstrated that romosozumab has binding affinity for human/monkey/rat sclerostin (CTD 4.2.1.1-1), inhibitory effect on human sclerostin binding to human LRP5/6 (CTD 4.2.1.1-2), and inhibitory effect on sclerostin's ability to inhibit mineralization in osteoblast-lineage cells (CTD 4.2.1.1-3), indicating that romosozumab has neutralizing activity against sclerostin.

The *in vivo* studies in which anti-sclerostin antibodies were administered to animal models of osteoporosis showed that (1) bone volume and bone strength improved; (2) at the time of accelerated bone formation, bone formation surface increased and resting bone surface decreased in the iliac cancellous bone; and (3) MBF surface increased, while resting bone surface and bone resorption surface decreased on trabecular surfaces in the lumbar vertebrae and on endocortical surfaces at the femoral diaphysis. These results suggests that romosozumab would promote modeling-based bone formation which requires activation of lining cells primarily on resting bone surfaces in the trabecular and cortical bone (CTD 4.2.1.1-6, CTD 4.2.1.1-12, *J Bone Miner Res.* 2017;32:788-801, *J Bone Miner Res.* 2015;30:1457-67). The promotion of bone formation peaked at a relatively early stage of romosozumab therapy, and decreased over time as treatment continued to a level in the control group (CTD 4.2.1.1-4, CTD 4.2.1.1-6). In rats, the vertebral osteoblast number increased, followed by decreases in osteoblast number and osteoblast density (CTD 4.2.3.7.3-2, CTD 4.2.3.7.3-3). Prior to diminishment of the bone formation promoting effect, osteoprogenitor cell number decreased, the mRNA expression of factors involved in regulation of cell division and cell cycle (i.e., p53, Rb, Cdkn1a, and c-Myc) fluctuated (CTD 4.2.3.7.3-2). These results indicated the possibility that, in the long-term treatment with romosozumab, a transcriptional change occurs to inhibit cell division and cell cycle progression, causing to decrease in the osteoprogenitor cell number, which results in decreases in osteoblastic density and bone formation indices, thereby attenuating romosozumab's bone formation promotion. Furthermore, in osteocytes, the mRNA expression of extracellular Wnt inhibitory factors (SOST and DKK1) against canonical Wnt signaling increased, suggesting a negative feedback loop in the Wnt signaling pathway (CTD 4.2.3.7.3-2).

The identified effects of romosozumab on bone resorption in OVX rats were decreases in serum TRACP5b, a marker of osteoclast number, and bone resorption indices such as osteoclast surface. Furthermore, osteoclast formation in *ex vivo* bone marrow cell culture decreased (CTD 4.2.1.1-4), and bone resorption indices on trabecular and endocortical surfaces decreased (CTD 4.2.1.1-5, CTD 4.2.1.1-6).

The identified effects of romosozumab on bone quality were more or less increases in the trabecular thickness and cortical thickness. Although romosozumab did not affect cortical porosity, trabecular number decreased as a result of increased trabecular thickness, and bone marrow cavity size decreased as a result of

increased cortical thickness. Bone volume was positively correlated with bone strength in OVX rats and OVX monkeys, suggesting that bone quality was maintained or improved. However, romosozumab did not increase osteoid thickness, indicating that romosozumab does not affect the dynamics of mineralization.

Based on the above, romosozumab primarily promotes modeling-based bone formation and inhibits bone resorption, thereby increasing bone volume and bone strength.

PMDA considers that the data have demonstrated the increased bone volume and bone strength caused by the bone formation promoting effects of romosozumab.

3.R.2 Secondary effects resulting from sclerostin inhibitory effect of romosozumab

The applicant's explanation about effects of romosozumab's sclerostin inhibition other than bone formation promotion:

While sclerostin is primarily expressed in osteocytes in humans, rats, and monkeys, it is also expressed in other cells such as chondrocytes in the epiphyseal plate and articular cartilage, vascular smooth muscle cells in calcified blood vessels and heart valves, and cementocytes in teeth (e.g., *Am J Hum Genet.* 2001;68:577-89, *J Heart Valve Dis.* 2013;22:317-25). Studies of mRNA expression of the *Sost* genes in normal tissues from mice, rats, monkeys, and humans showed that *Sost* mRNA was expressed mainly in the bones and aorta. In humans, *Sost* mRNA was expressed in the kidney (*Hum Mol Genet.* 2001;10:537-43, CTD 4.2.1.2-7, CTD 4.2.1.2-8).

Sclerostin expressed in epiphyseal plate chondrocytes is considered to negatively regulate chondrocyte maturation, hypertrophy, cartilaginous ossification, and longitudinal bone growth (*J Biol Chem.* 2005;280:19185-95, *J Dent Res.* 2009;88:569-74). Patients with sclerosteosis, who completely lack sclerostin, are of tall stature, while heterozygous carriers of the *Sost* mutation associated with decreased expression of sclerostin and patients with van Buchem disease are typically not of tall stature (e.g., *Clin Genet.* 2003;63:192-7, *J Bone Miner Res.* 2013;28:848-54). In the study using rat closed femur fracture models, when romosozumab was administered at a dose level corresponding to 19-fold the exposure levels at the clinically recommended dose, the rate of longitudinal growth increased slightly and transiently at Weeks 3 to 7 at the metaphysis of the femur opposite of the fractured bone; however, the change was minor, and the longitudinal growth rate returned to control levels at Week 9 (CTD 4.2.1.2-4). Patients with osteoporosis have epiphyseal growth plates already being closed, and therefore, this change is unlikely to occur.

Sclerostin is also known to be expressed in articular chondrocytes. Although the functions of sclerostin and canonical Wnt signaling in articular cartilage are unclear, a mouse model with excessive or lacking canonical Wnt signaling presented with cartilage degeneration or osteoarthrosis-like changes (e.g., *Arthritis Rheum.* 2007;56:4095-103, *Arthritis.* 2008;58:2053-64). Cartilage degeneration was more severe in *Sost*$^{-/-}$mice that underwent destabilization of the medial meniscus, suggesting that cartilage degeneration progresses depending on the degree of injury (*Arthritis Rheum.* 2013;65:721-31, *Arthritis Res Ther.* 2015;17:24). A rat

meniscus tear model receiving rat anti-sclerostin antibody subcutaneously or antigen-binding fragment intraarticularly presented with no effects on histopathology parameters including cartilage degeneration width and osteophyte size (CTD 4.2.1.2-5, CTD 4.2.1.2-6). While the results suggested that sclerostin is not likely to play a significant role in osteoarthrosis, the possibility remains that the administered antibody did not reach the lesion in the articular cartilage. Osteoarthrosis has not been reported in patients with sclerosteosis or van Buchem disease (*Clin Genet.* 2003;63:192-7).

Sclerostin is also expressed in the aorta, although its function is not clear. Because sclerostin is a mineralization inhibitor, the inhibition of sclerostin may induce or worsen vascular calcification. In a cross-reactivity study, romosozumab bound to the aorta of monkeys. However, in a 26-week repeated-dose toxicity study in monkeys, there were no macroscopic or histopathologic findings indicating vascular calcification (CTD 4.2.3.2-8). Following administration of romosozumab 30 mg/kg to OVX monkeys once weekly for 52 weeks, vascular calcification was not observed in X-ray images (CTD 4.2.1.1-6). An increased incidence of cardiovascular diseases associated with vascular calcification has not been reported in patients with sclerosteosis or van Buchem disease (*Clin Genet.* 2003;63:192-7).

Sclerostin expression was also seen in cementocytes of teeth of humans and mature mice (*J Periodontal Res.* 2010;45:246-54, *J Dent Res.* 2009;88:569-74). While canonical Wnt signaling is known to be important in tooth development, the function of sclerostin in mature teeth is unknown. Activation or inhibition of Wnt signaling was found to increase dentin thickness (*Biochem Biophys Res Commun.* 2012;424:170-5, *J Bone Miner Res.* 2014;29:892-901), and hypercementosis in molars of *Sost*$^{-/-}$mice was reported (*Int J Oral Sci.* 2014;6:70-6). Mature rodents are likely to be affected by Wnt signaling because their incisors continue to develop throughout life. A carcinogenicity study in rats indicated thickening of dentin in incisors, but romosozumab did not affect the incidence of nonneoplastic lesions such as abnormal dentin, microdont, molar wear, ameloblast degeneration, malformed teeth, and dents in teeth (CTD 4.2.3.4-1.1). While the effect of romosozumab cannot be ruled out in children whose deciduous teeth or permanent teeth are developing, obvious changes in cementum have not been reported in patients with sclerosteosis or van Buchem disease. It is therefore unlikely that adult patients with permanent teeth will be affected by romosozumab.

Theoretically, possible effects of sclerostin expression include longitudinal bone growth, osteoarthrosis, vascular calcification, and changes in teeth. Based on the data from the non-clinical studies, and findings in patients with sclerosteosis or van Buchem disease, which cause a lack of or low level of sclerostin, it is unlikely that the clinically recommended dose of romosozumab (210 mg once a month) will significantly affect adult patients with osteoporosis who have mature bone and teeth and cause clinical problems.

PMDA accepted the applicant's explanation and will continue to discuss potential concerns associated with *in vivo* inhibition of sclerostin in humans in Sections "7.R.2.5 Osteoarthritis" and "7.R.2.6 Cardiovascular events."

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The pharmacokinetics in rats of a single subcutaneous or intravenous dose of romosozumab was investigated. Because romosozumab induces the production of anti-drug antibodies in rodents, mouse or rat anti-sclerostin antibody was used in some rat studies. Based on toxicokinetics in toxicity studies in rats and monkeys, the pharmacokinetics of repeated subcutaneous doses of romosozumab was investigated. Serum romosozumab concentrations, m13C7 concentrations (mouse anti-sclerostin antibody), and r13C7 concentrations (rat anti-sclerostin antibody) were determined by ELISA. The lower limit of quantitation of serum romosozumab in each study was 5, 10, 99.2, 100 or 150 ng/mL in rats, and 10, 50.0, or 875 ng/mL in monkeys. The lower limits of quantitation of serum m13C7 concentration and serum r13C7 concentration in rats were 4.88 ng/mL and 100 ng/mL, respectively. Anti-drug antibodies and neutralizing antibodies in serum were detected by electrochemiluminescence (ECL) assay. Results from the main studies are presented in the following sections.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1, 4.2.3.6-3, and 4.2.3.7.3-1)

Table 6 shows pharmacokinetic parameters of a single subcutaneous or intravenous romosozumab, mouse anti-sclerostin antibody (m13C7), or rat anti-sclerostin antibody (r13C7) in male and female rats. The mean steady-state volume of distribution (V_{ss}) in rats following a single intravenous dose of m13C7 0.1 to 10 mg/kg was 36.8 to 58.7 mL/kg.

Table 6. Pharmacokinetic parameters of a single dose of romosozumab, m13C7, or r13C7 in rats

Study drug	Sex	Route of administration	Dose (mg/kg)	N	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}168\ h}$ (μg· h/mL)	CL (mL/h/kg)
Romosozumab	F	Subcutaneous (s.c.)	5[b)]	16[d)]	24.0	48	—	2070	2.42[h)]
			35[b)]	16[d)]	193	48	—	25,800	—
			35[c)]	16[d)]	184	48	—	22,700	—
		Intravenous (i.v.)	35[c)]	12[d)]	612	—	—	45,100	—
m13C7	M	s.c.	1	4	7.24 ± 1.11	24 [24, 72]	20.1 ± 1.40	481 ± 109[f)]	2.16 ± 0.496[h)]
		i.v.	0.1	4	2.94 ± 0.28	—	5.93 ± 0.854	23.1 ± 3.33[f)]	4.40 ± 0.617
			1	4	19.9 ± 9.9	2.0 [0, 24]	18.8 ± 0.937	472 ± 22.0[f)]	2.12 ± 0.095
			10	4	326 ± 22.5	—	28.2 ± 2.78	18,000 ± 1260[f)]	0.558 ± 0.037
r13C7	F[a)]	s.c.	100	31[e)]	403	96	—	112,000[g)]	—

Mean or mean ± standard deviation; t_{max} is median or median [range]; —, not calculated

C_{max}, maximum serum concentration; t_{max}, time to maximum serum concentration; $t_{1/2}$, elimination half-life; $AUC_{0\text{-}168\ h}$, area under the serum concentration-time curve from 0 to 168 hours post dose; CL, clearance

a) OVX rat; b) 10 mg/mL formulation; c) 70 mg/mL formulation; d) n = 4/time point; e) n = 5 to 8/time point; f) AUC_{inf} (area under the serum concentration-time curve, from 0 to infinity); g) $AUC_{0\text{-}672\ h}$, area under the serum concentration-time curve, from 0 to 672 hours post dose; h) CL/F, apparent clearance

4.1.2 Repeated-dose studies (CTD 4.2.1.1-5, 4.2.2.2-2, 4.2.3.2-1 to 2, 4.2.3.2-4, and 4.2.3.2-6 to 8)

Table 7 shows pharmacokinetic parameters of subcutaneous or intravenous doses of romosozumab administered to male and female rats once weekly. In the 1-month repeated-dose study, up to Day 99 including the follow-up period, anti-drug antibodies were detected in 13 of 24 animals at 10 mg/kg, 12 of 24 animals at 100 mg/kg, and 21 of 24 animals at 300 mg/kg. In the 6-month repeated-dose study, up to Week 26, anti-drug antibodies were detected in 13 of 20 animals at 3 mg/kg, 4 of 20 animals at 10 mg/kg, and 5 of 20 animals at 100 mg/kg. Neutralizing antibodies were not measured.

Table 7. Pharmacokinetic parameters of romosozumab in rats following repeated doses

Treatment period	Dose (mg/kg/week)	Route of administration	N	C_{max} (μg/mL)		$AUC_{0\text{-}168\ h}$ (μg·h/mL)	
				After initial dose	After repeated doses[a)]	After initial dose	After repeated doses[a)]
14 days	30	s.c.	16[c)]	204	315	24,400	41,700
	100		16[c)]	504	855	68,400	107,000
	300		16[c)]	1150	2090	158,000	254,000
	300	i.v.	16[c)]	6760	7990	437,000	608,000
1 month	10	s.c.	24[d)]	46.4	55.7	5400	5960
	100		24[d)]	519	1190	66,400	147,000
	300		24[d)]	1160	1540	157,000	176,000
6 months[b)]	3	s.c.	20[e)]	15.8	15.9	1420	931
	10		20[e)]	64.9	92.4	6930	10,700
	100		20[e)]	684	776	80,500	94,400

Mean

C_{max}, maximum serum concentration; $AUC_{0\text{-}168\ h}$, area under the serum concentration-time curve from 0 to 168 hours post dose

a) Assessment time point after repeated doses was Day 8, Day 22, and Day 183 for each treatment period (14 days, 1 month, and 6 months).

b) Anti-drug antibody positive animals were excluded from calculation of pharmacokinetic parameters.

c) n = 4/sex/time point; d) n = 3/sex/time point; e) n = 2/sex/time point

Table 8 shows pharmacokinetic parameters of subcutaneous or intravenous doses of romosozumab administered to male and female monkeys once weekly (or once a month in some studies). In the 1-month repeated-dose study, anti-drug antibodies were detected in 0 of 10 animals at 10 mg/kg, 2 of 10 animals at 30 mg/kg, 2 of 10 animals at 300 mg/kg (subcutaneous), and 2 of 10 animals at 300 mg/kg (intravenous) up to Day 99 including the follow-up period. In the 6-month repeated-dose study, anti-drug antibodies were detected in 3 of 12 animals at 3 mg/kg, 3 of 12 animals at 10 mg/kg, and 2 of 12 animals at 100 mg/kg up to Week 40 including the follow-up period. In the 1-year repeated-dose study, anti-drug antibodies were detected in 12 of 16 animals at 3 mg/kg, and 10 of 16 animals at 30 mg/kg up to Week 52. Among these animals, neutralizing antibodies were detected in 1 of 10 animals at 30 mg/kg, and 1 of 10 animals at 300 mg/kg (subcutaneous) in the 1 -month repeated-dose study; 1 of 12 animals at 3 mg/kg, 3 of 12 animals at 10 mg/kg, and 1 of 12 animals at 100 mg/kg in the 6-month repeated-dose study; and 10 of 16 animals at 3 mg/kg, and 1 of 16 animals at 30 mg/kg in the 1-year repeated-dose study.

Table 8. Pharmacokinetic parameters of romosozumab in monkeys following repeated doses

Treatment period	Dose (mg/kg/week)	Route of administration	Sex	N	C_{max} (μg/mL)		$AUC_{0\text{-}168\ h}$ (μg·h/mL)	
					After initial dose	After repeated doses[a)]	After initial dose	After repeated doses[a)]
14 days	30	s.c.	F	3	221 ± 6	353 ± 20	29,600 ± 2100	43,400 ± 3300
	100			3	913, 1040[g)]	1270 ± 140	120,000, 122,000[g)]	140,000 ± 63,000
	300			3	2400 ± 1210	3800 ± 1860	295,000 ± 150,000	487,000 ± 255,000
	300	i.v.		3	5180 ± 480	7290 ± 1010	413,000 ± 55,000	597,000[l)]
1 month	10	s.c.	F/M	10[e)]	67.5 ± 22.2	205 ± 82	8270 ± 2540	23,800 ± 10,500
	30			10[e)]	289 ± 56	569 ± 125	37,800 ± 5900	77,200 ± 21,800
	300			10[e)]	2500 ± 660	5180 ± 720	304,000 ± 46,000	645,000 ± 101,000
	300	i.v.		10[e)]	5910 ± 1600	7630 ± 1310	407,000 ± 75,000	588,000 ± 163,000
2 months	3[c)]	s.c.	F	3	17.7 ± 0.6	14.2 ± 2.3	2570 ± 440[j)]	1690 ± 280[j)]
	10[c)]			3	79.9 ± 6.3	60.0 ± 3.3	13,600 ± 1400[j)]	9890 ± 1330[j)]
	30[c)]			3	210 ± 18	163 ± 30	54,300 ± 6600[j)]	36,600 ± 14,700[j)]
6 months[b)]	3	s.c.	F/M	12[f)]	29.5 ± 5.04	30.6 ± 5.36[h)]	3060 ± 261	3490 ± 722[h)]
	10			12[f)]	107 ± 16.6	139 ± 27.0[i)]	13,100 ± 1980	17,100 ± 1920[i)]
	100			12[f)]	1590 ± 346	2280 ± 249	178,000 ± 30,500	30,1000 ± 45,700
1 year[b)]	3	s.c.	F[d)]	16	23.0 ± 1.26	32.3 ± 9.93	2930 ± 242[k)]	4130 ± 1520[k)]
	30			16	295 ± 34.8	538 ± 99.3	38,900 ± 4060[k)]	70,800 ± 13,600[k)]

Mean ± standard deviation; individual values are presented for n <3

C_{max}, maximum serum concentration; $AUC_{0\text{-}168\ h}$, area under the serum concentration-time curve from 0 to 168 hours post dose

a) Assessment time point after repeated doses was Day 8, Day 22, Day 29, Day 176, and Day 365 for each treatment period (14 days, 1 month, 2 months, 6 months, and 1 year).

b) Anti-drug antibody positive animals were excluded from calculation of pharmacokinetic parameters.

c) Administered once a month (mg/kg/month); d) OVX monkey; e) n = 5/sex; f) n = 6/sex; g) n = 2; h) n = 10; i) n = 9; j) AUC_{inf}, area under the serum concentration-time curve, from 0 to infinity; k) AUC_{last}, area under the serum concentration-time curve, from 0 to the final measuring time point; l) n = 1.

4.2 Distribution (CTD 4.2.3.5.2-1, 4.2.3.5.2-3)

Romosozumab 10, 60, and 300 mg/kg was subcutaneously administered to rats (n = 4/time point/group) once weekly, starting from 6 weeks prior to mating. The fetal-maternal serum romosozumab concentration ratio at 168 hours (gestational day 20) after the last dose (gestational day 13) was 0.89 at 10 mg/kg, 0.79 at 60 mg/kg, and 0.41 at 300 mg/kg. After romosozumab 30, 100, and 300 mg/kg was subcutaneously administered to pregnant rats (n = 4/time point/group) on gestational days 6 and 13, the fetal-maternal serum romosozumab concentration ratio at gestational day 19 was 0.80 at 30 mg/kg, 0.53 at 100 mg/kg, and 0.36 at 300 mg/kg.

4.3 Metabolism

No studies on the metabolism of romosozumab have been conducted.

4.4 Excretion

No studies on the excretion of romosozumab have been conducted.

4.R Outline of the review conducted by PMDA

4.R.1 The linearity and nonlinearity in the pharmacokinetics of romosozumab

The applicant's explanation:

Romosozumab is a humanized IgG2 monoclonal antibody that specifically binds to sclerostin. The elimination of romosozumab involves a target-mediated elimination pathway (saturable), mediated *in vivo* by specific binding to the target molecule of sclerostin, and the nonspecific elimination pathway (unsaturable), mediated by the reticuloendothelial system as with the metabolic process of endogenous immunoglobulins.

The results of a rat single-dose study showed that exposure ($AUC_{0\text{-}168\ h}$) tended to increase at a rate greater than the dose ratio within the lower dose range (0.1-10 mg/kg) studied, which suggested nonlinear pharmacokinetics (Table 6). On the other hand, the results of repeated-dose studies in rats or monkeys showed that exposure ($AUC_{0\text{-}168\ h}$) tended to increase in a dose-proportional manner in the higher dose range of 10 to 300 mg/kg, suggesting linear pharmacokinetics (Table 7 and Table 8). In clinical studies, namely a Japanese phase II study (Study 20101291) and a foreign phase II study (Study 20060326), the monthly doses of romosozumab 70 to 210 mg showed nonlinear pharmacokinetics within the dose range studied, and exposure tended to increase at a rate greater than the dose ratio.

Based on the above, at lower doses, the target-mediated elimination pathway is considered to be mainly involved, and be dose increase within the range causes binding to sclerostin saturate, resulting in increased exposure at a rate greater than the dose ratio. At higher doses, in contrast, binding to sclerostin having reached saturation suggests the predominant involvement of an unsaturable, nonspecific elimination pathway mediated by the reticuloendothelial system, and exposure increased in a dose-proportional manner. These pharmacokinetic characteristics have been seen in other IgG molecules as well (e.g., *J. Pharm Sci.* 2004;93:2645-68, *J. Pharm Sci.* 2012;101:4367-82).

PMDA accepted the applicant's explanation about the pharmacokinetic characteristics concerning the linearity and nonlinearity of romosozumab.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted the following toxicity studies: repeated-dose toxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, a local tolerance study, and other toxicity studies (e.g., studies to investigate the mechanism of action, and a cross reactivity study). Rats and cynomolgus monkeys were used in the toxicity studies of romosozumab because of the similar affinity of romosozumab to sclerostin in humans, rats, and cynomolgus monkeys. Data from some non-GLP studies were submitted as reference data.

5.1 Single-dose toxicity

No single-dose toxicity studies have been conducted. However, acute toxicity of romosozumab was evaluated based on data from single-dose intravenous safety pharmacology studies, and post-initial dose data from repeated-dose subcutaneous/intravenous toxicity studies in rats and cynomolgus monkeys. Results from the main studies are summarized in Table 9. No signs of deaths or acute toxicity were noted, and the approximate lethal dose was determined to be >300 mg/kg for regardless of the animal species and routes of administration.

Table 9. Summary of main single-dose toxicity studies

Study system	Route of administration	Dose of romosozumab (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male/female rat (SD)	i.v.	0,[a)] 30, 100, and 300	Acute toxicity in a safety pharmacology study (central nervous system): no toxic changes	>300	4.2.1.3-1
Male/female rat (SD)	s.c.	0,[a)] 10, 100, and 300	Acute toxicity in a 4-week repeated-dose subcutaneous toxicity study: no toxic changes	>300	4.2.3.2-2
Male/female cynomolgus monkey	s.c. and i.v.	0,[a)] 10, 30, 300 (s.c.), and 300 (i.v.)	Acute toxicity in a 4-week repeated-dose subcutaneous toxicity study: no toxic changes	>300	4.2.3.2-7

a) 10 mmol/L sodium acetate, 9% sucrose, 0.004% polysorbate 20 (pH5.2)

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted up to 26 weeks in rats and cynomolgus monkeys (Table 10). Main changes included increased bone formation caused by the pharmacological action of romosozumab, and changes assumed to be secondary effects (e.g., regenerative anemia accompanied by compensatory extramedullary hematopoiesis, increased platelet volume, decreased platelet count, increased serum phosphorus in rats; decreased serum calcium and decreased serum phosphorus in monkeys). However, no toxicologically significant changes were noted.

In male and female rats, exposure ($AUC_{0\text{-}168\ h}$) to romosozumab at the no-observed-adverse-effect level (NOAEL) (100 mg/kg) administered once weekly for 26 weeks was 66.7 mg·h/mL and 112 mg·h/mL, respectively, which are approximately 21 times and 35 times, respectively, the exposure level[21)] following administration of the clinically recommended dose (210 mg once a month) of romosozumab to humans. In male and female monkeys, exposure ($AUC_{0\text{-}\tau}$) to romosozumab at the NOAEL (100 mg/kg) administered once weekly for 26 weeks was 302 mg·h/mL and 300 mg·h/mL, respectively, which are approximately 94 times and 93 times, respectively, the exposure level[21)] following administration of the clinically recommended dose (210 mg once a month) of romosozumab to humans.

Table 10. Summary of repeated-dose toxicity study results

Study system	Route of administration	Treatment period	Dose of romosozumab (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
Male/female rat (SD)	s.c.	4 weeks (once weekly) + 10 weeks withdrawal	0,[a)] 10, 100, and 300[b)]	≥10 mg/kg;[g)] increased reticulocytes, decreased red blood cell count, increased bone formation markers (total ALP and OC), increased blood urea nitrogen, increased cortical and cancellous bone volume based on pQCT (area, volumetric BMD, and volumetric BMC), increased ossification in the sternum and tibia, increased splenic weight ≥100 mg/kg;[g)] decreased platelet count, increased platelet volume, and increased serum phosphorus Reversibility; reversible[h)]	300	4.2.3.2-2
Male/female rat (SD)	s.c.	26 weeks (once weekly) + 14 weeks	0,[a)] 3, 10, and 100[c)]	≥3 mg/kg;[g)] increased bone formation markers (total ALP and OC), increased ossification in the tibia, sternum, and lumbar vertebrae, decreased bone marrow cavity size, decreased platelet count, increased platelet volume ≥10 mg/kg;[g)] decreased red blood cell parameters (e.g., red	100	4.2.3.2-4

21) $AUC_{0\text{-}\tau}$ (12,888 μg·h/mL) for each dosing interval of romosozumab 210 mg once a month, calculated based on the data from the population pharmacokinetic analysis (CTD 5.3.3.5-1 to 3).

Study system	Route of administration	Treatment period	Dose of romosozumab (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
		withdrawal		blood cell count, hemoglobin, hematocrit value), increased reticulocytes, increased cortical and cancellous bone volume, thickening of the calvaria and long bones 100 mg/kg;[g] increased serum phosphorus, increased blood urea nitrogen, and increased serum globulin, etc. Reversibility; reversible[h]		
Male/female rat (SD)	s.c.	6 weeks (once weekly)	0,[a] 3, 10, and 50[d]	≥3 mg/kg;[i] increased cranial bone volume ≥10 mg/kg;[i] increased nasal cavity bone volume	—	4.2.3.2-3
Male/female cynomolgus monkey	s.c. and i.v.	4 weeks (once weekly) + 10 weeks withdrawal	0,[a] 10, 30, 300 (s.c.), and 300 (i.v.)[e]	≥10 mg/kg;[g] increased bone formation markers (total ALP, BAP, P1NP, and OC), increased BMD, increased ossification in the sternum and tibia, etc. ≥30 mg/kg;[g] decreased red blood cell parameters (red blood cell count, hemoglobin) 300 mg/kg;[g] decreased serum calcium Reversibility; reversible[h]	300	4.2.3.2-7
Male/female cynomolgus monkey	s.c.	26 weeks (once weekly) + 14 weeks withdrawal	0,[a] 3, 10, and 100[f]	≥3 mg/kg;[g] increased bone formation markers (total ALP, BAP, P1NP, and OC), increased cortical and cancellous bone volume, increased bone strength, increased ossification in the sternum, tibia, and lumbar vertebra (L1), decreased red blood cell parameters (red blood cell count, hematocrit value) 100 mg/kg;[g] decreased serum calcium and decreased serum phosphorus Reversibility; reversible[h]	100	4.2.3.2-8

a) 10 mmol/L sodium acetate, 9% sucrose, 0.004% polysorbate 20 (pH5.2)

b) Anti-drug antibodies were detected at the end of romosozumab therapy in 15 of 54 animals (10 mg/kg), 2 of 54 animals (100 mg/kg), and 12 of 54 animals (300 mg/kg), and at the end of the withdrawal period in 17 of 34 animals (10 mg/kg), 13 of 34 animals (100 mg/kg), and 27 of 34 animals (300 mg/kg).

c) Anti-drug antibodies were detected at the end of romosozumab therapy in 23 of 50 animals (3 mg/kg), 10 of 49 animals (10 mg/kg), and 8 of 49 animals (100 mg/kg), and at the end of the withdrawal period in 17 of 30 animals (3 mg/kg), 11 of 28 animals (10 mg/kg), and 15 of 29 animals (100 mg/kg). Of the anti-drug antibody-positive animals at Week 26, those with a serum romosozumab concentration of less than the lower limit of quantitation, or less than the half the mean value of anti-drug antibody-negative animals from each treatment group at Week 27 were excluded from the analysis at end of treatment. Of the anti-drug antibody-positive animals at Week 26, those with a serum romosozumab concentration of less than the lower limit of quantitation at Week 28 were excluded from the reversibility study analysis.

d) At the end of romosozumab therapy, anti-drug antibodies were detected in 17 of 45 animals (3 mg/kg), 5 of 36 animals (10 mg/kg), and 3 of 33 animals (50 mg/kg). Some animals were excluded on Days 22 and 43, based on presence/absence of anti-drug antibodies, level of anti-drug antibody response, and serum romosozumab concentration.

e) At the end of romosozumab therapy, anti-drug antibodies were detected in 1 of 10 animals in the romosozumab 30 mg/kg group (s.c.), and at the end of the withdrawal period, in 2 of 4 animals (30 mg/kg), and 2 of 4 animals (300 mg/kg) (s.c..), and 1 of 4 animals (100 mg/kg) (i.v.). At the end of the withdrawal period, neutralizing activity was also measured. Neutralizing antibodies were detected in 1 of 4 animals each in the 30 and 300 mg/kg groups (s.c.).

f) At the end of romosozumab therapy, anti-drug antibodies were detected in 2 of 12 animals (3 mg/kg), and 3 of 12 animals (10 mg/kg), and at the end of the withdrawal period, in 2 of 4 animals (10 mg/kg), and 2 of 4 animals (100 mg/kg). Among these animals, neutralizing antibodies were detected in 1 of 12 animals (3 mg/kg), and 2 of 12 animals (10 mg/kg) at the end of treatment, and in 2 of 4 animals (10 mg/kg), and 1 of 4 animals (100 mg/kg) at the end of the withdrawal period. Anti-drug antibody-positive animals were excluded from the analysis.

g) These were considered to be increased bone formation caused by the pharmacological action of romosozumab or changes assumed to be secondary effects.

h) Some lesions related to bone formation caused by the pharmacological action of romosozumab were determined to be the result of continued bone formation in the romosozumab elimination process. Other findings resolved, or tended to resolve.

i) These are assumed to be attributed to additional intramembranous ossification caused by the pharmacological action of romosozumab, and the pathology has been considered different from fibrous bone formation by undifferentiated mesenchymal cells.

5.3 Genotoxicity

Romosozumab is a recombinant protein composed of natural amino acids, and does not contain inorganic or synthesized organic linkers, or other nonprotein components. Thus romosozumab is unlikely to interact with DNA or other chromosome substances directly, and therefore, no genotoxicity studies were conducted.

5.4 Carcinogenicity (CTD 4.2.3.4.1-1)

A rat carcinogenicity study was conducted to evaluate the carcinogenic risk of romosozumab (Table 11). Another rat carcinogenicity study was conducted using IgG2 that is pharmacologically inactive, and immunogenic in rats but not immunogenic in humans (AMG 589) to evaluate the long-term effects as the consequences of lifetime exposure to a heteroantibody that is immunogenic (Table 12). No neoplastic changes were noted associated with treatment with romosozumab or AMG 589.

The exposure to once-weekly non-carcinogenic doses (50 mg/kg) of romosozumab in rats ($AUC_{0-\tau}$, 62,000 μg·h/mL) was estimated based on the Week 26 exposure level in the 26-week rat repeated-dose subcutaneous toxicity study (CTD 4.2.3.2-4), indicating that the exposure[21)] was approximately 19 times that to the clinically recommended dose (210 mg once a month) of romosozumab in humans.

Table 11. Summary of results from the carcinogenicity study with romosozumab

Study system	Route of administration	Treatment period	Major lesion	Dose	Romosozumab (mg/kg)[a)]				Non-carcinogenic dose (mg/kg)	CTD
					0[b)]	3	10	50		
				N	60/sex	60/sex	60/sex	F, 54; M, 60		
Male/ Female rat (SD)	s.c.	Male, 90-91 weeks Female, 98 weeks (once weekly)	Neoplastic lesion						50	4.2.3.4.1-1
			Tibia: osteosarcoma	M	0	0	0	1		
				F	0	0	0	0		
			Calvaria, femur, lumbar vertebrae, sternum: osteosarcoma	M	0	0	0	0		
				F	0	0	0	0		
			Other bone: osteosarcoma	M	0	0	0	1		
				F	0	0	0	0		
			Kidney: lipoma	M	0	1	0	0		
				F	1	0	0	3[c)]		
			Non-neoplastic lesion							
			Femur: osteoblast hypertrophy	M	0	0	1	0		
				F	0	0	0	0		
			Other non-neoplastic lesions	M F	≥3 mg/kg; increased ossification, increased bone volume, and their presumed secondary effects (extramedullary hemopoiesis in the liver and spleen) Treatment groups including control, inflammation at the injection site[d)]					

a) Anti-drug antibodies were measured at Week 13. Anti-drug antibodies were detected in 49 of 150 females and 105 of 149 males (3 mg/kg), 15 of 80 females and 22 of 79 males (10 mg/kg), and 20 of 79 females and 34 of 80 males (50 mg/kg). Among these animals, neutralizing antibodies were detected in 50 of 149 males (3 mg/kg), 10 of 79 males (10 mg/kg), 24 of 80 males (50 mg/kg), and 12 of 79 females (50 mg/kg). Anti-drug antibody-positive animals at Week 13 were removed from the study. When any group had >60/sex/group, animals were included by ascending order of animal number; when any group had <60/sex/group, anti-drug antibody-positive animals that tested negative for neutralizing antibodies were included by descending order of animal number.

b) 55 mmol/L acetate, 13mmol/L calcium, 6% sucrose, 0.006% polysorbate 20 (pH5.2)

c) Although the value is slightly greater than the historical control range for females (0%-4%), given that changes suggestive of precancerous lesion had not been noted, including in this study, and that characteristics and morphology of lipoma in the romosozumab group were similar to those observed in the controls, this was judged as a change not caused by romosozumab.

d) Mononuclear cell infiltration; the frequency and severity tended to be higher in the test substance treatment group.

Table 12. Summary of results from the carcinogenicity study with AMG 589

Male/ Female rat (SD)	s.c.	Male, 91 weeks Female, 98 weeks (once weekly)	Major lesion	Dose	AMG 589 (mg/kg)[a)]			Non-carcinogenic dose (mg/kg)	CTD
					0[b)]	0[c)]	50		
				N	60/sex	60/sex	60/sex		
			Neoplastic lesion	F M	None			50	4.2.3.4.1-2
			Non-neoplastic lesion		Inflammation at the injection site[d)]				

a) Anti-drug antibodies were measured at Week 13. Anti-drug antibodies were detected in 77 of 119 animals in the AMG 589 50 mg/kg group.
b) Physiological saline solution
c) 10 mmol/L sodium acetate, 9% sucrose, 0.004% polysorbate 20 (pH5.2)
d) Mononuclear cell infiltration; the frequency and severity tended to be higher in the test substance treatment group.

5.5 Reproductive and developmental toxicity

Romosozumab showed significant immunogenicity in rabbits including aggravated condition and necropsies caused by immune complex (CTD 4.2.3.2-5), and reproductive and developmental toxicity studies were therefore conducted in rats (Table 13). Romosozumab induced more frequent ossification failure in the arch of the sixth cervical vertebra in the 300 mg/kg group [see footnote f) of Table 13]. Furthermore, gross external malformation (digits) and skeletal malformation (including abnormalities in addition to digit malformations) were observed in a litter of fetuses from a dam treated with 300 mg/kg [see footnote g) of Table 13, and Section "5.R.3 External and skeletal malformations reported in the embryo-fetal development study"]. However, the extrapolation of these changes in rats to humans is considered unreasonable, and the NOAEL for reproductive and developmental toxicity in rats was thus determined as 300 mg/kg.

Maternal exposure of pregnant rats to romosozumab administered at the NOAEL (300 mg/kg) at gestational day 13 ($AUC_{0\text{-}168\ h}$, 179,760 μg·h/mL) was approximately 56 times that[21)] after the administration of the clinically recommended dose (210 mg, once a month) of romosozumab to humans. At gestational day 20, the serum romosozumab concentrations were 277 μg/mL (maternal), and 114 μg/mL (fetal) in the 300 mg/kg group. Maternal serum romosozumab concentrations were 1780 μg/mL prior to mating (Day 36), 539 to 1610 μg/mL at nursing day 21, and the mean serum romosozumab concentration in neonatal rats (lactation day 21) was 680 to 963 μg/mL.

Table 13. Summary of reproductive and developmental toxicity studies

Study type	Species/strain	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	CTD
Reproduction and embryo-fetal development study	M rat (SD)	s.c.	6 weeks prior to mating to 6 weeks post mating (once weekly)	Romosozumab 0,[a)] 10, 60, and 300[c)]	Parent animals: no toxic changes	Parent animals (general toxicity and reproductive toxicity)[j)]: 300	4.2.3.5.2-3
	F rat (SD)	s.c.	6 weeks prior to mating to gestational day 15 (once weekly)		Parent animals: no toxic changes Fetuses: 300 mg/kg/day; skeletal variations (ossification failure in the arch of the sixth cervical vertebra)[f)]	Parent animals (general toxicity and reproductive toxicity[j)]): 300 Embryo-fetal development: 300	

Study type	Species/strain	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	CTD
Embryo-fetal development study	F rat (SD)	s.c.	Gestational days 6-13 (once daily)	Romosozumab 0,[b] 10, 60, and 300[d]	Dams: no toxic changes Fetuses: 300 mg/kg/day; external malformations (extra digits and digits fused in fore and/or hindlimbs), skeletal malformation (extra toes, extra toe phalanges, enlarged tibia, metatarsal not-ossified, irregularly shaped ilium, broadened ribs, metacarpal not-ossified, incompletely ossified phalanx, misaligned metacarpals, enlarged ulna, extra digit, extra phalanx, fused phalanges, irregularly shaped metacarpal, misaligned metatarsals, or bent tibia),[g] skeletal variations (ossification failure in the arch of the sixth cervical vertebra)[f]	Parent animals (general toxicity): 300 Embryo-fetal development: 300	4.2.3.5.2-2
Study on prenatal and postnatal development and maternal function	F rat (SD)	s.c.	Dams: 6 weeks prior to mating to lactation day 20 (once daily)	Romosozumab 0,[a] 10, 60, and 300[e]	Dams: ≥60 mg/kg/day; decrease in feed intake (transient) 300 mg/kg/day; unkempt fur[h] F1 neonatal rats: ≥10 mg/kg/day, minor changes in femoral bone volume, and cortical bone shape[i]	Dams: (general toxicity): 300 F1 neonatal rat development: 300	4.2.3.5.3-1

a) 55 mmol/L acetate, 13 mmol/L calcium, 6% sucrose, 0.006% polysorbate 20 (pH5.2)

b) 10 mmol/L sodium acetate, 9% sucrose, 0.004% polysorbate 20 (pH5.2)

c) At week 4, anti-drug antibodies were detected in 20 of 60 males and 10 of 59 females (10 mg/kg), 29 of 60 males and 22 of 58 females (60 mg/kg), and 47 of 60 males and 33 of 59 females (300 mg/kg). Anti-drug antibodies were measured in males at Week 11, and were detected in 4 of 25 animals (10 mg/kg), 0 of 25 animals (60 mg/kg), and 11 of 25 animals (300 mg/kg). In females at gestational day 20 or 21, anti-drug antibodies were detected in 2 of 28 animals (10 mg/kg), 1 of 29 animals (60 mg/kg), and 9 of 29 animals (300 mg/kg). Some anti-drug antibody-positive animals at Week 4 were excluded from the study (to ensure a sufficient number of animals to be analyzed, animals that were anti-drug antibody-positive but had low anti-drug antibody response and high romosozumab serum concentrations were included in the analysis).

d) At gestational day 21, findings were noted in 6 of 24 animals (30 mg/kg), 5 of 25 animals (100 mg/kg), and 16 of 25 animals (300 mg/kg).

e) At Week 6, anti-drug antibodies were detected in 9 of 50 animals (10 mg/kg), 15 of 50 animals (60 mg/kg), and 28 of 50 animals (300 mg/kg). Some anti-drug antibody-positive animals at Week 6 were excluded from the study (to ensure a sufficient number of animals to be analyzed, animals that were anti-drug antibody-positive but had low anti-drug antibody response and high romosozumab serum concentrations were included in the analysis).

f) Regarding the increase in the frequency of ossification failure in the arch of the sixth cervical vertebra, no such changes were noted in newborn pups in the study on the effects on prenatal and postnatal development including maternal function. Given that the finding was a variation caused by delayed skeletal development in normal growth of rats, and in fact, the variation occurred in a non-human anatomical structure, it was judged to be of no toxicological significance.

g) While it exceeded the historical control range at the testing laboratory, given that anomalies attributable to loss-of-function mutation of the gene coding for sclerostin are limited to digits, and that the malformations were not observed in dams receiving higher concentrations of romosozumab, it was concluded that the finding was unrelated to romosozumab therapy.

h) During the mating period, transient decrease in feed intake was noted at ≥60 mg/kg, and unkempt fur was noted in many animals prior to mating, during pregnancy, and lactation period at 300 mg/kg. However, no effects of romosozumab therapy were found on maternal survival rate, body weight, body weight change, sexual cycle, reproductivity, birthing, lactation, nursing activity, or macroscopic findings; therefore, it was concluded that these changes were not toxicologically significant.

i) Assessment at lactation day 21 indicated that total and cortical/subcortical volumetric BMC, and BMD (males and females) as well as cancellous vBMC and vBMD (females) at the femoral metaphysis slightly decreased at ≥60 mg/kg. Cancellous vBMD increased in females in the 10 mg/kg group. There were slight decreases in indices of cortical bone morphology (e.g., cortical surface, periosteal perimeter and endosteal perimeter of cortical bone) in males of the romosozumab group. The above findings are not considered to be harmful effects.

j) To assess reproductivity, in addition to mating of males and females, and fertility, sperm motility, sperm concentration and reproductive organ weight were evaluated in males, and sexual cycle and uterine weight were evaluated in females.

5.6 Local tolerance (CTD 4.2.3.6-1, 4.2.3.6-2 to 3 [reference data])

In the local tolerance studies using male and female SD rats, investigation was performed with different concentrations of romosozumab (10 or 70 mg/mL),[22] and formulations produced by using drug substances manufactured by Process A (70 mg/mL sodium acetate formulation), and by Process B (64, 118, or 120 mg/mL calcium acetate formulation) (Table 14). The results indicated that local response was dependent on the concentration of the drug substance. There were no differences in local responses between the drug substances manufactured by Process A and B of nearly equal concentrations. The evaluation of injection sites in the repeated-dose toxicity study indicated that minor inflammatory cell infiltration occurred following the administration of romosozumab. These findings on local tolerance showed favorable tolerance to romosozumab with no serious irritation noted.

Table 14. Summary of local tolerance studies

Study system	Site of administration	Study design	Major findings	CTD
Male rat (SD)	s.c.	A single dose of 1.2 mL of the sodium acetate formulation (romosozumab 0[a] or 70 mg/mL), or a single dose of 1.2 mL of the calcium acetate formulation (romosozumab 0[b] or 120 mg/mL) was administered into the right scapular region.	≥70 mg/mL; granulomatous inflammation at the injection site (while frequency and severity increased according to the dose, no substantial differences existed between the vehicles.)	4.2.3.6-1
	s.c.	A single dose of 1.2 mL of the calcium acetate formulation (romosozumab 0,[b] 64, or 118 mg/mL) was administered into the left scapular region, and a single dose of vehicle into the right scapular region.	≥64 mg/mL, at the injection site, dose-dependent granulomatous inflammation, mixed cells infiltrating peripheral tissue, irregularly shaped proteinaceous material deposition, edema (scabs and protruded area noted macroscopically in 1 animal in the 118 mg/mL group), etc.	4.2.3.6-2 Reference data
Female rat (SD)	s.c. or i.v.	A single dose of romosozumab 0,[a] 5, or 35 mg/kg was subcutaneously administered, or a single dose of romosozumab 35 mg/kg was intravenously administered, and the injection site was observed over time (2, 24, 72, or 168 hours post dose).	≥5 mg/mL, inflammatory cell infiltration at the injection site (more severe at higher concentrations; the intensity peaked at 24 hours post dose before decreasing)	4.2.3.6-3 Reference data

a) 10 mmol/L sodium acetate, 9% sucrose, 0.004% polysorbate 20 (pH5.2)
b) 27 mmol/L acetic acid, 14 mmol/L calcium acetate, 6% sucrose, 0.006%polysorbate 20 (pH5.2)

5.7 Other toxicity studies

5.7.1 Cross reactivity study (CTD 4.2.3.7.7-1)

The cross-reactivity with normal tissues from human, cynomolgus monkey, rabbit, and rat was investigated. The results confirmed that binding of romosozumab to human, cynomolgus monkey, and rabbit osteocytes occurred, while specific binding of romosozumab to rat osteocytes was not observed. Binding of romosozumab to stromal fiber in the aorta or pulmonary artery was noted in a heart slice of 1 monkey. While the reason for romosozumab not binding to rat osteocytes was unclear, the applicant assured that rats have pharmacological sensitivity.

5.7.2 Evaluation of Fc effector functions

The applicant's explanation:

For the following reasons, expression of toxicity by romosozumab mediated by Fc effector functions is unlikely.

[22] Vehicle, 10 mmol/L acetate (adjusted to pH5.2 with sodium hydroxide), 9% sucrose, 0.004% polysorbate 20

- Romosozumab is an IgG2 antibody, which has low affinity for all Fcγ receptors involved in expression of Fc effector functions (*Nat Rev Drug Discov.* 2011;10:101-11).
- The antibody dependent cellular cytotoxicity (ADCC) activity of human IgG2 is very low or absent *in vitro* in the presence of human or cynomolgus monkey peripheral blood mononuclear cells (*J Immunol.* 2011;186:341-9, *J Immunol.* 2012;188:4405-11). IgG2 does not bind to complement C1q in an effective manner and cannot cause complement dependent cytotoxicity (CDC) in the presence of human complement (e.g., *J Exp Med.* 1988;168:127-42, *Front Immunol.* 2014;5:520).
- IgG2 activates complement pathway only at high epitope density (*Clin Exp Immunol.* 1991;84:1-8).
- CDC requires IgG hexamers arranged on cell surfaces (*Science.* 2014;343:1260-3).
- Sclerostin is a monomer, which has 1 epitope and binds to 1 molecule of romosozumab, and therefore, activation of complement pathways is not expected.
- In the repeated-dose toxicity studies of romosozumab up to 300 mg/kg in rats and cynomolgus monkeys, there were no signs of actions mediated by ADCC, antibody dependent cellular phagocytosis (ADCP), or CDC or any toxic changes in tissues in which sclerostin is expressed.

5.7.3 Mechanistic studies

Single- or repeated-dose subcutaneous toxicity studies were conducted using OVX rats to evaluate the effects of anti-sclerostin antibodies on transcription in the osteoblast-lineage cells (Table 15).

Table 15. Summary of the mechanistic studies

Study system	Study design	Major findings	CTD
Female rat (SD) (OVX at 6 months of age)	OVX rats received a single subcutaneous dose of rat anti-sclerostin antibody (r13C7) 0[a] or 100 mg/kg 2 months post-OVX. mRNA expression was analyzed by TaqMan and microarray methods, using osteocytes, osteoblasts, and lining cells sampled from the lumbar vertebrae by laser capture microdissection (LCM) at 6, 24, 72, and 168 hours post-dose.	Transcriptional profiles: ・ Transcriptional profiles were similar among osteocytes, osteoblasts, and lining cells. ・ At 168 hours post-dose, expression of Wnt target genes such as *Twist1* and extracellular matrix genes such as *Lox* and *Omd* increased (coincident with increased expression of Wnt target genes was the upregulation of numerous extracellular matrix genes). ・ Expression of the following genes increased: p53 target gene related to cell cycle arrest, *Cdkn1a* (p21) and *Cgref1*, and the gene related to B cell differentiation, *Cxcl12*. Based on the above, *in vivo* in osteocytes, osteoblasts, and lining cells, r13C7 affects regulation of canonical Wnt target genes involved in increased expression of extracellular matrix genes.	4.2.3.7.3-1
Female rat (SD) (OVX at 6 months of age)	OVX rats received subcutaneous doses of rat anti-sclerostin antibody (r13C7) 0,[a] 3, or 50 mg/kg once weekly from 2 months post-OVX for 26 weeks, followed by a withdrawal period of 12-18 weeks (a reversibility study sub-group was established in each group). Bone histomorphometry and immunohistology were performed on the lumbar vertebrae to evaluate osteoblast-lineage cell number. Also, mRNA expression was analyzed by TaqMan and microarray methods,[b] using osteocytes, osteoblasts, and lining cells sampled by LCM.	Bone histomorphometry: ・ Bone formation rate and osteoblast surface increased (peaked around Day 29) and recovered to the level of the control group by Day 183. As a result of drug withdrawal, the bone formation rate and osteoblast surface decreased, and recovered to the level of the control group by the end of the withdrawal period. ・ Osteoclast surface decreased in the treatment period, and increased in the withdrawal period. Immunohistology: ・ Total osteoblast cell number increased on Days 8 and 29 relative to the control group, and recovered to the levels of the control group by Day 183. ・ Osteoprogenitor cells decreased on Days 29 and 183 compared with the control group. Decreased osteoprogenitor cells were observed before decreases in osteoblasts or bone formation rate. Transcriptional profiles: ・ On Day 29, when bone formation rate peaked, increased expression of signaling pathways inhibiting cell cycle progression in osteocytes (e.g., TP53 [p53], CDKN1a [p21], CDKN2a, RB1 [Rb]), and decreased expression of signaling pathways promoting induction of mitogenesis (e.g., c-Myc, E2F1, and FOXM1) were observed. ・ Other observations included induction of extracellular inhibitors (e.g., SOST, DKK1) involved in canonical Wnt pathway, pathways such as TGF-β1 (TGFB1), Hippo (Lats2), and non-canonical Wnt (Wnt5b) (*Science.* 2002;296:1646-7, *Biochem Biophys Res Commun.* 2009;387:207-11). Based on the above, induction of mitogenesis and inhibition of cell cycle progression may contribute to the inhibition of bone formation observed with long-term r13C7 treatment.	4.2.3.7.3-3
Female/Male rat (SD)	Romosozumab 0[c] or 50 mg/kg was subcutaneously administered once weekly for 4 or 26 weeks, or rhPTH (1-34) 75 μg/kg was orally administered once daily for 4 or 26 weeks[d] At Weeks 4 and 26, immunohistology was performed to evaluate osteoblast-lineage cell number, and histomorphometry analysis was performed.	Immunohistology: ・ Osteoblast number increased in the rhPTH (1-34) group at Weeks 4 and 26. In the romosozumab group, osteoblast number increased at Week 4 and decreased at Week 26. The decrease in osteoblast number at Week 26 in the romosozumab group was correlated with the decrease in osteoprogenitor cell number. ・ Osteoblast density increased and osteoblast footprint decreased in the rhPTH (1-34) group. In the romosozumab group, osteoblast density decreased and osteoblast footprint increased at Week 26. ・ No effects on osteoblastic activity were noted in the rhPTH (1-34) group. Osteoblastic activity increased at Weeks 4 and 26 in the romosozumab group. Based on the above, osteoprogenitor cell number and osteoblast number increased up to Week 26 in the rhPTH (1-34) group, in contrast, in the romosozumab group, osteoblastic activity increased from Week 4, and osteoblast density and osteoprogenitor cell number decreased at Week 26.	4.2.3.7.3-2

a) 10 mmol/L sodium acetate, 9% sucrose, 0.004% polysorbate 20 (pH5.2)

b) Bone histomorphometry was performed on Days 8, 29, 85, 183, 197, 237, 267, and 309; osteoblast-lineage cell number on Days 8, 29, 183, 267, and 309; mRNA expression (microarray) on Days 8, 29, 85, 183, 237, and 309; and mRNA expression (Taqman) on Days 8, 183, and 309.

c) 55 mmol/L acetate, 13 mmol/L calcium, 6% sucrose, 0.006% polysorbate 20 (pH 5.2)

d) Anti-drug antibodies were measured on Day 29 in the 4-week treatment groups, and on Days 85 and 183 in the 26-week treatment groups. Anti-drug antibodies were detected in the following animals: on Day 29 (4-week treatment groups), 7 of 40 animals (romosozumab 3 mg/kg) and 11 of 36 animals (50 mg/kg); in the 26-week treatment groups, on Day 85, 26 of 100 animals (3 mg/kg) and 7 of 40 animals (50 mg/kg), and on Day

183, 1 of 24 animals (3 mg/kg) and 2 of 24 animals (50 mg/kg). In the 26-week treatment groups, anti-drug antibody-positive animals were excluded from the study on Day 85.

5.R Outline of the review conducted by PMDA

5.R.1 Carcinogenic risks

The applicant's explanation about the carcinogenic risks of romosozumab:

Romosozumab is a recombinant protein composed of natural amino acids, and does not contain inorganic or synthesized organic linkers or other nonprotein components. Therefore romosozumab has no possibility of interacting with DNA or chromosome substances directly. Furthermore, there have been no reports of increased incidence of cancer in humans or mice associated with loss-of-function mutations of the gene coding for sclerostin (e.g., *Ther Adv Musculoskelet Dis.* 2014;6:48-57, *J Bone Miner Res.* 2008;23:860-9). In the rat carcinogenicity study, osteosarcoma (proximal tibia and the skull) occurred in 3.7% (2 of 54) of the animals in the romosozumab 50 mg/kg group. However, there were no proliferative changes such as osteoblastic hyperplasia and foci of proliferative stromal cells, or continual changes such as benign bone tumors. In addition to histopathology evaluation, a highly sensitive X-ray examination was also performed. The results were not significantly higher than the historical control range (0%-3.33%) of the testing laboratory (CTD 4.2.3.4.1-1). Accordingly, the osteosarcoma that occurred in the romosozumab 50 mg/kg group is considered a spontaneous change rather than one associated with romosozumab therapy.

In a 2-year rat carcinogenicity study, the incidences of osteosarcoma accompanied by osteoblastic hyperplasia and stromal cell proliferation and of benign bone tumor increased with dose and treatment duration in the group that received rhPTH (1-34), an approved bone anabolic agent (e.g., *Toxicol Pathol.* 2002;30:312-21, *J Toxicol Sci.* 2012;37:617-29), indicating that rhPTH (1-34) is carcinogenic in rats. The results of the mechanistic studies of romosozumab [see Section "5.7.3 Mechanistic studies"] revealed that the mechanism of action of romosozumab in bone formation and osteoblast development differs from that of rhPTH (1-34). Osteoblastic density and osteoblast number steadily increased as a result of the continuous administration of rhPTH (1-34), whereas the bone formation promoting effect decreased after continuous administration of romosozumab [see Section "3.R.1 Mechanism of action of romosozumab"]. This difference in the mechanism may be a contributory factor to the absence of carcinogenicity in the romosozumab group.

PMDA's view:

The applicant's explanation is acceptable from a toxicological viewpoint. Although these toxicology study data are not suggestive of the carcinogenicity of romosozumab, safety in humans is to be discussed again in Section "7.R.2.9 Tumor necrosis factor (TNF)-mediated inflammatory diseases and malignant tumors."

5.R.2 Neurological risks associated with hyperostosis

The applicant's explanation:

An expected secondary effect of the pharmacological actions of romosozumab is an impact of hyperplasia of bone on the nervous system. In the rat 26-week repeated-dose toxicity study (dosing started at 13 weeks of

age[23]), which revealed thickening of the calvaria, spine, and long bones, general observation, periodic observation of detailed clinical condition, ophthalmological examination, or macroscopic and histopathological examinations of the brain, spinal cord, sciatic nerve, and optic nerve did not detect any change suggestive of neurological dysfunction or nerve compression (CTD 4.2.3.2-4). In a monkey 26-week repeated-dose toxicity study (dosing started at 3-5 years of age[24]), general observation, periodic observation of detailed clinical condition, ophthalmological examination, electrocardiography, blood pressure measurement, or macroscopic and histopathological examinations of the brain, spinal cord, sciatic nerve, and optic nerve did not indicate any change suggestive of neurological dysfunction or nerve compression (CTD 4.2.3.2-8). In the rat carcinogenicity study, which evaluated long-term treatment (dosing started at 8 weeks of age[25]), the results did not indicate any finding suggestive of neurological dysfunction or nerve compression (CTD 4.2.3.4-1.1). Furthermore, in sclerostin knockout mice, no neurological dysfunction has been reported. No findings suggestive of neurological risks were indicated in these repeated-dose toxicity studies. However, among patients with sclerosteosis or van Buchem disease that cause a lack of sclerostin or decreased expression of sclerostin, homozygous carriers of the *Sost* gene mutation have excessive bone deposition on periosteal and cortical surfaces, which mainly induces cranial nerve entrapment and causes facial palsy, hearing impairment, etc., leading to a complete lack of sclerostin (*J Bone Miner Res.* 2013;28;848-54, *J Clin Endocrinol Metab.* 2005;90:6392-5). Cranial nerve entrapment may be associated with the structure of the petrous part of the temporal bone in humans, which contains numerous foramina through which cranial nerves pass, and therefore humans are likely to be highly susceptible to this problem. However, in patients with reduced expression of sclerostin, who have intermediate levels of bone volume and bone formation markers, between those of homozygous carriers of the *Sost* gene mutation, and those of non-carriers, neurological effects were not necessarily characteristically present (*J Bone Miner Res.* 2011;26:2804-11, *J Bone Miner Res.* 2013;28:848-54). Based on the data on pharmacodynamic responses (e.g., serum P1NP) in patients who received a single subcutaneous dose of romosozumab at 0.1 to 10 mg/kg in the phase I study (Study 20060220), when the clinically recommended dose (210 mg once a month) of romosozumab is administered to humans, it is not thought that binding of romosozumab to sclerostin *in vivo* is saturated. Furthermore, the target patient population of romosozumab is skeletally-mature adults with osteoporosis, and excessive bone growth or neurological effects have not been reported in the clinical studies of romosozumab in humans. Thus, neurological risks associated with hyperostosis (excessive bone growth) are considered to be low when administering romosozumab in patients with osteoporosis who are at high risk of fracture.

While PMDA accepted the applicant's explanation that no changes suggestive of neurological risks were found in the non-clinical studies conducted, the neurological risks of romosozumab in humans are to be discussed again in Section "7.R.2.4 Hyperostosis."

23) Equivalent to 16 to 17 years of age in humans
24) Equivalent to 12 to 17 years of age in humans
25) Equivalent to 10 years of age in humans

5.R.3 External and skeletal malformations reported in the embryo-fetal development study

PMDA asked the applicant to explain the relationship between romosozumab therapy and external and skeletal malformations that occurred in the rat embryo-fetal development study (CTD 4.2.3.5.2-2).

The applicant's explanation:

In the rat embryo-fetal development study (CTD 4.2.3.5.2-2), external malformation (digital) and skeletal malformation (including non-digital anomalies) occurred in fetuses (7 of 16 fetuses from the same dam) from 1 of 22 dams receiving romosozumab 300 mg/kg. The frequency of the events was higher than the historical control range of the testing laboratory (0.04%). Furthermore, syndactyly occurred in 4% of sclerostin knockout mice and 75% of patients with sclerosteosis (*Clin Genet.* 1984;25:175-81, *Dev Biol*. 2013;38:90-105). Fetal exposure to romosozumab (AUC) during digital formation period[26)] (maternal-fetal transfer), taking into account placental transfer of IgG2 during rat organogenesis (when 300 mg/kg of IgG2 is intravenously administered to dams on gestational days 7 and 14, the fetal-to-maternal ratio of plasma IgG2 concentrations increased from 0.2% to 5.9% on gestational days 13-19 in a progressive manner. [*Birth Defects Res B Dev Reprod Toxicol.* 2014;101:178-88]), is estimated to be approximately 206 to 10,605 μg·h/mL. In light of the exposure level of 1416 μg·h/mL after administration of romosozumab 3 mg/kg, which showed a pharmacological effect on bone in the rat 26-week repeated-dose subcutaneous toxicity study (CTD 4.2.3.2-4), the estimated fetal exposure levels may be high enough to cause a pharmacological effect of romosozumab. From the standpoint of maternal-fetal transfer and the expression mechanism of romosozumab, the treatment may be related to digital malformation. However, in the preliminary study of embryo-fetal development in rats (CTD 4.2.3.5.2-1), rat fertility and embryo-fetal developmental toxicity study (CTD 4.2.3.5.2-3), and pre-and post-natal development study (CTD 4.2.3.5.3-1), these malformations did not occur in fetuses of other dams that exhibited blood exposure levels higher than that of the dam (83.9 μg/mL at gestational day 21) that had malformed fetuses, indicating that the malformations were not reproducible. Furthermore, in the rat embryo-fetal development study (CTD 4.2.3.5.2-2), in addition to digit malformations, skeletal variations occurred including metacarpal not-ossified, skeletal malformations in fore and/or hindlimbs, such as bent tibia, incompletely ossified phalanx, misaligned metacarpals, enlarged ulna, misaligned metatarsals, enlarged tibia, irregularly shaped metacarpal, broadened ribs, and irregularly shaped ilium. However, malformations in sclerostin knockout mice and in human patients with sclerosteosis are limited to digits, and no non-digital types of developmental skeletal malformations have been reported. Accordingly, it was concluded that the variations that occurred in the 7 fetuses from a litter in the rat embryo-fetal development study (CTD 4.2.3.5.2-2) were unrelated to romosozumab.

In humans, digits are formed in the first trimester. Placental transport of maternal immunoglobulin is very low in the first trimester (*Am J Obstet Gynecol.* 1961;82,167-71, *Hum Reprod.* 1995;10:3297-300), and the placental transport of IgG2 is inefficient (*Am J Reprod Immunol.* 1996;36,248-55, *Pediatr Allergy Immunol.* 2009;20:528-35). In patients with sclerosteosis, digital malformation occurred in homozygous carriers of the *Sost* gene mutation, which causes a complete lack of sclerostin (*Clin Genet.* 1984;25:175-81). In contrast,

26) In rats, digits form during late organogenesis, at around gestational days 13 to 17 (Developmental and reproductive toxicology: a practical approach. (Boca Raton, FL: CRC Press, Taylor & Francis; 2006. p147-97).

among heterozygous carriers, who have reduced sclerostin expression, digital malformations do not occur, suggesting that only complete lack of sclerostin throughout the period from conception to embryo-fetal development leads to digital malformation in humans (*J Bone Miner Res.* 2011;26:2804-11). Furthermore, based on the pharmacodynamic response data (e.g., serum P1NP) in patients who received a single subcutaneous dose of romosozumab at 0.1 to 10 mg/kg in a phase I study (Study 20060220), binding of romosozumab to sclerostin is not expected to reach saturation *in vivo* in humans at the clinically recommended dose (210 mg once a month). Therefore, the risk of romosozumab affecting the digital developmental process of the human fetus is considered low.

PMDA's view:
When assessing skeletal malformation that occurred in rat fetuses in the embryo-fetal development study (CTD 4.2.3.5.2-2), a relationship between external/skeletal malformations including digital malformations in rat fetuses and romosozumab has yet to be ruled out taking into consideration the following factors.

- While the variations occurred in the 7 fetuses from a litter, romosozumab can be transferred from the mother to the fetus across the placenta during organogenesis of rat digits;
- Similar digital malformations occurred in sclerostin knockout mice;
- The conditions including exposure to romosozumab are not clear in the fetuses with anomalies; and
- The results of the rat embryo-fetal development study were higher than the historical control range of the testing laboratory, and there were variations that had not been observed previously at the testing laboratory.

In humans, on the other hand, given extremely low level of immunoglobulin placental transport in the first trimester (digital formation period), and because the exposure level (60,500 μg·h/mL) after administration of the no-expression level (60 mg/kg) in the toxicity study that produced malformation results has 18.8-fold safety margin compared to the exposure level after administration of the clinically recommended dose (210 mg once a month) of romosozumab, the applicant considers that the risk of inducing digital malformations when administering romosozumab to pregnant women is low. While this explanation is acceptable, the events that occurred in the rat embryo-fetal development study (CTD 4.2.3.5.2-2) should be communicated to healthcare professionals via the package insert.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Formulations used in the major clinical studies of romosozumab are presented in Table 16. Changes were made to the manufacturing processes for the drug substance and drug product, comparability was evaluated in terms of the quality attributes, and the results demonstrated comparability of the drug substances and the drug product before and after the change [see Sections "2.1.4 Manufacturing process development," and "2.2.3 Manufacturing process development"]. The proposed formulation is the prefilled syringe (PFS)

(90 mg/mL) formulation produced from the drug substance manufactured by the proposed manufacturing process.

Table 16. Formulations used in major clinical studies

Manufacturing process of drug substance	Type of formulation (romosozumab concentration)	Phase (study ID)	
		Japanese study	Foreign study (including global studies)
Process A	Vial (70 mg/mL)	—	Phase I studies (Studies 20090378,[a] 20060220, 20060221, and 20[redacted]0223) Phase II study (Study 20060326)
Process B	PFS (70 mg/mL)	Phase II study (Study 20101291)	Phase I studies (Studies 20[redacted]0277 and 20110227) Phase II study (Study 20060326) Phase III studies (Studies 20070337,[b] 20110174,[b] 20080289, and 20120156)
	PFS (90 mg/mL)	—	Phase I studies (Studies 20[redacted]0277 and 20[redacted]0197) Phase III study (Study 20120156)
Proposed manufacturing process	PFS (90 mg/mL)	—	Phase I study (Study 20[redacted]0197)

—, not applicable
a) The phase I study including Japanese subjects living in the US
b) The global study including Japanese subjects

Serum romosozumab concentrations were determined by ELISA. The lower limit of quantitation was 50 ng/mL. Anti-drug antibodies and neutralizing antibodies in human serum were determined by ECL.

As biopharmaceutic evaluation data, data from a bioequivalence study conducted outside Japan (Study 20[redacted]0197), and as biopharmaceutic reference data, data from bioequivalence studies (Studies 20[redacted]0277, 20[redacted]1180, and 20[redacted]0418) and a relative bioavailability study (Study 20[redacted]0274) conducted outside Japan were submitted. Results from major studies are summarized in the following sections.

6.1.1 Bioequivalence study of formulations produced from drug substances at different manufacturing sites and/or by different manufacturing processes (CTD 5.3.1.2-2, Study 20[redacted]0197 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, parallel-group study was conducted in non-Japanese healthy adults (target sample size, 184 subjects; 92/group) to compare and evaluate the bioequivalence of formulations produced from drug substances at different manufacturing sites and/or by different manufacturing processes.

Subjects received a single subcutaneous dose of 210 mg of the PFS (90 mg/mL) formulation produced from the drug substance manufactured by the proposed manufacturing process (hereinafter referred to as "proposed formulation"), or a single subcutaneous dose of 210 mg of the PFS (90 mg/mL) formulation produced from the drug substance manufactured by Process B (hereinafter referred to as "Process B formulation"), followed by an 85-day follow-up period. Throughout the study period, calcium (≥500 mg/day and ≤2000 mg/day) and vitamin D (≥400 IU/day)[27] were administered as base treatment drugs.

A total of 188 subjects were randomized and received the study drug (92 subjects in the proposed formulation group, and 96 subjects in the Process B formulation group), and all were included in the safety

[27] Calcium and vitamin D (natural vitamin D) supplements were administered. The same shall apply hereinafter for base treatment drugs in this Review Report.

analysis set. Of these, 2 subjects in the proposed formulation group discontinued the study early and their pharmacokinetic parameters were therefore not calculated. Other than these 2 excluded, 186 subjects were included in the pharmacokinetic analysis set.

The pharmacokinetic results showed that the geometric mean ratio of the proposed formulation to Process B formulation with its 90% confidence interval (CI) for C_{max} was 0.92 [0.86, 0.98], and that for AUC_{last} was 0.91 [0.84, 0.99], and the proposed formulation and the Process B formulation were determined to be biologically equivalent.

The percentage of subjects who tested positive for anti-drug antibodies at least once by Day 85 was 6.5% (6 of 92 subjects) in the proposed formulation group, and 3.1% (3 of 96) in the Process B formulation group. Of these subjects, 1.1% (1 of 92) in the proposed formulation group, and 1.0% (1 of 96) in the Process B formulation group tested positive for neutralizing antibodies at Day 85.

Safety analyses revealed that the incidence of adverse events was 44.6% (41 of 92) and that of adverse reactions 18.5% (17 of 92) in the proposed formulation group, while in the Process B formulation group, the incidence of adverse events was 55.2% (53 of 96) and of adverse reactions 18.8% (18 of 96). There were no deaths or no adverse events leading to treatment discontinuation. A serious adverse event (palindromic rheumatism) occurred in 1 subject in the Process B formulation group, and the event was classified as an adverse reaction.

The laboratory examination results showed that albumin-corrected serum calcium level remained within the reference range in both groups. In both groups, serum intact parathyroid hormone (iPTH) levels increased from baseline and peaked on Day 29, and decreased to baseline by Day 57.

There were no changes in electrocardiogram (ECG) or vital signs that could cause clinical problems.

6.1.2 Bioequivalence study of formulations with different romosozumab concentrations (CTD 5.3.1.2-1, Study 20[redacted]0277 [[redacted] to [redacted] 20[redacted]]; Reference data)

A randomized, open-label, parallel-group study was conducted in non-Japanese healthy adults (target sample size, 160 subjects; 80/group) to compare and evaluate the bioequivalence of formulations with different romosozumab concentrations.

Subjects received a single subcutaneous dose of 210 mg of the PFS (90 mg/mL) formulation produced from the drug substance manufactured by Process B (hereinafter referred to as “90 mg/mL formulation”), or a single subcutaneous dose of 210 mg of the PFS (70 mg/mL) formulation produced from the drug substance manufactured by Process B (hereinafter referred to as “70 mg/mL formulation”), followed by an 85-day observation period.

A total of 172 subjects were randomized and received the study drug (85 in the 90 mg/mL formulation group, and 87 in the 70 mg/mL formulation group), and all were included in the safety analysis set. One subject in the 90 mg/mL formulation group and 5 subjects in the 70 mg/mL formulation group discontinued the study early and their pharmacokinetic parameters were therefore not calculated. Other than these 6 subjects excluded, the remaining 166 subjects were included in the pharmacokinetic analysis set.

The pharmacokinetic results showed that the geometric mean ratio of the 90 mg/mL formulation to the 70 mg/mL formulation with its 90% CI for C_{max} was 0.99 [0.91, 1.08], and that for AUC_{last} was 0.90 [0.81, 0.99], and the 90 mg/mL formulation and the 70 mg/mL formulation were determined to be biologically equivalent.

The percentage of subjects who tested positive for anti-drug antibodies at least once by Day 85 was 4.7% (4 of 85) in the 90 mg/mL formulation group, and 12.6% (11 of 87) in the 70 mg/mL formulation group. Of these subjects, 1.2% (1 of 85) in the 90 mg/mL formulation group and 3.4% (3 of 87) in the 70 mg/mL formulation group tested positive for neutralizing antibodies at Day 85.

The safety analyses revealed the incidences of adverse events and adverse reactions to be 40.0% (34 of 85) and 23.5% (20 of 85), respectively, in the 90 mg/mL formulation group, and 31.0% (27 of 87) and 24.1% (21 of 87), respectively, in the 70 mg/mL formulation group. There were no deaths or adverse events leading to treatment discontinuation. A serious adverse event (hemiplegic migraine) occurred in 1 subject in the 90 mg/mL formulation group, and a causal relationship to the study drug was ruled out for the event.

The laboratory examination showed albumin-corrected serum calcium level decreasing from baseline in both groups, reaching lowest levels at Day 29 and recovering to baseline by Day 85. In both groups, serum iPTH level increased from baseline to a peak at Day 29, and remained higher than baseline at Day 85.

There were no changes in vital signs or 12-lead ECG that could cause clinical problems.

6.2 Clinical pharmacology

The evaluation data submitted were results from a study in Japan (Study 20101291), 7 foreign studies (Studies 20090378,[28)] 20060220, 20060221, 20[redacted]0223, 20060326, 20080289, and 20120156), and 2 global studies (Studies 20070337 and 20110174). The reference data submitted included results from 4 foreign studies (Studies 20110227, 20090153, 20110253, and 20110142), and results from pharmacokinetic analysis. Results from the main studies are presented in the following sections.

[28)] A phase I study conducted in subjects including Japanese living in the US.

6.2.1 Studies in healthy adults

6.2.1.1 Phase I study in Japanese and non-Japanese healthy postmenopausal women (CTD 5.3.3.1-2, Study 20090378 [May to November 2010])

A randomized, double-blind, placebo-controlled study was conducted in Japanese and non-Japanese healthy postmenopausal women living in the US (target sample size, 30 subjects; 24 Japanese and 6 non-Japanese) to evaluate the safety, pharmacokinetics, and pharmacodynamics of a subcutaneous single-dose of romosozumab.

In Cohorts 1, 2, and 4 of Japanese women, subjects received a single subcutaneous dose of placebo, romosozumab 1, 3, or 5 mg/kg. In Cohort 3 of non-Japanese women, subjects received a single subcutaneous dose of placebo or romosozumab 3 mg/kg, followed by an 8-day observation period. In Cohorts 1, 2, and 4, subjects in each cohort (8 each) were randomized into placebo or romosozumab groups in a ratio of 1:3. In Cohort 3, 6 subjects were randomized into a placebo or romosozumab group in a ratio of 1:2.

All 30 subjects who were randomized and received the study drug (24 Japanese [6 in the placebo group and 18 in the romosozumab groups]; and 6 non-Japanese [2 in the placebo group and 4 in the romosozumab group]) were included in the safety analysis set, and 22 subjects in the romosozumab groups were included in the pharmacokinetic analysis set.

Table 17 shows pharmacokinetic parameters of a single subcutaneous dose of romosozumab.

Table 17. Pharmacokinetic parameters of a single subcutaneous dose of romosozumab

Dose	Population	N	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL/F (mL/day/kg)
1 mg/kg	Japanese	6	4.1 ± 1.5	64.7 ± 26.8	5.0 [5.0, 8.0]	5.82 ± 1.05	18.6 ± 10.0
3 mg/kg	Japanese	6	17.1 ± 4.7	347 ± 90	5.0 [3.0, 12]	6.31 ± 1.14	9.27 ± 2.64
3 mg/kg	Non-Japanese	4	18.6 ± 1.1	421 ± 147	5.0 [5.0, 7.0]	6.81 ± 2.69	7.91 ± 2.68
5 mg/kg	Japanese	6	33.8 ± 8.1	806 ± 323	5.0 [5.0, 7.0]	7.19 ± 1.55	6.98 ± 2.35

Mean ± standard deviation; t_{max} indicates the median [range].
C_{max}, maximum serum concentration; AUC_{inf}, area under the serum concentration-time curve, from 0 to infinity; t_{max}, time to maximum serum concentration; $t_{1/2}$, elimination half-life; CL/F, apparent clearance

Table 18 shows the percentage change from baseline in bone turnover markers as pharmacodynamic markers of romosozumab.

Table 18. Percentage change from baseline in bone turnover markers over time (%)

	Dose	Population	N	Day 3	Day 4	Day 8	Day 12	Day 22	Day 29	Day 43	Day 57
Serum P1NP	1 mg/kg	Japanese	6	−2.30 ± 5.77	2.11 ± 6.35	54.6 ± 13.3	59.2 ± 12.2	55.7 ± 12.0	36.9 ± 9.22	14.8 ± 6.20	2.34 ± 5.84
	3 mg/kg	Japanese	6	0.74 ± 3.83	8.02 ± 2.69	52.3 ± 10.6	75.4 ± 14.7	103 ± 18.3	85.1 ± 22.4	10.6 ± 17.3	−8.97 ± 6.76
	3 mg/kg	Non-Japanese	4	0.66 ± 2.25	18.5 ± 3.49	72.4 ± 15.3	118 ± 13.8	164 ± 35.6	127.0 ± 21.6	49.9 ± 21.2	15.0 ± 14.3
	5 mg/kg	Japanese	6	14.1 ± 6.74	29.7 ± 11.0	89.4 ± 19.1	132 ± 24.7	196 ± 29.8	169 ± 25.9	96.0 ± 19.3	9.74 ± 15.1
Serum CTX	1 mg/kg	Japanese	6	−0.71 ± 12.4	−12.7 ± 7.99	−10.5 ± 8.56	−16.2 ± 7.36	1.03 ± 12.9	2.96 ± 9.46	18.3 ± 10.2	8.66 ± 6.72
	3 mg/kg	Japanese	6	−16.5 ± 3.18	−26.1 ± 2.28	−35.9 ± 1.94	−33.4 ± 5.12	−29.0 ± 1.97	−17.3 ± 9.89	−25.2 ± 9.63	−11.4 ± 4.29
	3 mg/kg	Non-Japanese	4	−30.7 ± 7.93	−26.0 ± 10.8	−43.3 ± 9.96	−30.1 ± 11.9	−37.1 ± 9.93	−31.3 ± 13.9	−14.6 ± 11.6	−19.3 ± 11.2
	5 mg/kg	Japanese	6	−26.4 ± 6.54	−31.2 ± 5.60	−39.2 ± 5.13	−35.0 ± 7.42	−15.3 ± 18.9	0.30 ± 27.5	4.84 ± 22.2	31.7 ± 33.2

Mean ± standard deviation;
P1NP, type I procollagen-N-propeptide; CTX, type I collagen cross-linked C-telopeptide

Concerning anti-drug antibodies, no anti-drug antibody-positive subjects were found in the romosozumab groups at any time point.

The safety analysis in Japanese subjects revealed adverse events occurring in 6 of 6 subjects (placebo), 4 of 6 subjects (1 mg/kg), 3 of 6 subjects (3 mg/kg), and 6 of 6 subjects (5 mg/kg), and adverse reactions occurring in 2 of 6 subjects (placebo), 1 of 6 subjects (1 mg/kg), 2 of 6 subjects (3 mg/kg), and 1 of 6 subjects (5 mg/kg). In non-Japanese subjects, adverse events occurred in 2 of 2 subjects (placebo), and 4 of 4 subjects (3 mg/kg), while adverse reactions occurred in 0 of 2 subjects (placebo), and 0 of 6 subjects (3 mg/kg). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

The laboratory examination results showed that serum calcium level decreased from baseline in Japanese and non-Japanese subjects receiving romosozumab, and recovered nearly to baseline by Day 57. In Japanese and non-Japanese subjects receiving romosozumab, serum iPTH levels increased from baseline, and returned to baseline by Day 57.

There were no changes in vital signs or 12-lead ECG that could cause clinical problems.

6.2.2 Investigation in subjects with low bone mass and patients with osteoporosis

6.2.2.1 Phase I study in non-Japanese men with low bone mass, and non-Japanese postmenopausal women (CTD5.3.3.2-1, Study 20060221 [November 2007 to December 2008])

A randomized, double-blind, placebo-controlled, ascending multiple-dose study was conducted in non-Japanese men with low bone mass, and non-Japanese postmenopausal women (target sample size, 48 subjects; 16 men, and 32 women) to evaluate the safety, pharmacokinetics and pharmacodynamics of repeated subcutaneous doses of romosozumab. Major inclusion criteria were men aged 45 to 80 years or postmenopausal women who had no bone fracture history within 6 months prior to screening and a BMD T-score of ≥−2.5 and ≤−1 at the lumbar vertebrae or proximal femur.

This study consisted of a screening phase (up to 21 days), study drug treatment phase (3 months), and follow-on phase (3 months).

Cohorts 1 through 4 were of women. The subjects received placebo or romosozumab (1 or 2 mg/kg) once every 2 weeks (Q2W), or placebo or romosozumab (2 or 3 mg/kg) once every 4 weeks (Q4W) subcutaneously for 3 months. Cohorts 5 and 6 were of men, and the subjects received placebo or romosozumab 1 mg/kg Q2W, or placebo or romosozumab 3 mg/kg Q4W subcutaneously for 3 months. Subjects in each cohort (8 each) were randomized into placebo or romosozumab groups in a ratio of 1:3. Throughout the study period, calcium (≥500 mg/day) and vitamin D (≥400 IU/day and ≤1000 IU/day) were administered orally as base treatment drugs.

All 48 subjects who were randomized and received the study drug (12 in the placebo group and 36 in the romosozumab group) were included in the safety analysis set. Of these, 36 subjects in the romosozumab group were included in the pharmacodynamic analysis set. Two subjects in the romosozumab 1 mg/kg Q2W group (1 woman who tested positive for anti-drug antibodies in a previous study of romosozumab and 1 man withdrew consent), and 1 subject in the romosozumab 3 mg/kg Q4W group (1 woman unable to provide ≥2 sample specimen) were excluded from the pharmacodynamic analysis set, and the remaining 33 subjects were included in the pharmacokinetic analysis set.

Table 19 shows pharmacokinetic parameters of romosozumab administered subcutaneously for 3 months.

Table 19. Pharmacokinetic parameters of romosozumab administered subcutaneously for 3 months

Treatment group	Sex	N	Measuring time point	C_{max} (μg/mL)	AUC[a)] (μg·day/mL)	t_{max} (day)	$t_{1/2}$ (day)
1 mg/kg Q2W	F	5	Post first dose	6.8 ± 1.9	66 ± 16	3.0 [2.0, 5.0]	—
			Post third dose	14.2 ± 4.3	141 ± 41	3.0 [0, 5.0]	7.02 ± 3.52
	M	5	Post first dose	8.1 ± 1.6	71 ± 12	3.0 [3.0, 5.0]	—
			Post third dose	13.4 ± 4.4	136 ± 42	3.0 [3.0, 5.0]	6.77 ± 1.92
2 mg/kg Q2W	F	6	Post first dose	14.8 ± 6.0	152 ± 63	4.5 [3.0, 7.0]	—
			Post third dose	27.8 ± 8.4	321 ± 97	3.5 [3.0, 5.0]	9.32 ± 1.88
2 mg/kg Q4W	F	6	Post first dose	15.7 ± 4.6	202 ± 48	3.0 [3.0, 5.0]	—
			Post third dose	16.7 ± 3.3	231 ± 58	3.0 [1.0, 4.0]	6.51 ± 1.37
3 mg/kg Q4W	F	5	Post first dose	24.5 ± 6.8	340 ± 73	3.0 [3.0, 5.0]	—
			Post third dose	29.5 ± 8.7	462 ± 97	5.0 [2.0, 7.0]	6.84 ± 1.79
	M	6	Post first dose	27.7 ± 4.2	434 ± 81	5.0 [3.0, 5.0]	—
			Post third dose	37.1 ± 8.1	555 ± 181	3.0 [3.0, 5.0]	6.07 ± 1.50

Mean ± standard deviation; t_{max} is the median [range]; —, not calculated

C_{max}, maximum serum concentration; AUC, area under the serum concentration-time curve; t_{max}, time to maximum serum concentration; $t_{1/2}$, elimination half-life

a) $AUC_{0\text{-}14\ days}$ (area under the serum concentration-time curve, from 0 to Day 14 post dose) for the Q2W group; $AUC_{0\text{-}28\ days}$ (area under the serum concentration-time curve, 0 to Day 28 post-dose) for the Q4Wgroup

Table 20 shows the percentage change from baseline in bone turnover markers as pharmacodynamics markers.

Table 20. Percentage change from baseline in bone turnover markers (%)

Bone turnover marker		Treatment group	Sex	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 169
Bone formation markers	Serum P1NP	1 mg/kg Q2W	F	58.0 ± 11.5	81.5 ± 20.4	69.9 ± 20.5	51.7 ± 20.7	51.3 ± 15.3	35.6 ± 11.5	4.79 ± 7.31
			M	58.8 ± 12.5	88.2 ± 12.0	98.5 ± 17.2	77.0 ± 12.1	60.6 ± 14.7	54.1 ± 11.1	5.78 ± 9.42
		2 mg/kg Q2W	F	76.7 ± 21.3	118.2 ± 17.0	93.2 ± 20.3	95.2 ± 21.5	88.5 ± 15.1	79.8 ± 20.5	1.42 ± 6.81
		2 mg/kg Q4W	F	66.1 ± 14.6	26.4 ± 10.4	62.2 ± 24.0	3.28 ± 10.7	20.0 ± 13.2	−3.90 ± 10.1	−16.9 ± 7.34
		3 mg/kg Q4W	F	103.7 ± 7.37	74.5 ± 16.3	129 ± 21.1	77.0 ± 20.3	65.0 ± 21.8	24.9 ± 9.30	11.7 ± 11.5
			M	123.9 ± 39.1	115.1 ± 26.8	140 ± 31.5	74.2 ± 19.6	113.6 ± 19.1	44.4 ± 22.4	−7.07 ± 10.5
	Serum OC	1 mg/kg Q2W	F	23.6 ± 10.8	49.4 ± 16.0	45.5 ± 12.4	49.3 ± 10.5	39.5 ± 13.0	41.4 ± 11.9	−7.12 ± 7.84
			M	45.2 ± 13.5	55.6 ± 10.4	57.6 ± 13.4	69.2 ± 19.2	51.7 ± 16.4	48.7 ± 12.5	2.19 ± 10.8
		2 mg/kg Q2W	F	33.2 ± 9.05	81.7 ± 19.2	77.2 ± 14.9	70.8 ± 16.5	81.0 ± 20.7	63.7 ± 12.0	16.8 ± 12.4
		2 mg/kg Q4W	F	21.2 ± 6.94	39.5 ± 11.3	30.8 ± 14.4	−0.80 ± 15.2	28.0 ± 11.9	19.1 ± 9.44	−20.3 ± 8.66
		3 mg/kg Q4W	F	70.2 ± 15.2	90.1 ± 7.79	90.1 ± 17.1	74.7 ± 8.81	77.5 ± 7.93	77.2 ± 16.8	24.6 ± 12.8
			M	24.7 ± 5.35	79.5 ± 17.1	82.0 ± 14.9	81.2 ± 16.3	79.7 ± 20.0	81.9 ± 31.3	−13.7 ± 10.56
	Serum BAP	1 mg/kg Q2W	F	31.7 ± 14.4	56.1 ± 19.3	49.3 ± 14.0	41.4 ± 11.3	34.3 ± 11.3	26.0 ± 12.2	−1.37 ± 6.27
			M	15.6 ± 4.69	36.7 ± 10.5	27.6 ± 8.68	38.5 ± 12.2	25.5 ± 15.1	18.7 ± 9.63	−4.76 ± 5.36
		2 mg/kg Q2W	F	33.7 ± 8.61	65.1 ± 14.7	68.5 ± 12.8	65.3 ± 9.34	52.8 ± 7.72	69.9 ± 21.4	2.33 ± 4.19
		2 mg/kg Q4W	F	32.0 ± 6.28	36.5 ± 8.85	39.3 ± 10.5	38.1 ± 11.2	16.3 ± 6.39	7.70 ± 5.59	−5.72 ± 5.75
		3 mg/kg Q4W	F	52.0 ± 5.28	61.7 ± 13.2	66.7 ± 10.4	47.4 ± 6.06	44.7 ± 9.30	38.3 ± 4.20	16.3 ± 7.56
			M	46.4 ± 8.63	35.6 ± 13.8	52.3 ± 13.5	44.5 ± 11.6	47.5 ± 9.99	42.5 ± 14.5	−0.42 ± 6.39
Bone resorption marker	Serum CTX	1 mg/kg Q2W	F	−14.4 ± 9.41	0.310 ± 6.08	3.91 ± 9.40	14.4 ± 10.3	26.6 ± 14.9	15.0 ± 13.5	−1.13 ± 8.37
			M	−39.3 ± 2.85	−32.8 ± 4.85	−28.5 ± 6.07	−25.3 ± 12.3	−11.0 ± 18.1	−16.9 ± 16.8	−15.6 ± 11.7
		2 mg/kg Q2W	F	−35.3 ± 4.30	−25.4 ± 6.08	−34.0 ± 3.35	−23.7 ± 6.45	−18.2 ± 7.26	−13.1 ± 9.08	−0.920 ± 15.3
		2 mg/kg Q4W	F	−35.1 ± 8.69	−21.1 ± 8.86	−13.8 ± 15.1	−4.53 ± 18.0	−14.4 ± 11.8	8.97 ± 10.9	−9.38 ± 12.6
		3 mg/kg Q4W	F	−33.0 ± 7.65	−21.5 ± 11.0	−20.5 ± 12.7	−13.5 ± 15.7	−14.0 ± 13.6	13.8 ± 22.2	−0.270 ± 10.4
			M	−48.7 ± 5.56	−34.5 ± 8.14	−44.6 ± 7.31	−31.5 ± 7.89	−38.4 ± 4.37	−17.2 ± 10.1	−10.1 ± 9.54

Mean ± standard error; n = 6/group
P1NP, type I procollagen-N-propeptide; OC, osteocalcin; BAP, bone alkaline phosphatase; CTX, type I collagen cross-linked C-telopeptide

The number of subjects who tested positive for anti-drug antibodies at least once by the end of the follow-on phase (Month 6) were 2 of 6 women (romosozumab 1 mg/kg Q2W), 2 of 6 women (2 mg/kg Q2W), 2 of 6 women (2 mg/kg Q4W), 3 of 6 women (3 mg/kg Q4W), 1 of 6 men (1 mg/kg Q2W), and 3 of 6 men (3 mg/kg Q4W). Of these, 1 woman each (1 mg/kg Q2W and 2 mg/kg Q4W)) and 1 man (3 mg/kg Q4W) were neutralizing antibody-positive.

The safety analysis revealed that adverse events occurred in 8 of 8 women (placebo), 6 of 6 women (1 mg/kg Q2W), 6 of 6 women (2 mg/kg Q2W), 6 of 6 women (2 mg/kg Q4W), and 5 of 6 women (3 mg/kg Q4W), and adverse reactions occurred in 5 of 8 women (placebo), 1 of 6 women (1 mg/kg Q2W), 4 of 6 women (2 mg/kg Q2W), 1 of 6 women (2 mg/kg Q4W), and 3 of 6 women (3 mg/kg Q4W). Adverse events occurred in 2 of 4 men (placebo), 5 of 6 men (1 mg/kg Q2W), and 5 of 6 men (3 mg/kg Q4W), and adverse reactions in 1 of 4 men (placebo), 3 of 6 men (1 mg/kg Q2W), and 2 of 6 men (3 mg/kg Q4W).

There were no deaths. Serious adverse events occurred in 1 woman (haematochezia/haemorrhagic anaemia), and 1 man (coronary artery disease) in the romosozumab 3 mg/kg Q4W group. A causal relationship to the

study drug was ruled out for both events. An adverse event of pruritus in 1 woman in the romosozumab 3 mg/kg Q4W group led to treatment discontinuation and was assessed as an adverse reaction.

The laboratory examination showed serum total calcium level remaining >8.5 mg/dL in all romosozumab groups. Serum ionized calcium level remained >4.8 mg/dL in the romosozumab 2 mg/kg Q2W and 2 mg/kg Q4W groups, the concentrations dropped transiently to <4.8 mg/dL in men and women in other romosozumab groups. The post-baseline minimum serum ionized calcium levels were not dose dependent and were similar between men and women. In all romosozumab groups, serum iPTH level increased from baseline and returned to baseline by Days 71 to 141. Mild hypocalcaemia occurred in 1 subject in the romosozumab 3 mg/kg Q4W group and was assessed as an adverse reaction.

There were no changes in vital signs or 12-lead ECG that could cause clinical problems.

6.2.2.2 Japanese phase II study (CTD 5.3.5.1-3, Study 20101291 [October 2012 to January 2015])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in Japanese postmenopausal women with osteoporosis (target sample size, 220 subjects; 55/group) to evaluate the efficacy and safety of romosozumab [see Section "7.1.1 Japanese phase II study" for study design details, and efficacy and safety results].

Table 21 shows the time course of trough serum concentration representing the pharmacokinetics of romosozumab administered subcutaneously once a month for 12 months.

Table 21. Time course of trough serum concentration of romosozumab administered subcutaneously once a month for 12 months

	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
Romosozumab 70 mg	0.815 ± 0.567 (62)	0.777 ± 0.658 (60)	0.845 ± 0.681 (54)	0.911 ± 0.756 (54)	0.883 ± 0.878 (53)	0.884 ± 0.772 (54)
Romosozumab 140 mg	3.73 ± 2.21 (61)	4.21 ± 2.71 (62)	3.78 ± 2.50 (58)	4.45 ± 2.92 (61)	4.59 ± 3.12 (60)	4.50 ± 3.58 (62)
Romosozumab 210 mg	6.06 ± 2.67 (61)	8.30 ± 4.52 (59)	8.09 ± 5.77 (56)	9.04 ± 6.19 (55)	10.3 ± 6.29 (58)	10.4 ± 6.62 (57)

Mean ± standard deviation (number of subjects evaluated); unit, μg/mL

6.2.2.3 Foreign phase II study (CTD 5.3.5.1-2, Study 20060326 [June 2009 to March 2016])

A randomized, placebo- and active-controlled, parallel-group study was conducted in non-Japanese postmenopausal women with low bone mass (target sample size, 400 subjects; 50/group) to evaluate the efficacy and safety of romosozumab [see Section "7.1.2 Foreign phase II study" for study design details, and efficacy and safety results].

Table 22 shows the time course of trough serum concentration representing the pharmacokinetics of romosozumab administered subcutaneously once a month for 24 months in the initial treatment phase, and Table 23 shows that of romosozumab 210 mg administered subcutaneously once a month in the initial treatment and retreatment phases to subjects who proceeded to the retreatment phase.

Table 22. Time course of trough serum romosozumab in the initial treatment phase

	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 24
Romosozumab 70 mg Q1M[a)]	0.675 ± 0.518 (48)	0.757 ± 0.730 (45)	0.886 ± 0.925 (40)	0.713 ± 0.656 (37)	1.07 ± 0.972 (39)	0.943 ± 0.784 (36)	0.940 ± 0.812 (29)
Romosozumab 140 mg Q1M[a)]	2.92 ± 1.90 (47)	2.78 ± 1.95 (42)	3.54 ± 2.55 (41)	3.71 ± 3.23 (40)	3.98 ± 3.91 (42)	4.77 ± 4.25 (42)	6.05 ± 4.84 (33)
Romosozumab 210 mg Q1M[a)]	5.64 ± 2.89 (48)	5.92 ± 3.68 (42)	6.30 ± 4.25 (40)	7.20 ± 4.87 (43)	8.05 ± 4.64 (43)	9.32 ± 5.66 (44)	9.38 ± 5.55 (33)

Mean ± standard deviation (number of subjects evaluated); unit, μg/mL

a) Romosozumab 70 mg, 140 mg, or 210 mg was administered once a month

Table 23. Time course of trough serum romosozumab in the initial and retreatment phases

	Initial treatment phase[c)]						Retreatment phase[c)]				
	Month 1	Month 2	Month 6	Month 9	Month 12	Month 24	Month 37	Month 38	Month 42	Month 45	Month 48
Romosozumab 210 mg Q1M/placebo /romosozumab[a)]	6.33 ± 3.18 (18)	6.49 ± 4.04 (17)	7.49 ± 6.02 (19)	9.16 ± 5.77 (18)	10.4 ± 6.56 (19)	10.7 ± 6.79 (14)	6.49 ± 2.79 (12)	8.09 ± 3.98 (17)	10.5 ± 6.29 (18)	12.1 ± 7.63 (15)	10.2 ± 7.39 (15)
Romosozumab 210 mg Q1M/Dmab /romosozumab[b)]	4.92 ± 2.89 (20)	5.57 ± 3.98 (18)	6.57 ± 4.22 (17)	6.80 ± 3.82 (18)	7.63 ± 5.22 (19)	7.97 ± 4.75 (14)	4.70 ± 3.20 (11)	9.03 ± 5.45 (14)	10.7 ± 8.71 (15)	10.9 ± 7.75 (11)	6.67 ± 3.40 (14)

Mean ± standard deviation (number of subjects evaluated); unit, μg/mL

a) Romosozumab 210 mg once a month (initial treatment phase) → placebo once every 6 months (denosumab treatment phase) → romosozumab 210 mg once a month (retreatment phase)

b) Romosozumab 210 mg once a month (initial treatment phase) → denosumab once every 6 months (denosumab treatment phase) → romosozumab 210 mg once a month (retreatment phase)

c) In the initial treatment phase, the vial (70 mg/mL) formulation produced from the drug substance manufactured by Process A was used; in the retreatment phase, the PFS (70 mg/mL) formulation produced from the drug substance manufactured by Process B was used.

6.2.2.4 Global phase III study in postmenopausal women with osteoporosis (CTD 5.3.5.1-1, Study 20070337 [ongoing since March 2012, data cut-off in December 2015])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in Japanese and non-Japanese postmenopausal women with osteoporosis (target sample size, 6600 subjects; 3300/group) to evaluate the efficacy and safety of romosozumab [see Section "7.2.1 Global phase III study in postmenopausal women with osteoporosis" for study design details, and efficacy and safety results].

Table 24 shows the time course of trough serum concentration representing the pharmacokinetics of romosozumab 210 mg subcutaneously administered once a month for 12 months.

Table 24. Time course of trough serum concentration of romosozumab 210 mg subcutaneously administered once a month for 12 months

Month 1	Month 3	Month 6	Month 9	Month 12
5.93 ± 3.48 (325)	8.05 ± 5.51 (324)	8.46 ± 6.15 (366)	9.51 ± 6.37 (362)	9.87 ± 6.90 (381)

Mean ± standard deviation (number of subjects evaluated); unit, μg/mL

6.2.2.5 Global phase III study in men with osteoporosis (CTD 5.3.5.1-6, Study 20110174 [June 2014 to April 2016])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in Japanese and non-Japanese men with osteoporosis (target sample size, 225 subjects; 150 in the romosozumab group and 75 in the placebo group) to evaluate the efficacy and safety of romosozumab [see Section "7.2.2 Global phase III study in men with osteoporosis" for study design details, and efficacy and safety results].

Table 25 shows the time course of trough serum concentration representing the pharmacokinetics of romosozumab 210 mg subcutaneously administered once a month for 12 months.

Table 25. Time course of trough serum concentration of romosozumab 210 mg subcutaneously administered once a month for 12 months

Month 1	Month 3	Month 6	Month 12
6.22 ± 3.18 (152)	7.92 ± 4.84 (142)	7.95 ± 5.17 (128)	9.03 ± 5.51 (124)

Mean ± standard deviation (number of subjects evaluated); unit, μg/mL

6.2.3 Investigation of intrinsic factors

6.2.3.1 Pharmacokinetic study in patients with renal impairment (CTD 5.3.3.3-1, Study 20110227 [April 2013 to February 2014], Reference data)

An open-label, parallel group study was conducted in non-Japanese adult men and women (target sample size, 24 subjects) to evaluate the safety and pharmacokinetics of romosozumab in subjects with normal kidney function (eGFR,[29] ≥80 mL/min/1.73 m^2), and subjects with renal impairment (eGFR, 15-29 mL/min/1.73 m^2 [severe], <15 mL/min/1.73 m^2 [patients with end stage renal disease (ESRD) requiring hemodialysis]).

Subjects were treated with a single subcutaneous dose of romosozumab 210 mg. All subjects received 50000 IU of vitamin D orally at enrollment. Furthermore, subjects with normal kidney function received ≥500 mg/day of calcium and ≥400 IU/day of vitamin D orally at enrollment. Subjects with severe renal impairment or ESRD received ≥1000 mg/day of calcium and ≥800 IU/day of vitamin D if their albumin-corrected serum calcium level was <9.6 mg/dL or ≥500 mg/day of calcium and ≥400 IU/day of vitamin D orally at enrollment and the day before enrollment if ≥9.6 mg/dL. Subjects with severe renal impairment or ESRD received calcium (≥1000 mg/day) and vitamin D (≥800 IU/day) orally as basic medication throughout the study period.

All 24 subjects who received romosozumab (8 subjects each with normal renal function, severe renal impairment, and ESRD) were included in the safety and pharmacokinetic analysis set.

Table 26 shows pharmacokinetic parameters of a single subcutaneous dose of romosozumab 210 mg. The ratios of geometric mean C_{max} and AUC_{inf} between subjects with severe renal impairment and those with normal renal function with 90% CI were 1.313 [0.945, 1.824] and 1.425 [1.048, 1.937], respectively. The ratios of geometric mean of C_{max} and AUC_{inf} between the subjects with ESRD to those with normal renal function with 90% CI were 0.895 [0.638, 1.256] and 0.989 [0.723, 1.354], respectively.

Table 26. Pharmacokinetic parameters of a single subcutaneous dose of romosozumab 210 mg

	N	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	t_{max} (day)
Subjects with normal renal function	8	22.4 ± 10.3	445 ± 143	5.0 [3.0, 7.0]
Subjects with severe renal impairment	8	28.9 ± 10.8	642 ± 221	5.0 [3.0, 7.0]
Subjects with ESRD	8	19.8 ± 7.3	447 ± 154	5.0 [3.0, 7.0]

Mean ± standard deviation; t_{max} is the median [range]

C_{max}, maximum serum concentration; AUC_{inf}, area under the serum concentration-time curve, from 0 to infinity; t_{max}, time to maximum serum concentration

[29] Severity of renal impairment was classified based on the modified diet in renal disease (MDRD) formula using serum creatinine levels at screening (eGFR [mL/min/1.73 m^2] = 194 × serum $creatinine^{-1.094}$ × $age^{-0.287}$ × [0.739, for women]).

Anti-drug antibody testing revealed that 1 of 8 subjects with normal renal function was anti-drug antibody-positive at least once during the study period while none of the subjects with severe renal impairment or ESRD tested positive for anti-drug antibodies even once. Neutralizing antibodies were not detected in any of the subjects.

The safety analysis revealed that no adverse events or adverse reactions occurred in subjects with normal renal function (0 of 8 subjects). Of 8 subjects with severe renal impairment, 7 experienced adverse events and 5 experienced adverse reactions. Of 8 subjects with ESRD, 6 experienced adverse events and 6 experienced adverse reactions. There were no deaths or adverse events leading to treatment discontinuation. Serious adverse events occurred in 1 subject with severe renal impairment (anaemia) and in 1 subjects with ESRD (mitral valve disease). A causal relationship to the study drug was ruled out for both events.

The laboratory examination results showed that the lowest percentage change (mean) from baseline in albumin-corrected serum calcium level was −1.9% (Day 15) in subjects with normal renal function, −4.8% (Day 22) in subjects with severe renal impairment, and −12.9% (Day 22) in subjects with ESRD. While the serum calcium level returned to baseline by the end of the study period (Day 85) in subjects with normal renal function and those with severe renal impairment, the percentage change (mean) from baseline was −3.9% in subjects with ESRD. The highest percentage change (mean) from baseline in serum iPTH level was 94% (Day 29) in subjects with normal renal function, 150% (Day 29) in subjects with severe renal impairment, and 290% (Day 22) in subjects with ESRD. While the serum iPTH level decreased to baseline in subjects with normal renal function and patients with severe renal impairment by the end of the study period, the percentage change (mean) from baseline in subjects with ESRD was 119%. Hypocalcaemia occurred in 4 of 8 patients with severe renal impairment and 1 of 8 subjects with ESRD, and the event was assessed as an adverse reaction for all these patients.

There were no changes in vital signs or 12-lead ECG that could cause clinical problems.

6.2.4 Pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic (PPK) analysis (NONMEM version 7.2) was performed using serum romosozumab concentration data from 11 studies conducted in Japan and overseas in healthy subjects, subjects with low bone mass, and postmenopausal women with osteoporosis (phase I, Studies 20060220, 20060221, 20[redacted]0223, 20090378, 20[redacted]1180, 20[redacted]0277, 20110227, and 20110253; phase II, Studies 20060326 and 20101291; and phase III, Study 20070337). The data were obtained from 1459 subjects (341 healthy subjects [138 men and 203 women]; 12 men with low bone mass; 442 postmenopausal women with low bone mass; and 664 postmenopausal women with osteoporosis) measured at 13,346 time points.

The characteristics of the subjects in the PPK analysis (median value [minimum, maximum]) were age (66 [20, 89] years), body weight (61 [33, 109] kg), eGFR (80 [7, 144] mL/min/1.73 m^2), and BMD at the lumbar vertebrae (0.8 [0.53, 1.41] g/cm^2). The breakdown of race/ethnicity was: Caucasian, 51%; Japanese, 14%; Hispanic, 7%; black, 4%; non-Japanese Asian, 2%; and other, 21%.

An established basic model comprised 3 compartments, i.e., linear distribution to the peripheral compartment, parallel linear elimination in the central compartment, and non-linear target-mediated elimination in the peripheral compartment. Possible covariates to estimate parameters of individuals tested by the forward and backward selection methods were: baseline body weight, eGFR,[29] age, serum sclerostin concentration, sex, ethnicity (Japanese or non-Japanese), subject classification (healthy individuals, postmenopausal women with low bone mass, or postmenopausal women with osteoporosis), anti-drug antibody status, the manufacturing process of the drug substance (Process A or B), prior treatment with alendronate, and prior treatment with osteoporotic drugs. The covariates incorporated in the final model were: baseline body weight, eGFR, ethnicity, and the manufacturing process of the drug substance (Process A or B) for CL; and baseline body weight, age, and sex for the central compartment V_2.

Based on the examination of covariates in the final model, CL and V_2 were estimated to increase by approximately 18% and 20%, respectively, with every 10-kg increase in baseline body weight. In subjects with an eGFR of ≤80 mL/min/1.73 m^2, CL was estimated to decrease by approximately 5% with every 20-mL/min/1.73 m^2 decrease in eGFR. In subjects with an eGFR of >80 mL/min/1.73 m^2, CL was estimated to increase by approximately 4% with every 20-mL/min/1.73 m^2 increase in eGFR. Furthermore, CL was estimated to be higher in Japanese subjects than non-Japanese subjects by 11%, and was estimated to be lower in Process B-based formulation than in Process A-based formulation by 11%. In subjects aged >66 years, an age increase of 10 years would increase V_2 by approximately 11%. In addition, V_2 was estimated to be higher in women than in men by 24%. The ratios of mean C_{max} and AUC in patients with mild/moderate/severe renal impairment or subjects with ESRD (who were not scheduled to undergo hemodialysis during romosozumab therapy) to those in subjects with normal renal function and corresponding 90% CIs were estimated. The mean ratios (mild impairment to normal) of C_{max} and AUC were 1.04 [90% CI, 1.02, 1.06] and 1.08 [1.04, 1.12], respectively, the mean ratios (moderate impairment to normal) were 1.10 [1.07, 1.15] for C_{max} and 1.19 [1.12, 1.27] for AUC; the mean ratios (severe impairment to normal) were 1.20 [1.14, 1.26] for C_{max} and 1.36 [1.26, 1.48] for AUC; and the mean ratios (ESRD to normal) were 1.32 [1.23, 1.43] for C_{max} and 1.59 [1.43, 1.78] for AUC.

6.R Outline of the review conducted by PMDA

6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese populations

PMDA asked the applicant to explain the similarity in pharmacokinetics of romosozumab between Japanese and non-Japanese populations.

The applicant's explanation:

In the phase I study in healthy Japanese and non-Japanese postmenopausal women (Study 20090378), C_{max} (mean ± standard deviation) and AUC_{inf} (mean ± standard deviation) of romosozumab 3 mg/kg in Japanese subjects was 17.1 ± 4.7 μg/mL and 347 ± 90 μg·day/mL, respectively, while they were 18.6 ± 1.1 μg/mL and 421 ± 147 μg·day/mL, respectively, in non-Japanese subjects (Table 17). While it was difficult to strictly

compare data because of the small sample size of the study and large inter-individual variation, there were no clear differences in pharmacokinetics between Japanese and non-Japanese populations.

In the Japanese phase II study (Study 20101291) in postmenopausal women with osteoporosis and foreign phase II study (Study 20060326) in postmenopausal women with low bone mass, trough serum romosozumab (mean) at Months 1 to 12 following administration of romosozumab 210 mg once a month was 6.06 to 10.4 μg/mL in Japanese subjects and 5.64 to 9.32 μg/mL in non-Japanese subjects (Table 21 and 22). The trough values tended to be higher in Japanese subjects than in non-Japanese subjects by approximately 20%, suggesting that this difference may be attributed to the difference in body weight between Japanese and non-Japanese subjects (mean body weight at enrollment in both studies, 49.3 kg in Japanese subjects and 64.7 kg in non-Japanese subjects). A similar trend was observed in the global phase III study (Study 20110174) in men with osteoporosis. Trough serum romosozumab (mean) at Months 1 to 12 following the administration of romosozumab 210 mg once a month was 6.96 to 9.72 μg/mL in Japanese patients (mean weight at enrollment, 57.7 kg), and 6.09 to 8.93 μg/mL in non-Japanese patients (mean weight at enrollment, 73.5 kg), indicating that the trough value was higher in Japanese patients than in non-Japanese patients by approximately 15%.

The results of PPK analysis suggested that body weight was a covariate affecting the pharmacokinetics of romosozumab. In the range of body weight from 43 to 83 kg (corresponding to percentiles from 2.5th to 97.5th of body weight of the subjects in the PPK analysis), AUC was expected to vary 1.46-fold to 0.69-fold of 61 kg, the median body weight of 1459 subjects used for the analysis, suggesting that AUC would decrease with increasing body weight. However, in a simulation of the effect of AUC variation on BMD within the above-mentioned body weight range using a PK/PD model,[30)] the percentage change from baseline in BMD was estimated to range from 1.15-fold to 0.85-fold following the administration of romosozumab 210 mg for 12 months, suggesting that the change would not have a significant clinical impact.

PMDA's view:
The applicant explains that comparison of pharmacokinetics between Japanese and non-Japanese populations has shown a tendency of Japanese subjects to have greater exposure to romosozumab than non-Japanese subjects, which is primarily attributable to the difference in body weight. This explanation is acceptable. However, effects of different exposure levels on efficacy and safety are to be discussed further in Sections "7.R.1 Efficacy," and "7.R.2 Safety."

6.R.2 Administration of romosozumab in patients with renal impairment

The applicant's explanation:

30) A PK/PD analysis was conducted based on data of 662 subjects from the Japanese phase II study in postmenopausal women with osteoporosis (Study 20101291), and foreign phase II study in postmenopausal women with low bone mass (Study 20060326), and a semi-mechanistic bone turnover model was constructed for the effect of serum romosozumab concentration on bone turnover markers and BMD at the lumbar vertebrae in patients with osteoporosis.

Because of their high molecular weight, monoclonal antibodies are not excreted in urine. However, according to published literature, the degree of renal function affects the pharmacokinetics of some monoclonal antibodies (e.g., *J Clin Pharmacol.* 2010;50:754-66, *J Clin Pharmacol.* 2013;53:711-20). In order to investigate the pharmacokinetics of romosozumab in patients with renal impairment, Study 20110227 was conducted in patients with severe renal impairment and patients with ESRD. The geometric mean ratios (severe renal impairment or ESRD to normal renal function) for serum romosozumab C_{max} were 1.31 (severe renal impairment) and 0.90 (ESRD), while the geometric mean ratios for AUC_{inf} were 1.43 (severe renal impairment) and 0.99 (ESRD), indicating greater exposure of patients with severe renal impairment. There was no tendency for romosozumab exposure to increase in subjects with ESRD as compared to healthy adults. Subjects with ESRD who participated in the study underwent hemodialysis 3 days a week during the study period, and thus low exposure of subjects with ESRD would be partly due to hemodialysis. However, details are unknown.

Based on the PPK analysis results, the mean ratios (patients with renal impairment to subjects with normal renal function) for C_{max} were 1.04 (mild impairment), 1.10 (moderate impairment), 1.20 (severe impairment), and 1.32 (subjects with ESRD who were not scheduled to undergo hemodialysis during romosozumab therapy), and those for AUC were 1.08 (mild), 1.19 (moderate), 1.36 (severe), and 1.59 (ESRD), indicating that exposure increased with increasing severity of renal impairment. The effect of elevated AUC on BMD was investigated in subjects with ESRD, who had the greatest increase in AUC, using a PK/PD model.[30)] The percentage change from baseline in BMD following administration of romosozumab 210 mg for 12 months was estimated to be approximately 1.08-fold.

In phase II studies in postmenopausal women with osteoporosis conducted in and outside Japan (Studies 20060326 and 20101291), and a global phase III study (Study 20070337), the occurrence of adverse events was investigated on the basis of baseline eGFR (mL/min/1.73 m^2) classification (≥15 and <30; ≥30 and <60; ≥60 and <90; and ≥90; patients with eGFR <15 were excluded from the study). Although the limited number of patients with eGFR of ≥15 and <30 precluded a strict evaluation, there were no significant differences in the incidence of adverse events by severity of renal impairment (Table 92). However, patients with severe renal impairment or ESRD have declined ability to produce $1,25(OH)_2$ vitamin D, leading to decreased intestinal calcium absorption on demand. Romosozumab will promote bone formation causing to increase the demand for calcium. At the same time, romosozumab suppresses bone resorption causing to decrease calcium supply from bone, which will increase the risk of developing hypocalcaemia. Therefore, patients with severe renal impairment or ESRD are subject to careful administration, and this will be highlighted in the package insert.

PMDA's view:
The pharmacokinetic observation of romosozumab in patients with renal impairment in Study 20110227 and the PPK analysis revealed that romosozumab exposure increased with deteriorating renal function. In light of the limited number of subjects with osteoporosis particularly with severe renal impairment or ESRD in the

clinical studies and their high risk of developing hypocalcaemia, treatment with romosozumab in patients with renal impairment requires caution. Efficacy and safety in patients with renal impairment following administration of romosozumab are to be discussed further in Section "7.R.5.1 Patients with renal impairment".

6.R.3 Effects of antibody development on pharmacokinetics

The applicant's explanation about the effects of antibody development on the pharmacokinetics of romosozumab:

Table 27 shows trough serum romosozumab following subcutaneous administration of romosozumab 210 mg once a month for 12 months in the Japanese phase II study (Study 20101291), foreign phase II study (Study 20060326), and global phase III study in postmenopausal women with osteoporosis (Study 20070337) by anti-drug antibody and neutralizing antibody status. Trough values (mean) at Months 3, 6, and 9 tended to be lower in subjects who were anti-drug antibody-positive than those who were anti-drug antibody-negative by a maximum of 25%, and trough values at Month 12 were similar between subjects who tested positive and those who tested negative. Although the limited number of neutralizing antibody-positive subjects precluded strict comparison, trough values (mean) tended to be lower in neutralizing antibody-positive subjects than in neutralizing antibody-negative subjects.

Table 27. Trough serum romosozumab by antibody status (pooled data from Studies 20101291, 20060326, and 20070337)

Evaluation time point	Month 1	Month 3	Month 6	Month 9	Month 12
Negative for anti-drug antibodies	5.96 ± 3.33 (342)	8.23 ± 5.62 (339)	8.81 ± 6.13 (379)	9.82 ± 6.35 (369)	10.0 ± 6.70 (392)
Positive for anti-drug antibodies	5.77 ± 3.27 (91)	6.40 ± 4.44 (80)	6.63 ± 5.40 (85)	8.03 ± 5.54 (93)	8.98 ± 7.00 (89)
Positive for neutralizing antibodies	5.27 ± 3.47 (5)	4.76 ± 1.86 (3)	3.75 ± 3.11 (6)	4.61 ± 4.16 (5)	4.75 ± 4.39 (6)

Mean ± standard deviation (number of subjects evaluated); unit, μg/mL

PMDA's view:

The applicant compared trough serum romosozumab values by subject's antibody status based on the pooled data from Studies 20101291, 20060326, and 20070337. The result revealed difficulty in evaluating the effect of neutralizing antibody development on the pharmacokinetics of romosozumab because of the very limited number of neutralizing antibody-positive subjects. Given that trough values tended to be lower in subjects who tested positive for anti-drug antibodies or neutralizing antibodies than in subjects who tested negative for anti-drug antibodies, the effects of antibody development on the efficacy of romosozumab are to be discussed further in Section "7.R.1.3 Effects of antibody development on efficacy."

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from 6 studies summarized in Table 28. The applicant also submitted the results of 8 foreign clinical studies as reference data (Studies 20[redacted]0418, 20[redacted]1180, 20[redacted]0274, 20[redacted]0277, 20090153, 20110227, 20110253, and 20110142).

Table 28. List of clinical studies on efficacy and safety

Data	Location	Study ID	Phase	Subject	Number of subjects enrolled	Summary of dosage regimen	Major endpoint
Evaluation Data	Japan	20101291	II	Postmenopausal women with osteoporosis	252	Placebo or romosozumab (70 mg, 140 mg, or 210 mg) subcutaneously administered once a month for 12 months	Efficacy Safety
	Foreign	20060326	II	Postmenopausal women with low BMD	419	Initial treatment phase: Placebo or romosozumab (70 mg, 140 mg, or 210 mg) once a month (Q1M), or placebo or romosozumab (140 mg or 210 mg) once every 3 months (Q3M) for 24 months; In the active drug group, alendronate 70 mg orally once weekly for 12 months, followed by romosozumab 140 mg SC Q1M for 12 months, or teriparatide 20 μg SC once daily for 12 months (subjects randomized to teriparatide completed the study at Month 12.) Denosumab treatment phase: Placebo or denosumab 60 mg SC once every 6 months (Q6M) for 12 months Retreatment phase: romosozumab 210 mg SC Q1M for 12 months Follow-on phase: No intervention or single IV dose of zoledronic acid 5 mg	Efficacy Safety
	Global	20070337	III	Postmenopausal women with osteoporosis	7180	Placebo or romosozumab 210 mg SC Q1M for 12 months, followed by denosumab SC Q6M for 12 months	Efficacy Safety
	Global	20110174	III	Men with osteoporosis	245	Placebo or romosozumab 210 mg SC Q1M for 12 months	Efficacy Safety
	Foreign	20120156	III	Postmenopausal women with osteoporosis	294	Romosozumab 70 mg/mL formulation (210 mg) or its placebo, SC Q1M for 6 months; or romosozumab 90 mg/mL formulation (210 mg) or its placebo, SC Q1M for 6 months	Efficacy Safety
	Foreign	20080289	III	Postmenopausal women with osteoporosis	436	Romosozumab 210 mg SC Q1M for 12 months or teriparatide 20 μg SC once daily for 12 months	Efficacy Safety

Results from major studies are summarized in the following sections.

7.1 Phase II studies

7.1.1 Japanese phase II study (CTD 5.3.5.1-3, Study 20101291 [October 2012 to January 2015])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in postmenopausal women with osteoporosis (target sample size, 220 subjects; 55/group) to assess the efficacy and safety of romosozumab [for pharmacokinetics, see Section "6.2.2.2 Japanese phase II study"]. Major inclusion criteria were postmenopausal women aged 55 to 85 years; no history of vertebral fracture or proximal femoral fracture; and BMD T-score of ≤−2.5 at the lumbar vertebrae, proximal femur, or femoral neck. Subjects were excluded if BMD T-score at the lumbar vertebrae was ≤−4.0, BMD T-score at the proximal femur or femoral neck was ≤−3.5, or serum 25(OH) vitamin D was <20 ng/mL.

This study consisted of the screening phase (maximum of 35 days), treatment phase (12 months), and follow-on phase (3 months).

Placebo or romosozumab (70 mg, 140 mg, or 210 mg) was administered subcutaneously into the abdomen, thigh, or upper arm once a month. Throughout the study period, calcium (≥500 mg/day) and vitamin D[31] (≥600 IU/day) were administered orally as base treatment drugs.

All 252 subjects randomized (63/group) were included in the full analysis set (FAS). All 252 subjects (63/group) received the study drug and were included in the safety analysis set. In the FAS, 235 subjects (59 on placebo, 55 on romosozumab 70 mg, 62 on romosozumab 140 mg, and 59 on romosozumab 210 mg), received ≥10 doses of the study drug, had no missing baseline values, and had ≥1 post-baseline measurement data, and they were included in the primary efficacy analysis set. Of 17 subjects withdrawn from the study, 4 subjects were in the placebo group (consent withdrawal [4]), 8 subjects were in the romosozumab 70 mg group (consent withdrawal [7] and adverse events [1]), 1 subject was in the romosozumab 140 mg group (death [1]), and 4 subjects were in the romosozumab 210 mg group (consent withdrawal [3] and adverse events [1]).

As summarized in Table 29, the percentage change from baseline in BMD at the lumbar vertebrae at Month 12, the primary endpoint, significantly increased in all romosozumab groups compared to placebo.

Table 29. Percentage change from baseline in BMD at the lumbar vertebrae (L1-L4) at Month 12 (efficacy analysis set)

Endpoint	Placebo (59)	Romosozumab 70 mg (55)	Romosozumab 140 mg (62)	Romosozumab 210 mg (59)
Baseline T-score	−2.72 ± 0.50	−2.70 ± 0.59	−2.64 ± 0.65	−2.71 ± 0.41
Percentage change from baseline (%)	0.9 [0.1, 1.8]	8.4 [7.6, 9.3]	13.3 [12.1, 14.5]	16.9 [15.5, 18.4]
Between-group difference with placebo	—	7.5 [6.5, –]	12.4 [11.1, –]	16.0 [14.6, –]
P-value[a)]	—	<0.0001	<0.0001	<0.0001

Mean ± standard deviation; least squares mean [95% CI]
A mixed-effect model for repeated measures with baseline BMD, DXA machine type, interaction between DXA machine type and baseline BMD, office visit, treatment group, and interaction between office visit and treatment group as fixed effects, assuming within-subject unstructured variance-covariance structure
a) 1-sided significance level of 5%; multiplicity was adjusted based on a sequential test and Hochberg method.

The key secondary endpoints, the percentage change from baseline in BMD at the lumbar vertebrae, proximal femur, and femoral neck at Month 6 and Month 12 are presented in Table 30. Figure 1 shows the time course of the percentage change from baseline in bone turnover markers.

31) Natural vitamin D_3 was used. Where natural vitamin D_3 cannot be used, natural vitamin D_2 was used instead.

Table 30. Percentage change from baseline in BMD at Month 6 and Month 12 (efficacy analysis set)

Endpoint		Placebo (59)	Romosozumab 70 mg (55)	Romosozumab 140 mg (62)	Romosozumab 210 mg (59)
Lumbar vertebrae (L1-L4)	Baseline T-score	−2.72 ± 0.50	−2.70 ± 0.59	−2.64 ± 0.65	−2.71 ± 0.41
	Month 6 (%)	1.2 [0.5, 1.9]	6.5 [5.7, 7.2]	10.2 [9.2, 11.2]	13.1 [11.7, 14.5]
	Month 12 (%)	0.9 [0.1, 1.8]	8.4 [7.6, 9.3]	13.3 [12.1, 14.5]	16.9 [15.5, 18.4]
Proximal femur	Baseline T-score	−1.98 ± 0.58	−2.02 ± 0.57	−1.83 ± 0.68	−1.96 ± 0.66
	Month 6 (%)	0.6 [0.0, 1.3]	1.2 [0.5, 2.0]	2.3 [1.7, 2.9]	3.2 [2.5, 3.9]
	Month 12 (%)	0.6 [0.0, 1.3]	2.1 [1.4, 2.8]	3.2 [2.6, 3.9]	4.7 [4.0, 5.5]
Femoral neck	Baseline T-score	−2.30 ± 0.48	−2.32 ± 0.52	−2.26 ± 0.65	−2.31 ± 0.61
	Month 6 (%)	0.6 [−0.1, 1.4]	1.0 [0.1, 1.8]	1.9 [1.0, 2.9]	3.3 [2.1, 4.4]
	Month 12 (%)	0.3 [−0.6, 1.2]	1.9 [1.0, 2.7]	2.9 [2.1, 3.8]	3.8 [2.7, 4.9]

Mean ± standard deviation; least squares mean [95% CI]

A mixed-effect model for repeated measures with baseline BMD, DXA machine type, interaction between DXA machine type and baseline BMD, office visit, treatment group, and interaction between office visit and treatment group as fixed effects, assuming within-subject unstructured variance-covariance structure

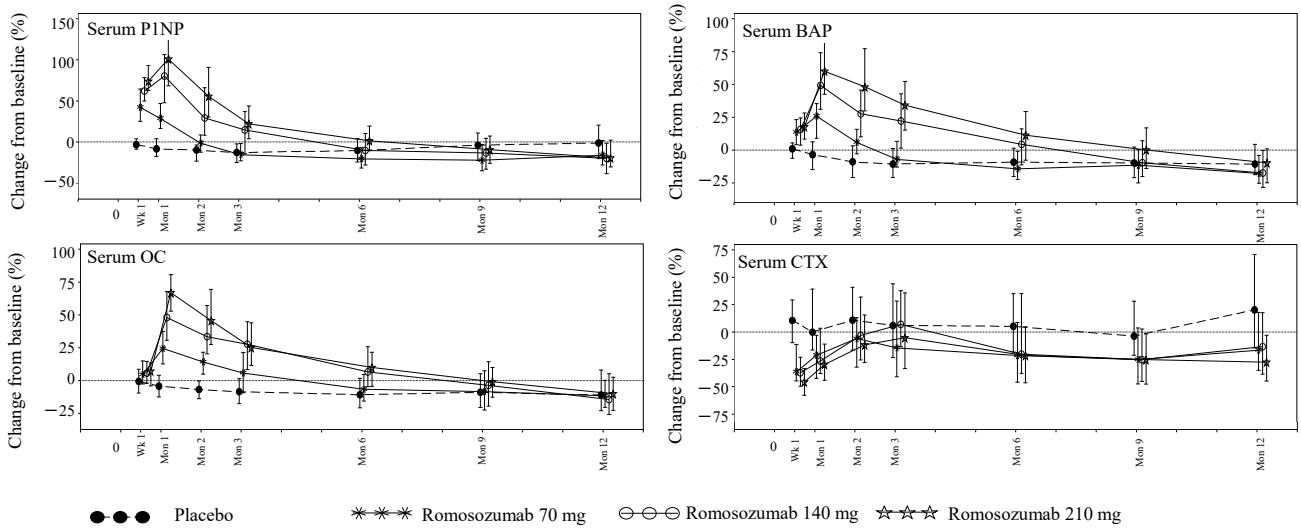

Figure 1. Time course of the percentage change from baseline in bone turnover markers to Month 12 (median and interquartile range) (efficacy analysis set)

The safety analysis revealed adverse events occurring at an incidence of ≥5% in any group during the treatment phase as shown in Table 31. Adverse reactions occurred in 1 subject in the placebo group (ventricular extrasystoles), 4 subjects in the romosozumab 70 mg group (administration site pain/injection site erythema, administration site reaction, injection site pain, and dizziness), 1 subject in the 140 mg group (injection site pruritus), and 1 subject in the 210 mg group (injection site bruising).

Table 31. Adverse events with an incidence of ≥5% in any group (safety analysis set)

	Placebo (63)	Romosozumab 70 mg (63)	Romosozumab 140 mg (63)	Romosozumab 210 mg (63)
All adverse events	68.3 (43)	77.8 (49)	71.4 (45)	74.6 (47)
Nasopharyngitis	12.7 (8)	27.0 (17)	25.4 (16)	31.7 (20)
Osteoarthritis	0 (0)	0 (0)	3.2 (2)	6.3 (4)
Spinal osteoarthritis	0 (0)	1.6 (1)	1.6 (1)	6.3 (4)
Cataract	0 (0)	0 (0)	0 (0)	6.3 (4)
Back pain	6.3 (4)	3.2 (2)	7.9 (5)	4.8 (3)
Abdominal pain upper	6.3 (4)	0 (0)	1.6 (1)	4.8 (3)
Ligament sprain	6.3 (4)	0 (0)	0 (0)	4.8 (3)
Hypertension	3.2 (2)	0 (0)	7.9 (5)	1.6 (1)
Eczema	1.6 (1)	6.3 (4)	4.8 (3)	1.6 (1)
Contusion	7.9 (5)	9.5 (6)	3.2 (2)	1.6 (1)
Dermatitis contact	1.6 (1)	6.3 (4)	1.6 (1)	0 (0)

Incidence, % (number of subjects); MedDRA ver.17.1

There were no deaths during the treatment phase. In the follow-on phase, 1 death occurred in the romosozumab 140 mg group (acute myocardial infarction), and a causal relationship to the study drug was ruled out.

The incidence of serious adverse events during the treatment phase was 6.3% in the placebo group (4 of 63 subjects; angina pectoris, endometrial hypertrophy, meniscus injury, and ventricular extrasystoles), 9.5% in the romosozumab 70 mg group (6 of 63 subjects; subarachnoid haemorrhage/atrioventricular block second degree, cellulitis, cholelithiasis, coronary artery stenosis, depression, and Parkinson's disease), 3.2% in the 140 mg group (2 of 63 subjects; cerebral infarction and large intestine polyp/post procedural haemorrhage), and 3.2% in the 210 mg group (2 of 63 subjects; angina unstable/cataract/vitreous haemorrhage, and breast cancer). One of the events in the placebo group (ventricular extrasystoles) was classified as an adverse reaction. During the follow-on phase, serious adverse events occurred in 2 subjects in the placebo group (heat illness and lumbar vertebral fracture), and 1 subject in the romosozumab 140 mg group (acute myocardial infarction). A causal relationship to the study drug was ruled out for all these events.

During the treatment phase, adverse events leading to treatment discontinuation occurred in 2 subjects in the 70 mg group (dizziness and subarachnoid haemorrhage), and 1 subject in the 210 mg group (hypochondriasis). Dizziness in 1 subject in the romosozumab 70 mg group was assessed as an adverse reaction. During the follow-on phase, vascular dementia in 1 subject in the romosozumab 70 mg group led to withdrawal from the study.

There were no changes in vital signs that could cause clinical problems.

7.1.2 Foreign phase II study (CTD 5.3.5.1-2, Study 20060326 [June 2009 to March 2016])

A randomized, placebo- and active-controlled, parallel-group study was conducted in postmenopausal women (target sample size, 400 subjects; 50/group) in the US, Canada, and other countries to evaluate the efficacy and safety of romosozumab [see Section "6.2.2.3 foreign phase II study" for pharmacokinetics]. Major inclusion criteria were postmenopausal women aged 55 to 85 years; no history of vertebral fracture or

fragility fracture of the carpal bones, humerus, proximal femur, or pelvis after age 50 years; and BMD T-score of ≥−3.5 and ≤−2.0 at the lumbar vertebrae, proximal femur, or femoral neck. Subjects were excluded if serum 25(OH) vitamin D was <20 ng/mL or albumin-corrected serum calcium level or serum iPTH level was not within the reference range.

This study consisted of the screening phase (maximum of 35 days), initial treatment phase (24 months), denosumab treatment phase (12 months), retreatment phase (12 months), and follow-on phase (24 months).

In the initial treatment phase, placebo or romosozumab (70 mg, 140 mg, or 210 mg) was administered subcutaneously once a month (Q1M), or placebo or romosozumab (140 mg or 210 mg) once every 3 months (Q3M) for 24 months. Placebo or each dose level of romosozumab was administered under the double-blinded conditions, while the dosing schedules were not blinded. The active control drug, alendronate or teriparatide, was administered under open-label conditions. Subjects in the ALN group received oral alendronate 70 mg once weekly for the first 12 months followed by subcutaneous romosozumab 140 mg once a month for 12 months. Subjects in the TPTD group received subcutaneous teriparatide 20 μg once daily for 12 months, and the study ended at Month 12.

In the denosumab treatment phase, subjects[32)] of all groups except the TPTD group of the initial treatment phase were randomized to placebo or the Dmab group, and placebo or denosumab 60 mg was administered subcutaneously once every 6 months for 12 months under double-blinded conditions.

In the retreatment phase, romosozumab 210 mg was administered subcutaneously once a month for 12 months under open-label conditions to subjects[33)] who were randomized either to romosozumab or to placebo in the initial treatment phase and completed the denosumab treatment phase.

In the follow-on phase, of the subjects who had completed the retreatment phase, those who received romosozumab in the initial treatment phase and denosumab in the denosumab treatment phase[34)] had no intervention (no-intervention group). The remaining subjects[35)] received a single intravenous injection of zoledronic acid 5 mg under open-label conditions (Zol group).

Throughout the study period, calcium (≥1000 mg/day) and vitamin D (≥800 IU/day) were administered orally as base treatment drugs. In addition, at the start of treatment in the retreatment phase (Month 36), vitamin D (50000-60000 IU) was given.

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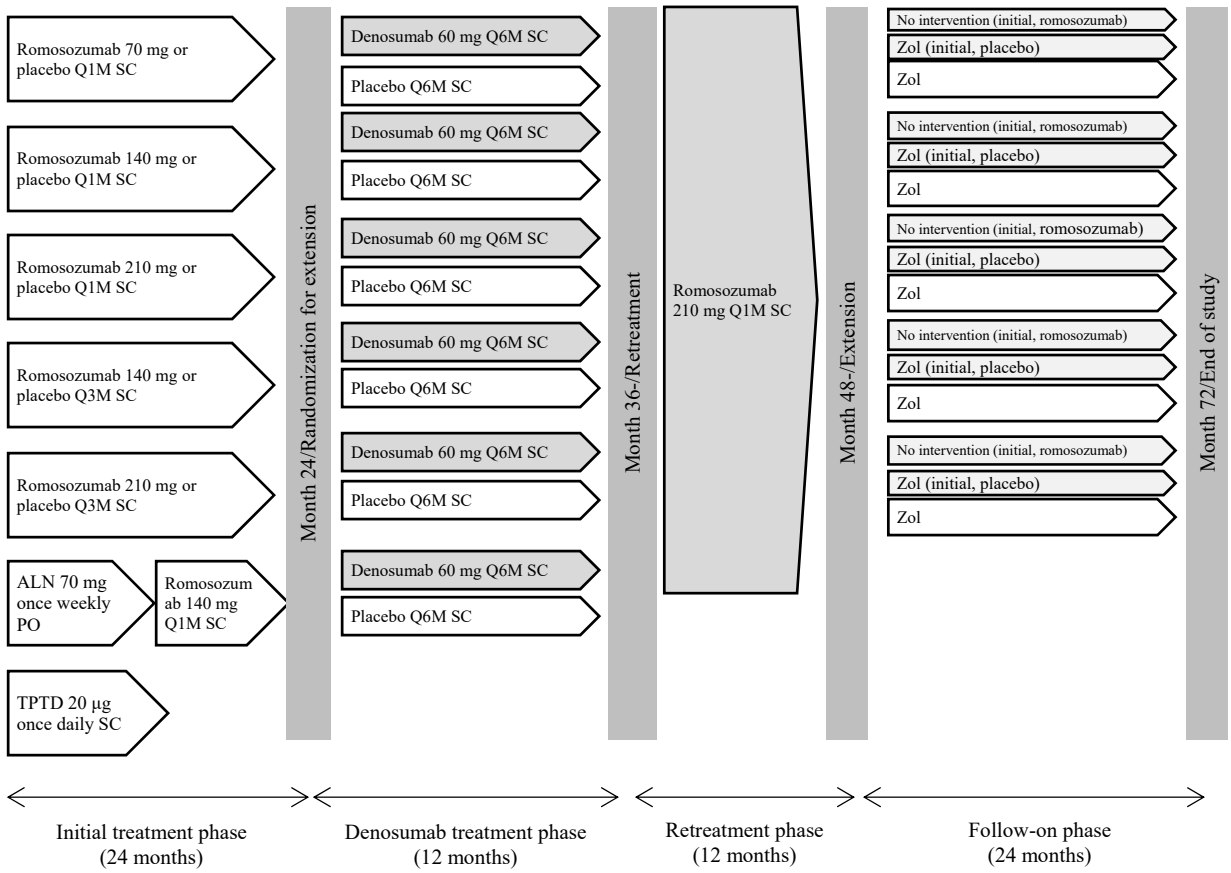
32) Subjects whose latest albumin-corrected serum calcium level in Month 21 to 24 were normal, with no history of clinical vertebral fracture or fragility fracture (the carpal bones, humerus, proximal femur, or pelvis) at Month 24, decreased percentage change from baseline in bone BMD at Month 18 of <7%, and no contraindication to denosumab

33) Subjects whose latest albumin-corrected serum calcium level in Month 30 to 36 were normal

34) Subjects who had no history of clinical vertebral fracture or fragility fracture (the carpal bones, humerus, proximal femur, or pelvis) in Months 24 to 48, with a BMD T-score of >−2.5 at Month 48 at the lumbar vertebrae, proximal femur, or femoral neck

35) Subjects with a condition contraindicated for zoledronic acid were excluded.

Figure 2 show the design and dosage regimen of Study 20060326.



Q1M, once a month; Q3M, once every 3 months; Q6M, once every 6 months; ALN, alendronate; TPTD, teriparatide (genetical recombination); Zol, zoledronic acid

Figure 2. Outline of the design and dosage regimen of Study 20060326

In the initial treatment phase, all 419 subjects who were randomized (52 in the placebo group, 51 in the romosozumab 70 mg Q1M group, 51 in the romosozumab 140 mg Q1M group, 52 in the romosozumab 210 mg Q1M group, 54 in the romosozumab 140 mg Q3M group, 53 in the romosozumab 210 mg Q3M group, 51 in the ALN group, and 55 in the TPTD group) were included in the FAS. Of the FAS, 402 subjects (50 in the placebo group, 49 in the romosozumab 70 mg Q1M group, 48 in the romosozumab 140 mg Q1M group, 50 in the romosozumab 210 mg Q1M group, 52 in the romosozumab 140 mg Q3M group, 53 in the romosozumab 210 mg Q3M group, 51 in the ALN group, and 49 in the TPTD group) who had baseline BMD and ≥1 post-baseline BMD measurement were included in the primary efficacy analysis set. Of the FAS, 410 subjects received the study drug (50 in the placebo group, 50 in the romosozumab 70 mg Q1M group, 48 in the romosozumab 140 mg Q1M group, 51 in the romosozumab 210 mg Q1M group, 53 in the romosozumab 140 mg Q3M group, 53 in the romosozumab 210 mg Q3M group, 51 in the ALN group, and 54 in the TPTD group), and all of them were included in the safety analysis set. During Months 0 to 12, 38 subjects withdrew from the study, of which 5 subjects were in the placebo group (consent withdrawal [3], adverse events [1], and death [1]), 6 subjects in the romosozumab 70 mg Q1M group (consent withdrawal [2], protocol deviation

[1], adverse events [1], death [1], and other [1]), 5 subjects in the romosozumab 140 mg Q1M group (consent withdrawal [4] and protocol deviation [1]), 3 subjects in the romosozumab 210 mg Q1M group (consent withdrawal [3]), 5 subjects in the 140 mg Q3M group (consent withdrawal [4] and lost to follow-up [1]), 3 subjects in the 210 mg Q3M group (consent withdrawal [2] and adverse events [1]), 2 subjects in the ALN group (consent withdrawal [1] and adverse events [1]), and 9 subjects in the TPTD group (consent withdrawal" [4], lost to follow-up [2], noncompliance [1], adverse events [1], and investigator's discretion [1]). During Months 12 to 24, 19 subjects withdrew from the study, of which 1 subject was in the placebo group (consent withdrawal), 5 subjects in the romosozumab 70 mg Q1M group (consent withdrawal [4] and adverse events [1]), 3 subjects in the romosozumab 140 mg Q1M group (consent withdrawal [2] and adverse events [1]), 1 subject in the romosozumab 210 mg Q1M group (consent withdrawal), 3 subjects in the 140 mg Q3M group (consent withdrawal [1], adverse events [1], and other [1]), 2 subjects in the 210 mg Q3M group (consent withdrawal [2]), and 4 subjects in the ALN-romosozumab 140 mg Q1M group (adverse events [1], consent withdrawal [2], and other [1]).

All 260 subjects who continued into the denosumab treatment phase (18 in the placebo/placebo group, 18 in the placebo/Dmab group, 93 in the romosozumab/placebo group, 90 in the romosozumab/Dmab group, 20 in the ALN-romosozumab 140 mg Q1M/placebo group, and 21 in the ALN-romosozumab 140 mg Q1M/Dmab group) were included in the FAS, which also served as the efficacy analysis set. In the FAS, 252 subjects received the study drug in the denosumab treatment phase (18 in the placebo/placebo group, 18 in the placebo/Dmab group, 90 in the romosozumab/placebo group, 88 in the romosozumab/Dmab group, 19 in the ALN-romosozumab 140 mg Q1M/placebo group, and 19 in the ALN-romosozumab 140 mg Q1M/Dmab group), and all of them were included in the safety analysis set. In the denosumab treatment phase, 12 subjects withdrew from the study, of which 1 subject was in the placebo/placebo group (protocol deviation), 5 subjects in the romosozumab/placebo group (noncompliance [1], adverse events [1], consent withdrawal [1], and other [2]), 2 subjects in the romosozumab/Dmab group (consent withdrawal [1] and other [1]), 2 subjects in the ALN-romosozumab 140 mg Q1M/placebo group (adverse events [1] and other [1]), and 2 subjects in the ALN-romosozumab 140 mg Q1M/Dmab group (other [2]).

All 167 subjects who proceeded to the retreatment phase (12 in the placebo/placebo/romosozumab 210 mg Q1M group, 16 in the placebo/Dmab/romosozumab 210 mg Q1M group, 72 in the romosozumab/placebo/romosozumab 210 mg Q1M group, and 67 in the romosozumab/Dmab/ romosozumab 210 mg Q1M group) were included in the FAS, which also served as the efficacy analysis set. All subjects in the FAS received the study drug in the retreatment phase, and all 167 subjects were included in the safety analysis set. During the retreatment phase, 11 subjects withdrew from the study, of which 2 subjects were in the placebo/Dmab/romosozumab 210 mg Q1M group (adverse events [1] and consent withdrawal [1]), 6 subjects in the romosozumab/placebo/romosozumab 210 mg Q1M group (adverse events [3], consent withdrawal [2], and lost to follow-up [1]), and 3 subjects in the romosozumab/Dmab/romosozumab 210 mg Q1M group (consent withdrawal [2] and other [1]).

All 141 subjects who proceeded to the follow-on phase (51 in the no-intervention group and 90 in the Zol group) were included in the FAS, which served as the efficacy analysis set. All the subjects were also included in the safety analysis set.[36] During the follow-on phase, 3 subjects withdrew from the study. Of these, 1 subject was in the no-intervention group (death) and the other 2 were in the Zol group (violation of inclusion/exclusion criteria [1] and consent withdrawal [1]).

Table 32 shows the percentage change from baseline in BMD at the lumbar vertebrae at Month 12, the primary endpoint of efficacy. The percentage change from baseline increased significantly in all romosozumab groups as compared to placebo.

Table 32. Percentage change from baseline in BMD at the lumbar vertebrae (L1-L4) at Month 12 (efficacy analysis set [a])

	Placebo	Romosozumab 70 mg Q1M	Romosozumab 140 mg Q1M	Romosozumab 210 mg Q1M	Romosozumab 140 mg Q3M	Romosozumab 210 mg Q3M	ALN	TPTD
Baseline T-score	−2.31 ± 0.66 (50)	−2.31 ± 0.78 (49)	−2.26 ± 0.78 (48)	−2.36 ± 0.59 (50)	−2.45 ± 0.70 (52)	−2.23 ± 0.68 (53)	−2.09 ± 0.69 (51)	−2.26 ± 0.57 (49)
Percentage change from baseline (%)	−0.1 [−1.2, 0.9] (47)	5.4 [4.3, 6.4] (44)	9.1 [8.0, 10.2] (46)	11.3 [10.3, 12.4] (49)	5.4 [4.4, 6.5] (49)	5.5 [4.4, 6.6] (51)	4.1 [3.0, 5.1] (47)	7.1 [6.1, 8.2] (46)
Between-group difference with placebo	—	5.5 [4.0, 7.0]	9.2 [7.8, 10.7]	11.5 [10.0, 12.9]	5.6 [4.1, 7.0]	5.6 [4.2, 7.1]	—	—
P-value[b]	—	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	—	—

Mean ± standard deviation; least squares mean [95% CI] (number of subjects evaluated); —, not calculated
A linear-mixed-effect model for repeated measures with baseline BMD, DXA machine type, interaction between DXA machine type and baseline BMD, geographic region, office visit, treatment group, and interaction between office visit and treatment group as covariates, assuming within-subject unstructured variance-covariance structure
a) Subjects with baseline values and ≥1 post-baseline measurement were analyzed
b) 2-sided significance level of 5%; the Hochberg method was used for multiplicity adjustment.

Figure 3 shows the time course of the percentage change from baseline in BMD at the lumbar vertebrae, proximal femur, and femoral neck from baseline to Month 24 (at the end of the initial treatment phase).

[36] Among subjects randomized to the Zol group, 3 subjects (romosozumab/placebo/romosozumab 210 mg Q1M group in the retreatment phase) did not receive zoledronic acid and thus data from these subjects were analyzed separately.

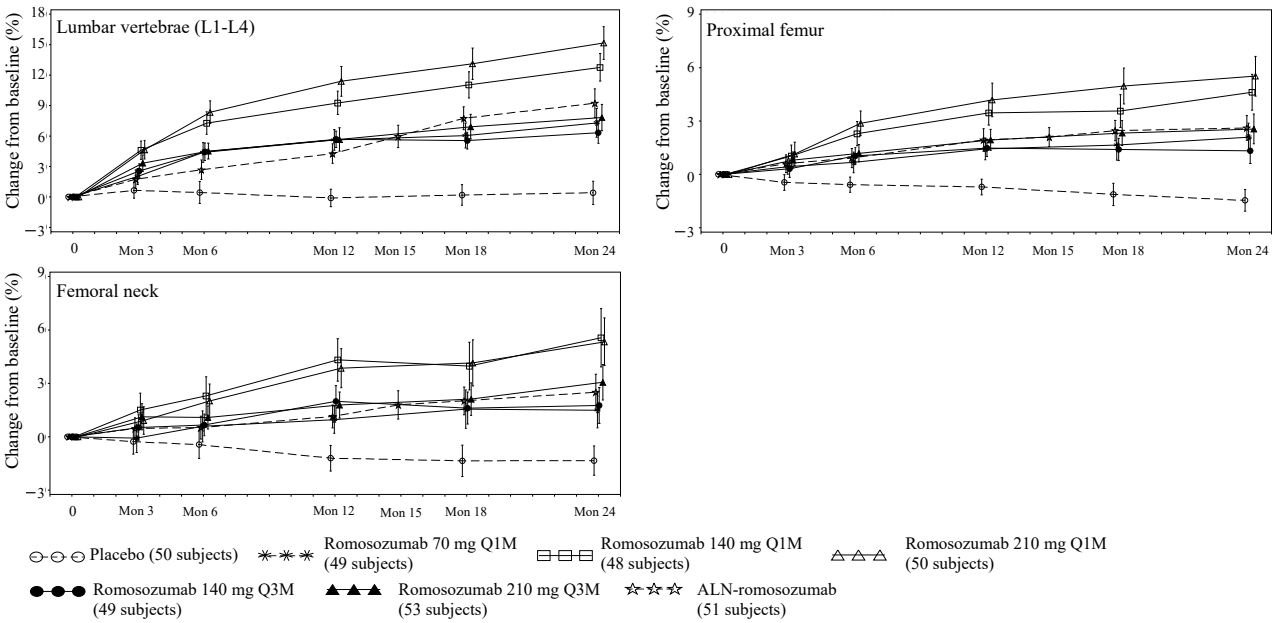


Figure 3. Time course of the percentage change from baseline in BMD to the end of the initial treatment phase (Month 24) (mean and its 95% CI) (efficacy analysis set)

Figure 4 shows the time course of the percentage change from baseline in bone turnover markers from baseline to Month 12.

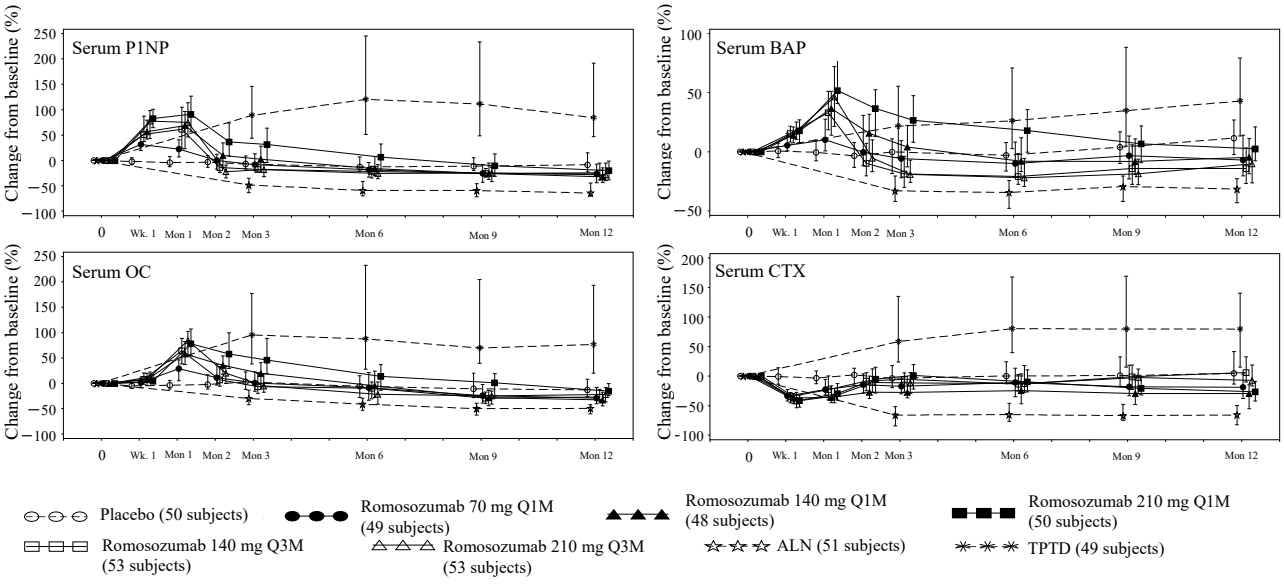


Figure 4. Percentage change from baseline in bone turnover markers to Month 12 (median and interquartile range) (efficacy analysis set)

Figures 5 and 6 show the time course of the percentage change from baseline in the BMD at the lumbar vertebrae, proximal femur and femoral neck, and bone turnover markers, respectively, from baseline to the end of the retreatment phase (Month 48). The results of subjects who proceeded to the denosumab and retreatment phases after receiving placebo or romosozumab 210 mg (Q1M) in the initial treatment phase are presented.

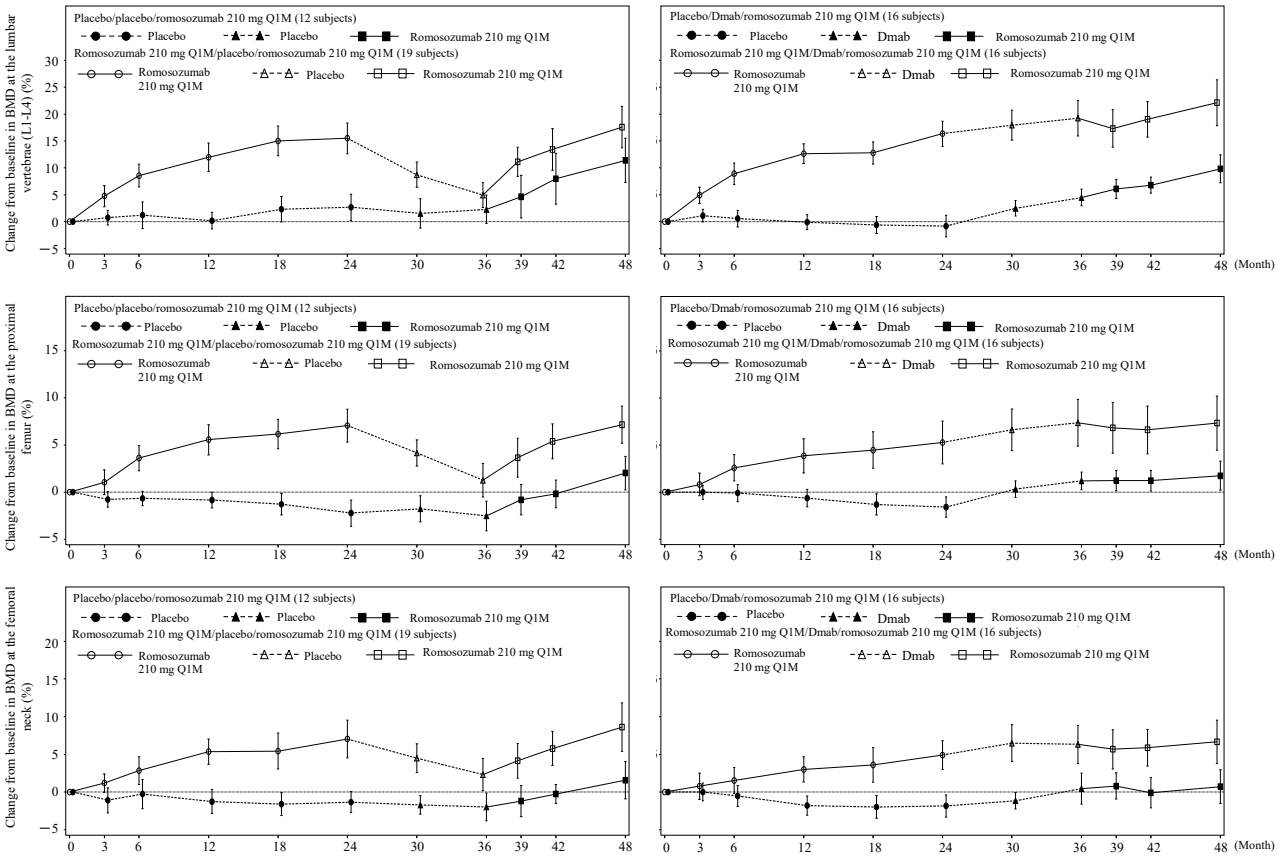


Figure 5. Time course of the percentage change from baseline in BMD to the end of the retreatment phase (Month 48) (mean and 95% CI) (efficacy analysis set)

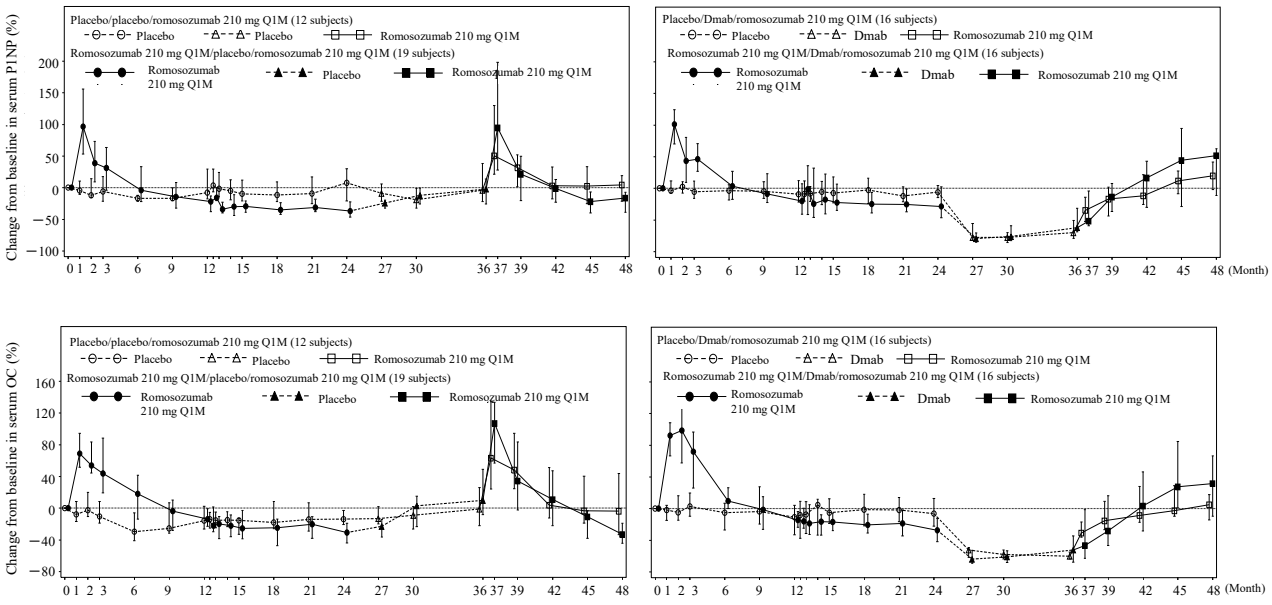


Figure 6. Time course of the percentage change from baseline in bone turnover markers to the end of the retreatment phase (Month 48) (median and interquartile range) (efficacy analysis set)

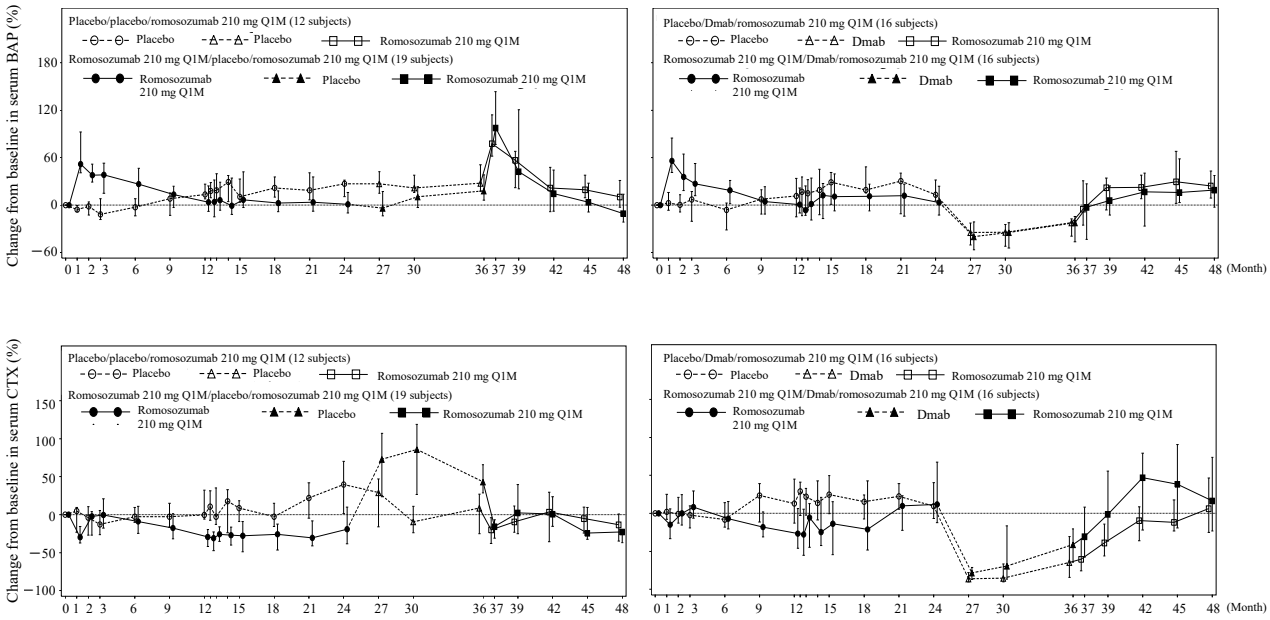


Figure 6. Time course of the percentage change from baseline in bone turnover markers to the end of the retreatment phase (Month 48) (median and interquartile range) (efficacy analysis set) (cont.)

The percentage change from baseline in BMD at the lumbar vertebrae, proximal femur, and femoral neck from baseline to the end of the follow-on phase (Month 72) are summarized in Table 33.

Table 33. Percentage change from baseline in BMD to the end of the follow-on phase (Month 72) (efficacy analysis set[a])

BMD	Evaluation time point	No intervention (51)	Zol (90)
Lumbar vertebrae (L1-L4)	Month 48	17.3 ± 7.1 (48)	14.2 ± 6.2 (80)
	Month 72	4.2 ± 6.3 (47)	12.8 ± 6.6 (77)
Proximal femur	Month 48	5.2 ± 3.4 (48)	4.2 ± 3.6 (79)
	Month 72	−1.6 ± 4.3 (46)	4.2 ± 4.8 (77)
Femoral neck	Month 48	5.3 ± 4.3 (48)	4.2 ± 4.9 (79)
	Month 72	−1.2 ± 4.8 (46)	4.4 ± 6.1 (77)

Mean ± standard deviation

a) Subjects with baseline values and ≥1 post-baseline measurement were analyzed.

Safety data in the initial treatment phase (for 12 or 24 months) showed adverse events with an incidence of ≥10% (for 12 months), and ≥15% (for 24 months) in any group, respectively (Table 34 and 35). Adverse reactions with an incidence of ≥5% in any group during the 24-month treatment period were injection site pain, injection site erythema, fatigue, and headache.

Table 34. Adverse events with an incidence of ≥10% in any group during the 12-month treatment period (at Month 12 analysis; safety analysis set)

(Initial treatment phase: safety analysis set) Adverse event	Placebo (50)	Romosozumab 70 mg Q1M (50)	Romosozumab 140 mg Q1M (48)	Romosozumab 210 mg Q1M (51)	Romosozumab 140 mg Q3M (53)	Romosozumab 210 mg Q3M (53)	ALN (51)	TPTD (54)
All adverse events	90.0 (45)	96.0 (48)	87.5 (42)	82.4 (42)	81.1 (43)	86.8 (46)	86.3 (44)	68.5 (37)
Nasopharyngitis	14.0 (7)	38.0 (19)	27.1 (13)	15.7 (8)	18.9 (10)	9.4 (5)	5.9 (3)	7.4 (4)
Gastroenteritis	6.0 (3)	6.0 (3)	8.3 (4)	15.7 (8)	3.8 (2)	9.4 (5)	3.9 (2)	1.9 (1)
Pain in extremity	4.0 (2)	20.0 (10)	10.4 (5)	11.8 (6)	13.2 (7)	5.7 (3)	3.9 (2)	9.3 (5)
Upper respiratory tract infection	2.0 (1)	8.0 (4)	2.1 (1)	11.8 (6)	1.9 (1)	0 (0)	3.9 (2)	1.9 (1)
Headache	16.0 (8)	8.0 (4)	6.3 (3)	9.8 (5)	13.2 (7)	5.7 (3)	7.8 (4)	5.6 (3)
Cough	4.0 (2)	16.0 (8)	8.3 (4)	7.8 (4)	5.7 (3)	1.9 (1)	7.8 (4)	0 (0)
Arthralgia	8.0 (4)	16.0 (8)	12.5 (6)	5.9 (3)	17.0 (9)	9.4 (5)	9.8 (5)	9.3 (5)
Back pain	6.0 (3)	10.0 (5)	14.6 (7)	5.9 (3)	7.5 (4)	13.2 (7)	9.8 (5)	5.6 (3)
Muscle spasms	0 (0)	0 (0)	2.1 (1)	5.9 (3)	3.8 (2)	0 (0)	2.0 (1)	14.8 (8)
Bronchitis	4.0 (2)	10.0 (5)	6.3 (3)	3.9 (2)	9.4 (5)	1.9 (1)	2.0 (1)	3.7 (2)
Fatigue	4.0 (2)	10.0 (5)	10.4 (5)	3.9 (2)	1.9 (1)	1.9 (1)	3.9 (2)	0 (0)
Nausea	4.0 (2)	16.0 (8)	4.2 (2)	0 (0)	3.8 (2)	0 (0)	2.0 (1)	9.3 (5)

Incidence, % (number of subjects); MedDRA ver.13.1

Table 35. Adverse events with an incidence of ≥15% in any group during the 24-month treatment period (Month 24 analysis; safety analysis set)

Adverse event	Placebo (50)	Romosozumab 70 mg Q1M (50)	Romosozumab 140 mg Q1M (49)	Romosozumab 210 mg Q1M (51)	Romosozumab 140 mg Q3M (52)	Romosozumab 210 mg Q3M (53)	ALN/romosozumab (51)
All adverse events	96.0 (48)	100.0 (50)	93.9 (46)	94.1 (48)	92.3 (48)	100 (53)	98.0 (50)
Nasopharyngitis	24.0 (12)	40.0 (20)	34.7 (17)	27.5 (14)	26.9 (14)	18.9 (10)	17.6 (9)
Gastroenteritis	6.0 (3)	8.0 (4)	8.2 (4)	17.6 (9)	3.8 (2)	9.4 (5)	7.8 (4)
Cough	8.0 (4)	16.0 (8)	16.3 (8)	15.7 (8)	9.6 (5)	5.7 (3)	11.8 (6)
Influenza	16.0 (8)	14.0 (7)	8.2 (4)	15.7 (8)	5.8 (3)	9.4 (5)	17.6 (9)
Upper respiratory tract infection	4.0 (2)	14.0 (7)	6.1 (3)	15.7 (8)	5.8 (3)	3.8 (2)	5.9 (3)
Arthralgia	24.0 (12)	22.0 (11)	14.3 (7)	13.7 (7)	21.2 (11)	17.0 (9)	21.6 (11)
Headache	16.0 (8)	10.0 (5)	6.1 (3)	13.7 (7)	17.3 (9)	7.5 (4)	11.8 (6)
Pain in extremity	8.0 (4)	24.0 (12)	12.2 (6)	11.8 (6)	15.4 (8)	9.4 (5)	5.9 (3)
Urinary tract infection	6.0 (3)	10.0 (5)	8.2 (4)	11.8 (6)	7.7 (4)	17.0 (9)	13.7 (7)
Back pain	18.0 (9)	16.0 (8)	24.5 (12)	9.8 (5)	15.4 (8)	17.0 (9)	23.5 (12)
Musculoskeletal pain	6.0 (3)	18.0 (9)	4.1 (2)	3.9 (2)	5.8 (3)	7.5 (4)	5.9 (3)
Nausea	6.0 (3)	18.0 (9)	6.1 (3)	2.0 (1)	3.8 (2)	0 (0)	2.0 (1)

Incidence, % (number of subjects); MedDRA ver.15.0

During the denosumab treatment phase (Months 24-36), adverse events occurred in 75.6% (96 of 127) of subjects in the placebo group, and 79.2% (99 of 125) of subjects in the Dmab group. Adverse events with an incidence of ≥5% in any group were nasopharyngitis (8.7% in the placebo group, and 12.0% in the Dmab group), arthralgia (3.9% in the placebo group, and 5.6% in the Dmab group), and back pain (2.4% in the placebo group, and 5.6% in the Dmab group).

The adverse events with an incidence of ≥5% in the entire study population during the retreatment phase (Months 36-48) are presented in Table 36.

Table 36. Adverse events with an incidence of ≥5% in the entire study population (retreatment phase, Months 36-48; safety analysis set)

Initial treatment phase (Months 0-24)	Placebo			Romosozumab			Entire study population (167)
Denosumab extension phase (Months 24-36)	Placebo	Dmab	Group total (27)	Placebo	Dmab	Group total (140)	
Retreatment phase (Months 36-48)	Romosozumab 210 mg (12)	Romosozumab 210 mg (15)		Romosozumab 210 mg (72)	Romosozumab 210 mg (68)		
All adverse events	100 (12)	80.0 (12)	88.9 (24)	81.9 (59)	85.3 (58)	84.3 (118)	84.4 (141)
Nasopharyngitis	25.0 (3)	20.0 (3)	22.2 (6)	11.1 (8)	14.7 (10)	12.9 (18)	14.4 (24)
Influenza	16.7 (2)	6.7 (1)	11.1 (3)	9.7 (7)	10.3 (7)	10.0 (14)	10.2 (17)
Back pain	16.7 (2)	0 (0)	7.4 (2)	8.3 (6)	11.8 (8)	10.0 (14)	9.6 (16)
Arthralgia	16.7 (2)	0 (0)	7.4 (2)	6.9 (5)	11.8 (8)	9.3 (13)	9.0 (15)
Hypertension	16.7 (2)	6.7 (1)	11.1 (3)	4.2 (3)	8.8 (6)	6.4 (9)	7.2 (12)
Diarrhoea	16.7 (2)	0 (0)	7.4 (2)	2.8 (2)	7.4 (5)	5.0 (7)	5.4 (9)
Pain in extremity	8.3 (1)	13.3 (2)	11.1 (3)	5.6 (4)	2.9 (2)	4.3 (6)	5.4 (9)

Incidence, % (number of subjects); MedDRA ver.16.1

Adverse events with an incidence of ≥10% in the Zol group during the follow-on phase (Months 48-72) are presented in Table 37.

Table 37. Adverse events with an incidence of ≥10% in the Zol group during the follow-on phase (follow-on phase, Months 48-72; safety analysis set)

Adverse event	No intervention (51)	Zol (87)
All adverse events	72.5 (37)	83.9 (73)
Influenza like illness	0 (0)	16.1 (14)
Myalgia	0 (0)	13.8 (12)
Arthralgia	3.9 (2)	12.6 (11)
Influenza	2.0 (1)	12.6 (11)
Nasopharyngitis	7.8 (4)	11.5 (10)

Incidence, % (number of subjects); MedDRA ver.18.1

During Months 0 to 12 of the initial treatment phase, 1 death (colon cancer) occurred in the placebo group, and 1 death (postoperative ileus) occurred in the romosozumab 70 mg Q1M group. A causal relationship to the study drug was ruled out for both events. No deaths occurred during Months 12 to 24 of the initial treatment phase, denosumab treatment phase (Months 24-36), or retreatment phase (Months 36-48). During the follow-on phase (Months 48-72), 1 subject in the no-intervention group died (cardio-respiratory arrest), but a causal relationship to the study drug was ruled out for the event.

The incidence of serious adverse events during Months 0 to 12 of the initial treatment phase was 14.0% (7 of 50) in the placebo group, 10.0% (5 of 50) in the romosozumab 70 mg Q1M group, 2.1% (1 of 48) in the romosozumab 140 mg Q1M group, 9.8% (5 of 51) in the romosozumab 210 mg Q1M group, 7.5% (4 of 53) in the romosozumab 140 mg Q3M group, 3.8% (2 of 53) in the romosozumab 210 mg Q3M group, 7.8% (4 of 51) in the ALN group, and 9.3% (5 of 54) in the TPTD group. A causal relationship to the study drug was ruled out for all these events. During Months 12 to 24 of the initial treatment phase, the incidence of serious adverse events was 9.3% (4 of 43) in the placebo group, 9.5% (4 of 42) in the romosozumab 70 mg Q1M group, 13.6% (6 of 44) in the romosozumab 140 mg Q1M group, 2.2% (1 of 46) in the romosozumab 210 mg Q1M group, 12.8% (6 of 47) in the romosozumab 140 mg Q3M group, 4.3% (2 of 47) in the romosozumab 210 mg Q3M group, and 8.3% (4 of 48) in the ALN-romosozumab 140 mg Q1M group. A serious adverse event of nephrolithiasis in 1 subject of the romosozumab 140 mg Q3M group was assessed as an adverse reaction. During the denosumab treatment phase (Months 24-36), serious adverse events occurred in 5.5% of

subjects in the placebo group (7 of 127; 2 in the placebo/placebo group, 3 in the romosozumab/placebo group, and 2 in the ALN-romosozumab 140 mg Q1M/placebo group), and 6.4% of subjects in the Dmab group (8 of 125; 1 in the placebo/Dmab group and 7 in the romosozumab/Dmab group). A causal relationship to the study drug was ruled out for all events. In the retreatment phase (Months 36-48), the incidence of serious adverse events was 6.7% (1 of 15) in the placebo/Dmab/romosozumab 210 mg Q1M group, 4.2% (3 of 72) in the romosozumab/placebo/romosozumab 210 mg Q1M group, and 4.4% (3 of 68) in the romosozumab/Dmab/romosozumab 210 mg Q1M group. A causal relationship to the study drug was ruled out for all events. During the follow-on phase (Months 48-72), serious adverse events occurred in 15.7% (8 of 51) of subjects in the no-intervention group, and 13.8% (12 of 87) of subjects in the Zol group. Serious iridocyclitis in 1 subject of the Zol group was assessed as an adverse reaction.

The incidence of adverse events leading to treatment discontinuation during Months 0 to 12 of the initial treatment phase was 4.0% (2 of 50) in the placebo group, 4.0% (2 of 50) in the romosozumab 70 mg Q1M group, 2.1% (1 of 48) in the romosozumab 140 mg Q1M group, 3.9% (2 of 51) in the romosozumab 210 mg Q1M group, 1.9% (1 of 53) in the romosozumab 210 mg Q3M group, and 3.9% (2 of 51) in the ALN group, and 5.6% (3 of 54) in the TPTD group. Pain in extremity in 1 subject of the romosozumab 140 mg Q1M group, dizziness/hypoaesthesia/muscle spasms/paraesthesia in 1 subject of the romosozumab 210 mg Q1M group, and dizziness in 1 subject of the TPTD group were assessed as adverse reactions. During Months 12 to 24 of the initial treatment phase, the incidence of adverse events leading to treatment discontinuation was 2.3% (1 of 43) in the placebo group, 2.4% (1 of 42) in the romosozumab 70 mg Q1M group, 4.5% (2 of 44) in the romosozumab 140 mg Q1M group, 2.2% (1 of 46) in the romosozumab 210 mg Q1M group, 4.3% (2 of 47) in the romosozumab 140 mg Q3M group, 2.1% (1 of 47) in the romosozumab 210 mg Q3M group, and 2.1% (1 of 48) in the ALN-romosozumab group. A causal relationship to the study drug was ruled out for all events. During the denosumab treatment phase (Months 24-36), adverse events leading to treatment discontinuation occurred in 1.6% of subjects in the placebo group (2 of 127; 1 each in the romosozumab/placebo group and the ALN-romosozumab 140 mg Q1M/placebo group), and a causal relationship to the study drug was ruled out for events. During the retreatment phase (Months 36-48), the incidence of adverse events leading to treatment discontinuation was 6.7% (1 of 15) in the placebo/Dmab/romosozumab 210 mg Q1M group, 2.8% (2 of 72) in the romosozumab/placebo/romosozumab 210 mg Q1M group, and 1.5% (1 of 68) in the romosozumab/Dmab/romosozumab 210 mg Q1M group. Dermatitis allergic/injection site rash and injection site rash in 1 subject each in the romosozumab/placebo/romosozumab 210 mg Q1M group were assessed as adverse reactions. No adverse events leading to treatment discontinuation (or withdrawal from the study) occurred in the follow-on phase (Months 48-72).

There were no changes in ECG or vital signs that could cause clinical problems.

7.2 Global phase III studies

7.2.1 Global phase III study in postmenopausal women with osteoporosis (CTD 5.3.5.1-1, Study 20070337 [March 2012 to December 2016])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in postmenopausal Japanese and non-Japanese[37)] women with osteoporosis (target sample size, 6600 subjects; 3300/group) to evaluate the efficacy and safety of romosozumab [see Section "6.2.2.4 Global phase III study in postmenopausal women with osteoporosis" for pharmacokinetics]. Major inclusion criteria were postmenopausal women aged 55 to 90 years; no history of proximal femoral fracture or absence of severe vertebral fracture or ≥3 moderate vertebral fractures; and BMD T-score of >−3.5 and ≤−2.5 at the proximal femur or femoral neck. Subjects were excluded if the serum 25(OH) vitamin D was <20 ng/mL or albumin-corrected serum calcium level or serum iPTH level was not within the reference range.

This study consisted of a screening phase (up to 35 days), double-blind phase (12 months), open-label phase (12 months), and extension phase (12 months). This section summarizes the results up to the open-label phase.

In the double-blind phase, placebo or romosozumab 210 mg was administered subcutaneously into the abdomen, thigh, or upper arm once a month. In the open-label phase and extension phase, denosumab 60 mg was administered subcutaneously once every 6 months in all groups. Subjects with a screening serum 25(OH) vitamin D level of ≥20 ng/mL and ≤40 ng/mL were to receive 50,000 to 60,000 IU of vitamin D[31)] within 1 week of the first dose of study drug treatment (initial loading). Subjects with a screening serum 25(OH) vitamin D level of >40 ng/mL received an initial loading dose at the investigator's discretion. Throughout the study period, calcium (≥500-1000 mg/day) and vitamin D[31)] (≥600-800 IU/day) were administered orally as base treatment drugs. Hereinafter in this section, data from the double-blind phase are expressed as either "the placebo group" or "the romosozumab group," while data from the double-blind and open-label phases are expressed as "the placebo/Dmab group" or "the romosozumab/Dmab group."

All 7180 subjects randomized (3591 [245 Japanese] in the placebo group, and 3589 [247 Japanese] in the romosozumab group) were included in the FAS, which also served as the primary efficacy analysis set. In the FAS, 7157 subjects received the study drug[38)] (3576 [244 Japanese] in the placebo group, and 3591 [245 Japanese] in the romosozumab group) and were included in the safety analysis set. During the double-blind phase, 790 subjects withdrew from the study. Of these, 386 subjects were in the placebo group (253 [15 Japanese] due to "consent withdrawal," 39 [8 Japanese] due to adverse events, 20 due to death, 21 due to lost to follow-up, 16 due to noncompliance, 6 [1 Japanese] due to violation of inclusion/exclusion criteria, 3 due to protocol deviation, 2 due to alternative therapy required, 2 [1 Japanese] due to investigator's discretion, and 24 due to other reasons); and 404 subjects were in the romosozumab group (261 [22 Japanese] due to

37) The US, Poland, the Czech Republic, Hungary, Lithuania, Estonia, Latvia, Romania, UK, Denmark, Germany, Spain, Switzerland, Belgium, Columbia, Brazil, Argentina, the Dominican Republic, Mexico, Hong Kong, India, Canada, Australia, and New Zealand

38) In the double-blind phase (12 months), subjects who received ≥1 dose of the study drug; in the total treatment period (24 months), subjects who received ≥1 dose in each of the double-blind phase and open-label phase

consent withdrawal, 39 [5 Japanese] due to adverse events, 27 [1 Japanese] due to death, 22 due to lost to follow-up, 9 [1 Japanese] due to noncompliance, 7 [3 Japanese] due to violation of inclusion/exclusion criteria, 2 due to protocol deviation, 2 due to alternative therapy required, 1 due to investigator's discretion, and 34 due to other reasons). During the open-label phase, 364 subjects withdrew from the study. Of these, 173 subjects were in the placebo/Dmab group (61 [4 Japanese] due to consent withdrawal, 24 due to death, 17 due to noncompliance, 14 due to adverse events, 21 [1 Japanese] due to lost to follow-up, 13 [1 Japanese] due to investigator's discretion, 2 due to violation of inclusion/exclusion criteria, 1 due to protocol deviation, and 20 due to other reasons); and 191 subjects were in the romosozumab/Dmab group (85 [9 Japanese] due to consent withdrawal, 22 [1 Japanese] due to death, 19 [2 Japanese] due to investigator's discretion, 27 [2 Japanese] due to lost to follow-up, 8 [3 Japanese] due to adverse events, 6 due to noncompliance, 2 due to alternative therapy required, 1 due to violation of inclusion/exclusion criteria, 1 due to protocol deviation, and 20 [2 Japanese] due to other reasons).

Table 38 summarizes the incidence of new vertebral fracture at Months 12 and 24, the primary efficacy endpoint. The incidence of fracture decreased significantly in the romosozumab/Dmab group as compared to the placebo/Dmab group at both time points in the entire study population.

Table 38. The incidence of new vertebral fracture (efficacy analysis set[a])

Entire study population	Placebo/Dmab (3591)	Romosozumab/Dmab (3589)	Risk ratio[b] [95% CI]	*P*-value[c]
Month 12	1.8 (59/3322)	0.5 (16/3321)	0.27 [0.16, 0.47]	<0.001
Month 24	2.5 (84/3327)	0.6 (21/3325)	0.25 [0.16, 0.40]	<0.001
Japanese subpopulation	Placebo/Dmab (245)	Romosozumab/Dmab (247)	Risk ratio[b] [95% CI]	
Month 12	3.7 (9/243)	1.7 (4/237)	0.45 [0.15, 1.33]	
Month 24	4.5 (11/243)	1.7 (4/237)	0.37 [0.13, 1.09]	

Incidence of fracture, % (number of subjects with fractures/number of subjects evaluated); LOCF

a) Subjects with baseline vertebral fracture assessment and at least 1 post-baseline vertebral fracture assessment were analyzed.

b) Based on the Mantel-Haenszel method stratified by age and prevalent vertebral fracture.

c) Based on a logistic regression model with treatment as the main effect, and age and prevalent vertebral fracture as covariates, *p*-value was calculated based on a score test; at 2-sided significance level of 5%

The key secondary endpoints, the incidence of vertebral fracture (Table 39), and cumulative incidence of clinical and other fractures (Table 40) at Months 12 and 24 are presented. Table 41 shows the percentage change from baseline in BMD.

Table 39. The incidence of vertebral fracture (efficacy analysis set[a])

Entire study population		Placebo/Dmab (3591)	Romosozumab/Dmab (3589)	Risk ratio[b] [95% CI]
Vertebral fracture (New or worsening)[c]	Month 12	1.8 (59/3322)	0.5 (17/3321)	0.29 [0.17, 0.49]
	Month 24	2.5 (84/3327)	0.7 (22/3325)	0.26 [0.16, 0.42]
Multiple vertebral fractures (New or worsening)[d]	Month 12	0.3 (9/3322)	<0.1 (1/3321)	0.11 [0.01, 0.87]
	Month 24	0.5 (17/3327)	<0.1 (1/3325)	0.06 [0.01, 0.44]
Japanese subpopulation		Placebo/Dmab (245)	Romosozumab/Dmab (247)	Risk ratio[b] [95% CI]
Vertebral fracture (New or worsening)[c]	Month 12	3.7 (9/243)	2.1 (5/237)	0.56 [0.20, 1.54]
	Month 24	4.5 (11/243)	2.1 (5/237)	0.47 [0.17, 1.26]
Multiple vertebral fractures (New or worsening)[d]	Month 12	1.6 (4/243)	0.4 (1/237)	0.28 [0.03, 2.42]
	Month 24	2.5 (6/243)	0.4 (1/237)	0.19 [0.02, 1.54]

Incidence of fracture, % (number of subjects with fracture/number of subjects evaluated); LOCF

a) Subjects with baseline vertebral fracture assessment and at least 1 post-baseline vertebral fracture assessment were analyzed.

b) Based on the Mantel-Haenszel method stratified by age and prevalent vertebral fracture

c) New vertebral fracture or worsening of vertebral fracture; d) multiple new vertebral fractures or worsening of vertebral fracture

Table 40. The cumulative incidence of clinical and other fractures (FAS)

Entire study population		Placebo/Dmab (3591)	Romosozumab/Dmab (3589)	Hazard ratio[a] [95% CI]
Clinical fractures[b]	Month 12	2.5 (90/3591)	1.6 (58/3589)	0.64 [0.46, 0.89]
	Month 24	4.1 (147/3591)	2.8 (99/3589)	0.67 [0.52, 0.87]
All nonvertebral fractures	Month 12	2.1 (75/3591)	1.6 (56/3589)	0.75 [0.53, 1.05]
	Month 24	3.6 (129/3591)	2.7 (96/3589)	0.75 [0.57, 0.97]
Major nonvertebral fractures[c]	Month 12	1.5 (55/3591)	1.0 (37/3589)	0.67 [0.44, 1.02]
	Month 24	2.8 (101/3591)	1.9 (67/3589)	0.67 [0.49, 0.91]
Proximal femur fracture	Month 12	0.4 (13/3591)	0.2 (7/3589)	0.54 [0.22, 1.35]
	Month 24	0.6 (22/3591)	0.3 (11/3589)	0.50 [0.24, 1.04]
Major osteoporotic fractures[d]	Month 12	1.8 (63/3591)	1.1 (38/3589)	0.60 [0.40, 0.90]
	Month 24	3.1 (110/3591)	1.9 (68/3589)	0.62 [0.46, 0.84]
Japanese subpopulation		Placebo/Dmab (245)	Romosozumab/Dmab (247)	Hazard ratio[a] [95% CI]
Clinical fractures[b]	Month 12	4.5 (11/245)	2.0 (5/247)	0.50 [0.17, 1.44]
	Month 24	6.1 (15/245)	2.8 (7/247)	0.52 [0.21, 1.27]
All nonvertebral fractures	Month 12	3.3 (8/245)	1.6 (4/247)	0.54 [0.16, 1.80]
	Month 24	4.9 (12/245)	2.4 (6/247)	0.54 [0.20, 1.45]
Major nonvertebral fractures[c]	Month 12	1.2 (3/245)	0.8 (2/247)	0.75 [0.13, 4.51]
	Month 24	2.4 (6/245)	1.2 (3/247)	0.56 [0.14, 2.26]
Proximal femur fractures	Month 12	0.4 (1/245)	0 (0/247)	—
	Month 24	0.8 (2/245)	0 (0/247)	—
Major osteoporotic fractures[d]	Month 12	2.0 (5/245)	1.2 (3/247)	0.69 [0.16, 2.88]
	Month 24	2.9 (7/245)	1.6 (4/247)	0.66 [0.19, 2.27]

Cumulative incidence of fracture, % (number of subjects with fractures/number of subjects evaluated); LOCF; —, not calculated

a) A Cox proportional hazards model stratified by age and prevalent vertebral fracture was used.

b) Clinical vertebral and clinical nonvertebral fractures are included; c) Fractures of the pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and proximal femur; d) Nonvertebral and clinical fractures of the proximal femur, wrist joint, and humerus

Table 41. Percentage change from baseline in BMD (%) (efficacy analysis set[a])

Entire study population	Treatment group	Baseline T-score	Change from baseline at Month 12	Change from baseline at Month 24
Lumbar vertebrae (L1-L4)	Placebo/Dmab	−2.71 ± 1.04 (3174)	0.4 [0.2, 0.5] (3148)	5.5 [5.3, 5.7] (2877)
	Romosozumab/Dmab	−2.73 ± 1.04 (3170)	13.1 [12.8, 13.3] (3151)	16.6 [16.3, 16.8] (2861)
Proximal femur	Placebo/Dmab	−2.46 ± 0.47 (3251)	0.3 [0.1, 0.4] (3210)	3.2 [3.1, 3.3] (2918)
	Romosozumab/Dmab	−2.48 ± 0.47 (3238)	6.0 [5.9, 6.2] (3197)	8.5 [8.3, 8.7] (2903)
Femoral neck	Placebo/Dmab	−2.74 ± 0.30 (3251)	0.3 [0.1, 0.5] (3210)	5.5 [5.2, 5.7] (3197)
	Romosozumab/Dmab	−2.75 ± 0.28 (3238)	5.5 [5.2, 5.7] (3197)	7.3 [7.0, 7.5] (2903)
Japanese subpopulation	Treatment group	Baseline T-score	Change from baseline at Month 12	Change from baseline at Month 24
Lumbar vertebrae (L1-L4)	Placebo/Dmab	−2.45 ± 0.83 (230)	0.3 [−0.2, 0.7] (230)	7.3 [6.7, 7.8] (205)
	Romosozumab/Dmab	−2.42 ± 0.90 (217)	15.2 [14.4, 16.0] (216)	20.2 [19.3, 21.2] (190)
Proximal femur	Placebo/Dmab	−2.44 ± 0.47 (241)	0.5 [0.1, 0.9] (241)	2.9 [2.4, 3.4] (205)
	Romosozumab/Dmab	−2.45 ± 0.48 (234)	5.3 [4.8, 5.8] (232)	7.9 [7.2, 8.5] (200)
Femoral neck	Placebo/Dmab	−2.82 ± 0.30 (241)	0.8 [0.2, 1.5] (241)	3.6 [2.8, 4.4] (205)
	Romosozumab/Dmab	−2.84 ± 0.31 (234)	5.4 [4.7, 6.1] (232)	7.9 [6.9, 8.8] (200)

Mean ± standard deviation; least squares mean [95% CI]; LOCF
Analysis of covariance with treatment group, age, prevalent vertebral fracture, baseline BMD, DXA machine type, interaction between DXA machine type and baseline BMD as covariates
a) Subjects with baseline values and ≥1 post-baseline measurement were analyzed.

According to the safety analysis, the occurrence of adverse events with an incidence of ≥5% in any group in the entire study population, adverse events with an incidence of ≥5% in any group in the Japanese subpopulation and matching adverse reactions in the double-blind phase is as shown in Table 42.

Table 42. Adverse events with an incidence of ≥5% in any group and the incidence of matching adverse reactions (double-blind phase [12 months]; safety analysis set)

Adverse event	Entire study population			
	Placebo (3576)		Romosozumab (3581)	
	Adverse event	Adverse reaction	Adverse event	Adverse reaction
All adverse events	79.7 (2850)	13.8 (494)	78.4 (2806)	16.6 (596)
Arthralgia	12.0 (429)	1.7 (62)	13.0 (467)	2.0 (72)
Nasopharyngitis	12.2 (438)	1.0 (34)	12.8 (459)	1.0 (36)
Back pain	10.6 (378)	0.6 (20)	10.5 (375)	0.7 (24)
Pain in extremity	8.4 (302)	1.1 (38)	7.8 (279)	1.6 (56)
Fall	8.9 (318)	0 (0)	7.1 (254)	<0.1 (1)
Headache	5.7 (205)	0.5 (19)	6.5 (233)	0.6 (22)
Hypertension	7.2 (259)	0.2 (6)	6.3 (225)	0.2 (7)
Viral upper respiratory tract infection	6.3 (277)	0.6 (21)	5.8 (206)	0.8 (28)
Osteoarthritis	6.2 (220)	0.3 (10)	5.2 (186)	0.2 (8)
Influenza	5.1 (182)	0.1 (4)	4.7 (169)	<0.1 (2)
Adverse event	Japanese subpopulation			
	Placebo (244 subjects)		Romosozumab (245 subjects)	
	Adverse event	Adverse reaction	Adverse event	Adverse reaction
All adverse events	77.9 (190)	7.0 (17)	81.6 (200)	7.8 (19)
Nasopharyngitis	25.8 (63)	0 (0)	29.4 (72)	0.1 (1)
Back pain	7.0 (17)	0.8 (2)	10.6 (26)	0.4 (1)
Constipation	7.4 (18)	0 (0)	7.8 (19)	0 (0)
Contusion	5.7 (14)	0 (0)	7.8 (19)	0 (0)
Fall	7.0 (17)	0 (0)	6.1 (15)	0 (0)
Osteoarthritis	6.1 (15)	0 (0)	5.7 (14)	0 (0)

Incidence, % (number of subjects); MedDRA ver.18.1

Table 43 shows the occurrence of adverse events with an incidence of ≥5% in any group in the entire study population, adverse events with an incidence of ≥5% in any group in the Japanese subpopulation, and matching adverse reactions in the double-blind phase and open-label phase.

Table 43. Adverse events with an incidence of ≥5% in any group and the incidence of matching adverse reactions (double-blind phase + open-label phase [24 months]; safety analysis set)

Adverse event	Entire study population			
	Placebo/Dmab (3576)		Romosozumab/Dmab (358)	
	Adverse event	Adverse reaction	Adverse event	Adverse reaction
All adverse events	85.8 (3069)	15.6 (557)	85.3 (3053)	18.2 (65.3)
Arthralgia	15.8 (565)	1.9 (67)	16.3 (585)	2.2 (79)
Nasopharyngitis	15.3 (546)	1.0 (36)	15.6 (557)	1.1 (39)
Back pain	14.4 (516)	0.6 (22)	12.9 (463)	0.7 (26)
Fall	12.8 (457)	0 (0)	10.8 (387)	<0.1 (1)
Pain in extremity	10.2 (363)	1.1 (39)	10.1 (362)	1.6 (59)
Hypertension	9.8 (352)	0.2 (6)	9.2 (328)	0.3 (9)
Headache	6.7 (241)	0.6 (22)	7.6 (272)	0.7 (26)
Osteoarthritis	8.3 (298)	0.3 (10)	7.6 (272)	0.3 (10)
Musculoskeletal pain	6.1 (192)	0.9 (32)	6.4 (228)	0.9 (31)
Viral upper respiratory tract infection	7.0 (249)	0.6 (21)	6.2 (223)	0.8 (28)
Upper respiratory tract infection	6.3 (225)	0.2 (7)	6.2 (221)	0.1 (4)
Influenza	6.1 (217)	0.1 (5)	5.9 (211)	<0.1 (2)
Urinary tract infection	6.3 (226)	0.2 (8)	5.7 (204)	0.1 (4)
Dizziness	5.4 (192)	0.6 (21)	5.4 (194)	0.6 (23)
Muscle spasms	5.1 (181)	0.4 (13)	5.3 (189)	0.6 (22)
Constipation	5.3 (188)	0.3 (9)	4.8 (171)	0.2 (6)
Adverse event	Japanese subpopulation			
	Placebo/Dmab (244)		Romosozumab/Dmab (245)	
	Adverse event	Adverse reaction	Adverse event	Adverse reaction
All adverse events	88.1 (215)	10.2 (25)	87.3 (214)	9.8 (24)
Nasopharyngitis	33.2 (81)	0 (0)	37.6 (92)	0.4 (1)
Back pain	11.1 (27)	0.8 (2)	12.2 (30)	0.4 (1)
Constipation	8.6 (21)	0 (0)	11.0 (27)	0 (0)
Contusion	9.4 (23)	0 (0)	11.8 (29)	0 (0)
Fall	9.8 (24)	0 (0)	10.6 (26)	0 (0)
Osteoarthritis	10.7 (26)	0 (0)	9.0 (22)	0.4 (1)
Arthralgia	5.7 (14)	0.8 (2)	6.1 (15)	0.4 (1)
Hypertension	4.9 (12)	0.4 (1)	6.1 (15)	0.4 (1)
Eczema	7.0 (17)	0.4 (1)	6.5 (16)	0 (0)
Dental caries	4.5 (11)	0 (0)	5.7 (14)	0 (0)
Dizziness	4.9 (12)	0 (0)	5.3 (13)	1.2 (3)
Periodontitis	4.9 (12)	0 (0)	5.3 (13)	0.4 (1)
Periarthritis	6.6 (16)	0 (0)	4.5 (11)	0 (0)

Incidence, % (number of subjects); MedDRA ver.18.1

During the double-blind phase, death occurred in 23 subjects in the placebo group and 29 subjects in the romosozumab group. Sudden death in 1 subject in the placebo group and deep vein thrombosis in 1 subject in the romosozumab group were assessed as adverse reactions. One Japanese subject in the romosozumab group died (cardiac failure congestive), but a causal relationship to the study drug was ruled out. In the open-label phase, death occurred in 24 subjects in the placebo/Dmab group and 23 subjects in the romosozumab/Dmab group. Lung neoplasm malignant in 1 subject in the romosozumab/Dmab group was assessed as an adverse reaction. One Japanese subject in the romosozumab/Dmab group died (multi-organ failure), but a causal relationship to the study drug was ruled out.

During the double-blind phase, serious adverse events occurred in 8.7% (312 of 3576) of subjects in the placebo group, and 9.6% (344 of 3581) of subjects in the romosozumab group. Serious adverse events assessed as adverse reactions that had occurred in 13 subjects in the placebo group were chronic kidney disease (2 subjects), lung neoplasm malignant/sudden death, cholestasis/hepatocellular injury, breast cancer female, intraocular melanoma, rectal cancer stage II, diverticular perforation, pancreatitis acute, transaminases increased, liver function test abnormal, cardiac failure congestive, and bronchiectasis, and

those occurring in 16 subjects in the romosozumab group were clostridium difficile colitis, hepatitis viral, pharyngitis bacterial, pneumonia, sinusitis, dermatitis, dermatitis allergic, psoriasis, rash macular, laryngeal squamous cell carcinoma, plasma cell myeloma, abdominal pain, non-cardiac chest pain, hypersensitivity, transaminases increased, and deep vein thrombosis in 1 subject each. In Japanese subjects, serious adverse events occurred in 6.6% (16 of 244) of subjects in the placebo group, and 6.1% (15 of 245) of subjects in the romosozumab group, and a causal relationship to the study drug was ruled out for all these events. During the open-label phase, serious adverse events occurred in 9.0% (279 of 3112[39)]) in the placebo/Dmab group, and 9.0% (279 of 3087[39)]) in the romosozumab/Dmab group. Serious adverse events assessed as adverse reaction in 1 each of 7 subjects in the placebo/Dmab group were herpes zoster, pneumonia bacterial, plasma cell myeloma, adenocarcinoma of colon, aortic valve stenosis, atrial fibrillation, and pain in jaw; and those occurring in 15 subjects in the romosozumab/Dmab group were abscess limb, cellulitis, angiocentric lymphoma, gastric cancer, lung neoplasm malignant, pancreatic carcinoma, and large intestine polyp (Japanese), toothache, mucosal dryness, pernicious anaemia (Japanese), cataract, osteoarthritis (Japanese), osteonecrosis of jaw (Japanese), cognitive disorder, and chronic obstructive pulmonary disease were classified as adverse reactions. In Japanese subjects, serious adverse events occurred in 6.9% (15 of 218) of subjects in the placebo/Dmab group, and 9.5% (20 of 211) of subjects in the romosozumab/Dmab group, and events that occurred in 4 of the subjects in the romosozumab/Dmab group were assessed as adverse reactions.

Adverse events leading to treatment discontinuation occurred in 2.6% (94 of 3576) of subjects in the placebo group, and 2.9% (103 of 3581) of subjects in the romosozumab group in the double-blind phase. Events in 46 subjects in the placebo group[40)] and 54 subjects in the romosozumab group[41)] were assessed as adverse reactions. In Japanese subjects, adverse events leading to treatment discontinuation occurred in 4.9% (12 of 244) of subjects in the placebo group and 2.9% (7 of 245) of subjects in the romosozumab group. Events in 4 subjects in the placebo group and 2 subjects in the romosozumab group were assessed as adverse reactions. During the open-label phase, adverse events leading to treatment discontinuation occurred in 0.5% (16 of 3112) of subjects in the placebo/Dmab group and 0.6% (19 of 3087) of subjects in the romosozumab/Dmab group. Adverse reactions were eczema/fatigue/oedema/sensation of foreign body/urinary retention/visual acuity reduced/pain in jaw/joint swelling, rash, pain in jaw, and abdominal pain in 4 subjects in the placebo/Dmab group and angiocentric lymphoma, pancreatic carcinoma, pain in extremity, dyspepsia, herpes

39) Incidence of serious adverse events in subjects who received ≥1 dose of the study drug in the open-label phase.

40) Musculoskeletal pain (4), cardiac failure congestive (2), pruritus generalised (2), arthralgia/asthenia/dizziness/malaise/pyrexia (1), arthralgia/erythema/fatigue (1), spinal pain/arthralgia/diarrhoea (1), asthenia/hyperhidrosis/hypoaesthesia (1), back pain/musculoskeletal pain (1) (Japanese), muscular weakness/somnolence (1), arthralgia/myalgia (1), hot flush/tachycardia (1), amnesia/non-cardiac chest pain (1), musculoskeletal pain/spinal pain (1), dizziness/bone pain (1), hepatocellular injury/cholestasis (1), diarrhoea/fatigue (1), injection site bruising/injection site pain (1), dermatitis atopic (1), dermatitis allergic (1), liver function test abnormal (1), polymyalgia rheumatica (1), hepatic enzyme increased (1), breast cancer female (1), muscle spasms (1), rash pruritic (1), pain in extremity (1) (Japanese), eczema (1) (Japanese), back pain (1) (Japanese), rectal cancer stage II (1), injection site pain (1), myalgia (1), lung neoplasm malignant (1), eye naevus (1), cough (1), dizziness (1), fatigue (1), diverticular perforation (1), palpitations (1), skin lesion (1), osteoarthritis (1), and chronic kidney disease (1)

41) Arthralgia (3), dermatitis allergic (3), pain in extremity (3), bone pain (2), fatigue (2), nausea (2), musculoskeletal pain (2), dyspnoea exertional/headache/hypoaesthesia/non-cardiac chest pain/osteoarthritis/pain/pain in extremity/pruritus generalised (1), abdominal pain lower/abdominal pain upper/diarrhoea/vomiting/alanine aminotransferase increased (1) (Japanese), arthralgia/arthropathy/back pain (1) (Japanese), injection site erythema/somnolence/dry skin (1), muscular weakness/pain in extremity (1), abdominal pain/nausea (1), dyspnoea/palpitations (1), arthralgia/myalgia (1), bone pain/pain in extremity (1), back pain/pain in extremity (1), pain in extremity/spinal pain (1), diarrhoea/pollakiuria (1), pruritus/rash (1), hypersensitivity (1), chest pain (1), erythema multiforme (1), gastrooesophageal reflux disease (1), systemic lupus erythematosus (1), headache (1), atrial flutter (1), rash (1), rash maculo-papular (1), drug eruption (1), gastrointestinal haemorrhage (1), tinnitus (1), laryngeal squamous cell carcinoma (1), clostridium difficile colitis (1), age-related macular degeneration (1), skin disorder (1), asthma (1), injection site pain (1), rash macular (1), injection site reaction (1), musculoskeletal stiffness (1), tooth disorder (1), and costochondritis (1)

zoster, and paraesthesia in 6 subjects in the romosozumab/Dmab group. In Japanese subjects, adverse events leading to treatment discontinuation occurred in 0% (0 of 218) of subjects in the placebo/Dmab group and 1.4% (3 of 211) of subjects in the romosozumab/Dmab group, and a causal relationship to the study drug was ruled out for all events.

There were no changes in ECG or vital signs that could cause clinical problems.

7.2.2 Global phase III study in men with osteoporosis (CTD 5.3.5.1-6, Study 20110174 [June 2014 to April 2016])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in Japanese and non-Japanese[42)] men with osteoporosis (target sample size, 225 subjects; 150 in the romosozumab group, and 75 in the placebo group) to evaluate the efficacy and safety of romosozumab [see Section "6.2.2.5 Global phase III study in men with osteoporosis" for pharmacokinetics]. Major inclusion criteria were men aged 55 to 90 years who had no history of proximal femur fracture and met one of the following criteria: (1) BMD T-score of ≤−2.5 at the lumbar vertebrae, proximal femur, or femoral neck, or (2) BMD T-score of ≤−1.5 at the lumbar vertebrae, proximal femur, or femoral neck, with a history of fragility nonvertebral fracture or vertebral fracture. Subjects were excluded if the BMD T-score at the proximal femur or femoral neck was ≤−3.5, or the serum 25(OH) vitamin D was <20 ng/mL or albumin-corrected serum calcium level or serum iPTH level was not within the reference range.

This study consisted of the screening phase (up to of 35 days), treatment phase (12 months), and follow-on phase (3 months).

Placebo or romosozumab 210 mg was administered subcutaneously into the abdomen, thigh, or upper arm once a month. Subjects with a screening serum 25(OH) vitamin D level of ≥20 ng/mL and ≤40 ng/mL were to receive 50,000 to 60,000 IU of vitamin D[31)] within 1 week of the first dose of study drug treatment (initial loading). If the screening serum 25(OH) vitamin D level was >40 ng/mL, an initial loading dose was administered at the investigator's discretion. Throughout the study period, calcium (≥500-1000 mg/day) and vitamin D[31)] (≥600-800 IU/day) were administered orally as base treatment drugs.

All 245 subjects randomized (82 [9 Japanese] in the placebo group, and 163 [18 Japanese] in the romosozumab group) were included in the FAS, and 244 subjects of the FAS, who received ≥1 dose of the study drug (81 [9 Japanese] in the placebo group and 163 [18 Japanese] in the romosozumab group) were included in the safety analysis set. In the FAS, 236 subjects (79 [9 Japanese] in the placebo group and 157 [18 Japanese] in the romosozumab group), who had baseline BMD and ≥1 post-baseline BMD measurement were included in the primary efficacy analysis set. During the treatment phase, 14 subjects (non-Japanese) withdrew from the study. Of these, 3 subjects were in the placebo group (consent withdrawal [1], lost to

42) The US, Belgium, the Czech Republic, Denmark, Poland, Russia, Switzerland, Columbia, and Mexico

follow-up [1], and death [1]), and 11 subjects were in the romosozumab group (consent withdrawal [7], violation of inclusion/exclusion criteria [2], lost to follow-up [1], and death [1]).

Table 44 summarizes the primary efficacy endpoint, i.e., the percentage change from baseline in BMD at the lumbar vertebrae at Month 12. The percentage change significantly increased in the romosozumab group as compared to placebo in the entire study population.

Table 44. Percentage change from baseline in BMD at the lumbar vertebrae (L1-L4) at Month 12 (efficacy analysis set)

Entire study population	Placebo (79)	Romosozumab (157)	Between-group difference	*P*-value[a)]
Baseline T-score	−2.31 ± 1.44	−2.19 ± 1.16	—	—
Change from baseline (%)	1.2 [0.2, 2.2]	12.1 [11.2, 13.0]	10.9 [9.6, 12.2]	<0.0001
Japanese subpopulation	Placebo (9)	Romosozumab (18)	Between-group difference	
Baseline T-score	−2.15 ± 2.62	−2.46 ± 1.07	—	
Change from baseline (%)	1.7 [−1.6, 5.0]	13.5 [10.7, 16.4]	11.8 [7.2, 16.4]	

Mean ± standard deviation; least squares mean [95% CI]; LOCF; —, not calculated
Analysis of covariance with treatment group, baseline BMD, baseline testosterone level, and geographic region as the main effects, and DXA machine type, and interaction between DXA machine type and baseline BMD as covariates
a) 2-sided significance level of 5%

A key secondary endpoint, the percentage change from baseline in BMD at the lumbar vertebrae, proximal femur, and femoral neck at Month 6 and Month 12 are presented in Table 45.

Table 45. Percentage change from baseline in BMD at Months 6 and 12 (efficacy analysis set)

Entire study population		Placebo	Romosozumab	Between-group difference
Lumbar vertebrae (L1-L4)	Baseline T-score	−2.31 ± 1.44 (79)	−2.19 ± 1.16 (157)	—
	Change from baseline (%) at Month 6	0.3 [−0.6, 1.2] (78)	9.0 [8.2, 9.7] (156)	8.7 [7.6, 9.7]
	Change from baseline (%) at Month 12	1.2 [0.2, 2.2] (78)	12.1 [11.2, 13.0] (156)	10.9 [9.6, 12.2]
Proximal femur	Baseline T-score	−1.92 ± 0.66 (79)	−1.91 ± 0.60 (158)	—
	Change from baseline (%) at Month 6	0.2 [−0.2, 0.7] (78)	1.6 [1.2, 2.0] (157)	1.4 [0.8, 2.0]
	Change from baseline (%) at Month 12	−0.5 [−1.1, 0.1] (79)	2.5 [2.1, 2.9] (158)	3.0 [2.3, 3.7]
Femoral neck	Baseline T-score	−2.30 ± 0.52 (79)	−2.33 ± 0.52 (158)	—
	Change from baseline (%) at Month 6	0.0 [−0.7, 0.7] (78)	1.2 [0.6, 1.8] (157)	1.3 [0.4, 2.1]
	Change from baseline (%) at Month 12	−0.2 [−1.0, 0.6] (79)	2.2 [1.5, 2.9] (158)	2.4 [1.5, 3.3]
Japanese subpopulation		Placebo	Romosozumab	Between-group difference
Lumbar vertebrae (L1-L4)	Baseline T-score	−2.15 ± 2.62 (9)	−2.46 ± 1.07 (18)	—
	Change from baseline (%) at Month 6	−1.2 [−4.5, 2.1] (9)	10.5 [7.7, 13.3] (18)	11.7 [7.1, 16.3]
	Change from baseline (%) at Month 12	1.7 [−1.6, 5.0] (9)	13.5 [10.7, 16.4] (18)	11.8 [7.2, 16.4]
Proximal femur	Baseline T-score	−2.37 ± 0.47 (9)	−2.15 ± 0.46 (18)	—
	Change from baseline (%) at Month 6	1.3 [−0.6, 3.1] (9)	1.0 [−0.1, 2.0] (18)	−0.3 [−2.5, 2.0]
	Change from baseline (%) at Month 12	0.9 [−1.0, 2.7] (9)	2.1 [0.9, 3.3] (18)	1.2 [−1.1, 3.6]
Femoral neck	Baseline T-score	−2.49 ± 0.17 (9)	−2.40 ± 0.37 (18)	—
	Change from baseline (%) at Month 6	1.0 [−0.5, 2.6] (9)	1.0 [−0.6, 2.5] (18)	−0.1 [−2.4, 2.3]
	Change from baseline (%) at Month 12	0.8 [−1.4, 3.0] (9)	1.4 [−0.3, 3.1] (18)	0.6 [−2.3, 3.5]

Mean ± standard deviation; least squares mean [95% CI]; LOCF; —, not calculated
Analysis of covariance with treatment group, baseline BMD, baseline testosterone level, and geographic region as the main effects, and DXA machine type, and interaction between DXA machine type and baseline BMD as covariates

The safety analysis revealed the incidences of adverse events that occurred in ≥4 subjects in any group of the entire study population and the matching adverse reactions during the treatment phase, as shown in Table 46. In the Japanese subpopulation, the incidence of adverse events was 88.9% (8 of 9) and that of adverse reactions was 0% (0 of 9) in the placebo group, while the incidence of adverse events was 77.8% (14 of 18), and that of adverse reactions was 0% (0 of 18) in the romosozumab group. In the Japanese subpopulation,

adverse events that occurred in ≥2 subjects in any group were nasopharyngitis (22.2% [2 of 9] in the placebo group, and 38.9% [7 of 18] in the romosozumab group), constipation (11.1% [1 of 9] in the placebo group and 16.7% [3 of 18] in the romosozumab group), pharyngitis (0% [0 of 9] in the placebo group, and 11.1% [2 of 18] in the romosozumab group), upper respiratory tract infection bacterial (22.2% [2 of 9] in the placebo group, and 5.6% [1 of 18] in the romosozumab group), and tonsillitis (22.2% [2 of 9] in the placebo group, and 0% [0 of 18] in the romosozumab group). There were no adverse reactions.

Table 46. The incidence of adverse events that occurred in ≥4 subjects in any group and matching adverse reactions (safety analysis set)

Adverse event	Placebo (81)		Romosozumab (163)	
	Adverse event	Adverse reaction	Adverse event	Adverse reaction
All adverse events	80.2 (65)	8.6 (7)	75.5 (123)	11.7 (19)
Nasopharyngitis	27.2 (22)	1.2 (1)	21.5 (35)	0.6 (1)
Back pain	4.9 (4)	0 (0)	7.4 (12)	0 (0)
Hypertension	6.2 (5)	0 (0)	7.4 (12)	0 (0)
Headache	7.4 (6)	0 (0)	6.1 (10)	1.2 (2)
Constipation	1.2 (1)	0 (0)	5.5 (9)	0.6 (1)
Arthralgia	8.6 (7)	0 (0)	4.9 (8)	0 (0)
Osteoarthritis	1.2 (1)	0 (0)	4.9 (8)	0 (0)
Procedural pain	7.4 (6)	0 (0)	4.9 (8)	0.6 (1)
Pain in extremity	2.5 (2)	0 (0)	3.7 (6)	0 (0)
Benign prostatic hyperplasia	0 (0)	0 (0)	3.1 (5)	0.6 (1)
Cough	1.2 (1)	0 (0)	3.1 (5)	0 (0)
Dizziness	1.2 (1)	0 (0)	3.1 (5)	0.6 (1)
Fall	2.5 (2)	0 (0)	3.1 (5)	0 (0)
Influenza like illness	0 (0)	0 (0)	3.1 (5)	0 (0)
Musculoskeletal pain	0 (0)	0 (0)	3.1 (5)	0.6 (1)
Pneumonia	0 (0)	0 (0)	3.1 (5)	0 (0)
Upper respiratory tract infection	4.9 (4)	0 (0)	3.1 (5)	0 (0)
Diarrhoea	4.9 (4)	1.2 (1)	2.5 (4)	0.6 (1)
Injection site pain	0 (0)	0 (0)	2.5 (4)	2.5 (4)
Pharyngitis	1.2 (1)	0 (0)	2.5 (4)	0 (0)
Muscle spasms	6.2 (5)	1.2 (1)	1.8 (3)	0 (0)
Myalgia	6.2 (5)	0 (0)	1.8 (3)	0.6 (1)
Fatigue	4.9 (4)	1.2 (1)	1.2 (2)	0 (0)

Incidence, % (number of subjects); MedDRA ver.18.1

During the treatment phase, deaths occurred in 1 subject (death) in the placebo group and 2 subjects (cardio-respiratory arrest and death in 1 subject each) in the romosozumab group. However, a causal relationship to the study drug was ruled out for all these events. No deaths occurred in the Japanese subpopulation. There were no deaths in the follow-on phase.

During the treatment phase, serious adverse events occurred in 12.3% of subjects in the placebo group, and 12.9% of subjects in the romosozumab group. A causal relationship to the study drug was ruled out for all events. In the Japanese subpopulation, serious adverse events occurred in 1 subject (cardiac valvulopathy) in the placebo group, and 2 subjects in the romosozumab group (Wolff-Parkinson-White syndrome and cholecystitis). A causal relationship to the study drug was ruled out for all these events. During the follow-on phase, serious adverse events occurred in 1 subject in the placebo group and 3 subjects in the romosozumab group, and a causal relationship to the study drug was ruled out for all events.

During the treatment phase, adverse events leading to treatment discontinuation occurred in 1.2% (1 of 81) of subjects in the placebo group and 3.1% (5 of 163) of subjects in the romosozumab group and the events in 2

subjects (dizziness, headache/non-cardiac chest pain) in the romosozumab group were assessed as adverse reactions. No adverse events leading to treatment discontinuation occurred in Japanese subjects. In the follow-on phase, no adverse events leading to treatment discontinuation occurred.

There were no changes in ECG or vital signs that could cause clinical problems.

7.3 Foreign phase III study

7.3.1 Foreign phase III study to compare formulations (CTD 5.3.5.1-4, Study 20120156 [December 2013 to December 2014])

A randomized, double-blind, parallel-group study was conducted in postmenopausal women with osteoporosis (target sample size, 272 subjects; 50 in the placebo group, 111 in the romosozumab 70 mg/mL group, 111 in the romosozumab 90 mg/mL group) in the US, Poland, and the Czech Republic to evaluate the efficacy and safety of the romosozumab 70 mg/mL formulation for clinical studies and the romosozumab 90 mg/mL formulation intended for commercial release. Major inclusion criteria were postmenopausal women aged 55 to 90 years with no history of proximal femur fracture; a BMD T-score of ≤−2.5 at the lumbar vertebrae, proximal femur, or femoral neck; a history of fragility fracture or ≥2 clinical risk factors for fracture including (1) aged ≥70 years, (2) BMD T-score of ≤−3.0 at the lumbar vertebrae, proximal femur, or femoral neck, (3) smoking, (4) daily alcohol consumption of ≥3 drinks, (5) parental history of fragility fracture, and (6) body weight of ≤56 kg. Subjects were excluded if the BMD T-score at the proximal femur or femoral neck was ≤−3.5, the serum 25(OH) vitamin D was <20 ng/mL or albumin-corrected serum calcium level or serum iPTH level was not within the reference range.

This study consisted of the screening phase (maximum of 35 days), treatment phase (6 months), and follow-on phase (3 months).

Romosozumab 70 mg/mL formulation (210 mg) or matching placebo (3 prefilled syringes), or romosozumab 90 mg/mL formulation (210 mg) or matching placebo (2 prefilled syringes) was administered subcutaneously into the abdomen, thigh, or upper arm once a month. Subjects with a screening serum 25(OH) vitamin D level of ≥20 ng/mL and ≤40 ng/mL were to receive 50,000 to 60,000 IU vitamin D[31)] within 1 week of the first dose of study drug treatment (initial loading). If the screening serum 25(OH) vitamin D level was >40 ng/mL, an initial loading dose was administered at the investigator's discretion. Throughout the study period, calcium (≥500-1000 mg/day) and vitamin D[31)] (≥600-800 IU/day) were administered orally as base treatment drugs.

All 294 subjects randomized (53 in the placebo group, 118 in the romosozumab 70 mg/mL group, and 123 in the romosozumab 90 mg/mL group) were included in the FAS. All 294 subjects who received the study drug (52[43)] in the placebo group, 119[43)] in the romosozumab 70 mg/mL group, and 123 in the romosozumab 90 mg/mL group) were included in the safety analysis set. In the FAS, 273 subjects (46 in the placebo group,

[43)] One of subjects randomized to the placebo group erroneously received 1 dose of romosozumab 70 mg/mL. The data of this subject were included in the romosozumab 70 mg/mL group in the safety analysis set.

110 in the romosozumab 70 mg/mL group, and 117 in the romosozumab 90 mg/mL group), who had baseline BMD and ≥1 post-baseline BMD measurement, were included in the primary efficacy analysis set. During the treatment phase, 15 subjects withdrew from the study. Of these, 6 subjects were in the placebo group (consent withdrawal [5] and lost to follow-up [1]), 5 subjects in the romosozumab 70 mg/mL group (consent withdrawal [4] and lost to follow-up [1]), and 4 subjects in the romosozumab 90 mg/mL group (consent withdrawal [3] and lost to follow-up [1]).

Table 47 shows the percentage change from baseline in BMD at the lumbar vertebrae at Month 6, the primary efficacy endpoint. The difference in the percentage change from baseline [95% CI] between the romosozumab 70 mg/mL and 90 mg/mL groups was −0.4% [−1.5, 0.7]. The lower limit of 95% CI is greater than the noninferiority limit (−2.0%[44)]) specified in advance, demonstrating the noninferiority of romosozumab 90 mg/mL to romosozumab 70 mg/mL.

The least squares mean [95% CI] for percentage change from baseline in BMD at the lumbar vertebrae at Month 6 in the per-protocol set[45)] was evaluated as a sensitivity analysis, and was 0.7% [−0.5, 2.0] in the placebo group, 9.6% [8.8, 10.4] in the romosozumab 70 mg/mL group, and 9.3% [8.5, 10.0] in the romosozumab 90 mg/mL group. The between-group difference [95% CI] was therefore −0.3% [−1.5, 0.8].

Table 47. Percentage change from baseline in BMD at the lumbar vertebrae (L1-L4) at Month 6 (efficacy analysis set)

	Placebo (46)	Romosozumab 70 mg/mL (110)	Romosozumab 90 mg/mL (117)	Between-group difference, Romosozumab 70 mg/mL and 90 mg/mL
Baseline T-score	−2.83 ± 1.06	−2.96 ± 0.97	−3.04 ± 0.70	—
Change from baseline T-score (%)	0.8 [−0.4, 2.1]	9.6 [8.8, 10.4]	9.2 [8.4, 10.0]	−0.4 [−1.5, 0.7]

Mean ± standard deviation; least squares mean [95% CI]; LOCF; —, not calculated
Analysis of covariance with treatment group, and baseline T-score for BMD at the lumbar vertebrae (L1-L4) as the main effects

The key secondary endpoints, the percentage change from baseline in BMD at the proximal femur and femoral neck at Month 6 are presented in Table 48.

Table 48. Percentage change from baseline in BMD at the proximal femur and femoral neck at Month 6 (efficacy analysis set)

		Placebo (46)	Romosozumab 70 mg/mL (110)	Romosozumab 90 mg/mL (116)
Proximal femur	Baseline T-score	−2.07 ± 0.67	−1.81 ± 0.69	−1.85 ± 0.64
	Change from baseline (%)	−0.0 [−0.9, 0.8]	3.9 [3.4, 4.4]	3.4 [2.9, 4.0]
Femoral neck	Baseline T-score	−2.31 ± 0.54	−2.13 ± 0.62	−2.03 ± 0.60
	Change from baseline (%)	−0.5 [−1.5, 0.5]	3.1 [2.5, 3.8]	2.6 [2.0, 3.3]

Mean ± standard deviation; least squares mean [95% CI]; LOCF
Analysis of covariance with treatment group, and baseline T-score for BMD at the lumbar vertebrae (L1-L4) as the main effects

The safety analysis revealed adverse events with an incidence of ≥5% in any group and matching adverse reactions in the treatment phase, as presented in Table 49.

44) Based on the results of the between-group difference in the percentage change from baseline in BMD at the lumbar vertebrae at Month 6 from the foreign phase II study (Study 20060326), which compared the romosozumab 210 mg Q1M group (70 mg/mL formulation) and placebo, 30% of the lower limit of 95% CI for the between-group difference, 7.95% [6.6, 9.3] was specified.

45) In the primary efficacy analysis set, 269 subjects (44 in the placebo group, 109 in the romosozumab 70 mg/mL group, 116 in the romosozumab 90 mg/mL group), who received ≥5 doses of the study drug assigned at randomization, and did not violate any inclusion/exclusion criteria, were included in the per-protocol set.

Table 49. Adverse events with an incidence of ≥5% in any group and matching adverse reaction (safety analysis set)

Adverse event	Placebo (52)		Romosozumab 70 mg/mL (119)		Romosozumab 90 mg/mL (123)	
	Adverse event	Adverse reaction	Adverse event	Adverse reaction	Adverse event	Adverse reaction
All adverse events	57.7 (30)	19.2 (10)	54.6 (65)	19.3 (23)	58.5 (72)	18.7 (23)
Nasopharyngitis	5.8 (3)	0 (0)	7.6 (9)	0.8 (1)	15.4 (19)	0 (0)
Urinary tract infection	1.9 (1)	0 (0)	0.8 (1)	0.8 (1)	5.7 (7)	0 (0)
Injection site erythema	0 (0)	0 (0)	1.7 (2)	1.7 (2)	5.7 (7)	5.7 (7)
Injection site pain	0 (0)	0 (0)	5.9 (7)	5.9 (7)	2.4 (3)	2.4 (3)
Upper respiratory tract infection	5.8 (3)	0 (0)	0.8 (1)	0 (0)	1.6 (2)	0 (0)
Headache	5.8 (3)	3.8 (2)	1.7 (2)	0 (0)	1.6 (2)	0 (0)

Incidence, % (number of subjects); MedDRA ver.17.1

Death occurred in 1 subject (death) in the placebo group during the treatment phase, but a causal relationship to the study drug was ruled out. There were no deaths during the follow-on phase.

During the treatment phase, serious adverse events occurred in 7.7% (4 of 52) of subjects in the placebo group, 5.0% (6 of 119) of subjects in the romosozumab 70 mg/mL group, and 2.4% (3 of 123) of subjects in the romosozumab 90 mg/mL group. A causal relationship to the study drug was ruled out for all these events. During the follow-on phase, serious adverse events occurred in 5.8% (3 of 52) of subjects in the placebo group, and 1.7% (2 of 119) of subjects in the romosozumab 70 mg/mL group. A causal relationship to the study drug was ruled out for all these events. There were no serious adverse events in the romosozumab 90 mg/mL group.

During the treatment phase, adverse events leading to treatment discontinuation occurred in 3.8% (2 of 52) of subjects in the placebo group, 1.7% (2 of 119) of subjects in the romosozumab 70 mg/mL group, and 2.4% (3 of 123) of subjects in the romosozumab 90 mg/mL group. Headache/spinal osteoarthritis and constipation/headache in 2 subjects in the placebo group, urinary tract inflammation in 1 subject in the romosozumab 70 mg/mL, and injection site hypersensitivity in 2 subjects in the romosozumab 90 mg/mL group were assessed as adverse reactions.

There were no changes in ECG or vital signs that could cause clinical problems.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy in postmenopausal women with osteoporosis

The applicant's explanation:

The global phase III study (Study 20070337) in postmenopausal women with osteoporosis demonstrated superior efficacy of romosozumab to placebo at Month 12 in the entire study population. Romosozumab/Dmab was superior to placebo/Dmab at Month 24 in terms of the incidence of new vertebral fracture, which was the primary endpoint. The risk ratio [95% CI] was 0.27 [0.16, 0.47] for Month 12, and 0.25 [0.16, 0.40] for Month 24 (Table 38). The incidence of all nonvertebral fractures, one of the secondary endpoints, was lower in the romosozumab group (Month 12) and in the romosozumab/Dmab group (Month

24) than controls. The hazard ratio [95% CI] was 0.75 [0.53, 1.05] (Month 12), and 0.75 [0.57, 0.97] (Month 24) (Table 40).

Efficacy evaluation in the Japanese subpopulation focused on extrinsic ethnic factors related to osteoporosis. Osteoporosis is internationally defined as a disease characterized by low bone mass, decreased bone strength, and an increased risk of fracture. There are no significant differences in the causes or pathological condition of osteoporosis between Japanese and non-Japanese populations. In recent years, the incidence of vertebral fracture in Japanese people has been decreasing, while the incidence of fracture at the proximal femur is on the rise, indicating that the trends in the incidence of different types of fracture are becoming similar to those of Europeans and Americans. Both the World Health Organization (WHO) criteria for diagnosis of osteoporosis (*WHO Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level.* Summary Meeting Report, Brussels, Belgium, 5-7 May 2004, Geneva, Switzerland: WHO Press; 2007) and Japan's diagnostic criteria for primary osteoporosis (*J Bone Miner Metab.* 2013;31:247-57) state that osteoporosis should be diagnosed based on the presence of fragility fracture and reduction in BMD compared with the average BMD value for young adults. In addition, non-traumatic vertebral fracture is diagnosed based on the extent of vertebral body height reduction on radiographs both in and outside Japan. Although cut-off values vary from country to country depending on their medical economy and other factors, many countries including Japan employ the score of the Fracture Risk Assessment Tool (FRAX) to determine the intervention threshold. FRAX allows estimation of 10-year risks of major osteoporotic fracture and proximal femoral fracture based on low BMD, prior osteoporotic fracture, long-term use of glucocorticoid, age, and other fracture risks. The purpose of prevention and treatment of osteoporosis is to prevent fractures. Treatment options for osteoporosis include diet-, exercise-, and drug-based therapies. While recommended daily intake levels differ between countries, all countries emphasize the intake of sufficient levels of calcium and vitamin D. Standard medications for osteoporosis include antiresorptive agents such as bisphosphonates and selective estrogen receptor modulators, or teriparatide (bone anabolic agent), and therapeutic agents do not differ significantly between Japan and other countries.

In the global phase III study (Study 20070337) in postmenopausal women with osteoporosis, baseline subject characteristics of the Japanese subpopulation and entire study population are shown in Table 50. Compared with the entire study population, body weight and body mass index (BMI) tended to be lower, and BMD T-score at the lumbar vertebrae tended to be higher in the Japanese subpopulation.

Table 50. Baseline subject characteristics in the Japanese subpopulation and the entire study population (Study 20070337; FAS)

Subject characteristics			Japanese subpopulation		Entire study population	
			Placebo (245)	Romosozumab (247)	Placebo (3591)	Romosozumab (3589)
Age (years)			70.4 ± 6.6	71.3 ± 6.8	70.8 ± 6.9	70.9 ± 7.0
Height (cm)			150.6 ± 5.5	150.2 ± 5.6	153.1 ± 7.4	153.2 ± 7.3
Body weight (kg)			48.40 ± 6.50	47.44 ± 6.43	57.96 ± 11.10	57.91 ± 10.83
BMI (kg/m^2)			21.37 ± 2.84	21.06 ± 2.93	24.74 ± 4.42	24.66 ± 4.30
BMD T-score	Lumbar vertebrae		−2.45 ± 0.82 (232)	−2.41 ± 0.90 (229)	−2.71 ± 1.04 (3481)	−2.72 ± 1.04 (3498)
	Proximal femur		−2.44 ± 0.47 (245)	−2.44 ± 0.48 (247)	−2.46 ± 0.47 (3590)	−2.48 ± 0.47 (3589)
	Femoral neck		−2.82 ± 0.30 (245)	−2.84 ± 0.30 (247)	−2.74 ± 0.29 (3590)	−2.76 ± 0.28 (3589)
Prevalent vertebral fracture		With	46 (18.8)	59 (23.9)	645 (18.0)	672 (18.7)
		Without	193 (78.8)	186 (75.3)	2839 (79.1)	2795 (77.9)
		Unknown	6 (2.4)	2 (0.8)	107 (3.0)	122 (3.4)
History of osteoporotic fracture on or after age 45		With	94 (38.4)	95 (38.5)	1258 (35.0)	1270 (35.4)
		Without	151 (61.6)	152 (61.5)	2333 (65.0)	2319 (64.6)
Corrected serum calcium (mg/dL)			9.43 ± 0.35 (244)	9.47 ± 0.36 (245)	9.75 ± 0.38 (3584)	9.73 ± 0.38 (3582)
Serum 25 (OH) vitamin D (ng/dL)			29.6 ± 7.3 (244)	30.6 ± 7.9 (245)	29.5 ± 11.5 (3584)	29.6 ± 10.6 (3581)

Mean ± standard deviation; number of subjects (%) for prevalent vertebral fracture and history of osteoporotic fracture on or after age 45

In the Japanese subpopulation, the primary endpoint, i.e., the incidence of new vertebral fracture and the secondary endpoints, i.e., the incidences of clinical fracture (nonvertebral and clinical vertebral fractures) and of all nonvertebral fractures were lower in the romosozumab group (Month 12) and in the romosozumab/Dmab group (Month 24) than controls, as with the entire study population (Table 38 and Table 40). The percentage change from baseline in BMD at the lumbar vertebrae, proximal femur, and femoral neck at Months 12 and 24, the secondary endpoints, were higher in the romosozumab group (Month 12), and in the romosozumab/Dmab group (Month 24) than controls in the Japanese subpopulation, as with the entire study population (Table 41). The influence of differences in subject characteristics between the entire study population and the Japanese subpopulation on the efficacy of romosozumab were assessed based on a subgroup analysis by baseline BMI and BMD T-score at the lumbar vertebrae. The results indicated no significant differences in fracture risk reduction between the Japanese subpopulation and the entire study population (Table 51).

Table 51. The incidences of new vertebral fracture at Month 12 by subject characteristics (Study 20070337; efficacy analysis set)

	Japanese subpopulation				Entire study population			
	Subject characteristics	Placebo	Romosozumab	Risk ratio[a)] [95% CI]	Subject characteristics	Placebo	Romosozumab	Risk ratio[a)] [95% CI]
BMI (kg/m^2)	≤19.8	2.5 (2/81)	1.1 (1/90)	0.45 [0.04, 4.87]	≤22.5	2.0 (22/1107)	0.5 (6/1105)	0.26 [0.11, 0.66]
	>19.8 ≤22.4	5.8 (5/86)	2.9 (2/69)	0.50 [0.10, 2.49]	>22.5 ≤26.1	1.6 (18/1145)	0.4 (4/1123)	0.23 [0.08, 0.67]
	>22.4	2.6 (2/76)	1.3 (1/78)	0.49 [0.05, 5.26]	>26.1	1.8 (19/1067)	0.6 (6/1087)	0.31 [0.12, 0.77]
BMD T-score at the lumbar vertebrae	≤−3.0	6.9 (4/58)	3.1 (2/65)	0.45 [0.08, 2.35]	≤−3.0	2.6 (35/1337)	0.9 (12/1402)	0.33 [0.17, 0.62]
	>−3.0 ≤−2.5	5.0 (3/60)	0 (0/47)	—	>−3.0 ≤−2.5	1.8 (11/619)	0 (0/639)	—
	>−2.5	0.9 (1/113)	0.9 (1/109)	1.04 [0.07, 16.37]	>−2.5	0.7 (9/1272)	0.2 (3/1205)	0.34 [0.09, 1.27]

Incidence of new vertebral fracture, % (number of subjects with fractures/number of subjects evaluated); —, not calculated
a) Based on the Mantel-Haenszel method stratified by age and prevalent vertebral fracture

The results of Study 20070337 demonstrated the fracture risk reduction effect of romosozumab in the entire

study population, and romosozumab will have promising efficacy in the Japanese subpopulation as well.

PMDA's view:
The results of the global phase III study (Study 20070337) in postmenopausal women with osteoporosis demonstrated the superiority of romosozumab to the placebo group in the incidence of new vertebral fracture, which was the primary endpoint. Accordingly, the efficacy of romosozumab in reducing the risk of fracture in postmenopausal women with osteoporosis has been proven.

The efficacy of romosozumab did not differ significantly between Japanese and non-Japanese subjects by extrinsic ethnic factor and there were no particular factors affecting the evaluation of global studies of romosozumab. In Study 20070337, the incidences of new vertebral fracture at Months 12 and 24, the primary endpoint, while point estimates for the risk ratio tend to be larger in the Japanese subpopulation than in the entire study population, the risk ratio decreased in the romosozumab/Dmab group relative to controls, a trend similar to that seen in the entire study population. Furthermore, romosozumab will have a promising effect in fracture risk reduction in Japanese postmenopausal women with osteoporosis as with the entire study population, given that (1) no significant differences were seen in the percentage change from baseline in BMD at the respective sites between the Japanese subpopulation and the entire study population; (2) no significant differences were detected between the subgroups in the subgroup analysis by subject characteristics that had differed between the Japanese subpopulation and entire study population; and (3) the dose-response relationship for the percentage change from baseline in BMD at the lumbar vertebrae showed a similar trend between the foreign phase II study (Study 20060326) and Japanese phase II study (Study 20101291). With regard to intrinsic ethnic factors, while romosozumab exposure tended to be higher in Japanese subjects than in non-Japanese subjects [see Section "6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese populations"], based on the results of Study 20070337 described above, the observed difference in romosozumab exposure is unlikely to influence the efficacy of romosozumab.

7.R.1.2 Efficacy in men with osteoporosis

The applicant's explanation:
The global phase III study (Study 20110174) in men with osteoporosis demonstrated the superiority of romosozumab to placebo in the entire study population in the percentage change from baseline in BMD at the lumbar vertebrae at Month 12, the primary endpoint (Table 44).

Efficacy in the Japanese subpopulation was evaluated as follows. Table 52 shows the baseline subject characteristics of the Japanese subpopulation and the entire study population in Study 20110174. Body weight, BMI, and BMD T-score at the proximal femur tended to be lower in the Japanese subpopulation than those in the entire study population.

Table 52. Baseline subject characteristics of the Japanese subpopulation and entire study population (Study 20110174; FAS)

Subject characteristics		Japanese subpopulation		Entire study population	
		Placebo (9)	Romosozumab (18)	Placebo (82)	Romosozumab (163)
Age (years)		75.3 ± 3.0	75.0 ± 7.0	71.5 ± 6.9	72.4 ± 7.4
Height (cm)		162.8 ± 6.7	161.3 ± 9.0	168.6 ± 8.0	168.4 ± 9.1
Body weight (kg)		53.22 ± 6.33	57.62 ± 7.12	70.84 ± 13.58	71.74 ± 13.43
BMI (kg/m^2)		20.17 ± 2.78	22.18 ± 2.49	24.84 ± 3.99	25.23 ± 3.82
BMD T-score	Lumbar vertebrae	−2.15 ± 2.62	−2.46 ± 1.07	−2.33 ± 1.41	−2.22 ± 1.19
	Proximal femur	−2.37 ± 0.47	−2.15 ± 0.46	−1.92 ± 0.65	−1.92 ± 0.59
	Femoral neck	−2.49 ± 0.17	−2.40 ± 0.37	−2.30 ± 0.52	−2.34 ± 0.52
Corrected serum calcium (mg/dL)		9.53 ± 0.23	9.59 ± 0.39	9.62 ± 0.33	9.59 ± 0.33
Serum 25 (OH) vitamin D (ng/dL)		26.7 ± 6.8	26.9 ± 4.8	28.1 ± 5.9	28.9 ± 8.5

Mean ± standard deviation

As with in the entire study population, the percentage changes from baseline in BMD at the lumbar vertebrae, proximal femur, and femoral neck at Month 12 were higher in the romosozumab group than in the placebo group in the Japanese subpopulation (Table 45). The effects of differences in subject characteristics between the entire study population and the Japanese subpopulation on the efficacy of romosozumab were evaluated based on the subgroup analysis by baseline BMI and BMD T-score at the proximal femur. The percentage change from baseline in BMD at the lumbar vertebrae at Month 12 increased in all subgroups both in the Japanese subpopulation and in the entire study population (Table 53), and similar trends were observed in the percentage changes from baseline in BMD at the proximal femur and femoral neck.

Table 53. Percentage changes from baseline in BMD at the lumbar vertebrae (L1-L4) at Month 12 by subject characteristics (%) (Study 2011174; efficacy analysis set)

	Japanese subpopulation			Entire study population			
	Subject characteristics	Placebo (9)	Romosozumab (18)	Subject characteristics	Placebo (79)	Romosozumab (157)	Between-group difference
BMI (kg/m^2)	≤21.7	2.3 (−0.3, 5.9) (6)	10.8 (7.6, 29.9) (8)	≤23.2	1.0 [−0.9, 2.9] (26)	13.8 [11.9, 15.8] (53)	12.9 [10.6, 15.1]
	>21.7	−2.5 (−3.4, 5.8) (3)	16.3 (11.2, 18.8) (10)	>23.2 ≤26.6	0.9 [−0.7, 2.6] (27)	12.6 [11.0, 14.2] (53)	11.7 [9.4, 13.9]
				>26.6	1.9 [0.1, 3.7] (26)	9.4 [8.1, 10.6] (51)	7.5 [5.4, 9.6]
BMD T-score at the proximal femur	≤−2.5	1.1, 5.4 (2)	14.9 (10.6, 23.6) (4)	≤−2.5	−3.0 [−7.1, 1.2] (14)	13.3 [10.5, 16.1] (21)	16.3 [11.6, 20.9]
	>−2.5	0.0 (−3.4, 5.9) (7)	11.9 (5.2, 21.8) (14)	>−2.5	1.7 [0.6, 2.7] (65)	11.9 [10.9, 12.8] (136)	10.2 [8.9, 11.5]

Median (minimum, maximum); least squares mean [95% CI] (number of subjects evaluated); individual values are presented for n <3

The small number of subjects in the Japanese subpopulation precludes a precise data interpretation. However, based on the increase in BMD following administration of romosozumab in the entire study population, romosozumab is expected to increase BMD in the Japanese subpopulation as well.

The percentage change from baseline in BMD of men with osteoporosis in Study 20110174 was compared with that of postmenopausal women with osteoporosis in Study 20070337 (global phase III study) to evaluate romosozumab's effect on fracture reduction in men with osteoporosis. The dosage regimen used in Study 20110174 was the same as that of Study 20070337 because the studies conducted in healthy adults (Studies

20[redacted]1180[46] and 20[redacted]0277) suggested that there were no differences in pharmacokinetics and safety between healthy men and women. The comparison of baseline patient characteristics between men (Study 20110174) and women (Study 20070337) identified no significant differences in patient characteristics between the 2 studies, except height and body weight, and the baseline BMD T-scores at the lumbar vertebrae, proximal femur, and femoral neck that tended to be higher in men than in women (Table 54).

Table 54. Baseline subject characteristics of men (Study 20110174) and women (Study 20070337)

Subject characteristics		Men (Study 20110174)		Women (Study 20070337)	
		Placebo (82)	Romosozumab (163)	Placebo (3591)	Romosozumab (3589)
Age (years)		71.5 ± 6.9	72.4 ± 7.4	70.8 ± 6.9	70.9 ± 7.0
Height (cm)		168.6 ± 8.0	168.4 ± 9.1	153.1 ± 7.4	153.2 ± 7.3
Body weight (kg)		70.84 ± 13.58	71.74 ± 13.43	57.96 ± 11.10	57.91 ± 10.83
BMI (kg/m^2)		24.84 ± 3.99	25.23 ± 3.82	24.74 ± 4.42	24.66 ± 4.30
BMD T-score	Lumbar vertebrae	−2.33 ± 1.41 (82)	−2.22 ± 1.19 (163)	−2.71 ± 1.04 (3481)	−2.72 ± 1.04 (3498)
	Proximal femur	−1.92 ± 0.65 (82)	−1.92 ± 0.59 (163)	−2.46 ± 0.47 (3590)	−2.48 ± 0.47 (3589)
	Femoral neck	−2.30 ± 0.52 (82)	−2.34 ± 0.52 (163)	−2.74 ± 0.29 (3590)	−2.76 ± 0.28 (3589)
Corrected serum calcium (mg/dL)		9.62 ± 0.33 (82)	9.59 ± 0.33 (163)	9.75 ± 0.38 (3584)	9.73 ± 0.38 (3582)
Serum 25 (OH) vitamin D (ng/dL)		28.1 ± 5.9 (82)	28.9 ± 8.5 (163)	29.5 ± 11.5 (3584)	29.6 ± 10.6 (3581)

Mean ± standard deviation

Table 55 shows the percentage change from baseline in BMD at Month 12 in men (Study 20110174) and women (Study 20070337). In both studies, BMD at the lumbar vertebrae, proximal femur, and femoral neck increased in the romosozumab group as compared with the placebo group. The percentage change from baseline in BMD was greater in the romosozumab group of Study 20070337 than in the romosozumab group of Study 20110174. The results were considered attributable to lower baseline BMD T-scores in women than in men.

Table 55. Percentage change from baseline in BMD at Month 12 in men (Study 20110174) and women (Study 20070337) (%) (efficacy analysis set)

Site	Men (Study 20110174)		Women (Study 20070337)	
	Placebo	Romosozumab	Placebo	Romosozumab
Lumbar vertebrae (L1-L4)	1.2 [0.2, 2.2] (79)	12.1 [11.2, 13.0] (157)	0.4 [0.2, 0.5] (3148)	13.1 [12.8, 13.3] (3151)
Proximal femur	−0.5 [−1.1, 0.1] (79)	2.5 [2.1, 2.9] (158)	0.3 [0.1, 0.4] (3210)	6.0 [5.9, 6.2] (3197)
Femoral neck	−0.2 [−1.0, 0.6] (79)	2.2 [1.5, 2.9] (158)	0.3 [0.1, 0.5] (3210)	5.5 [5.2, 5.7] (3197)

Least squares mean [95% CI] (number of subjects evaluated)

As shown above, men with osteoporosis experienced similar BMD increases to postmenopausal women with osteoporosis, and therefore romosozumab is expected to reduce the risk of fracture in men with osteoporosis as well.

PMDA's view:

The global phase III study (Study 20110174) in men with osteoporosis demonstrated romosozumab's

46) A phase I study in non-Japanese healthy men and women (target sample size, 136 subjects) to assess the bioequivalence of 70 mg/mL PFS formulation and 120 mg/mL PFS formulation produced from Process B drug substance when administering a single subcutaneous dose of romosozumab 210 mg.

superiority to placebo in the primary endpoint, i.e., the percentage change from baseline in BMD at the lumbar vertebrae at Month 12. Romosozumab has been shown to increase BMD in men with osteoporosis.

In terms of efficacy in Japanese patients, (1) there are no particular influential factors on the evaluation of global studies [see Section "7.R.1.1 Efficacy in postmenopausal women with osteoporosis"]; (2) no significant differences were seen between the Japanese subpopulation and the entire study population in the primary endpoint of Study 20110174, i.e., the percentage change from baseline in BMD at the lumbar vertebrae at Month 12; and (3) the subgroup analyses on some subject characteristics tended to show difference between the Japanese subpopulation and entire study population but proved consistent increase in BMD at the lumbar vertebrae across the subgroups. Accordingly, romosozumab is expected to increase BMD in Japanese men with osteoporosis as well as in the entire study population.

The percentage changes from baseline in BMD at the proximal femur and femoral neck tended were low in men with osteoporosis as compared with postmenopausal women with osteoporosis, while the reason remains unclear. However, the percentage changes were greater in the romosozumab group than in the placebo group both in men and women, and the values at the lumbar vertebrae were similar between men and women. Romosozumab is thus expected to have fracture reduction effect to a certain degree in men with osteoporosis as well.

7.R.1.3 Effects of antibody development on efficacy

The applicant's explanation:

The percentage change from baseline in BMD at the lumbar vertebrae up to Month 15 was evaluated by antibody status using data from postmenopausal women with osteoporosis in the romosozumab group of the global phase III study (Study 20070337) and from men with osteoporosis in the romosozumab group of the global phase III study (Study 20110174). No significant differences were seen between antibody-positive and antibody-negative subjects (Table 56). The percentage changes from baseline in BMD at the proximal femur and femoral neck showed a similar trend.

Table 56. Percentage changes from baseline in BMD at the lumbar vertebrae (L1-L4) by antibody status (romosozumab group[a)] in Study 20070337 and the romosozumab group[b)] in Study 20110174)

	Endpoint	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies
Study 20070337	Baseline T-score	−2.7 ± 1.0 (2534)	−2.8 ± 1.0 (636)	−2.7 ± 1.0 (25)
	Change from baseline at Month 12 (%)	13.1 ± 6.0 (2510)	13.1 ± 5.9 (631)	11.6 ± 5.0 (25)
	Change from baseline at Month 24 (%)	16.7 ± 7.0 (2267)	16.7 ± 7.2 (588)	15.1 ± 7.7 (23)
Study 20110174	Baseline T-score	−2.2 ± 1.2 (125)	−2.2 ± 1.2 (32)	−3.0 (1)
	Change from baseline at Month 6 (%)	9.0 ± 4.7 (124)	9.2 ± 4.0 (32)	14.1 (1)
	Change from baseline at Month 12 (%)	12.7 ± 5.9 (117)	12.7 ± 5.1 (30)	18.9 (1)

Mean ±standard deviation (number of subjects evaluated)

a) Subjects with BMD data at the lumbar vertebrae from baseline and through Month 24, and antibody data through Month 15

b) Subjects with BMD data at the lumbar vertebrae from baseline and through Month 12, and antibody data through Month 15

In the foreign phase II study (Study 20060326), no association was observed between the dose/dosing interval and the proportion of anti-drug or neutralizing antibody-positive subjects in the initial treatment phase (Months 0-24). As shown in Table 57, the percentage change from baseline in BMD at the lumbar vertebrae through Month 27 by antibody status indicated no significant differences. The percentage changes from baseline in BMD at the lumbar vertebrae in the retreatment phase (Months 36-48) by antibody status was examined. Although the analysis was based on a small number of neutralizing antibody-positive subjects, there was no trend towards a decrease in the percentage change from baseline in BMD at the lumbar vertebrae in anti-drug antibody-positive subjects as compared to those who tested negative for anti-drug antibodies (Table 58). The percentage changes from baseline in BMD at the proximal femur and femoral neck showed a similar trend.

Table 57. Percentage changes from baseline in BMD at the lumbar vertebrae (L1-L4) by antibody status (romosozumab group[a)] in the initial treatment phase of Study 20060326)

	Romosozumab 70 mg Q1M (49)			Romosozumab 140 mg Q1M (48)			Romosozumab 210 mg Q1M (50)		
	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies
Baseline T-score	−2.4 ± 0.6 (36)	−2.2 ± 1.1 (13)	—	−2.2 ± 0.8 (41)	−2.4 ± 0.3 (7)	—	−2.3 ± 0.6 (42)	−2.5 ± 0.7 (8)	−1.5 (1)
Change from baseline at Month 24 (%)	7.1 ± 4.4 (27)	7.5 ± 3.9 (11)	—	12.7 ± 4.6 (36)	12.3 ± 2.8 (7)	—	14.8 ± 5.9 (40)	16.5 ± 3.8 (8)	20.9 (1)

	Romosozumab 140 mg Q3M (52)			Romosozumab 210 mg Q3M (53)		
	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies
Baseline T-score	−2.4 ± 0.7 (37)	−2.7 ± 0.7 (15)	−2.9 ± 0.3 (5)	−2.3 ± 0.7 (36)	−2.1 ± 0.7 (17)	−2.0 ± 0.6 (5)
Change from baseline at Month 24 (%)	6.3 ± 2.8 (31)	6.4 ± 4.8 (12)	3.5 ± 3.7 (4)	8.3 ± 4.9 (32)	6.8 ± 3.5 (16)	5.7 ± 4.1 (5)

Mean ±standard deviation (number of subjects evaluated); —, not applicable

a) Subjects with BMD data at the lumbar vertebrae from baseline through Month 24 and antibody data up to Month 27

Table 58. Percentage changes from baseline in BMD at the lumbar vertebrae (L1-L4) by antibody status (retreatment phase[a)] of Study 20060326)

	Romosozumab 210 mg Q1M/Dmab/ Romosozumab 210 mg (16)		Romosozumab 210 mg Q1M/placebo/ Romosozumab 210 mg (19)		Placebo/Dmab/ Romosozumab 210 mg (16)		Placebo/placebo/ Romosozumab 210 mg (12)	
	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Negative for anti-drug antibodies	Positive for anti-drug antibodies
Baseline T-score	−2.3 ± 0.6 (14)	−3.3, −2.6 (2)	−2.4 ± 0.5 (16)	−2.5 ± 0.9 (3)	−2.3 ± 0.5 (12)	−2.5 ± 0.4 (4)	−2.3 ± 0.7 (9)	−2.3 ± 0.6 (3)
Change from baseline at Month 48 (%)	21.9 ± 7.7 (12)	18.3, 28.9 (2)	17.1 ± 7.9 (13)	19.8 ± 3.0 (3)	8.8 ± 4.1 (10)	13.3 ± 3.1 (3)	9.4 ± 4.5 (8)	19.2, 19.3 (2)

Mean ±standard deviation (number of subjects evaluated); individual values are presented for n <3

a) Subjects with BMD data at the lumbar vertebrae from baseline through Month 48 and antibody data up to Month 48

A neutralizing antibody-based analysis was not performed because there was only 1 subject who tested positive for anti-drug antibodies and positive for neutralizing antibodies (romosozumab 210 mg Q1M/placebo/romosozumab 210 mg group) in the retreatment phase.

In the Japanese phase II study (Study 20101291), there were no dose-related trends in the proportion of anti-drug or neutralizing antibody-positive subjects through Month 15. The results of the percentage changes from baseline in BMD at the lumbar vertebrae up to Month 15 by antibody status indicated no significant

differences (Table 59). The percentage changes from baseline in BMD at the proximal femur and femoral neck showed a similar trend.

Table 59. Percentage changes from baseline in BMD at the lumbar vertebrae (L1-L4) by antibody status (romosozumab group[a)] of Study 20101291)

	Romosozumab 70 mg (63)			Romosozumab 140 mg (63)			Romosozumab 210 mg (63)		
	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies	Negative for anti-drug antibodies	Positive for anti-drug antibodies	Positive for neutralizing antibodies
Baseline T-score	−2.7 ± 0.6 (43)	−2.8 ± 0.4 (20)	−2.9 ± 0.6 (3)	−2.6 ± 0.7 (41)	−2.7 ± 0.6 (22)	−3.0 ± 0.3 (5)	−2.7 ± 0.4 (48)	−2.7 ± 0.4 (15)	−3.0 (1)
Change from baseline at Month 6 (%)	6.4 ± 2.8 (43)	6.2 ± 2.6 (20)	7.1 ± 1.2 (3)	10.1 ± 4.4 (41)	10.5 ± 3.1 (22)	10.1 ± 3.4 (5)	12.8 ± 5.0 (48)	13.0 ± 6.8 (15)	18.1 (1)
Change from baseline at Month 12 (%)	8.5 ± 4.1 (39)	7.9 ± 2.2 (18)	5.3, 8.0 (2)	13.3 ± 5.1 (41)	12.8 ± 4.6 (22)	9.0 ± 4.5 (5)	17.0 ± 5.1 (45)	16.6 ± 7.2 (14)	20.4 (1)

Mean ± standard deviation (number of subjects evaluated)
a) Subjects with BMD data at the lumbar vertebrae from baseline through Month 12 and antibody data through Month 15

In the foreign phase III (Study 20120156) formulation comparison study, the proportion of anti-drug or neutralizing antibody-positive subjects through Month 9 did not differ significantly between the romosozumab 70 mg/mL formulation (for clinical studies) and 90 mg/mL formulation (intended for commercial release).

PMDA's view:

The small number of anti-drug or neutralizing antibody-positive subjects in some clinical studies precludes strict comparison. However, the results of Japanese and foreign studies show that romosozumab tends to be effective also in patients who have antibodies.

7.R.2 Safety

The applicant's explanation:

Table 60 shows the occurrence of adverse events in the Japanese subpopulation and the entire study population at Months 12 and 24 in the global phase III study (Study 20070337) in postmenopausal women with osteoporosis. The occurrence of adverse events with an incidence of ≥5% in any treatment group and matching adverse reactions are shown in Table 42 and 43. No significant differences were observed between groups.

Table 60. Incidence of adverse events in the Japanese subpopulation and entire study population (Study 20070337; safety analysis set)

Double-blind phase (12 months)	Japanese subpopulation		Entire study population	
	Placebo (244)	Romosozumab (245)	Placebo (3576)	Romosozumab (3581)
All adverse events	77.9 (190)	81.6 (200)	79.7 (2850)	78.4 (2806)
All adverse reactions	7.0 (17)	7.8 (19)	13.8 (494)	16.6 (596)
Serious adverse events	6.6 (16)	6.1 (15)	8.7 (312)	9.6 (344)
Adverse events leading to treatment discontinuation	4.9 (12)	2.9 (7)	2.6 (94)	2.9 (103)
Adverse events leading to study withdrawal	3.7 (9)	2.4 (6)	1.4 (50)	1.2 (44)
Deaths	0 (0)	0.4 (1)	0.6 (23)	0.8 (29)
Double-blind phase + open-label phase (24 months)	Japanese subpopulation		Entire study population	
	Placebo/Dmab (244)	Romosozumab/Dmab (245)	Placebo/Dmab (3576)	Romosozumab/Dmab (3581)
All adverse events	88.1 (215)	87.3 (214)	85.8 (3069)	85.3 (3053)
All adverse reactions	10.2 (25)	9.8 (24)	15.6 (557)	18.2 (653)
Serious adverse events	11.5 (28)	13.9 (34)	15.1 (540)	15.8 (565)
Adverse events leading to treatment discontinuation	4.9 (12)	4.1 (10)	3.1 (110)	3.4 (122)
Adverse events leading to study withdrawal	3.7 (9)	3.7 (9)	1.6 (56)	1.5 (52)
Deaths	0 (0)	0.8 (2)	1.3 (47)	1.5 (52)

Incidence, % (number of subjects)

A subgroup analysis was performed on baseline BMI and BMD T-score at the lumbar vertebrae, as these are the subject characteristics that tended to show different results between the Japanese subpopulation and entire study population. Both in the Japanese subpopulation and in the entire population, the incidences of adverse events at Month 12 did not differ significantly between the romosozumab and placebo groups in any of the subgroups (Table 61).

Table 61. Incidence of adverse events by subject characteristics (Study 20070337, double-blind phase [12 months]; safety analysis set)

	Japanese subpopulation			Entire study population		
	Subject characteristics	Placebo (244)	Romosozumab (245)	Subject characteristics	Placebo (3576)	Romosozumab (3581)
BMI (kg/m^2)	≤19.8	73.2 (60/82)	74.7 (68/91)	≤22.5	77.4 (913/1179)	78.9 (935/1185)
	>19.8 ≤22.4	76.7 (66/86)	90.3 (65/72)	>22.5 ≤26.1	80.1 (984/1229)	78.3 (959/1224)
	>22.4	84.2 (64/76)	81.7 (67/82)	>26.1	81.5 (950/1165)	77.8 (906/1165)
BMD T-score at the lumbar vertebrae	≤−3.0	81.0 (47/58)	85.1 (57/67)	≤−3.0	77.9 (1115/1431)	77.3 (1154/1492)
	>−3.0 ≤−2.5	77.0 (47/61)	81.3 (39/48)	>−3.0 ≤−2.5	80.5 (540/671)	79.4 (547/689)
	>−2.5	77.0 (87/113)	80.7 (92/114)	>−2.5	81.5 (1115/1368)	80.0 (1053/1317)

Incidence, % (number of subjects with adverse events/number of subjects analyzed)

Based on the above, there are no significant differences in terms of safety between the Japanese subpopulation and the entire study population in Study 20070337.

The occurrence of adverse events was investigated in the pooled safety analysis set[47] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis (Table 62). The incidences of adverse events were similar between the groups, and no adverse events occurred at a ≥2% higher incidence in the romosozumab group than in the placebo group. Sudden death in 1 subject in the placebo group and deep vein thrombosis in 1 subject in the romosozumab group in Study 20070337 resulted in death, and were assessed as adverse reactions. The incidences of adverse events by time to onset indicated no significant differences between onset times or between treatment groups.

Table 62. Incidence of adverse events by onset time (pooled safety analysis set comprising subjects in the placebo and romosozumab 210 mg groups)

	Months 0-3		Months 3-6		Months 6-9		Months 9-12		Months 0-12	
	Placebo (3689)	Romosozumab (3695)	Placebo (3556)	Romosozumab (3558)	Placebo (3456)	Romosozumab (3463)	Placebo (3372)	Romosozumab (3381)	Placebo (3689)	Romosozumab (3695)
All adverse events	50.7 (1870)	52.1 (1924)	49.2 (1748)	49.4 (1758)	47.7 (1648)	45.9 (1589)	46.1 (1556)	43.2 (1461)	79.6 (2938)	78.4 (2896)
All adverse reactions	8.3 (306)	9.7 (360)	4.4 (155)	5.6 (201)	3.2 (109)	4.5 (156)	2.3 (79)	3.0 (102)	13.6 (501)	16.3 (604)
Serious adverse events	3.0 (109)	2.5 (92)	2.7 (95)	3.2 (113)	2.3 (81)	2.9 (100)	2.3 (79)	2.6 (88)	8.8 (323)	9.5 (352)
Adverse events leading to treatment discontinuation	1.5 (56)	1.4 (50)	0.6 (20)	0.9 (32)	0.3 (12)	0.6 (20)	0.3 (9)	0.1 (5)	2.6 (96)	2.9 (106)
Adverse events leading to study withdrawal	0.7 (26)	0.7 (25)	0.3 (11)	0.2 (6)	0.1 (5)	0.4 (13)	0.2 (8)	<0.1 (3)	1.4 (50)	1.2 (45)
Deaths	<0.1 (2)	<0.1 (3)	0.3 (9)	0.3 (10)	0.3 (10)	0.2 (6)	<0.1 (3)	0.3(10)	0.7 (24)	0.8 (29)

Incidence, % (number of subjects)

Table 63 presents the incidence rates of adverse events in the pooled safety analysis set[48] comprising subjects from studies in postmenopausal women with osteoporosis. There were no dose-related trends in the incidence rates of adverse events.

Table 63. Incidence of adverse events (pooled safety analysis set of studies in postmenopausal women with osteoporosis)

	Placebo (3741)	Romosozumab 70 mg (113)	Romosozumab 140 mg (112)	Romosozumab 210 mg (4155)	Romosozumab total (4485)
All adverse events	215.4 (2969)	263.5 (99)	196.7 (91)	209.0 (3193)	211.2 (3484)
All adverse reactions	16.0 (512)	18.1 (22)	17.2 (21)	20.5 (697)	19.9 (760)
Serious adverse events	9.7 (329)	10.3 (15)	6.6 (10)	10.3 (379)	10.0 (418)
Adverse events leading to treatment discontinuation	2.8 (99)	3.3 (5)	1.9 (3)	3.1 (118)	3.0 (130)
Adverse events leading to study withdrawal	1.4 (50)	1.3 (2)	0.6 (1)	1.2 (45)	1.1 (50)
Deaths	0.7 (24)	0.7 (1)	0 (0)	0.8 (30)	0.7 (31)

Incidence rate, number of subjects experiencing events/100 person-years (number of subjects)

The safety of romosozumab in long-term treatment (≥12 months) was evaluated. The incidences of adverse events from Months 0 to 12 and Months 12 to 24 in the initial treatment phase (Months 0-24) of the foreign phase II study (Study 20060326) were similar between the placebo and romosozumab groups (Table 64). Deaths occurred in 2 subjects (colon cancer [1] in the placebo group, and postoperative ileus [1] subject in

47) A pooled analysis set comprising subjects in the placebo and romosozumab 210 mg groups of 12-month placebo-controlled phase II and III studies in postmenopausal women with osteoporosis (Studies 20070337, 20060326, and 20101291)

48) A pooled analysis set comprising subjects in the placebo and romosozumab groups of phase II and III studies in postmenopausal women with osteoporosis: Studies 20070337 (12 months), 20060326 (24 months), 20101291 (12 months), 20080289 (12 months [see footnote 51]), and 20120156 (6 months)

the romosozumab 70 mg Q1M group) during Months 0 to 12, while no deaths occurred during Months 12 to 24.

Table 64. Incidence of adverse events by onset time in the initial treatment phase (Months 0-24) of Study 20060326 (safety analysis set)

Months 0-12								
	Placebo (50)	Romosozumab 70 mg Q1M (50)	Romosozumab 140 mg Q1M (48)	Romosozumab 210 mg Q1M (51)	Romosozumab 140 mg Q3M (53)	Romosozumab 210 mg Q3M (53)	ALN (51)	TPTD (54)
All adverse events	90.0 (45)	96.0 (48)	87.5 (42)	82.4 (42)	81.1 (43)	86.8 (46)	86.4 (44)	68.5 (37)
All adverse reactions	12.0 (6)	38.0 (19)	39.6 (19)	13.7 (7)	15.1 (8)	13.2 (7)	11.8 (6)	22.2 (12)
Serious adverse events	14.0 (7)	10.0 (5)	2.1 (1)	9.8 (5)	7.5 (4)	3.8 (2)	7.8 (4)	9.3 (5)
Adverse events leading to treatment discontinuation	4.0 (2)	4.0 (2)	2.1 (1)	3.9 (2)	0 (0)	1.9 (1)	3.9 (2)	5.6 (3)
Adverse events leading to study withdrawal	0 (0)	2.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.9 (1)
Months 12-24								
	Placebo (43)	Romosozumab 70 mg Q1M (42)	Romosozumab 140 mg Q1M (44)	Romosozumab 210 mg Q1M (46)	Romosozumab 140 mg Q3M (47)	Romosozumab 210 mg Q3M (47)	ALN /romosozumab (48)	
All adverse events	83.7 (36)	90.5 (38)	88.6 (39)	80.4 (37)	89.4 (42)	85.1 (40)	93.8 (45)	
All adverse reactions	2.3 (1)	2.4 (1)	6.8 (3)	2.2 (1)	4.3 (2)	4.3 (2)	12.5 (6)	
Serious adverse events	7.0 (3)	9.5 (4)	13.6 (6)	2.2 (1)	12.8 (6)	4.3 (2)	10.4 (5)	
Adverse events leading to treatment discontinuation	2.3 (1)	2.4 (1)	4.5 (2)	2.2 (1)	4.3 (2)	0 (0)	4.2 (2)	
Adverse events leading to study withdrawal	0 (0)	2.4 (1)	2.3 (1)	0 (0)	0 (0)	0 (0)	2.1 (1)	

Incidence, % (number of subjects)
ALN, alendronate; TPTD, teriparatide (genetical recombination)

The safety of romosozumab in men with osteoporosis was evaluated in the global phase III study (Study 20110174). Table 65 shows the incidences of adverse events in the Japanese subpopulation and the entire study population. As indicated in Section “7.2.2 Global phase III study in men with osteoporosis” and Table 46, the incidence of adverse events that occurred in ≥4 subjects in any group in the entire study population (≥2 in the Japanese subpopulation) and matching adverse reactions did not differ significantly between the Japanese subpopulation and the entire study population.

Table 65. Incidence of adverse events in the Japanese subpopulation and entire study population (Study 20110174; safety analysis set)

	Japanese subpopulation		Entire study population	
	Placebo (9)	Romosozumab (18)	Placebo (81)	Romosozumab (163)
All adverse events	88.9 (8)	77.8 (14)	80.2 (65)	75.5 (123)
All adverse reactions	0 (0)	0 (0)	8.6 (7)	11.7 (19)
Serious adverse events	11.1 (1)	11.1 (2)	12.3 (10)	12.9 (21)
Serious adverse reactions	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	1.2 (1)	3.1 (5)
Adverse reactions leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	1.2 (2)
Deaths	0 (0)	0 (0)	1.2 (1)	0.6 (1)

Incidence, % (number of subjects)

A subgroup analysis was performed on baseline BMI and BMD T-score at the proximal femur, which are the subject characteristics that tended to show different results between the Japanese subpopulation and entire study population. Both in the Japanese subpopulation and in the entire study population, the incidences of adverse events did not differ significantly between the romosozumab and placebo groups in any of the subgroups (Table 66).

Table 66. Incidence of adverse events by subject characteristics (Study 20110174; safety analysis set)

	Japanese subpopulation			Entire study population		
	Subject characteristics	Placebo (9)	Romosozumab (18)	Subject characteristics	Placebo (81)	Romosozumab (163)
BMI (kg/m^2)	≤21.7	83.3 (5/6)	75.0 (6/8)	≤23.2	74.1 (20/27)	77.8 (42/54)
	>21.7	100.0 (3/3)	80.0 (8/10)	>23.2 ≤26.6	78.6 (22/28)	73.2 (41/56)
				>26.6	88.5 (23/26)	75.5 (40/53)
BMD T-score at the proximal femur	≤−2.5	50.0 (1/2)	75.0 (3/4)	≤−2.5	78.6 (11/14)	81.8 (18/22)
	>−2.5	100.0 (7/7)	78.6 (11/14)	>−2.5	80.6 (54/67)	74.5 (105/141)

Incidence, % (number of subjects with adverse events/number of subjects analyzed)

Accordingly, although the small number of subjects in the Japanese subpopulation precludes full data interpretation, Study 20110174 revealed no significant differences between the Japanese subpopulation and the entire study population in terms of the safety of romosozumab.

The incidences of adverse events, adverse reactions, serious adverse events, adverse events leading to treatment discontinuation, and adverse events resulting in deaths in the romosozumab group of men with osteoporosis (Study 20110174; Table 65) were similar to those of the romosozumab group of postmenopausal women with osteoporosis (pooled safety analysis set comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies;[47] Table 62). This suggests no significant differences in the safety profiles of romosozumab between men with osteoporosis and postmenopausal women with osteoporosis.

PMDA's view:
While Japanese subjects tended to have higher exposure to romosozumab than non-Japanese subjects [see Section "6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese populations], the safety evaluation of romosozumab based primarily on the incidences of adverse events demonstrated no significant safety-related differences of potential clinical concern between the Japanese subpopulation and the entire

study population in the global phase III studies (Studies 20070337 and 20110174). As the applicant explained, there were no particular safety concerns in men with osteoporosis as compared with postmenopausal women with osteoporosis.

The following sections discuss adverse events of interest post-treatment with romosozumab, taking into account the action mechanism of romosozumab and data from domestic and foreign clinical studies. The safety of romosozumab is considered acceptable, on the premise that safety advice is properly given to healthcare professionals based on the discussions below.

7.R.2.1 Hypocalcaemia

The applicant's explanation:

Serum calcium level may decrease due to increases in calcium demands for matrix mineralization as a result of stimulated bone formation following administration of romosozumab. The occurrence of hypocalcaemia was therefore examined.

In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, hypocalcaemia-related events[49)] occurred in 0 of 3689 subjects in the placebo group, and 1 of 3695 subjects in the romosozumab group. The event in 1 subject in the romosozumab group was hypocalcaemia. It occurred in the double-blind phase (a period of 12 months) of Study 20070337 and was reported as non-serious and moderate. This subject was hospitalized on Day 336 (1 day post-dose of romosozumab) due to serious cardiac failure congestive and the subject's condition was complicated by obstruction lung disease (serious), encephalopathy, fall, and pulmonary hypertension. On Day 339 (4 days post-dose of romosozumab), the subject experienced hypocalcaemia (measurements unknown). A causal relationship to the study drug was ruled out for the event, and calcium and vitamin D formulations were given. None of Japanese subjects experienced hypocalcaemia-related events.

In Foreign Study 20080289,[50)] a study in postmenopausal women with osteoporosis who are at high risk of fractures, hypocalcaemia-related events occurred in 3 of 218 subjects (blood calcium decreased in 2 subjects, and hypocalcaemia in 1 subject) in the romosozumab group. All of them were non-serious. The 1 subject experiencing hypocalcaemia had symptomatic hypocalcaemia accompanied by constipation and asthenia on Day 48 (19 days post-dose of romosozumab). Symptomatic hypocalcaemia was reported as a mild adverse reaction. Of blood calcium decreased in the 2 subjects, 1 occurred on Day 34 (34 days post-dose of romosozumab), and the other on Day 185 (37 days post-dose of romosozumab). Both adverse events of blood

49) The following MedDRA preferred terms (PTs): adjusted calcium decreased, blood calcium decreased, calcium deficiency, calcium ionised decreased, Chvostek's sign, hypocalcaemia, hypocalcaemic seizure, and Trousseau's sign

50) A randomized, open-label, teriparatide-controlled, parallel-group study in non-Japanese postmenopausal women with osteoporosis who were at high risk of fractures (target sample size, 400 subjects; 200/group) to evaluate the efficacy and safety of romosozumab. Main inclusion criteria were postmenopausal women aged 55 to 95 years; previously treated with oral bisphosphonate for ≥3 years prior to screening (for the latest 1 year period, alendronate 70 mg once weekly, or equivalent dosage regimen); history of vertebral fracture at any time, or nonvertebral fracture after age 50 years; and BMD T-score of ≤−2.50 at the lumbar vertebrae, proximal femur, or femoral neck. Subjects received subcutaneous injections of romosozumab 210 mg once a month, or teriparatide 20 μg once daily for 12 months.

calcium decreased were mild and asymptomatic, and a causal relationship to the study drug was ruled out for both events. No hypocalcaemia-related events led to treatment discontinuation or study withdrawal.

In Foreign Study 20110142,[51)] a study in patients with osteoporosis who were at high risk of fractures, hypocalcaemia-related events occurred in 1 of 2040 subjects (hypocalcaemia) in the romosozumab group, and 1 of 2014 subjects (hypocalcaemia) in the alendronate group during the double-blind phase. Both events were non-serious.

The initial treatment phase (Months 0-24) of the foreign phase II study (Study 20060326), the foreign phase III study (Study 20120156) to compare formulations, and the global phase III study (Study 20110174) in men with osteoporosis revealed no hypocalcaemia-related events.

The time course of albumin-corrected serum calcium was studied in the pooled safety analysis set[47)] comprising subjects in the placebo or romosozumab 210 mg group of 12-month studies in postmenopausal women with osteoporosis. Albumin-corrected serum calcium reached the lowest level (median) by Month 1 in the romosozumab group. The percentage changes (median) from baseline at Month 1 were 0.0% in the placebo group and −2.2% in the romosozumab group, then gradually recovered to 0.0% in the placebo group and −1.0% in the romosozumab group by Month 12. Post-baseline decrease in the albumin-corrected serum calcium level of Common Terminology Criteria for Adverse Events (CTCAE)[52)] Grade 1 occurred in 3 of 3689 subjects in the placebo group and 7 of 3695 subjects in the romosozumab group, while that of CTCAE Grade 2 occurred in 1 of 3689 subjects in the placebo group and 7 of 3695 subjects in the romosozumab group. None of the subjects in the romosozumab group experienced decreased albumin-corrected serum calcium of CTCAE Grade 3 or 4. Among these subjects who experienced decreased albumin-corrected serum calcium level, there were no particular trends in the time period of decrease. Table 67 shows the percentage changes from baseline in albumin-corrected serum calcium level in the bone turnover marker substudy[53)] of Study 20070337. In the romosozumab group, the percentage change reached lowest level between Day 14 to

51) A randomized, double-blind, alendronate-controlled/open-label parallel-group study in non-Japanese postmenopausal women with osteoporosis who were at high risk of fractures (target sample size, 4000 subjects; 2000/group) to evaluate the efficacy and safety of romosozumab. Main inclusion criteria were postmenopausal women aged 55 to 90 years, (1) with history of vertebral fractures (≥1 moderate or severe, or ≥2 mild), and BMD T-score of ≤−2.5 at the proximal femur or femoral neck; OR (2) history of proximal femur fracture in 3 to 24 months prior to randomization, or history of ≥2 moderate or severe vertebral fractures, and BMD T-score of ≤−2.0 at the proximal femur or femoral neck. Subjects received subcutaneous injections of romosozumab 210 mg once a month, or oral doses of alendronate 70 mg once weekly during the double-blind phase (12 months), and then all subjects received oral doses of alendronate 70 mg once weekly (the treatment groups were described as the romosozumab/ALN group, and ALN/ALN group in this Review Report). The primary analysis was performed when clinical fractures had occurred in ≥330 subjects and all subjects had received doses for 24 months. The study continued until ≥440 subjects had experienced a nonvertebral fracture.

52) CTCAE Grades for hypocalcaemia:
Grade 1, albumin-corrected serum calcium of ≥8.0 mg/dL and <lower limit of normal (LLN), or serum ionized calcium of ≥1.0 mmol/L and <LLN;
Grade 2, albumin-corrected serum calcium of 7.0 and <8.0 mg/dL, or serum ionized calcium of ≥0.9 and <1.0 mmol/L; or symptomatic;
Grade 3, albumin-corrected serum calcium of ≥6.0 and <7.0 mg/dL, or serum ionized calcium of ≥0.8 and <0.9 mmol/L; or hospitalization indicated;
Grade 4, albumin-corrected serum calcium of <6.0 mg/dL, or serum ionized calcium of <0.8 mmol/L; or life-threatening consequences;

53) A substudy was conducted to investigate bone turnover markers (target sample size, approximately 150 subjects). Informed consent for the substudy was obtained from 130 subjects. Of these, 129 subjects had baseline values and ≥1 post-baseline measurement (65 in the placebo/Dmab group, and 64 in the romosozumab/Dmab group) and were analyzed. No Japanese subjects were enrolled in the substudy.

Month 1, then recovered to near baseline by Month 6 plus 14 days. In the calcium substudy[54)] of Study 20070337, no albumin-corrected serum calcium level was <7.5 mg/dL on Day 14 in any treatment group.

Table 67. Percentage changes from baseline in albumin-corrected serum calcium level (%) (Study 20070337; bone turnover marker substudy)

	Baseline[a)]	Day 14	Month 1	Month 3	Month 3 + 14 days	Month 6	Month 6 + 14 days
Placebo	9.70 (8.7, 10.5) (65)	0.0 (−8.7, 9.2) (58)	0.0 (−9.6, 13.8) (64)	0.0 (−8.2, 10.3) (61)	−1.0 (−6.1, 11.5) (57)	0.0 (−7.8, 11.5) (59)	0.3 (−9.5, 9.2) (54)
Romosozumab	9.70 (8.7, 10.5) (64)	−3.0 (−10.3, 4.7) (56)	−3.1 (−10.0, 7.1) (60)	−2.1 (−11.0, 4.3) (58)	−2.1 (−9.7, 5.2) (57)	−1.9 (−7.3, 5.3) (62)	−1.0 (−8.4, 6.1) (56)

Median (minimum, maximum) (number of subjects evaluated)
a) Unit, mg/dL

In the pooled safety analysis set[48)] comprising subjects from studies in postmenopausal women with osteoporosis, the incidence rate of CTCAE Grade ≥1 decrease in albumin-corrected serum calcium level (number of subjects with events/100 person-years) was 0.1 in the placebo group, 1.3 in the romosozumab 70 mg group, 0.0 in the romosozumab 140 mg group, 0.7 in the romosozumab 210 mg group, and 0.6 in all romosozumab-treated subjects.

In Study 20110174 in men with osteoporosis, the percentage change from baseline in albumin-corrected serum calcium level (median) at Month 1 was 0.0% in the placebo group and −2.2% in the romosozumab group, indicating a mild decrease. The decreased calcium gradually recovered to −0.9% in the placebo group and −1.3% in the romosozumab group by Month 12. The maximum post-baseline decrease in albumin-corrected serum calcium of CTCAE Grade ≥1 occurred in 1 subject in the romosozumab group.

In the study of pharmacokinetics in patients with renal impairment (Study 20110227), hypocalcaemia occurred in 1 of 8 subjects with severe renal impairment and 4 of 8 subjects with ESRD. On Days 6 to 7, 2 episodes of CTCAE Grade 3 hypocalcaemia occurred in 1 subjects with ESRD, and both were asymptomatic. Other events were CTCAE Grade ≤2. The lowest percentage change from baseline (mean) in albumin-corrected serum calcium level was −1.9% (Day 15) in healthy subjects, −4.8% (Day 22) in subjects with severe renal impairment, and −12.9% (Day 22) in subjects with ESRD.

As mentioned above, clinical studies conducted in and outside Japan in subjects with osteoporosis revealed that serum calcium level tend to transiently decrease following administration of romosozumab and reach lowest roughly 1 month post-dose. The incidences of hypocalcaemia-related events in the romosozumab group was low, and all events were transient and asymptomatic. Furthermore, no subject had a decrease in albumin-corrected serum calcium level of CTCAE Grade ≥3 However, CTCAE Grade 1 or 2 decreases in albumin-corrected serum calcium level occurred in some subjects in clinical studies conducted in Japan or overseas, hypocalcaemia occurred in many subjects with severe renal impairment or ESRD, and hypocalcaemia may result in serious outcomes if it worsens. Therefore, romosozumab will be contraindicated in patients with hypocalcaemia. In addition, healthcare professionals will be advised to monitor patients

54) A calcium substudy was conducted to investigate hypocalcaemia (target sample size, approximately 920 subjects). A total of 1687 subjects (854 in the placebo group, 833 in the romosozumab group), including 82 Japanese subjects (41/group) were analyzed.

closely for signs or symptoms of hypocalcaemia and to supplement patients appropriately with calcium and vitamin D at the discretion of the physician during treatment with romosozumab. Furthermore, data on the occurrence of hypocalcaemia will continuously be gathered in the post-marketing setting.

PMDA's view:

In clinical studies conducted in and outside Japan, only a few romosozumab-treated subjects developed adverse events of hypocalcaemia. No hypocalcaemia events were serious, and no events were severe in severity. However, patients with hypocalcaemia were excluded from the studies, and calcium and vitamin D were co-administered as base treatment drugs throughout the study period. Therefore, these factors may have contributed to maintaining serum calcium level. Given that transient decreases in albumin-corrected serum calcium level have occurred in the studies at the beginning of treatment with romosozumab, patients must be carefully monitored for hypocalcaemia following administration of romosozumab. Romosozumab should therefore be contraindicated in patients with hypocalcaemia. In addition, it is necessary to provide cautionary statements to the effect that patients with hypocalcaemia or bone/mineral metabolism disorders such as magnesium and iPTH should be treated before starting romosozumab therapy; and that appropriate levels of calcium and vitamin D should be given during romosozumab therapy for the treatment or prevention of hypocalcaemia. In the pharmacokinetic study conducted in patients with renal impairment, hypocalcaemia occurred at a certain incidence in subjects with severe renal impairment or ESRD. Therefore, using the package insert or other relevant materials, the applicant should appropriately advise healthcare professionals to exercise caution when considering administering romosozumab to subjects with severe renal impairment or ESRD [see Section "7.R.5.1 Patients with renal impairment"]. Furthermore, information on the incidence of hypocalcaemia should continuously be gathered, and incidence in patients with or without renal impairment should also be evaluated. The above issues will be finalized taking into account the comments from the Expert Discussion.

7.R.2.2 Hypersensitivity

The applicant's explanation:

In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, the incidence of hypersensitivity-related events[55)] was 6.9% (253 of 3689) in the placebo group and 6.7% (249 of 3695) in the romosozumab group. The incidence of adverse reactions was 0.6% (22 of 3689) in the placebo group and 1.5% (55 of 3695) in the romosozumab group. A serious adverse event of anaphylactic reaction occurred in 1 subject in the placebo group. In the romosozumab group, 10 serious adverse events occurred in 7 subjects (rash macular [2 events]/dermatitis exfoliative/angioedema [1], circulatory collapse [1], hypersensitivity [1], dermatitis allergic [1], alveolitis allergic [1 Japanese], immune thrombocytopenic purpura [1], and dermatitis [1]). Of these, 5 events in 4 subjects in the romosozumab group were assessed as adverse reactions (rash macular [2 events], hypersensitivity [1], dermatitis allergic [1], and dermatitis [1]) and were resolved. One subject in the romosozumab group died due to circulatory collapse; however, a causal relationship to the study drug was

55) Standardized MedDRA Queries (SMQ) "Hypersensitivity"

ruled out. Adverse events leading to treatment discontinuation occurred in 6 subjects in the placebo group (dermatitis allergic, dermatitis atopic, eczema, gingival swelling, rash pruritic, and rhinitis allergic in 1 subject each) and 11 subjects in the romosozumab group (dermatitis allergic [3], rash [2], drug eruption [1], erythema multiforme/eye swelling [1], hypersensitivity [1], injection site rash [1], rash macular [1], and rash maculo-papular [1]). All events were assessed as adverse reactions except for rhinitis allergic and gingival swelling in 2 subjects in the placebo group, and eye swelling in 1 subject in the romosozumab group. Adverse events leading to study withdrawal occurred in 2 subjects in the placebo group (eczema and dermatitis allergic in 1 each) and 2 subjects in the romosozumab group (alveolitis allergic [Japanese] and drug eruption in 1 each). Among these events, eczema in 1 subject in the placebo group and drug eruption in 1 subject in the romosozumab group were assessed as adverse reactions. The incidence of hypersensitivity-related events that occurred within 2 days post-dose was 0.9% (32 of 3689) in the placebo group and 1.3% (48 of 3695) in the romosozumab group; and 3 to 7 days post-dose was 1.0% (38 of 3689) in the placebo group and 1.5% (54 of 3695) in the romosozumab group. The incidence of hypersensitivity-related events in Japanese subjects was 12.4% (38 of 307) in the placebo group and 9.4% (29 of 308) in the romosozumab group. A causal relationship to the study drug was ruled out for all the events in the romosozumab group.

In the pooled safety analysis set[48)] comprising subjects from the studies in postmenopausal women with osteoporosis was 7.6 in the placebo group, the incidence rate of hypersensitivity-related events (number of subjects with events/100 person-years) was 14.2 in the romosozumab 70 mg group, 8.8 in the romosozumab 140 mg group, 7.4 in the romosozumab 210 mg group, and 7.7 in all romosozumab-treated subjects.

In Study 20110174 conducted in men with osteoporosis, the incidence of hypersensitivity-related events was 4.9% (4 of 81 subjects) in the placebo group, 4.9% (8 of 163 subjects) in the romosozumab group. Dermatitis allergic and injection site hypersensitivity in 2 subjects in the romosozumab group were assessed as adverse reactions. No serious adverse events occurred. In Japanese subjects, hypersensitivity-related events occurred in 1 of 9 subjects in the placebo group (application site dermatitis), and 2 of 18 subjects in the romosozumab group (allergic pharyngitis and rhinitis allergic). A causal relationship to the study drug was ruled out for all these events.

During the double-blind phase of Study 20070337 (12 months), no events meeting the diagnostic criteria for anaphylaxis in the World Allergy Organization Guidelines 2012 (*Curr Opin AllergyClin Immunol.* 2012;12:389-399) were reported.

In phase II and III studies conducted in and outside Japan, the romosozumab 70 mg/mL formulation was evaluated [see Section “6.1 Summary of biopharmaceutic studies and associated analytical methods”]. In Foreign Study 20110156, a study to evaluate the noninferiority of the 90 mg/mL formulation (for commercial release) in comparison with the 70 mg/mL formulation (for clinical studies) in terms of the percentage change in BMD at the lumbar vertebrae, the incidence of hypersensitivity-related events[55)] was 5.8% (3 of

52) in the placebo group, 2.5% (3 of 119) in the 70 mg/mL group, and 11.4% (14 of 123) in the 90 mg/mL group. The results indicate higher incidence in the 90 mg/mL group than in the 70 mg/mL group. Dermatitis allergic (1) and injection site hypersensitivity (1) that occurred in 2 subjects in the 70 mg/mL group and injection site hypersensitivity (2), eczema/rash (1), rash pruritic (1), rhinitis allergic (1), and pruritus (1) in 6 subjects in the 90 mg/mL group were assessed as adverse reactions. While the 2 subjects with injection site hypersensitivity in the 90 mg/mL group discontinued treatment, no serious adverse events were reported. There was no increase in concentration-dependent risk of romosozumab, and the romosozumab 90 mg/mL formulation was also well tolerated. It is important to use 2 injections of the 90 mg/mL formulation instead of 3 injections of the 70 mg/mL formulation to mitigate injection-associated burden on patients.

As discussed above, based on the data from clinical studies in and outside Japan, overall, the incidence of hypersensitivity-related events was not necessarily higher in the romosozumab group than in the placebo group. However, romosozumab is a monoclonal antibody, and clinically significant hypersensitivity reactions such as angioedema, erythema multiforme, and urticaria occurred in the romosozumab group. Relevant cautionary advice will be given to healthcare professionals via the package insert or other materials.

PMDA's view:
In clinical studies in and outside Japan, hypersensitivity-related serious adverse events and events leading to treatment discontinuation occurred more frequently in the romosozumab group than in the placebo group. In addition, hypersensitivity-related events occurred more frequently in subjects who received the 90 mg/mL formulation (intended for commercial release) than in those who received the 70 mg/mL formulation (for clinical studies). These facts in the occurrence of hypersensitivity should be presented in the package insert. This matter will be finalized taking into account the comments from the Expert Discussion.

7.R.2.3 Injection site reactions

The applicant's explanation:
In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, the incidence of injection site reaction-related events[56)] was 2.9% (107 of 3689) in the placebo group and 5.2% (192 of 3695) in the romosozumab group. The incidence of adverse reactions was 1.5% (54 of 3689) in the placebo group and 3.5% (130 of 3695) in the romosozumab group. There were no serious adverse events related to injection site reactions. The majority of the events were mild or moderate in severity, and severe injection site reactions (adverse reactions of injection site pain) occurred in 1 subject each in the placebo and romosozumab groups. Adverse events leading to treatment discontinuation occurred in 2 subjects in the placebo group (injection site bruising/injection site pain [1 Japanese] and injection site pain [1]), and 5 subjects in the romosozumab group (injection site erythema [2], injection site pain [1], injection site rash [1], and injection site reaction [1]). All these events were assessed as adverse reactions except for those that occurred in 2 subjects in the romosozumab group (injection site erythema and injection site rash). Adverse events leading to study

56) Data were gathered according to the preferred term list, which was defined by the applicant in advance.

withdrawal occurred in 2 subjects in the placebo group (injection site bruising/injection site pain [1] and injection site pain [1]), and 1 subject in the romosozumab group (injection site pain), and all these events were assessed as adverse reactions. In Japanese subjects, the incidence of injection site reaction-related events was 1.3% (4 of 307) in the placebo group, and 3.2% (10 of 308) in the romosozumab group. The events in 3 subjects (injection site pain [3]) in the placebo group, and in 7 subjects (injection site pain [2], injection site bruising [2], injection site erythema/injection site swelling [1], injection site erythema/injection site pruritus [1], and injection site erythema/injection site pain [1]) in the romosozumab group were assessed as adverse reaction.

In the pooled safety analysis set[48)] comprising subjects from studies in postmenopausal women with osteoporosis, the incidence rate of injection site reaction-related events (number of subjects with events/100 person-years) was 3.1 in the placebo group, 11.2 in the romosozumab 70 mg group, 10.2 in the romosozumab 140 mg group, 6.3 in the romosozumab 210 mg group, and 6.6 in all romosozumab-treated subjects.

In Study 20110174 in men with osteoporosis, the incidence of injection site reaction-related events was 3.7% (3 of 81) in the placebo group and 5.5% (9 of 163) in the romosozumab group. All these events were assessed as adverse reactions. No serious adverse events or events severe in severity were reported. In Japanese subjects, no injection site reaction-related events occurred.

As discussed above, based on the data from clinical studies in and outside Japan, the incidence of injection site reactions was higher in the romosozumab group than in the control group. However, all the events were non-serious and resolved, and thus clinically acceptable.

PMDA's view:
Injection site reactions occurred more frequently in the romosozumab group than in the placebo group. As the applicant explained, taking into account the severity of injection site reactions observed in clinical studies, it is unlikely that injection site reactions become a clinically significant problem. However, information on the occurrence of injection site reactions should be provided in the package insert.

7.R.2.4 Hyperostosis

The applicant's explanation:

Neurological disorders associated with hyperostosis have been reported in patients with sclerosteosis or van Buchem disease. In addition to the evaluations in non-clinical studies [see Section "5.R.2 Neurological risks associated with hyperostosis"], the occurrence of hyperostosis in clinical studies was also investigated.

In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, the incidences of hyperostosis-related events[57)] was 0.8% (29 of 3689) in the placebo group and 0.5% (19 of 3695) in the romosozumab group, showing similar results between the groups. An adverse reaction observed was exostosis in 1 subject in the placebo group and 2 subjects in the romosozumab group. Major adverse events were lumbar spinal stenosis (8 in the placebo group and 9 in the romosozumab group), exostosis (13 in the placebo group and 6 in the romosozumab group), and spinal column stenosis (7 in the placebo group and 3 in the romosozumab group). Serious adverse events occurred in 5 subjects in the placebo group (spinal column stenosis [3] and lumbar spinal stenosis [2]) and 1 subject in the romosozumab group (spinal column stenosis). A causal relationship to the study drug was ruled out for all the serious events. No adverse events leading to treatment discontinuation occurred. Lumbar spinal stenosis led to study withdrawal in 1 subject in the placebo group, and a causal relationship to the study drug was ruled out. The incidence of events falling under a MedDRA high level group term (HLGT) of "spinal cord and nerve root disorders" was 1.8% (65 of 3689) in the placebo group and 1.8% (66 of 3695) in the romosozumab group; "cranial nerve disorders (excluding neoplasms)" 0.4% (14 of 3689) in the placebo group and 0.3% (11 of 3695) in the romosozumab group; and "hearing disorders" 0.9% (32 of 3689) in the placebo group, and 0.8% (30 of 3695) in the romosozumab group, indicating similar results between the treatment groups. In Japanese subjects, the incidence of hyperostosis-related events was 2.6% (8 of 307) in the placebo group and 3.2% (10 of 308) in the romosozumab group. A causal relationship to the study drug was ruled out for all these events. No serious adverse events were reported. The incidences of events falling under the MedDRA HLGTs of "spinal cord and nerve root disorders," "cranial nerve disorders (excluding neoplasms)," and "hearing disorders" were similar between the treatment groups.

In the pooled safety analysis set[48)] comprising subjects from studies in postmenopausal women with osteoporosis, the incidence rate of hyperostosis-related events (number of subjects with events/100 person-years) was 0.8 in the placebo group, 2.7 in the romosozumab 70 mg group, 0.6 in the romosozumab 140 mg group, 0.5 in the romosozumab 210 mg group, and 0.6 in all romosozumab-treated subjects.

In Study 20110174 conducted in men with osteoporosis, no hyperostosis-related events were reported.

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57) Events falling under MedDRA PTs of acquired foramen magnum stenosis, acral overgrowth, bone formation increased, cervical spinal stenosis, enostosis, exostosis, exostosis of external ear canal, exostosis of jaw, extraskeletal ossification, foramen magnum stenosis, high turnover osteopathy, intracranial pressure increased, lumbar spinal stenosis, macrogenia, melorheostosis, senile ankylosing vertebral hyperostosis, spinal column stenosis, vertebral foraminal stenosis, and vertebral osteophyte.

To evaluate the effects of excessively increased BMD post-dose of romosozumab on safety, the incidence of adverse events by the maximum T-score (0-1, 1-2, or >2) in post-dose BMD (at the lumbar vertebrae, proximal femur, or femoral neck) in Study 20070337 was examined. There were no significant differences in the incidences of adverse events between treatment groups within each subgroup (Table 68). Hyperostosis-related events occurred only in 1 subject in the placebo group and 2 subjects in the romosozumab group in the subgroup with the maximum post-dose BMD T-score of 0 to 1.

Table 68. Incidences of adverse events by post-dose maximum BMD T-score (Study 20070337; safety analysis set)

	Maximum BMD T-score 0-1		Maximum BMD T-score 1-2		Maximum BMD T-score >2	
	Placebo (40)	Romosozumab (127)	Placebo (6)	Romosozumab (31)	Placebo (1)	Romosozumab (14)
All adverse events	75.0 (30)	84.3 (107)	83.3 (5)	80.6 (25)	100 (1)	85.7 (12)
All adverse reactions	12.5 (5)	18.1 (23)	16.7 (1)	6.5 (2)	0 (0)	28.6 (4)
Serious adverse events	12.5 (5)	10.2 (13)	16.7 (1)	0 (0)	100 (1)	21.4 (3)
Adverse events leading to treatment discontinuation	5.0 (2)	1.6 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to study withdrawal	2.5 (1)	0.8 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperostosis-related events	2.5 (1)	1.6 (2)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence, % (number of subjects)

One of potential events of hyperostosis is hearing loss due to nerve compression. An audiology substudy[58)] was therefore conducted in Study 20070337. Hearing loss was confirmed when any one of the following American Speech-Language-Hearing Association (ASHA) criteria for ototoxicity was met: (1) a ≥20 dB hearing threshold shift at any single frequency; (2) a ≥10 dB hearing threshold shift at any 2 adjacent frequencies; or (3) loss of response at 3 consecutive frequencies where responses were previously obtained. The incidence of hearing loss at Month 12 was 23.4% (43 of 184) in the placebo group, and 25.8% (54 of 209) in the romosozumab group, showing similarity between the treatment groups. The change from baseline in hearing threshold (least squares mean change from baseline in pure-tone audiometry threshold) at Month 12 was 0.3 (178) in the placebo group, and 1.0 (204) in the romosozumab group. There were no significant differences between the treatment groups.

PMDA asked the applicant to explain the risk of developing hyperostosis in pediatric patients before epiphyseal closure treated with romosozumab.

The applicant's explanation:
In patients with sclerosteosis, who completely lack sclerostin, craniosclerosis and cranial nerve entrapment cause irreversible damage. The use of romosozumab in children aged <10 years pose a significant potential risk because their cranium continue to grow rapidly. In addition, sclerostin is reported to be expressed by hypertrophic chondrocytes in the growth plate. Patients with sclerosteosis are characterized by tall stature due to lack of sclerostin, and romosozumab may affect the longitudinal growth of bones in children before epiphyseal closure. Sclerostin is also reported to be expressed by cementocytes in the teeth. While symptoms such as tooth malformation or hypercementosis have not been reported in patients with sclerosteosis or van

58) An audiology substudy was conducted to investigate the effects on hearing loss and hearing ability (target sample size, approximately 400 subjects), and 498 subjects were analyzed (243 subjects in the placebo group, and 255 subjects in the romosozumab group). No Japanese subjects were enrolled in this substudy.

Buchem disease, there is a potential risk associated with the use of romosozumab in children whose teeth are still actively developing. The efficacy and safety of romosozumab in pediatric patients have not been evaluated, and its impact remains unknown. The safety of romosozumab in low birth weight babies, newborns, infants, young children and children has not been established, and this fact will be communicated to healthcare professionals.

PMDA's view:
The action mechanism of romosozumab may induce hyperostosis. However, clinical study data of adults in and outside Japan do not indicate significant problems in terms of the risk of hyperostosis associated with romosozumab therapy. Given that no changes suggestive of neurological risks associated with hyperostosis have been reported in the non-clinical studies [see Section "5.R.2 Neurological risks associated with hyperostosis"], a written caution on hyperostosis in the package insert, etc. is not necessary at this point. However, during the post-marketing use of romosozumab, close attention should be given to the occurrence of hyperostosis and accompanying neurological disorders, and whether to give new cautionary advice should be discussed immediately as necessary. This will be finalized taking into account the comments from the Expert Discussion.

7.R.2.5 Osteoarthritis

The applicant's explanation:
It has been suggested that sclerostin is expressed in articular cartilage, and that canonical Wnt signaling is involved in the formation and maintenance of articular cartilage (*Arthritis Rheum.* 2007;56:4095-103, *Arthritis.* 2008;58:2053-64). Therefore, the incidence of osteoarthritis in clinical studies was investigated in addition to evaluations in non-clinical studies [see Section "3.R.2 Secondary effects resulting from sclerostin inhibitory effect of romosozumab"].

In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, the incidence of osteoarthritis-related events[59)] was 8.7% (320 of 3689) in the placebo group and 7.9% (291 of 3695) in the romosozumab group. The incidence of adverse reactions was 0.4% (15 of 3689) in the placebo group and 0.4% (16 of 3695) in the romosozumab group, showing similarity between the groups. Serious adverse events occurred in 17 subjects in the placebo group (osteoarthritis [15 including 2 Japanese] and spinal osteoarthritis [2]), and 7 subjects in the romosozumab group (osteoarthritis [6] and arthropathy [1]). A causal relationship to the study drug was ruled out for all these serious adverse events. Adverse events leading to treatment discontinuation occurred in 2 subjects in the placebo group (osteoarthritis [2]), and 3 subjects in the romosozumab group (osteoarthritis [2] and arthropathy [1 Japanese]). Osteoarthritis in 1 subject in the placebo group, osteoarthritis in 1 subject and arthropathy in 1 Japanese subject in the romosozumab group were assessed as adverse reactions. Adverse events leading to study withdrawal occurred in 2 subjects in the romosozumab group (osteoarthritis [1] and

59) Events classified as MedDRA PTs, ankle arthroplasty, arthritis, arthropathy, exostosis, facet joint syndrome, hip arthroplasty, joint arthroplasty, knee arthroplasty, monarthritis, nodal osteoarthritis, osteoarthritis, osteoarthropathy, polyarthritis, rapidly progressive osteoarthritis, shoulder arthroplasty, spinal osteoarthritis, and vertebral osteophyte.

arthropathy [1 Japanese]), and all of these events were assessed as adverse reactions. The incidence of osteoarthritis-related events in the Japanese phase II study (Study 20101291) in Japanese postmenopausal women with osteoporosis was 0% (0 of 63) in the placebo group, 1.6% (1 of 63) in the romosozumab 70 mg group, 3.2% (2 of 63) in the romosozumab 140 mg group, and 15.9% (10 of 63) in the romosozumab 210 mg group, indicating a trend towards a dose-dependent increase. Adverse events observed in the romosozumab groups were spinal osteoarthritis, osteoarthritis, arthritis, and facet joint syndrome, and a causal relationship to the study drug was ruled out for all these events. There were no serious adverse events, and none of the adverse events were severe. No adverse events led to treatment discontinuation. While majority of the events were mild, moderate adverse events occurred in 5 subjects in the romosozumab 210 mg group. In the romosozumab 210 mg group, 5 of 10 subjects had a history of osteoarthritis. Meanwhile, in the initial treatment phase (Months 0-24) of the foreign phase II study (Study 20060326) in non-Japanese postmenopausal women with low BMD, the incidence of osteoarthritis-related events was 12.0% (6 of 50) in the placebo group, 12.0% (6 of 50) in the romosozumab 70 mg Q1M group, 10.2% (5 of 49) in the romosozumab 140 mg Q1M group, and 3.9% (2 of 51) in the romosozumab 210 mg Q1M group. There was no trend towards a dose-dependent increase. Furthermore, the incidence of osteoarthritis-related events in the Japanese subpopulation in Study 20070337 was 10.2% (25 of 244) in the placebo group and 10.2% (25 of 245) in the romosozumab group, showing similarity between the groups.

In the pooled safety analysis set[48)] comprising subjects from studies in postmenopausal women with osteoporosis, the incidence rate of osteoarthritis-related events (number of subjects with events/100 person-years) was 9.6 in the placebo group, 4.8 in the romosozumab 70 mg group, 4.6 in the romosozumab 140 mg group, 8.5 in the romosozumab 210 mg group, and 8.2 in all romosozumab-treated subjects.

In Study 20110174, a study in men with osteoporosis, the incidence of osteoarthritis-related events was similar between the treatment groups, i.e., 4.9% (4 of 81) in the placebo group and 4.9% (8 of 163) in the romosozumab group. A causal relationship to the study drug was ruled out for all these events. A serious adverse event occurred in 1 subject in the romosozumab group (osteoarthritis), and a causal relationship to the study drug was ruled out for this event. No adverse events led to treatment discontinuation or study withdrawal. No osteoarthritis-related events occurred in Japanese subjects.

Furthermore, in an osteoarthritis substudy[60)] in Study 20070337, the progression of gonarthrosis was investigated. The incidence of osteoarthritis-related events in the substudy was 12.0% (21 of 175) in the placebo group and 7.7% (13 of 168) in the romosozumab group. The change from baseline (least squares mean ± standard error) in Western Ontario and McMaster Universities Arthritis Index (WOMAC) total score at Month 12 was −1.3 ± 1.6 (122) in the placebo group and −2.2 ± 1.6 (123) in the romosozumab group, showing no significant differences between the groups. The incidence of worsening of gonarthrosis (defined as an increase in total WOMAC score ≥10 points) was 20.5% (25 of 122) in the placebo group, and 17.1%

60) An osteoarthritis substudy (target sample size, approximately 300 subjects) was conducted to investigate the progress of gonarthrosis, and 343 subjects (175 subjects in the placebo group, and 168 subjects in the romosozumab group) were analyzed. No Japanese subjects were enrolled in the substudy.

(21 of 123) in the romosozumab group, showing similarity between the groups. No marked progression of gonarthrosis was noted in the romosozumab group.

Based on the results from clinical studies in and outside Japan, romosozumab is unlikely to increase the risk of developing osteoarthritis.

PMDA's view:
As the applicant explains, the results of domestic and foreign clinical studies suggest that there are no particular concerns regarding an increased risk of osteoarthritis following administration of romosozumab. Given that the results of non-clinical studies also raise no particular concerns regarding an increased risk of osteoarthritis [see Section "3.R.2 Secondary effects resulting from sclerostin inhibitory effect of romosozumab"], it is not necessary to give specific cautionary advice at this point. However, the incidence of osteoarthritis-related events should be further monitored.

7.R.2.6 Cardiovascular events

The applicant's explanation:
Sclerostin is known to be expressed in the calcified foci of the aorta and blood vessels (*PLoS One.* 2011;6:e19595). Therefore, the incidence of cardiovascular events in clinical studies was reviewed as with in non-clinical studies [see Section "3.R.2 Secondary effects resulting from sclerostin inhibitory effect of romosozumab"].

In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, the incidence of adverse events falling under the MedDRA System Organ Class (SOC) of "cardiac disorders" was 4.6% (170 of 3689) in the placebo group and 4.9% (181 of 3695) in the romosozumab group, while the incidence of adverse reactions falling under "cardiac disorders" was 0.2% (9 of 3689 subjects) in the placebo group and 0.2% (8 of 3695 subjects) in the romosozumab group, indicating similarity between the treatment groups. Overall, the incidence of adverse events by PT was similar between the treatment groups. Adverse events with an incidence of ≥0.5% in any group were palpitations (0.7% [27 of 3689] in the placebo group and 0.7% [26 of 3695] in the romosozumab group), and atrial fibrillation (0.4% [16 of 3689] in the placebo group, and 0.5% [18 of 3695] in the romosozumab group). The incidence of serious adverse events was 1.1% (42 of 3689) in the placebo group and 1.3% (48 of 3695) in the romosozumab group. Cardiac failure congestive (1) and ventricular extrasystoles (1 Japanese) in the placebo group were assessed as adverse reactions.

In the pooled safety analysis set[48)] comprising subjects from studies in postmenopausal women with osteoporosis, the incidence rate of adverse events falling under the MedDRA SOC of "cardiac disorders" (number of subjects with events/100 person-years) was 5.0 in the placebo group, 2.7 in the romosozumab 70 mg group, 5.5 in the romosozumab 140 mg group, 5.3 in the romosozumab 210 mg group, and 5.1 in all romosozumab-treated subjects. The incidence rate of serious adverse events (number of subjects with

events/100 person-years) of “cardiac disorders” was 1.2 in the placebo group, 1.3 in the romosozumab 70 mg group, 1.3 in the romosozumab 140 mg group, 1.4 in the romosozumab 210 mg group, and 1.4 in all romosozumab-treated subjects.

In Study 20110174 conducted in men with osteoporosis, the incidence of adverse events falling under the MedDRA SOC of “cardiac disorders” was 8.6% (7 of 81) in the placebo group and 5.5% (9 of 163) in the romosozumab group. A causal relationship to the study drug was ruled out for all these events. Overall, the incidence of adverse events by PT was similar between the treatment groups. Adverse events of cardiac disorders that occurred in ≥2 subjects in any group were angina pectoris (0% [0 of 81] in the placebo group, and 1.2% [2 of 163] in the romosozumab group), and myocardial ischaemia (0% [0 of 81] in the placebo group, and 1.2% [2 of 163] in the romosozumab group). Serious adverse events occurred in 1.2% of subjects (1 of 81) in the placebo group, and 3.7% (6 of 163) in the romosozumab group.

In Studies 20070337 and 20110174, all deaths and serious adverse events that were deemed by the investigator to be of potential cardiovascular origin or etiology were adjudicated by the independent adjudication committee established by the sponsor. Table 69 shows the incidence of serious cardiovascular events during the double-blind phase (12 months) in Studies 20070337 and 20110174. In Japanese subjects, cardiovascular death occurred in 1 subject in the romosozumab group (congestive cardiomyopathy), and serious cardiovascular events occurred in 1 subject in the placebo group (cerebral infarction), and 2 subjects in the romosozumab group (cerebral haemorrhage and acute myocardial infarction) in Study 20070337. A causal relationship to the study drug was ruled out for all these events. In Study 20110174, no serious cardiovascular events or cardiovascular deaths occurred in Japanese subjects. Many serious cardiovascular events occurred in the romosozumab group in Study 20110174, but a causal relationship to the study drug was ruled out for all these events. The small numbers of subjects analyzed and those experiencing events allow only limited interpretation.

Table 69. Incidence of serious cardiovascular events (Studies 20070337 and 20110174)

	Study 20070337		Study 20110174	
	Placebo (3576)	Romosozumab (3581)	Placebo (81)	Romosozumab (163)
Serious cardiovascular events	1.3 (46)	1.3 (46)	2.5 (2)	4.9 (8)
Cardiovascular deaths	0.4 (15)	0.5 (17)	1.2 (1)	1.2 (2)
Cardiac ischemic events	0.4 (16)	0.4 (16)	0 (0)	1.8 (3)
Cardiac failure	0.1 (5)	0.2 (7)	0 (0)	0.6 (1)
Cerebrovascular events	0.3 (11)	0.3 (10)	1.2 (1)	1.8 (3)
Peripheral ischemic events not requiring revascularization	<0.1 (1)	0.1 (4)	0 (0)	0 (0)

Incidence, % (number of subjects)

In Foreign Study 20110142[51)] conducted in postmenopausal women with osteoporosis at high risk of fractures, cardiovascular adjudication was performed in a similar manner by an independent adjudication committee. Table 70 shows the incidence of adverse events assessed as serious cardiovascular events. An imbalance in the incidence of serious cardiovascular events up to Month 12 was seen between the

romosozumab group and the control group treated with ALN, and was primarily attributed to the incidences of cardiac ischemic events and cerebrovascular events. Presumed cardiovascular-related risk factors, namely, subject characteristics including age, smoking history, and medical history of hypercholesterolemia, hypertension, diabetes mellitus, and cardiovascular diseases were similar across the treatment groups.

Table 70. Incidence of serious cardiovascular events (Foreign Study 20110142)

	Up to Month 12		Up to the primary analysis[a)]	
	ALN (2014)	Romosozumab (2040)	ALN/ALN (2014)	Romosozumab/ALN (2040)
Serious cardiovascular events	1.9 (38)	2.5 (50)	6.1 (122)	6.5 (133)
Cardiovascular deaths	0.6 (12)	0.8 (17)	2.7 (55)	2.8 (58)
Cardiac ischemic events	0.3 (6)	0.8 (16)	1.0 (20)	1.5 (30)
Cardiac failure	0.4 (8)	0.2 (4)	1.1 (23)	0.6 (12)
Cerebrovascular events	0.3 (7)	0.8 (16)	1.3 (27)	2.2 (45)
Revascularization	0.2 (5)	0.1 (3)	0.5 (10)	0.3 (6)
Peripheral ischemic events not requiring revascularization	<0.1 (2)	0 (0)	0.2 (5)	<0.1 (2)

Incidence, % (number of subjects)
ALN, alendronate
a) The time point by which clinical fractures had occurred in ≥330 subjects and all subjects had received doses for 24 months.

The incidence of serious cardiovascular events in the 2 large-scale fracture reduction trials (Study 20070337 and Foreign Study 20110142[51)]) was examined by defining Meta-analysis of Positively Adjudicated Cardiovascular Adverse Events (MACE)[61)] post-hoc. The incidence of MACE up to Month 12 in Study 20070337 was 0.8% (29 of 3576) in the placebo group and 0.8% (30 of 3581) in the romosozumab group, indicating similarity between the treatment groups. In contrast, in Foreign Study 20110142, the incidence of MACE was 1.1% (22 of 2014) in the ALN group and 2.0% (41 of 2040) in the romosozumab group, revealing more frequent MACE observed in the romosozumab group than in the ALN group. The trend was similar to that for serious cardiovascular events. There were differences in subject characteristics between Foreign Study 20110142 and Study 20070337, namely, age and the percentage of subjects with medical history of hypertension or cardiovascular diseases were higher in Foreign Study 20110142 than in Study 2007033. The incidence of serious cardiovascular events by each subject characteristics revealed no marked differences between the romosozumab and control groups in any subgroups of subject characteristics in either study (Table 71).

61) Cardiovascular death; myocardial infarction, a cardiac ischemic event; and stroke, a cerebrovascular event (hemorrhagic stroke, ischaemic cerebral infarction, and other stroke)

Table 71. Incidence of serious cardiovascular events by subject characteristics (Study 20070337 and Foreign Study 20110142; for 12 months)

		Study 20070337		Study 20110142	
		Placebo (3576)	Romosozumab (3581)	ALN (2014)	Romosozumab (2040)
Age	<75 years	0.8 (20/2461)	0.7 (17/2464)	1.7 (16/965)	1.7 (17/972)
	≥75 years	2.3 (26/1115)	2.6 (29/1117)	2.1 (22/1049)	3.1 (33/1068)
History of hypertension	Y	2.0 (38/1919)	1.9 (36/1890)	2.6 (32/1227)	3.4 (42/1248)
	N	0.5 (8/1657)	0.6 (10/1691)	0.8 (6/787)	1.0 (8/792)
History of cardiovascular diseases	Y	1.7 (40/2331)	1.6 (38/2327)	2.3 (34/1456)	3.1 (46/1497)
	N	0.5 (6/1245)	0.6 (8/1254)	0.7 (4/558)	0.7 (4/543)
History of cerebrovascular disorder	Y	3.2 (6/190)	4.0 (7/173)	3.3 (6/183)	4.8 (7/147)
	N	1.2 (40/3386)	1.1 (39/3408)	1.7 (32/1831)	2.3 (43/1893)

Incidence, % (number of subjects)

Furthermore, in subjects in the analysis set of Study 20070337 who had met the inclusion criteria of Foreign Study 20110142 (BMD T-score of ≤−2.5 at the proximal femur or femoral neck and a history of ≥1 moderate or severe vertebral fracture(s) or ≥2 vertebral fracture of any severity), the incidence of serious cardiovascular events was 0.9% (3 of 319) in the placebo group and 1.4% (5 of 354) in the romosozumab group. Although the limited number of subjects precluded adequate interpretation, the results showed a trend similar to that in the entire study population of Study 20070337.

Based on the above, no risk factors in the romosozumab group were identified for the between-group imbalances in the incidence of serious cardiovascular events reported in Foreign Study 20110142.

An association of alendronate or other bisphosphonates with a decreased or increased cardiovascular risks has been reported, but it remains controversial. In this situation, interpretation of the result of the control group is difficult in terms of cardiovascular risks. The incidence rate of serious cardiovascular adverse events in Foreign Study 20110142 was 20 subjects/1000 person-years in the ALN group and 26 subjects/1000 person-years in the romosozumab group. In particular, the incidence rate of cardiac ischemic events was 3 subjects/1000 person-years in the ALN group and 8 subjects/1000 person-years in the romosozumab group, and cerebrovascular events 4 subjects/1000 person-years in the ALN group and 8 subjects/1000 person-years in the romosozumab group. These rates are similar to or lower than the reported incidence rate of cardiovascular diseases, myocardial infarction, or stroke in elderly women in general or postmenopausal women with osteoporosis (e.g., *Osteoporos Int.* 2014;25:757-62, *J Bone Miner Res.* 2005;20:1912-20). The subjects in these reports had different characteristics such as age and other clinical risk factors, and their region, evaluation period, definition and confirmation method of cardiovascular event outcome, and statistical methods were also different from those of subjects in Foreign Study 20110142. Although this condition precludes direct comparison, the incidence rates of these events in Foreign Study 20110142 are of no clinical concerns.

The results of the pharmacology and toxicity studies in rats and monkeys (CTD 4.2.1.3-2, 4.2.3.2-8, 4.2.1.1-6, and 4.2.3.4.1-1) suggested that inhibition of sclerostin would not change the start of aging-related vascular

calcification or the progression of existing medial calcification of vessels. Furthermore, the results of additional non-clinical studies presented below demonstrate that romosozumab is not likely to have significant effects on cardiovascular functions or cause harmful cardiovascular events.

- Using results from public database, genome-wide association studies (GWAS) from the UK Biobank, the association of the single nucleotide polymorphism (SNP) with stroke or myocardial infarction was examined. SNP rs2741856 is an SNP most significantly linked to BMD at the *Sost* locus. The genetic modification to reduce sclerostin expression by SNP rs2741856 had significant positive bone physiological effects but no effect on the risk of myocardial infarction or stroke.
- In an *in vitro* human platelet activation assay, romosozumab did not activate platelets.
- In isolated human coronary artery specimens, neither romosozumab nor sclerostin affected vasoconstriction.
- Expression of sclerostin was examined using immunohistochemical staining in atherosclerotic lesions (plaques) from endarterectomy specimens of human carotid or femoral arteries. In the majority of the plaques, sclerostin expression was not observed. In sclerostin-expressed specimens, the expression was observed in the media part of the plaque sites. The expression was downregulated compared to the media of normal aorta, and sclerostin expression was not observed in the media or adventitia, which are associated with plaque rupture or erosion. Sclerostin expression was not associated with age at endarterectomy, history of arterial diseases, pro-inflammatory cytokine profiles, intra-plaque hemorrhage, macrophage infiltration, collagen content, smooth muscle cell content, or lipid core size.
- Mouse anti-sclerostin antibody (m13C7) was administered to apolipoprotein E-deficient (*ApoE*$^{-/-}$) mice (mouse model of atherosclerosis). No increases in plaque volume or calcified plaque volume were observed. Necrosis and fibro-cartilaginous metaplasia did not occur. Furthermore, anti-sclerostin antibody did not affect aortic atherosclerotic plaque-related gene transcription, histological features, or pro-inflammatory cytokines in circulating blood.

In Foreign Study 20110142, the primary endpoints were the incidence of new vertebral fracture up to Month 24, and incidence of clinical fracture up to the primary analysis. It was found that fractures were significantly reduced in the romosozumab group compared with the ALN group. Based on this result and above discussions, the benefit-risk balance of romosozumab for osteoporosis with a high risk of fracture is considered favorable. On the other hand, patients with osteoporosis are relatively older, and thus a certain proportion of patients already have influential factors in the risk of cardiovascular diseases. For this reason, the benefit-risk balance of romosozumab therapy should be examined carefully patient by patient to ascertain the patient's suitability for romosozumab therapy, in particular, patients at high risk of myocardial infarction or stroke. Physicians are required to determine whether to prescribe romosozumab after due consideration of risks for cardiovascular events for individual patients and are expected to response promptly to cardiovascular symptoms, if any. Therefore, the imbalance observed in the incidences of cardiovascular events including cardiac ischemic events and cerebrovascular disorders in the foreign clinical studies will be communicated to healthcare professionals via the package insert.

PMDA's view:
In Foreign Study 20110142, serious cardiovascular events occurred in the romosozumab group more frequently than in the ALN group. In contrast, in the phase III study (Study 20070337), which was a major study with participation of Japanese subjects, there were no marked differences in the incidence of cardiovascular events between the romosozumab group and the placebo group. Non-clinical studies did not identify particular effects of romosozumab on the cardiovascular system.

Given the demonstrated superiority of romosozumab to placebo and ALN in fracture risk reduction in Study 20070337 and Foreign Study 20110142, the safety profiles of romosozumab related to cardiovascular events are clinically acceptable from the standpoint of its benefit-risk balance. Nevertheless, importance should be given to the results of serious cardiovascular events reported in Foreign Study 20110142 particularly for the selection of medication for osteoporosis. Appropriate cautionary advice should be given in the package insert of romosozumab along with the results of Foreign Study 20110142 for physicians to refer for the selection of a drug. Post-marketing data should be gathered on cardiovascular events following administration of romosozumab to be compared against other osteoporotic drugs. This issue will be finalized taking into account the comments from the Expert Discussion.

7.R.2.7 Osteonecrosis of jaw

The applicant's explanation:
Osteonecrosis of jaw has been reported in patients with osteoporosis who received long-term bisphosphonate therapy. Because romosozumab also inhibits bone resorption, the incidence of osteonecrosis of jaw was investigated.

In Study 20070337 in postmenopausal women with osteoporosis, positively adjudicated[62)] osteonecrosis of jaw occurred in 1 subject in the romosozumab group during the double-blind phase, and 1 Japanese subject in the romosozumab/Dmab group during the open-label phase. The subject in the romosozumab group experiencing osteonecrosis of jaw during the double-blind phase was a woman aged 6[redacted] years with no prior bisphosphonate therapy, prior chemotherapy, prior radiation therapy, or history of cancer. She had impaired healing on Day 363. Because of non-traumatic tooth injury identified in 2 teeth, the subject had 4 teeth extracted and had them replaced with dentures on Day 109. However, a wound formed on the mucous membrane of the palate led to bone exposure at a site different from the site of tooth extracted. The condition remained uncured 4 months later and was confirmed as delayed healing of the gum. The subject underwent a cauterization on the same day, and the gum healed 12 days later. Although osteonecrosis of jaw was a serious adverse event leading to treatment discontinuation, it was mild in severity and was attributed to continuous use of ill-fitting dentures. A causal relationship to the study drug was ruled out for the event. The subject in the romosozumab/Dmab group who developed osteonecrosis of jaw during the open-label phase was a

62) In Studies 20070337, 20060326, 20080289, 20110174, and 20110142, adverse events that were considered potentially to be osteonecrosis of jaw, or atypical femur fracture, identified through predefined MedDRA PTs, were adjudicated by the independent adjudication committee established by the sponsor. In Study 20101291, adjudication of events was not performed.

Japanese woman aged 6[redacted] years. The subject had a previous non-serious adverse event of periodontitis and received no previous bisphosphonate therapy, chemotherapy, or radiation therapy, and had no history of cancer. She experienced osteonecrosis of jaw 66 days post-initial dose of denosumab. Approximately 1 month after the start of denosumab treatment, the subject had a diagnosis of acute apical periodontitis in the maxillary right cuspid tooth, and the tooth was removed. Impaired healing of the tooth extraction site and bone exposure occurred 22 days after tooth extraction, and the condition was diagnosed as osteonecrosis of jaw. The subject received antibacterial drugs; however, the event remained unresolved as of 545 days after the onset. This serious event was moderate in severity, resulting in study withdrawal. Osteonecrosis of jaw was assessed as an adverse reaction caused by denosumab administered during the open-label phase. A causal relationship to romosozumab, which was administered during the double-blind phase, was ruled out. In Studies 20060326, 20080289, and 20110174, no subjects with positively adjudicated osteonecrosis of jaw were reported.

In Foreign Study 20110142[51)] in patients with osteoporosis who are at high risk of fracture, positively adjudicated osteonecrosis of jaw occurred in 3 subjects. The event occurred during or after the open-label alendronate treatment that followed a year-long treatment with either romosozumab (2 subjects) or alendronate (1 subject). The event occurred at Month 22, Month 27, or 55 months after discontinuation of open-label alendronate treatment that lasted for 12 months. A causal relationship to alendronate during the open-label phase could not be ruled out for the event in 1 of the subjects who received alendronate during the double-blind phase and experienced the event at Month 22.

Based on the above findings, the causes of osteonecrosis of jaw in the studies are unknown, and the event occurred in only a small number of subjects. However, given romosozumab's inhibitory activity on bone resorption and the possibility of increased risk of osteonecrosis of jaw, cautionary advice will be given in the package insert, etc.

PMDA's view:
Osteonecrosis of jaw has been reported, albeit in a small number of subjects, in the clinical studies in and outside Japan. In light of the limited treatment duration in the clinical studies and romosozumab's bone resorption inhibitory activity, the package insert, as practiced for other antiresorptive agents, should highlight the concern about a risk of osteonecrosis of jaw caused by romosozumab.

7.R.2.8 Atypical femoral fractures

The applicant's explanation:
Atypical femoral fracture was reported from patients with osteoporosis who had received long-term bisphosphonate therapy. Because romosozumab also inhibits bone resorption, the occurrence of atypical femoral fractures was investigated.

In Study 20070337 in postmenopausal women with osteoporosis, 1 subject (femur fracture) in the romosozumab group during the double-blind phase had positively adjudicated[62)] atypical femoral fracture. The subject was a woman aged 6[redacted] years with no prior treatment with bisphosphonate or denosumab. She fell from a standing position on Day 101 and suffered a right femoral diaphysis fracture that required hospitalization. The radiography revealed a non-comminuted, simple, transverse fracture, or short oblique fracture at the subtrochanteric or diaphyseal areas of the femur, which healed after osteosynthesis. This adverse event was assessed as serious but did not lead to treatment discontinuation. A causal relationship to romosozumab was ruled out because the patient had pain in the fracture site prior to the start of the study, serum 25(OH) vitamin D was as low as 19.2 ng/mL at screening, and the onset was Month 3.5. In Studies 20060326, 20080289, and 20110174, there were no subjects experiencing positively adjudicated atypical femoral fracture.

In Foreign Study 20110142[51)] in patients with osteoporosis who are at high risk of fracture, positively adjudicated atypical femoral fracture occurred in 7 subjects. The event occurred during the open-label alendronate phase that followed a year-long treatment with either romosozumab (3 subjects) or alendronate (4 subjects), i.e., after approximately 4 months, 5 months, 1 year 4 months (2 subjects), 1 year 9 months, 2 years, or 2 years 8 months of the open-label alendronate phase. The subject who had the event after 4 months of the open-label phase had received alendronate during the double-blind phase, and a causal relationship to alendronate in the open-label and double-blind phases could not be ruled out. One of the subjects who had the event after 1 year 4 months of the open-label phase had received romosozumab during the double-blind phase, and a causal relationship to alendronate in the open-label phase could not be ruled out. The subject who had the event after 2 years of the open-label phase had received alendronate during the double-blind phase, and a causal relationship to alendronate in the open-label phase could not be ruled out.

Based on the above findings, atypical femoral fracture occurred in only a small number of subjects in the clinical studies in and outside Japan. However, given romosozumab's bone resorption inhibitory activity and the possibility of increased risk of atypical femoral fracture, cautionary advice will be given in the package insert, etc.

PMDA's view:
Atypical femoral fracture has been reported, albeit in a small number of subjects, in the romosozumab group of clinical studies in and outside Japan. In light of the limited treatment duration in the clinical studies and romosozumab's bone resorption inhibitory activity, the package insert, as practiced for other antiresorptive agents, should highlight the concern about a risk of atypical femoral fracture caused by romosozumab.

7.R.2.9 Tumor necrosis factor (TNF)-mediated inflammatory diseases and malignant tumors

The applicant's explanation:
Some studies have suggested that sclerostin functions as a negative regulator in tumor necrosis factor (TNF)-α production in the synovial membrane, and expression of sclerostin in synovial cells in patients with

rheumatoid arthritis has been reported (*Sci Transl Med.* 2016;8:330). The occurrence of TNF-mediated inflammatory diseases was investigated.

In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, the incidence of TNF-mediated inflammatory diseases[63)] was 0.4% (14 of 3689) in the placebo group, and 0.2% (7 of 3695) in the romosozumab group. Psoriasis in 3 subjects in the placebo group and psoriasis in 1 subject in the romosozumab group were assessed as adverse reactions. Regardless of a history of TNF-mediated inflammatory diseases, the incidence was lower in the romosozumab group than in the placebo group. Serious psoriatic arthropathy occurred in 1 subject in the placebo group and serious psoriasis in 2 subjects in the romosozumab group. Serious psoriasis in 1 subject in the romosozumab group was assessed as an adverse reaction. No adverse events led to treatment discontinuation or study withdrawal.

In the pooled safety analysis set[48)] comprising subjects from the studies in postmenopausal women with osteoporosis, the incidence rate (number of subjects with events/100 person-years) of TNF-mediated inflammatory diseases was 0.4 in the placebo group, 0.7 in the romosozumab 70 mg group, 0.6 in the romosozumab 140 mg group, 0.2 in the romosozumab 210 mg group, and 0.2 in all romosozumab-treated subjects. While no rheumatoid arthritis occurred in the romosozumab groups, palindromic rheumatism occurred in 1 subject in the romosozumab group of Study 20070337. The subject was a woman aged 7[redacted] years with a history of palindromic rheumatism. Non-serious palindromic rheumatism worsened during Days 76 to 128, and a causal relationship to the study drug was ruled out. In a foreign phase I study (Study 20[redacted]0197) in healthy adult women, palindromic rheumatism occurred in 1 subject (woman aged 6[redacted] years) 10 days post-dose, and the event was assessed as a serious adverse reaction.

In Study 20110174 in men with osteoporosis, TNF-mediated inflammatory diseases occurred in 1.2% (2 of 163) of subjects in the romosozumab group, and a causal relationship to the study drug was ruled out for both subjects. No serious adverse events occurred, and no adverse events led to treatment discontinuation or study withdrawal.

In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, The incidence of SMQ “malignant or unspecified tumors” was 1.9% (71 of 3689) in the placebo group, and 1.7% (61 of 3695) in the romosozumab group, showing similarity between the treatment groups. Adverse events with an incidence of ≥0.2% in any

63) Events classified as MedDRA PTs, acute disseminated encephalomyelitis, acute haemorrhagic ulcerative colitis, ankylosing spondylitis, autoimmune arthritis, autoimmune colitis, autoimmune uveitis, axial spondyloarthritis, cardiac sarcoidosis, cerebral sarcoidosis, chronic inflammatory demyelinating polyradiculoneuropathy, Crohn’s disease, cutaneous sarcoidosis, dermatitis psoriasiform, erythrodermic psoriasis, Felty’s syndrome, guttate psoriasis, hidradenitis, inflammatory bowel disease, juvenile idiopathic arthritis, juvenile psoriatic arthritis, juvenile spondyloarthritis, laryngeal rheumatoid arthritis, liver sarcoidosis, Marburg’s variant multiple sclerosis, multiple sclerosis, multiple sclerosis relapse, multiple sclerosis relapse prophylaxis, muscular sarcoidosis, nail psoriasis, ocular sarcoidosis, Pelizaeus-Merzbacher disease, primary progressive multiple sclerosis, progressive multifocal leukoencephalopathy, progressive multiple sclerosis, progressive relapsing multiple sclerosis, psoriasis, psoriatic arthropathy, pulmonary sarcoidosis, pustular psoriasis, rebound psoriasis, relapsing-remitting multiple sclerosis, rheumatoid arthritis, rheumatoid lung, rheumatoid neutrophilic dermatosis, rheumatoid nodule, rheumatoid scleritis, rheumatoid vasculitis, sarcoidosis, secondary progressive multiple sclerosis, seronegative arthritis, spondyloarthropathy, and Still’s disease adult onset.

treatment group were basal cell carcinoma (0.5% [17 of 3689] in the placebo group, and 0.2% [7 of 3695] in the romosozumab group), and thyroid neoplasm (0.3% [10 of 3689] in the placebo group, and 0.2% [7 of 3695] in the romosozumab group).

In the pooled safety analysis set[48)] comprising subjects from studies in postmenopausal women with osteoporosis, The incidence rate (number of subjects with events/100 person-years) of an SMQ of "malignant or unspecified tumors" was 2.0 in the placebo group, 0.0 in the romosozumab 70 mg group, 1.3 in the romosozumab 140 mg group, 1.8 in the romosozumab 210 mg group, and 1.7 in all romosozumab-treated subjects. Deaths occurred in 4 subjects in the romosozumab 210 mg group (lung neoplasm malignant [4]), and a causal relationship to the study drug was ruled out for the event of 4 subjects. The event occurred after 47 to 132 days of romosozumab therapy. All 4 subjects were current or former smokers, and 1 of them had a history of basal cell carcinoma. Another subject had a family history of unspecified cancer.

In Study 20110174 in men with osteoporosis, the incidence of an SMQ of "malignant or unspecified tumors" was 2.5% (2 of 81) in the placebo group, and 1.8% (3 of 163) in the romosozumab group, showing similarity between the treatment groups. In the follow-on phase, serious basal cell carcinoma in the romosozumab group was reported, and the outcome was reported as resolved. A causal relationship to the study drug was ruled out.

Accordingly, there were no particular concerns in terms of the occurrence of TNF-mediated inflammatory diseases or malignant tumors based on the data from the clinical studies conducted in and outside Japan.

PMDA's view:
Based on the results from clinical studies conducted in Japan or overseas, no particular concerns have been raised regarding TNF-mediated inflammatory diseases or malignant tumors that could cause clinical problems up to the present.

7.R.2.10 Antibody production

The applicant's explanation:
In the pooled safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, and in the pooled safety analysis set[48)] comprising subjects from studies in postmenopausal women with osteoporosis, the occurrence of adverse events, serious adverse events, the SMQ of "hypersensitivity," injection site reaction-related events,[56)] and of an HLGT of "autoimmune disorders" was investigated based on the antibody status. There were no trends toward increased incidence of any adverse events in subjects who tested positive for antibodies (Table 72 and 73).

Table 72. Incidence of adverse events by antibody status (pooled safety analysis set comprising subjects in the placebo and romosozumab 210 mg[a])

	Negative for anti-drug antibodies (2821)	Positive for anti-drug antibodies[b] (669)	Positive for neutralizing antibodies (27)
All adverse events	80.1 (2261)	79.1 (529)	77.8 (21)
All adverse reactions	15.8 (446)	19.0 (127)	11.1 (3)
Serious adverse events	9.7 (274)	8.2 (55)	11.1 (3)
SMQ "hypersensitivity"	7.0 (197)	7.2 (48)	3.7 (1)
Injection site reaction-related events	5.0 (141)	6.9 (46)	7.4 (2)
HLGT "autoimmune disorders"	0.9 (26)	0.7 (5)	0 (0)

Incidence, % (number of subjects)

a) Subjects with antibody data post-baseline by Month 15

b) Among subjects who tested negative at baseline for anti-drug antibodies, or had missing measurements, those who tested positive by Month 15 in ≥1 test (excluding 22 subjects who tested positive at baseline)

Table 73. Incidence of adverse events by antibody status (pooled safety analysis set comprising subjects from studies in postmenopausal women with osteoporosis, pooled romosozumab-treated subjects[a])

	Negative for anti-drug antibodies (3411)	Positive for anti-drug antibodies[b] (852)	Positive for neutralizing antibodies (49)
All adverse events	212.5 (2708)	201.3 (664)	183.3 (38)
All adverse reactions	19.0 (566)	21.9 (163)	22.5 (11)
Serious adverse events	10.0 (325)	8.0 (68)	9.6 (5)
SMQ "hypersensitivity"	7.8 (253)	7.5 (63)	5.4 (3)
Injection site reaction-related events	6.2 (202)	8.3 (68)	15.7 (8)
HLGT "autoimmune disorders"	0.8 (28)	0.7 (6)	0 (0)

Incidence rate, number of subjects with events/100 person-years (number of subjects)

a) Subjects with antibody data post-baseline by Month 27 (Study 20060326), by Month 15 (Studies 20070337 and 20101291), by Month 12 (Study 20080289), and by Month 9 (Study 20120156)

b) Among subjects who tested negative at baseline for anti-drug antibodies, or had missing measurements, those who tested positive in ≥1 test by Month 27 (Study 20060326), by Month 15 (Studies 20070337 and 20101291), by Month 12 (Study 20080289), and by Month 9 (Study 20120156) (excluding 24 subjects who tested positive at baseline)

In Study 20110174 in men with osteoporosis, the incidence of adverse events, serious adverse events, the SMQ of "hypersensitivity," injection site reaction-related events,[56] and the HLGT of "autoimmune disorders" by antibody status was as outlined in Table 74.

Table 74. Incidence of adverse events by antibody status (Study 20110174; safety analysis set[a])

	Negative for anti-drug antibodies (130)	Positive for anti-drug antibodies[b] (28)	Positive for neutralizing antibodies (1)
All adverse events	74.6 (97)	82.1 (23)	100.0 (1)
All adverse reactions	10.0 (13)	14.3 (4)	0 (0)
Serious adverse events	13.8 (18)	17.9 (5)	0 (0)
SMQ "hypersensitivity"	4.6 (6)	7.1 (2)	0 (0)
Injection site reaction-related events	4.6 (6)	7.1 (2)	0 (0)
HLGT "autoimmune disorders"	0.8 (1)	0 (0)	0 (0)

Incidence, % (number of subjects)

a) Subjects with antibody data post-baseline by Month 15

b) Among subjects who tested negative at baseline for anti-drug antibodies, or had missing measurements, those who tested positive by Month 15 in ≥1 test (excluding 4 subjects who tested positive at baseline)

In Study 20060326, 140 subjects received romosozumab during the initial treatment phase (Months 0-24). In the retreatment phase (Months 36-48), anti-drug antibodies were detected in 11 of 33 subjects who tested positive for anti-drug antibodies in ≥1 test during the initial treatment phase and 2 of 107 subjects who tested negative for anti-drug antibodies during the initial treatment phase. Of 8 subjects who tested positive for anti-drug antibodies at Month 36 (including 2 who tested positive for neutralizing antibodies), 5 subjects

were anti-drug antibody-positive also during the retreatment phase (including 1 who tested positive for neutralizing antibodies). The incidence of adverse events in the retreatment phase was similar regardless of antibody status, and was 73.7% (14 of 19) in anti-drug antibody-positive subjects and 84.8% (117 of 138) in anti-drug antibody-negative subjects.

Based on the above findings, no effects of anti-drug antibody development on safety parameters were detected.

PMDA's view:
Although a precise analysis was precluded by the limited number of subjects who tested positive for anti-drug antibodies or neutralizing antibodies in some clinical studies, there were no differences in the effects of romosozumab therapy on safety parameters between anti-drug antibody-positive and negative subjects.

7.R.3 Clinical positioning and indication of romosozumab

7.R.3.1 Clinical positioning of romosozumab

The applicant's explanation:
For patients with osteoporosis who are at high risk of fracture, and it is particularly important to provide treatment that can improve bone volume and strength rapidly and reduce the risk of fracture. Recently, a working group on Goal-Directed Treatment for Osteoporosis, established by the American Society for Bone and Mineral Research (ASBMR) and the United States National Osteoporosis Foundation (NOF) has released a progress report. The report proposes to consider that patients with recent fracture or patients with a T-score substantially below −2.5 be initially treated with therapeutic agents which are able to reduce fracture risk rapidly and increase BMD, pointing out that the use of bone anabolic agents followed by antiresorptive agents is the optimal treatment sequence (*J Bone Miner Res.* 2017;32:3-10). Therapeutic agents for the treatment of osteoporosis and prophylaxis for osteoporotic fractures include antiresorptive agents (bisphosphonates, selective estrogen receptor modulators, and denosumab), bone anabolic agents (teriparatide, a PTH analogue), activated vitamin D_3 and vitamin K_2 formulations, with bisphosphonates as standard treatment. In major clinical studies for conventional osteoporotic drugs, it typically takes 2 to 3 years to demonstrate a fracture reduction effect (e.g., *Bone.* 49 2011;605-12). In contrast, romosozumab reduced the incidence of new vertebral fracture by 73% by Month 12 (Table 38). In addition, romosozumab rapidly increases BMD. In Study 20070337, the percentage change from baseline in BMD T-score at the lumbar vertebrae and proximal femur after 1 year of treatment with romosozumab was similar to the increase in BMD which was achieved by denosumab after approximately 4.5 years in the lumbar vertebrae, and 3 years in the proximal femur (*N Engl J Med.* 2009;361:756-65). Teriparatide, a bone anabolic agent, promotes bone remodeling, thereby promoting bone formation and bone resorption. In contrast, romosozumab promotes bone formation and inhibit bone resorption by inhibiting sclerostin. In Studies 20060326 and 20080289, the percentage changes from baseline in BMD at the lumbar vertebrae, proximal femur, and

femoral neck were assessed up to Month 12 in the romosozumab group and teriparatide group. At all sites, BMD increased in the romosozumab group as compared with the teriparatide group.

The above discussions and findings suggest that romosozumab will serve as a new treatment option for patients with osteoporosis who are at high risk of fracture.

7.R.3.2 Indication

The applicant's explanation:

Although the global phase III study (Study 20070337) was conducted in postmenopausal women with osteoporosis, the proposed indication was "osteoporosis with a high risk of fracture" for the following reasons.

While there is no clinically unified definition of "osteoporosis with a high risk of fracture" in Japan or overseas, fracture risk factors include history of fracture, age, and low BMD. The efficacy of romosozumab in patients with osteoporosis with a high risk of fracture in Studies 20070337 and 20110174 was assessed based on the following definitions: (1) ≥1 of the following independent risk factors specified in the diagnostic criteria for primary osteoporosis (FY 2012 revised edition) (Japanese Society for Bone and Mineral Research and Japan Osteoporosis Society Joint Review Committee for the Revision of the Diagnostic Criteria for Primary Osteoporosis) is met: "BMD of <−3.3 standard deviation at the lumbar vertebrae;" "≥2 prevalent vertebral fractures;" and "a Grade 3 prevalent vertebral fracture assessed by semi-quantitative evaluation method;" or (2) WHO classification of severe osteoporosis (patients with BMD T-score of ≤−2.5 standard deviation, and ≥1 fragility fracture). The between-group difference vs placebo in the incidence of new vertebral fracture, and the percentage change from baseline in BMD were consistent with the entire study population based on either definition of "osteoporosis with a high risk of fracture," demonstrating the efficacy of romosozumab in the treatment of patients with osteoporosis with a high risk of fracture (Table 75 and 76).

Table 75. Incidence of new vertebral fracture in patients with osteoporosis with a high risk of fracture (Study 20070337)

	12-month treatment			24-month treatment		
Fracture risk	Placebo	Romosozumab	Risk ratio[a)] [95% CI]	Placebo	Romosozumab	Risk ratio[a)] [95% CI]
Entire study population	1.8 (59/3322)	0.5 (16/3321)	0.27 [0.16, 0.47]	2.5 (84/3591)	0.6 (21/3325)	0.25 [0.16, 0.40]
High risk group 1[b)]	3.4 (36/1070)	0.6 (7/1083)	0.19 [0.09, 0.43]	4.7 (50/1072)	0.8 (9/1085)	0.18 [0.09, 0.36]
Non-high risk group 1	1.0 (23/2252)	0.4 (9/2238)	0.39 [0.18, 0.85]	1.5 (34/2255)	0.5 (12/2240)	0.35 [0.18, 0.68]
High risk group 2[c)]	2.5 (20/786)	1.0 (8/818)	0.38 [0.17, 0.87]	3.9 (31/787)	1.1 (9/818)	0.28 [0.13, 0.58]
Non-high risk group 2	1.5 (39/2536)	0.3 (8/2503)	0.21 [0.10, 0.45]	2.1 (53/2540)	0.5 (12/2507)	0.23 [0.12, 0.43]

Incidence of fractures, % (number of subjects with fractures/number of subjects evaluated)

a) Based on the Mantel-Haenszel method stratified by age and prevalent vertebral fracture.

b) ≥1 of the following independent risk factors specified in the diagnostic criteria for primary osteoporosis (FY 2012 revised edition) (Japanese Society for Bone and Mineral Research and Japan Osteoporosis Society Joint Review Committee for the Revision of the Diagnostic Criteria for Primary Osteoporosis) is met: "BMD of <−3.3 standard deviation at the lumbar vertebrae"; "≥2 prevalent vertebral fractures"; and "Grade 3 prevalent vertebral fracture by semi-quantitative evaluation method"

c) WHO classification of severe osteoporosis (patients with BMD T-score of ≤−2.5 standard deviation, and ≥1 fragility fracture)

Table 76. Between-group difference from the placebo group in the percentage change from baseline in patients with osteoporosis with a high risk of fracture (%) (Studies 20070337 and 20110174)

	Evaluation time point	Entire study population	High risk group 1[a)]	Non-high risk group 1	High risk group 2[b)]	Non-high risk group 2
Study 20070337						
Lumbar vertebrae (L1-L4)	Month 12	12.7 [12.4, 12.9]	14.9 [14.5, 15.4]	11.6 [11.3, 11.8]	12.5 [12.0, 13.0]	12.7 [12.5, 13.0]
	Month 24	11.1 [10.8, 11.4]	13.0 [12.4, 13.6]	10.1 [9.8, 10.5]	10.7 [10.1, 11.4]	11.2 [10.9, 11.5]
Proximal femur	Month 12	5.8 [5.6, 6.0]	6.9 [6.5, 7.2]	5.3 [5.1, 5.5]	5.7 [5.3, 6.0]	5.8 [5.6, 6.0]
	Month 24	5.3 [5.1, 5.5]	6.3 [5.9, 6.7]	4.8 [4.6, 5.1]	5.0 [4.5, 5.4]	5.4 [5.2, 5.6]
Femoral neck	Month 12	5.2 [4.9, 5.4]	6.1 [5.7, 6.5]	4.7 [4.5, 5.0]	5.1 [4.6, 5.5]	5.2 [4.9, 5.4]
	Month 24	4.9 [4.7, 5.2]	5.7 [5.3, 6.2]	4.5 [4.2, 4.8]	4.8 [4.3, 5.4]	5.0 [4.7, 5.2]
Study 20110174						
Lumbar vertebrae (L1-L4)	Month 12	10.9 [9.6, 12.2]	15.4 [11.9, 18.8]	10.1 [8.7, 11.5]	11.1 [8.8, 13.4]	10.7 [9.1, 12.3]
Proximal femur	Month 12	3.0 [2.3, 3.7]	2.9 [1.1, 4.6]	3.2 [2.4, 4.1]	3.8 [2.4, 5.1]	2.5 [1.7, 3.3]
Femoral neck	Month 12	2.4 [1.5, 3.3]	1.9 [−0.7, 4.5]	2.4 [1.4, 3.5]	3.1 [1.3, 4.8]	1.9 [0.8, 2.9]

Least squares mean [95% CI]
a) See the footnote b) of Table 75.
b) See the footnote c) of Table 75.

Table 77 shows the percentage change from baseline in BMD by baseline BMD T-score.

Table 77. Percentage change from baseline in BMD at Month 12 by baseline BMD T-score (Studies 20070337 and 20110174)

	Baseline T-score	Placebo	Romosozumab	Between-group difference
Study 20070337				
Lumbar vertebrae (L1-L4)	≤−3.0	0.5 [0.2, 0.7] (1302)	15.1 [14.7, 15.5] (1350)	14.6 [14.2, 15.0]
	>−3.0 and ≤−2.5	0.7 [0.1, 1.3] (606)	13.1 [12.4, 13.8] (628)	12.4 [11.9, 12.9]
	>−2.5	0.3 [0.1, 0.5] (1240)	11.0 [10.7, 11.3] (1173)	10.7 [10.3, 11.0]
Proximal femur	≤−3.0	0.6 [0.0, 1.2] (389)	7.4 [6.8, 8.1] (402)	6.8 [6.2, 7.5]
	>−3.0 and ≤−2.5	0.3 [0.0, 0.6] (1273)	6.7 [6.4, 7.0] (1294)	6.4 [6.1, 6.7]
	>−2.5	0.1 [−0.1, 0.3] (1548)	5.1 [4.9, 5.3] (1501)	5.0 [4.8, 5.2]
Study 20110174				
Lumbar vertebrae (L1-L4)	≤−3.0	0.4 [−1.9, 2.7] (25)	15.1 [12.7, 17.5] (38)	14.7 [12.0, 17.4]
	>−3.0 and ≤−2.5	0.3 [−5.2, 5.7] (19)	10.3 [5.3, 15.2] (34)	10.0 [6.9, 13.1]
	>−2.5	1.1 [−0.4, 2.7] (35)	10.7 [9.5, 11.8] (85)	9.5 [7.7, 11.4]

Least squares mean [95% CI] (number of subjects evaluated)

In Foreign Study 20080289[50)] in postmenopausal women with osteoporosis with a high risk of fracture, the least squares mean [95% CI] for the percentage change from baseline in BMD (%) at the proximal femur at Month 12 was 2.6 [2.2, 3.0] (206 subjects) in the romosozumab group, −0.6 [−1.0, −0.2] (209 subjects) in the teriparatide group, with a between-group difference of 3.2 [2.7, 3.8], indicating a significant increase in BMD in the romosozumab group as compared with the teriparatide group. A similar trend was observed in the percentage changes from baseline in BMD at the lumbar vertebrae and femoral neck. In Foreign Study 20110142[51)] in postmenopausal women with osteoporosis with a high risk of fracture, the incidences of new vertebral fracture up to Month 24 and clinical fracture up to the primary analysis significantly decreased in the romosozumab/ALN group as compared with the ALN/ALN group.

The incidence of adverse events in the high risk group and the entire study population (Table 78) indicates that the safety profiles in the high risk group are similar to those in the entire study population.

Table 78. Incidence of adverse events in patients with osteoporosis with a high risk of fracture (Studies 20070337 and 20110174; 12 months)

	Entire study population		High risk group 1[a)]		High risk group 2[b)]	
Study 20070337						
	Placebo (3576)	Romosozumab (3581)	Placebo (1149)	Romosozumab (1159)	Placebo (860)	Romosozumab (890)
All adverse events	79.7 (2850)	78.4 (2806)	78.1 (897)	76.5 (887)	81.4 (700)	79.3 (706)
All adverse reactions	13.8 (494)	16.6 (596)	13.6 (156)	17.4 (202)	14.4 (124)	15.8 (141)
Serious adverse events	8.7 (312)	9.6 (344)	8.4 (96)	8.9 (103)	9.7 (83)	10.3 (92)
Adverse events leading to treatment discontinuation	2.6 (94)	2.9 (103)	2.7 (31)	2.4 (28)	2.8 (24)	3.3 (29)
Adverse events leading to study withdrawal	1.4 (50)	1.2 (44)	1.5 (17)	0.9 (11)	1.6 (14)	1.6 (14)
Deaths	0.6 (23)	0.8 (29)	0.4 (5)	0.9 (10)	0.3 (3)	0.8 (7)
Study 20110174						
	Placebo (81)	Romosozumab (163)	Placebo (18)	Romosozumab (23)	Placebo (32)	Romosozumab (50)
All adverse events	80.2 (65)	75.5 (123)	72.2 (13)	65.2 (15)	87.5 (28)	76.0 (38)
All adverse reactions	8.6 (7)	11.7 (19)	0 (0)	8.7 (2)	6.3 (2)	12.0 (6)
Serious adverse events	12.3 (10)	12.9 (21)	22.2 (4)	0 (0)	15.6 (5)	12.0 (6)
Adverse events leading to treatment discontinuation	1.2 (1)	3.1 (5)	5.6 (1)	0 (0)	3.1 (1)	2.0 (1)
Deaths	1.2 (1)	0.6 (1)	5.6 (1)	0 (0)	3.1 (1)	2.0 (1)

Incidence, % (number of subjects)
a) See the footnote b) of Table 75.
b) See the footnote c) of Table 75.

The patient population excluded in Study 20070337 (i.e., patients with a BMD T-score of ≤−3.5 at the proximal femur or femoral neck or patients with a history of proximal femur fracture) was included in Foreign Study 20080289[50)] in postmenopausal women with osteoporosis with a high risk of fracture. In the subgroup with a history of proximal femur fracture or with BMD T-score of ≤−3.5 at the proximal femur or femoral neck, the percentage change from baseline in BMD at Month 6 and Month 12 at the proximal femur, femoral neck, or lumbar vertebrae was slightly greater than that in the remaining subgroups (subjects with no history of proximal femur fracture, and BMD T-score >−3.5 at the proximal femur and femoral neck). The percentage change from baseline in BMD was greater in the romosozumab group than in the teriparatide group in all subgroups (Table 79).

Table 79. Percentage change from baseline in BMD in the subgroup with a history of proximal femur fracture, or with a BMD T-score of ≤−3.5 (Study 20080289)

		Subgroup with history of proximal femur fracture, or with BMD T-score ≤−3.5		Other subgroups	
		Romosozumab (19)	Teriparatide (20)	Romosozumab (199)	Teriparatide (198)
Proximal femur	Baseline T-score	−3.4 ± 0.5 (18)	−3.2 ± 0.9 (20)	−2.1 ± 0.7 (189)	−2.1 ± 0.6 (189)
	Change from baseline at Month 6 (%)	2.8 [0.7, 4.8] (17)	1.2 [−0.7, 3.2] (20)	2.2 [1.8, 2.6] (186)	−1.0 [−1.4, −0.6] (183)
	Change from baseline at Month 12 (%)	4.4 [2.3, 6.5] (17)	2.2 [0.2, 4.2] (18)	2.7 [2.2, 3.1] (180)	−0.8 [−1.2, −0.3] (184)
Femoral neck	Baseline T-score	−3.5 ± 0.5 (18)	−3.3 ± 0.8 (20)	−2.4 ± 0.6 (188)	−2.3 ± 0.6 (189)
	Change from baseline at Month 6 (%)	2.6 [0.2, 5.1] (17)	0.5 [−1.8, 2.7] (20)	2.0 [1.4, 2.6] (186)	−1.2 [−1.8, −0.6] (183)
	Change from baseline at Month 12 (%)	4.1 [1.3, 6.9] (17)	3.3 [0.6, 5.9] (18)	3.1 [2.4, 3.7] (180)	−0.6 [−1.2, 0.0] (184)
Lumbar vertebrae (L1-L4)	Baseline T-score	−3.3 ± 1.1 (18)	−3.5 ± 1.3 (20s)	−2.8 ± 1.1 (188)	−2.8 ± 1.0 (189)
	Change from baseline at Month 6 (%)	7.9 [4.9, 10.9] (18)	5.1 [2.2, 8.0] (19)	7.2 [6.6, 7.8] (185)	3.3 [2.7, 3.9] (185)
	Change from baseline at Month 12 (%)	10.0 [6.8, 13.2] (17)	8.1 [5.0, 11.1] (18)	9.8 [9.1, 10.5] (180)	5.1 [4.4, 5.8] (183)

Mean ± standard deviation; least squares mean [95% CI] (number of subjects evaluated)

Based on the above, romosozumab reduces the risk of fracture regardless of its extent, without making difference in safety. It is important to increase bone volume and reduce fracture risk quickly, particularly in patients with a high risk of fracture. Therefore, “osteoporosis with a high risk of fracture” appropriately describes the indication of romosozumab.

PMDA’s view on the clinical positioning and indication:
The global phase III study (Study 20070337) in postmenopausal women with osteoporosis demonstrated that romosozumab is effective in reducing the risk of new vertebral fracture. Romosozumab is also expected to have efficacy to a certain extent in men with osteoporosis [see Section “7.R.1 Efficacy”]. The safety in the use of romosozumab in postmenopausal women with osteoporosis and men with osteoporosis is acceptable with appropriate cautionary advice given to healthcare professionals [see Section “7.R.2 Safety”]. Accordingly, romosozumab is expected to be a new treatment option for patients with osteoporosis.

In the explanation about the reason for defining the indication of romosozumab as “osteoporosis with a high risk of fracture,” the applicant asserted the importance of early increase in bone volume and fracture risk mitigation particularly in patients with a high risk of fracture, which is acceptable. Furthermore, the safety profiles in relation to cardiovascular events in romosozumab-treated patients are clinically acceptable, but serious cardiovascular events were reported in Foreign Study 20110142 [see Section “7.R.2.6 Cardiovascular events”]. Given this, the applicant’s explanation that romosozumab is particularly useful in patients with a relatively high risk of fracture is fairly reasonable.

Study 20070337, a pivotal confirmatory study of romosozumab, was conducted in postmenopausal women with osteoporosis without taking into account the level of fracture risk. In addition, the trends towards an increase in BMD and a decrease in the incidence of fracture were observed consistently in both the subgroups

with a high risk of fracture and in the entire study population in this study, and the safety profile of romosozumab did not differ significantly. Whether “a high risk of fracture” should be added to the indication will be finalized taking into account the comments from the Expert Discussion.

7.R.4 Dosage and administration

7.R.4.1 Dosage and administration and treatment duration

The applicant’s explanation:

Among the romosozumab Q1M groups in the foreign phase II study (Study 20060326), the increase in BMD at the lumbar vertebrae, proximal femur, and femoral neck was greater in the romosozumab 210 mg Q1M group than in the 70 mg Q1M and 140 mg Q1M groups. Bone formation markers (serum P1NP, serum BAP, and serum OC) also indicated highest increase in the 210 mg Q1M group, and the values remained above baseline for the longest time in this group. Conversely, there was only a weak dose-dependent decrease in bone resorption marker (serum CTX). These findings suggest that, in once-a-month treatment, although the romosozumab 210 mg regimen had a strong effect on the promotion of bone formation as compared with the romosozumab 140 mg regimen, there was no dose-dependent inhibitory effect on bone resorption. To evaluate the dose interval, the Q3M group and Q1M group in Study 20060326 were compared. The percentage change in BMD and bone turnover markers in the romosozumab 140 mg Q3M and 210 mg Q3M groups was lower than that in the romosozumab 140 mg Q1M and 210 mg Q1M groups. Data were similar between the 210 mg Q3M group and the 70 mg Q1M group. There were no trends towards an increase in the incidence of adverse events in the romosozumab 210 mg Q1M group as compared with other dose levels of the once-a-month treatment groups or the once every 3 months treatment groups [see Section “7.1.2 Foreign phase II study”].

In the foreign phase II study (Study 20060326), during the initial treatment phase (Months 0-24), the increases in BMD at the lumbar vertebrae, proximal femur, and femoral neck were maintained up to Month 24 in all romosozumab Q1M groups, with the degree of increase more significant in the first 12 months (

Table 80). Bone formation markers (serum P1NP, serum BAP, and serum OC) peaked at Month 1, then decreased to near baseline or below baseline levels at Months 9 to 12, and thereafter remained at these levels throughout the treatment period. The bone resorption marker (serum CTX) overall remained below baseline levels up to Month 24 (Table 81).

These findings suggest that romosozumab promotes bone formation and inhibits bone resorption most significantly in the first 12 months after the start of treatment. As shown in Table 82, the incidence of adverse events during Months 0 to 12 and Months 12 to 24 in Study 20060326 did not indicate any safety concerns associated with extension of treatment duration.

Based on these findings, the regimen of romosozumab 210 mg once a month for 12 months was chosen for phase II studies conducted thereafter, the retreatment phase of Study 20060326, and phase III studies.

Table 80. Percentage change from baseline in BMD at the lumbar vertebrae up to Month 24 (%) (Study 20060326)

Evaluation time point	Placebo (50)	Romosozumab 70 mg Q1M (49)	Romosozumab 140 mg Q1M (48)	Romosozumab 210 mg Q1M (50)
Month 3	0.5 [−0.4, 1.4] (50)	1.9 [1.0, 2.8] (49)	4.4 [3.5, 5.3] (48)	4.5 [3.6, 5.4] (50)
Month 6	0.2 [−0.8, 1.2] (49)	4.0 [3.0, 5.1] (43)	7.0 [6.0, 8.1] (47)	8.2 [7.2, 9.2] (50)
Month 12	−0.1 [−1.2, 1.0] (48)	5.3 [4.2, 6.4] (44)	9.0 [7.9, 10.2] (46)	11.3 [10.2, 12.4] (48)
Month 18	0.2 [−0.9, 1.4] (46)	5.8 [4.6, 7.0] (43)	10.9 [9.6, 12.1] (44)	13.0 [11.8, 14.1] (47)
Month 24	0.5 [−0.8, 1.8] (46)	6.9 [5.6, 8.3] (38)	12.5 [11.2, 13.9] (43)	15.1 [13.8, 16.4] (48)

Least squares mean [95% CI] (number of subjects evaluated)

Table 81. Time course of the percentage change from baseline in bone turnover markers (%) (Study 20060326; efficacy analysis set)

Bone turnover marker	Evaluation time point	Week 1	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24
Bone formation marker	Serum P1NP	81.7 ± 28.2 (50)	97.7 ± 56.8 (50)	31.3 ± 44.0 (50)	11.1 ± 39.4 (50)	0.5 ± 49.0 (49)	−11.8 ± 43.2 (48)	−19.0 ± 29.9 (48)	−22.7 ± 31.2 (43)
	Serum BAP	17.7 ± 15.7 (50)	63.5 ± 34.5 (50)	31.8 ± 39.4 (50)	17.8 ± 31.5 (49)	14.4 ± 35.7 (49)	12.7 ± 35.7 (48)	13.8 ± 32.0 (48)	9.1 ± 31.1 (43)
	Serum OC	8.8 ± 20.6 (50)	83.3 ± 50.0 (50)	50.3 ± 54.9 (50)	14.6 ± 38.1 (49)	0.7 ± 35.7 (49)	−8.3 ± 38.7 (48)	−16.1 ± 38.6 (48)	−21.2 ± 25.8 (43)
Bone resorption marker	Serum CTX	−41.8 ± 16.9 (50)	−26.0 ± 21.7 (50)	0.0 ± 29.4 (50)	−3.7 ± 34.9 (50)	−9.6 ± 44.5 (49)	−13.9 ± 53.7 (48)	−15.3 ± 40.3 (48)	2.1 ± 47.0 (43)

Mean ± standard deviation (number of subjects evaluated)

Table 82. Incidence of adverse events in Months 0-12 and Months 12-24 (Study 20060326)

	Months 0-12			Months 12-24		
	Placebo (50)	Romosozumab 210 mg Q1M (51)	Romosozumab -treated total (255)	Placebo (43)	Romosozumab 210 mg Q1M (46)	Romosozumab -treated total (226)
All adverse events	90.0 (45)	82.4 (42)	86.7 (221)	83.7 (36)	80.4 (37)	86.7 (196)
All adverse reactions	12.0 (6)	13.7 (7)	23.5 (60)	2.3 (1)	2.2 (1)	4.0 (9)
Serious adverse events	14.0 (7)	9.8 (5)	6.7 (17)	7.0 (3)	2.2 (1)	8.4 (19)
Adverse events leading to treatment discontinuation	4.0 (2)	3.9 (2)	2.4 (6)	2.3 (1)	2.2 (1)	2.7 (6)
Adverse events leading to study withdrawal	0 (0)	0 (0)	0.4 (1)	0 (0)	0 (0)	0.9 (2)
Deaths	2.0 (1)	0 (0)	0.4 (1)	0 (0)	0 (0)	0 (0)
Hypocalcaemia-related events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SMQ “hypersensitivity”	8.0 (4)	7.8 (4)	9.0 (23)	7.0 (3)	4.3 (2)	5.8 (13)
Injection site reaction-related events	4.0 (2)	5.9 (3)	12.5 (32)	0 (0)	0 (0)	4.0 (9)
SMQ “malignant or unspecified tumors”	4.0 (2)	2.0 (1)	0.8 (2)	2.3 (1)	2.2 (1)	1.3 (3)
Hyperostosis-related events	4.0 (2)	0 (0)	1.6 (4)	0 (0)	0 (0)	0.4 (1)
Osteoarthritis-related events	10.0 (5)	0 (0)	3.5 (9)	4.7 (2)	4.3 (2)	8.8 (20)

Incidence, % (number of subjects)

In the global phase III study (Study 20070337), the incidence of new vertebral fracture in subjects receiving romosozumab 210 mg once a month for 12 months was evaluated. The results demonstrated that romosozumab was effective in reducing the risk of fracture. In the global phase III study (Study 20110174) in men with osteoporosis, the percentage change from baseline in BMD at the lumbar vertebrae in subjects receiving romosozumab 210 mg once a month for 12 months was significantly higher than in those receiving placebo, indicating that romosozumab increased BMD in men as did in women [see Section “7.R.1 Efficacy”].

In Japanese subjects, in the Japanese phase II study (Study 20101291), similarly to the foreign phase II study (Study 20060326), a once-a-month dose of romosozumab 210 mg was found to be the optimum regimen to achieve maximum efficacy without increasing adverse events. Furthermore, in the global phase III study (Study 20070337) in postmenopausal women with osteoporosis, a comparison of the reduction in the risk of fracture in subjects receiving romosozumab 210 mg once a month for 12 months was performed between the Japanese subpopulation and the entire study population. The results were consistent between the populations (Table 38 and 40). In the global phase III study (Study 20110174) in men with osteoporosis, the percentage change from baseline in BMD at the lumbar vertebrae in subjects receiving romosozumab 210 mg once a month for 12 months was similar between the Japanese subpopulation and the entire study population (Table 44). Based on these findings, it is appropriate to select the regimen of romosozumab 210 mg once a month for 12 months for the treatment of Japanese patients with osteoporosis. In the application, the applicant specified “once a month for 12 times” in the “Proposed Dosage and Administration” section; however, this was modified to “once a month for 12 months” in the reviewing process.

Because the specified treatment duration for romosozumab is 12 months, PMDA asked the applicant to explain about the need for other pharmacotherapy after the completion of romosozumab therapy and selection of medications.

The applicant’s explanation:
In Study 20060326 in subjects receiving romosozumab during the initial treatment phase (Months 0-24) and placebo during the denosumab treatment phase, the BMD at the lumbar vertebrae, proximal femur, and femoral neck increased in the initial treatment phase, and then decreased (Figure 5). Among bone turnover markers, serum P1NP decreased to below baseline at Month 24, and returned to near baseline by Month 36. Serum CTX was near baseline levels at Month 24, increased to above baseline when receiving placebo, and then returned to near baseline by Month 36 (Figure 6). In the follow-on phase (Months 48-72), similar trends were observed in subjects of the “no-intervention” group. The effects of romosozumab on BMD and bone turnover markers were reversible. In contrast, in subjects receiving romosozumab during the initial treatment phase (Months 0-24) and denosumab during the denosumab treatment phase, bone formation and bone resorption markers decreased and BMD continuously increased (Figures 5 and 6). Based on these findings, it is necessary to continue treatment of osteoporosis after treatment with romosozumab. There have been reports of transient above-baseline increases in bone resorption markers, decreases in BMD, and multiple vertebral fractures after the discontinuation of denosumab, an antiresorptive agent. To estimate the risk of fracture after discontinuation of romosozumab therapy, the incidence of fracture during the denosumab treatment phase in Study 20060326 was evaluated. The incidence was 3.9% (5 of 127) in the romosozumab/placebo group, and 3.2% (4 of 125) in the romosozumab/Dmab group, with no significant differences between the groups. Vertebral fracture was reported in 2 subjects in the romosozumab/Dmab group; however, no multiple vertebral fracture was reported in either of the groups. As for the selection of medication following romosozumab therapy, in Studies 20060326 and 20070337, it was possible to maintain BMD by switching to denosumab or zoledronic acid, antiresorptive agents (Tables 25 and 34). Although

other osteoporotic drugs (e.g., selective estrogen receptor modulators and activated vitamin D_3 formulations) have not been evaluated, these agents are assumed to be useful in mitigating increased bone resorption following discontinuation of romosozumab therapy. However, the efficacy and safety of treatment followed by teriparatide, a bone anabolic agent, are unknown.

Accordingly, the package insert will remind possible decrease in BMD after discontinuation of romosozumab and advise healthcare professionals to continue with an appropriate osteoporosis therapy after the completion of romosozumab therapy.

PMDA's view:
The dosage regimen of romosozumab
In the foreign phase II study (Study 20060326), there were no trends towards increased incidence of adverse events in the romosozumab 210 mg Q1M group as compared with other dose levels of the once-a-month treatment groups or the once every 3 months treatment groups. In Study 20060326 and the Japanese phase II study (Study 20101291), the increase in BMD was greater in the romosozumab 210 mg Q1M group than in the 70 mg Q1M and 140 mg Q1M groups. In the global phase III study (Study 20070337), the incidence of new vertebral fracture up to Month 12 in subjects receiving romosozumab 210 mg once a month was evaluated. The results demonstrated that romosozumab group was superior to placebo. Given these results, a once-a-month dose of romosozumab 210 mg is the appropriate regimen.

The treatment duration of romosozumab
In the foreign phase II study (Study 20060326), BMD increased following romosozumab 210 mg once a month for 24 months, and there were no particular safety problems. In contrast, based on the time course of bone formation markers, the applicant concluded that the pharmacological action of romosozumab is expected to be most effective in the first 12 months of treatment. Accordingly, a phase III study was conducted with a treatment period of 12 months, and the results demonstrated the efficacy of romosozumab. Therefore, a treatment duration of 12 months is acceptable. The applicant intends to remind in the package insert of possible changes in BMD and bone turnover markers after discontinuation of romosozumab as well as the need for an appropriate osteoporosis therapy after the completion of the 12-month romosozumab therapy, which is also agreeable. The appropriateness of the dosage regimen and cautionary statements will be finalized taking into account the comments from the Expert Discussion.

7.R.4.2 Retreatment

The applicant's explanation:
Table 83 shows the percentage change from the start of the retreatment phase (Months 36-48) in BMD at the lumbar vertebrae during the phase in Study 20060326. In subjects receiving placebo during the denosumab treatment phase (Months 24-36), BMD at the lumbar vertebrae increased in the retreatment phase as in the initial treatment phase of romosozumab (the percentage change from baseline in BMD at the lumbar vertebrae in the romosozumab 210 mg Q1M group during the initial treatment phase was 4.6 ± 3.2% [50

subjects] at Month 3, 8.3 ± 3.9% [50 subjects] at Month 6, and 11.3 ± 5.0% [49 subjects] at Month 12). In subjects receiving denosumab during the denosumab treatment phase, BMD at the lumbar vertebrae increased regardless of the treatment group in the initial treatment phase (Months 0-24), while the percentage increase in BMD was smaller than that in subjects receiving placebo during the denosumab phase. The time course data show that the greatest percentage change from baseline in BMD at the lumbar vertebrae occurred in subjects receiving romosozumab or denosumab for 48 months throughout the study period (Table 84). The percentage change in BMD at the proximal femur and femoral neck during the retreatment phase showed similar trends as the BMD at the lumbar vertebrae.

Table 83. Time course of the percentage change from the start of retreatment phase (Month 36) up to the end of the retreatment phase in BMD at the lumbar vertebrae (L1-L4) (%) (Study 20060326)

Initial treatment phase (Months 0-24)	Placebo		Romosozumab	
Denosumab treatment phase (Months 24-36)	Placebo	Dmab	Placebo	Dmab
Retreatment phase (Months 36-48)	Romosozumab 210 mg (12)	Romosozumab 210 mg (16)	Romosozumab 210 mg (72)	Romosozumab 210 mg (67)
T-score at the start of retreatment phase (Month 36)	−2.13 ± 0.70 (12)	−2.01 ± 0.48 (16)	−2.15 ± 0.75 (72)	−1.37 ± 0.87 (67)
Month 39	2.5 ± 3.3 (11)	1.6 ± 2.6 (16)	6.6 ± 3.1 (70)	0.0 ± 2.5 (65)
Month 42	6.0 ± 4.2 (11)	2.5 ± 2.4 (14)	9.6 ± 3.4 (67)	0.2 ± 3.0 (63)
Month 48	9.1 ± 4.5 (11)	5.3 ± 3.5 (13)	13.1 ± 4.0 (64)	2.4 ± 3.7 (62)

Mean ± standard deviation (number of subjects evaluated); Dmab, denosumab (genetical recombination)

Table 84. Time course of the percentage change from baseline up to the end of the retreatment phase in BMD at the lumbar vertebrae (L1-L4) (%) (Study 20060326)

Initial treatment phase (Months 0-24)	Placebo		Romosozumab	
Denosumab treatment phase (Months 24-36)	Placebo	Dmab	Placebo	Dmab
Retreatment phase (Months 36-48)	Romosozumab 210 mg (12)	Romosozumab 210 mg (16)	Romosozumab 210 mg (72)	Romosozumab 210 mg (67)
Baseline T-score	−2.29 ± 0.62 (12)	−2.35 ± 0.44 (16)	−2.35 ± 0.65 (72)	−2.42 ± 0.59 (67)
Month 12	0.2 ± 2.4 (12)	−0.1 ± 2.6 (16)	8.4 ± 4.7 (71)	8.0 ± 4.5 (67)
Month 24	2.7 ± 3.9 (12)	−0.8 ± 3.7 (16)	11.0 ± 5.7 (72)	10.6 ± 5.6 (66)
Month 36	2.3 ± 4.1 (12)	4.5 ± 2.9 (16)	2.8 ± 4.9 (72)	14.4 ± 6.3 (67)
Month 39	4.7 ± 5.5 (10)	6.1 ± 3.3 (16)	9.0 ± 5.3 (63)	14.2 ± 5.6 (63)
Month 42	8.0 ± 6.6 (10)	6.8 ± 2.6 (14)	11.9 ± 5.7 (60)	14.4 ± 6.0 (61)
Month 48	11.4 ± 5.7 (10)	9.8 ± 4.3 (13)	15.9 ± 6.8 (57)	17.3 ± 6.8 (60)

Mean ± standard deviation (number of subjects evaluated); Dmab, denosumab (genetical recombination)

Figure 6 shows the time course of the percentage change from baseline in bone turnover markers during the retreatment phase. Romosozumab increased bone formation markers regardless of the treatment groups during the initial treatment phase and denosumab treatment phase. In subjects receiving placebo during the denosumab treatment phase, a rapid increase in serum P1NP and decrease in serum CTX were noted. In the retreatment phase, the markers exhibited similar changes as in the initial treatment phase. In subjects receiving denosumab during the denosumab treatment phase, the serum P1NP and serum CTX levels decreased during the denosumab treatment phase first, and gradually started increasing during the retreatment phase, reaching near baseline levels by Month 42. Thereafter, the serum P1NP levels continuously increased up to Month 48, while the serum CTX levels remained near baseline.

Data from Study 20060326 demonstrated that the increase in BMD and change in bone turnover markers in subjects receiving romosozumab as retreatment after 12-month placebo treatment were similar to those in

subjects receiving romosozumab as initial treatment. In addition, BMD increase from the start of the retreatment phase in subjects receiving romosozumab as retreatment after 12-month denosumab treatment was less than that in subjects receiving romosozumab as initial treatment. However, the increase in BMD from baseline at the end of the retreatment phase (Month 48) was greater than that in subjects receiving romosozumab as retreatment after placebo treatment.

Table 85 outlines the incidence of adverse events in the retreatment phase (Months 36-48), showing no differences based on romosozumab therapy history. No new deaths occurred during the retreatment phase. In the group with a history of romosozumab therapy, CTCAE Grade 1 decrease in albumin-corrected serum calcium level occurred in 1 subject. However, the event was not assessed as a hypocalcaemia-related event and resolved without treatment.

Based on the data from Study 20060326, the safety profiles of romosozumab retreatment were not considered to differ markedly from those of initial romosozumab therapy.

Table 85. Incidence of adverse events during the retreatment phase (Months 36-48) (safety analysis set)

Initial treatment phase (Months 0-24)	Placebo			Romosozumab			Entire study population
Denosumab treatment phase (Months 24-36)	Placebo	Dmab	Total (27)	Placebo	Dmab	Total (140)	
Retreatment phase (Months 36-48)	Romosozumab 210 mg (12)	Romosozumab 210 mg (15)		Romosozumab 210 mg (72)	Romosozumab 210 mg (68)		Romosozumab 210 mg (167)
All adverse events	100.0 (12)	80.0 (12)	88.9 (24)	83.3 (60)	85.3 (58)	84.3 (118)	85.0 (142)
All adverse reactions	0 (0)	20.0 (3)	11.1 (3)	13.9 (10)	13.2 (9)	13.6 (19)	13.2 (22)
Serious adverse events	0 (0)	6.7 (1)	3.7 (1)	5.6 (4)	4.4 (3)	5.0 (7)	4.8 (8)
Adverse events leading to treatment discontinuation	0 (0)	6.7 (1)	3.7 (1)	4.2 (3)	1.5 (1)	2.9 (4)	3.0 (5)
Adverse events leading to study withdrawal	0 (0)	6.7 (1)	3.7 (1)	4.2 (3)	1.5 (1)	2.9 (4)	3.0 (5)
Hypocalcaemia-related events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SMQ “hypersensitivity”	8.3 (1)	6.7 (1)	7.4 (2)	6.9 (5)	8.8 (6)	7.9 (11)	7.8 (13)
Injection site reaction-related events	0 (0)	13.3 (2)	7.4 (2)	8.3 (6)	5.9 (4)	7.1 (10)	7.2 (12)
Hyperostosis-related events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence, % (number of subjects); MedDRA ver.18.1; final analysis; Dmab, denosumab (genetical recombination)

Based on the above findings, following 12-month initial treatment with romosozumab, if treatment is discontinued or treatment is switched to other osteoporotic drugs, and then the subject was diagnosed to be at high risk of fracture again, romosozumab retreatment is considered to be an effective option from the standpoints of efficacy and safety.

PMDA’s view:

Although only a limited number of subjects received retreatment with romosozumab in the clinical studies, there are no particular concerns regarding the efficacy and safety of romosozumab in the retreatment phase as compared with those in the initial treatment phase. While very little is known regarding the optimal timing for retreatment, there are no compelling reasons for restricting retreatment with romosozumab in patients who are found to require retreatment, provided that appropriate osteoporotic treatment was given to the

patient following initial romosozumab therapy. The above issues will be finalized taking into account the comments from the Expert Discussion.

7.R.4.3 Initial loading of high dose vitamin D

The applicant's explanation:

In the initial treatment phase of Study 20060326 in postmenopausal women with low BMD, BMD increased rapidly after administration of romosozumab. At the time, albumin-corrected serum calcium level decreased slightly within the reference range and remained stable, while serum iPTH level rose in a transient manner, suggesting a compensatory response to increases in calcium and other mineral demand associated with bone volume increase. Taking these results into consideration, in the retreatment phase of Study 20060326 and the phase III studies (Studies 20070337 and 20110174), the initial loading dose of vitamin D were administered to promote intestinal absorption of calcium, increase calcium use for mineralization, and suppress any compensatory and transient serum iPTH increase in the early stage of bone volume increase following administration of romosozumab, thereby maximizing the efficacy of romosozumab. Subjects with a screening serum 25(OH) vitamin D level of ≥20 ng/mL and ≤40 ng/mL were to receive 50,000 to 60,000 IU of vitamin D within 1 week of the first dose of study drug treatment. If the screening serum 25(OH) vitamin D level was >40 ng/mL, the initial loading dose was administered at the investigator's discretion. In Study 20060326 and the phase III studies (Studies 20070337 and 20110174), calcium and vitamin D were also administered as base treatment drugs throughout the study period, separately from the initial loading dose.

Table 86 shows the percentage change from baseline in albumin-corrected serum calcium level in studies in which initial vitamin D loading was performed (Studies 20070337 and 20110174), and in studies in which initial loading was not performed (the initial treatment phase of Study 20060326, and Study 20101291). Albumin-corrected serum calcium reached lowest level by Month 1, and there were no significant differences in percentage change between the studies with or without initial vitamin D loading.

Table 86. Percentage change from baseline in albumin-corrected serum calcium level following administration of romosozumab 210 mg once a month (%) (Studies 20101291, 20060326, 20070337, and 20110174)

		Baseline	Day 7	Month 1	Month 3	Month 6	Month 12
Without initial loading of vitamin D	Study 20101291	9.30 (8.7, 10.1) (63)	−1.1 (−12.2, 3.2) (63)	−3.2 (−11.5, 7.9) (63)	−2.2 (−11.2, 6.5) (60)	−1.1 (−10.5, 9.2) (60)	1.1 (−7.9, 8.9) (59)
	Study 20060326	9.60 (8.9, 10.3) (51)	—	−3.1 (−8.2, 10.1) (49)	−3.1 (−13.0, 10.1) (49)	−1.6 (−6.3, 10.1) (50)	0.0 (−6.2, 13.8) (48)
With initial loading of vitamin D	Study 20070337	9.70 (7.9, 12.9) (3581)	—	−2.2 (−22.0, 26.6) (3425)	−2.1 (−27.6, 22.5) (3337)	−1.0 (−22.8, 20.3) (3242)	−1.0 (−22.0, 26.2) (3124)
	Study 20110174	9.60 (8.4, 10.5) (163)	—	−2.1 (−17.7, 7.5) (160)	—	−2.0 (−10.6, 12.1) (154)	−1.1 (−9.4, 7.8) (147)

Unit, mg/dL; median (minimum, maximum) (number of subjects evaluated); —, not calculated

The effects of initial vitamin D loading in Study 20070337 on efficacy and safety were evaluated. In the entire study population of Study 20070337, of subjects with a baseline serum 25(OH) vitamin D level of ≥20 ng/mL and ≤40 ng/mL, 83.0% (2711 of 3267) in the placebo group and 83.2% (2708 of 3254) in the

romosozumab group received an initial vitamin D loading dose, and 17.0% (556 of 3267) in the placebo group and 16.8% (546 of 3254) in the romosozumab group did not receive an initial vitamin D loading dose. Of subjects with a baseline serum 25(OH) vitamin D level of >40 ng/mL, 21.3% (67 of 315) in the placebo group and 19.2% (62 of 323) in the romosozumab group received an initial vitamin D loading dose, and 78.7% (248 of 315) in the placebo group and 80.8% (261 of 323) in the romosozumab group did not receive an initial vitamin D loading dose. Two of 3591 subjects in the placebo group and 4 of 3589 subjects in the romosozumab group had a baseline serum 25(OH) vitamin D level of <20 ng/mL. Of these, 2 in the romosozumab group received an initial vitamin D loading dose.

Table 87 shows the efficacy of romosozumab with or without initial vitamin D loading. The incidence of new vertebral fracture in Study 20070337 decreased regardless of initial vitamin D loading (Table 87).

Table 87. Incidence of new vertebral fracture with or without initial vitamin D loading (Study 20070337)

	With initial loading			Without initial loading		
	Placebo	Romosozumab	Risk ratio[a)] [95% CI]	Placebo	Romosozumab	Risk ratio[a)] [95% CI]
12 months after start of study	1.8 (47/2582)	0.5 (12/2568)	0.25 [0.14, 0.48]	1.6 (12/740)	0.5 (4/753)	0.33 [0.11, 1.02]
24 months after start of study	2.7 (69/2586)	0.6 (16/2571)	0.23 [0.13, 0.40]	2.0 (15/741)	0.7 (5/754)	0.33 [0.12, 0.90]

Incidence of new vertebral fracture, % (number of subjects with fractures/number of subjects evaluated)
a) Based on the Mantel-Haenszel method stratified by age and prevalent vertebral fracture.

Table 88 shows the percentage change from baseline in BMD at the lumbar vertebrae at Month 12 with or without initial vitamin D loading, indicating that initial vitamin D loading did not affect the percentage change from baseline in BMD in any study or any site evaluated. Similar trends were observed in the percentage change from baseline in BMD at the proximal femur and femoral neck.

Table 88. Percentage change from baseline in BMD at the lumbar vertebrae (L1-L4) at Month 12 with or without initial vitamin D loading (%)

Clinical study	Evaluation time point	With initial loading		Without initial loading	
		Placebo	Romosozumab	Placebo	Romosozumab
20070337	Baseline T-score	−2.71 ± 1.03 (2461)	−2.70 ± 1.04 (2440)	−2.74 ± 1.06 (687)	−2.82 ± 1.02 (711)
	Month 12	0.3 [0.2, 0.5] (2461)	13.0 [12.8, 13.3] (2440)	0.6 [0.3, 0.9] (687)	13.2 [12.7, 13.6] (711)
20110174	Baseline T-score	−2.24 ± 1.49 (62)	−2.24 ± 1.16 (115)	−2.57 ± 1.22 (17)	−2.06 ± 1.17 (42)
	Month 12	1.2 [0.0, 2.3] (62)	11.6 [10.6, 12.5] (115)	1.3 [−1.0, 3.6] (17)	13.3 [11.0, 15.6] (42)

Mean ± standard deviation; least squares mean [95% CI] (number of subjects evaluated); LOCF

Table 89 shows the safety of romosozumab with or without initial vitamin D loading. The incidences of adverse events in Study 20070337 indicate no significant differences by initial vitamin D loading status.

Table 89. Incidence of adverse events by with or without initial loading of high dose vitamin D (Study 20070337, for 12 months)

	With initial loading		Without initial loading	
	Placebo (2772)	Romosozumab (2774)	Placebo (804)	Romosozumab (807)
All adverse events	80.0 (2217)	78.8 (2187)	78.7 (633)	76.7 (619)
All adverse reactions	14.0 (388)	17.1 (475)	13.2 (106)	15.0 (121)
Serious adverse events	8.6 (239)	9.4 (262)	9.1 (73)	10.2 (82)
Adverse events leading to treatment discontinuation	2.6 (72)	2.8 (78)	2.7 (22)	3.1 (25)
Adverse events leading to study withdrawal	1.3 (37)	1.3 (36)	1.6 (13)	1.0 (8)
Deaths	0.6 (18)	0.8 (21)	0.6 (5)	1.0 (8)
Hypocalcaemia-related events	0 (0)	0 (0)	0 (0)	0.1 (1)

Incidence, % (number of subjects)

Table 90 shows the percentage change from baseline in albumin-corrected serum calcium and serum iPTH levels in the target population in the bone turnover marker substudy[53)] in Study 20070337. After the start of romosozumab therapy, a transient decrease in albumin-corrected serum calcium level, and a transient increase in serum iPTH levels were observed; however, there were no significant differences regardless of initial vitamin D loading. In the calcium substudy,[54)] albumin-corrected serum calcium level slightly decreased in the romosozumab group on Day 14 regardless of initial vitamin D loading. The percentage change (median) was −2.1% (531 subjects) with initial vitamin D loading, and −2.1% (125 subjects) without initial loading, and gradually returned to near baseline levels by Month 12.

Table 90. Percentage change from baseline in albumin-corrected serum calcium and serum iPTH levels with or without initial vitamin D loading (%) (Study 20070337; bone turnover marker substudy)

Albumin-corrected serum calcium (mg/dL)				
	With initial loading		Without initial loading	
Evaluation time point	Placebo (48)	Romosozumab (40)	Placebo (17)	Romosozumab (24)
Baseline	9.7 (8.7, 10.5) (48)	9.7 (8.7, 10.5) (40)	9.8 (8.9, 10.5) (17)	9.6 (9.0, 10.5) (24)
Day 14	0.0 (−6.2, 9.2) (43)	−3.1 (−10.3, 4.7) (34)	0.0 (−8.7, 2.6) (15)	−2.1 (−7.6, 4.2) (22)
Month 1	0.0 (−8.1, 13.8) (48)	−3.1 (−10.0, 7.1) (39)	−0.5 (−9.6, 1.1) (16)	−3.0 (−9.6, 2.2) (21)
Month 3	0.3 (−8.2, 10.3) (46)	−2.1 (−11.0, 4.3) (36)	0.0 (−3.9, 5.1) (15)	−2.1 (−9.5, 2.1) (22)
Month 3 + 14 days	−0.5 (−6.1, 11.5) (44)	−2.1 (−9.7, 5.2) (36)	−1.0 (−5.8, 5.6) (13)	−2.0 (−9.5, 3.3) (21)
Month 6	0.0 (−7.2, 11.5) (45)	−1.5 (−6.2, 5.3) (39)	−1.5 (−7.8, 5.2) (14)	−2.1 (−7.3, 2.2) (23)
Month 6 + 14 days	1.0 (−9.1, 9.2) (40)	−1.0 (−8.4, 6.1) (36)	0.0 (−9.5, 7.2) (14)	−1.0 (−5.7, 4.3) (20)
Month 12	0.0 (−8.1, 8.0) (45)	−1.0 (−8.4, 10.3) (38)	−1.0 (−7.2, 6.7) (16)	−1.0 (−11.4, 3.1) (22)
Serum iPTH (pg/mL)				
	With initial loading		Without initial loading	
Evaluation time point	Placebo (42)	Romosozumab (38)	Placebo (15)	Romosozumab (19)
Baseline	44.7 (14.0, 111.2) (42)	43.2 (10.5, 207.5) (38)	33.2 (18.9, 84.2) (15)	45.2 (12.3, 108.9) (19)
Day 14	0.0 (−42.3, 176.8) (39)	48.4 (−25.2, 197.3) (33)	28.2 (−33.0, 210.2) (13)	32.3 (−18.6, 156.8) (17)
Month 1	0.1 (−49.0, 152.1) (40)	32.4 (−18.9, 499.0) (36)	19.0 (−51.4, 185.0) (14)	40.4 (−14.4, 121.6) (15)
Month 3	5.2 (−37.4, 93.5) (39)	28.9 (−25.8, 308.3) (35)	21.9 (−50.7, 85.7) (12)	51.0 (−18.7, 153.4) (16)
Month 3 + 14 days	6.1 (−36.9, 86.5) (39)	48.6 (−16.3, 633.2) (33)	16.4 (−24.1, 64.9) (12)	55.5 (2.6, 114.1) (19 subjects)
Month 6	5.3 (−55.0, 94.2) (39)	27.2 (−32.0, 276.5) (36)	31.6 (−12.8, 69.9) (11)	32.9 (−37.8, 96.3) (17)
Month 6 + 14 days	7.4 (−53.2, 173.5) (37)	34.1 (−39.5, 457.6) (34)	26.9 (−5.8, 103.5) (13)	41.5 (−31.9, 98.2) (17)
Month 12	5.4 (−66.5, 117.8) (37)	29.8 (−54.0, 447.6) (33)	19.1 (−38.7, 92.5) (13)	31.2 (−36.7, 71.4) (16)

Median (minimum, maximum) (number of subjects evaluated)

In Study 20101291, in which initial vitamin D loading was not performed, decreases in albumin-corrected serum calcium level of CTCAE Grade ≥1 occurred in 1 subject in the romosozumab 70 mg group (Day 190) and 1 subject in the romosozumab 210 mg group (Day 57). Both were CTCAE Grade 1. During the initial treatment phase (Months 0-24) of Study 20060326, decreases in albumin-corrected serum calcium level of CTCAE Grade ≥1 occurred only in 1 subject in the romosozumab 70 mg Q1M group (Month 9; CTCAE Grade 2). In Study 20070337, initial vitamin D loading was performed, and hypocalcaemia occurred only in 1 subject in the romosozumab group. However, the subject was found not to have received an initial vitamin D loading dose. In the calcium substudy[54)] of Study 20070337, among groups with initial vitamin D loading, decreases in albumin-corrected serum calcium level of CTCAE Grade ≥1 occurred in 0.1% (1 of 682) of subjects (CTCAE Grade 4) in the placebo group, and 0.5% (3 of 661) of subjects (CTCAE Grade 1 [2] and CTCAE Grade 2 [1]) in the romosozumab group. Among groups without initial vitamin D loading, decreases in albumin-corrected serum calcium level of CTCAE Grade ≥1 occurred in 0.6% (1 of 172) of subjects (CTCAE Grade 1) in the placebo group, and 1.7% (3 of 172) of subjects (CTCAE Grade 2 [3]) in the romosozumab group.

Based on these findings indicate no marked differences in efficacy or safety in clinical studies in and outside Japan regardless of initial vitamin D loading. In all studies, the extent of decrease in albumin-corrected serum calcium level was small following administration of romosozumab. The events were not accompanied by serious hypocalcaemia and were transient changes with increased compensatory serum iPTH levels. Therefore, in the use of romosozumab in the clinical settings, initial vitamin D loading may be omitted when vitamin D and calcium are supplemented as base treatment, as practiced in the used of other osteoporotic drugs.

PMDA's view:

As explained by the applicant, in the clinical studies of romosozumab, the extent of decrease in albumin-corrected serum calcium level was small after administration of romosozumab, even without initial vitamin D loading. This suggests that suitable supplementation of vitamin D and calcium throughout the study period may have prevented hypocalcaemia, which causes clinical problems. However, after administration of romosozumab, a compensatory increase in serum iPTH levels occurred and may have inhibited decreases in serum calcium. Therefore, hypocalcaemia or disorders of bone/mineral metabolism such as of magnesium and iPTH should be treated prior to romosozumab therapy, and this should be highlighted in the package insert. The above issues will be finalized taking into account the comments from the Expert Discussion.

7.R.5 Special populations

7.R.5.1 Patients with renal impairment

The applicant's explanation:

The incidence of new vertebral fracture by renal function[29)] (baseline eGFR [mL/min/1.73 m^2] classification of ≥30 and <60; ≥60 and <90; and ≥90]) in the global phase III study (Study 20070337) in postmenopausal women with osteoporosis is presented in Table 91. Baseline eGFR was not likely to affect the risk ratio for the decrease in the incidence of new vertebral fracture in the romosozumab group as compared to placebo. None of the enrolled subjects fell in the classification of <30 mL/min/1.73 m^2.

Table 91. Incidence of new vertebral fracture by renal function (Study 20070337; efficacy analysis set)

Renal function	Month 12			Month 24		
	Placebo	Romosozumab	Risk ratio[a)] [95% CI]	Placebo/Dmab	Romosozumab /Dmab	Risk ratio[a)] [95% CI]
30≤ eGFR <60	2.1 (12/581)	0.6 (4/664)	0.28 [0.09, 0.86]	3.3 (19/582)	0.9 (6/665)	0.27 [0.11, 0.66]
60≤ eGFR <90	1.5 (35/2337)	0.4 (10/2248)	0.30 [0.15, 0.60]	2.1 (49/2341)	0.5 (12/2249)	0.26 [0.14, 0.48]
90≤ eGFR	3.0 (12/396)	0.5 (2/400)	0.16 [0.04, 0.70]	4.0 (16/396)	0.7 (3/402)	0.18 [0.05, 0.60]

Incidence of fractures, % (number of subjects with fractures/number of subjects evaluated); LOCF; Dmab, denosumab (genetical recombination)
a) Based on the Mantel-Haenszel method stratified by age and prevalent vertebral fracture.

Table 92 shows the incidence of adverse events in the safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis by renal function (baseline eGFR classification, ≥15 and <30; ≥30 and <60; ≥60 and <90; and ≥90). Because there were only a few subjects in some subgroups, adequate evaluation is difficult. However, the incidence of adverse events, adverse reactions, serious adverse events, adverse events leading to treatment discontinuation,

adverse events leading to study withdrawal, adverse events resulting in deaths, and adverse events of interest was generally similar between treatment groups in each subgroup by renal function and between subgroups by renal function in each treatment group.

Table 92. Incidence of adverse events by renal function (pooled safety analysis set comprising subjects in the placebo and romosozumab 210 mg group)

	15≤ eGFR <30		30≤ eGFR <60		60≤ eGFR <90		90≤ eGFR	
	Placebo (8)	Romosozumab (10)	Placebo (635)	Romosozumab (740)	Placebo (2598)	Romosozumab (2475)	Placebo (447)	Romosozumab (470)
All adverse events	100.0 (8)	90.0 (9)	80.3 (510)	77.7 (575)	79.3 (2060)	77.9 (1928)	80.3 (359)	81.7 (384)
All adverse reactions	25.0 (2)	10.0 (1)	14.8 (94)	15.1 (112)	13.5 (352)	17.0 (421)	11.6 (52)	14.9 (70)
Serious adverse events	25.0 (2)	20.0 (2)	10.7 (68)	12.8 (95)	8.7 (226)	8.6 (214)	6.0 (27)	8.7 (41)
Adverse events leading to treatment discontinuation	25.0 (2)	0 (0)	3.5 (22)	3.4 (25)	2.4 (62)	2.6 (64)	2.2 (10)	3.6 (17)
Adverse events leading to study withdrawal	12.5 (1)	0 (0)	2.0 (13)	1.6 (12)	1.2 (30)	0.9 (23)	1.3 (6)	2.1 (10)
Deaths	0 (0)	20.0 (2)	0.6 (4)	1.1 (8)	0.7 (19)	0.7 (18)	0.2 (1)	0.2 (1)
Hypocalcaemia-related events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<0.1 (1)	0 (0)	0 (0)
SMQ “hypersensitivity”	25.0 (2)	0 (0)	6.3 (40)	5.0 (37)	6.7 (174)	7.0 (173)	8.3 (37)	8.3 (39)
Injection site reaction-related events	25.0 (2)	0 (0)	2.4 (15)	3.8 (28)	2.9 (75)	5.7 (140)	3.4 (15)	5.1 (24)
Hyperostosis-related events	0 (0)	0 (0)	0.6 (4)	0.3 (2)	0.7 (19)	0.5 (12)	1.3 (6)	1.1 (5)

Incidence, % (number of subjects)

In the safety analysis set[47)] comprising subjects in the placebo and romosozumab 210 mg groups of 12-month studies in postmenopausal women with osteoporosis, hypocalcaemia occurred in 1 subject in the romosozumab group in the subgroup with eGFR of ≥60 and <90. In the initial treatment phase (Months 0-24) and retreatment phase (Months 36-48) of Study 20060326 and in Study 20120156, no hypocalcaemia was reported.

Safety results from the pharmacokinetic study in patients with renal impairment (Study 20110227) are outlined in Section “6.2.3.1 Pharmacokinetic study in patients with renal impairment.” Adverse events that occurred at a high frequency in Study 20110227 were hypocalcaemia in 5 subjects (1 with severe renal impairment, and 4 with ESRD), and hyperparathyroidism secondary in 4 subjects (with severe renal impairment). With the exception in 1 subject with ESRD who experienced 2 events of CTCAE Grade 3 asymptomatic hypocalcaemia, hypocalcaemia was CTCAE Grade ≤2. The lowest percentage change from baseline (mean) in albumin-corrected serum calcium level was reached by Day 15 in healthy subjects (−1.9%), and by Day 22 in subjects with severe renal impairment (−4.8%) and in subjects with ESRD (−12.9%), and then returned to near baseline levels. The percentage change from baseline (mean) in serum iPTH level at Day 29 was 94% in healthy subjects, 150% in subjects with severe renal impairment, and 287% in subjects with ESRD. Thereafter, serum iPTH level returned to near baseline levels in healthy subjects and subjects with severe renal impairment by the end of the study (Day 85), while serum iPTH level remained high in subjects with ESRD, and the percentage change from baseline (mean) in serum iPTH level at the end of the study was 13% in healthy subjects, 41% in subjects with severe renal impairment, and 119% in subjects with ESRD.

Although there were no particular differences in the incidence of adverse events by the degree of renal function in major clinical studies conducted in and outside Japan, in the pharmacokinetics study in patients with renal impairment (Study 20110227), marked decreases in serum calcium level and marked increases in serum iPTH levels occurred in subjects with severe renal impairment and subjects with ESRD as compared to subjects with normal renal function. Taking into account the risk of developing hypocalcaemia in subjects with renal impairment [see Section "6.R.2 Administration of romosozumab in patients with renal impairment"], the draft package insert will specify patients with severe renal impairment and those with ESRD as patients requiring careful administration of romosozumab along with cautionary advice.

PMDA's view:
Patients with renal impairment have reduced production of $1,25(OH)_2$ vitamin D and low intestinal absorption of calcium on demand. Given this and because of the action mechanism of romosozumab, the risk of hypocalcaemia following romosozumab therapy is likely to increase in patients with renal impairment. In the evaluation using the pooled safety analysis set[47)] comprising subjects from studies in postmenopausal women with osteoporosis, there were no clear trends in the incidence of adverse events including hypocalcaemia in relation to the stage of renal impairment. However, only a limited number of subjects with severe renal impairment or ESRD were evaluated in these clinical studies. Furthermore, in the pharmacokinetics study in patients with renal impairment (Study 20110227), hypocalcaemia occurred in subjects with severe renal impairment and subjects with ESRD. Given that the serum calcium level is lower in these subjects than in healthy adults, together with the results of the study and the findings of the PPK analysis indicated that exposure increased as renal function deteriorated [see Section "6.R.2 Administration of romosozumab in patients with renal impairment"], it is appropriate to specify patients with severe renal impairment and patients with ESRD as patients requiring careful administration of romosozumab. Because only a limited number of patients with severe renal impairment or ESRD have received romosozumab, safety data of romosozumab in patients with renal impairment (particularly the incidence of hypocalcaemia) should be gathered in the post-marketing setting. These issues, including the adequacy of cautionary advice, will be finalized taking into account the comments from the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant's explanation:
Based on the data from major clinical studies conducted in and outside Japan, the following issues should be the focus of the risk management plan of romosozumab: hypocalcaemia, hypersensitivity, immunogenicity, hyperostosis, osteonecrosis of jaw, atypical femoral fracture, cardiovascular events, fetal risk, and safety of romosozumab therapy in patients with renal impairment. Furthermore, the applicant plans to carry out a post-marketing database survey as an additional pharmacovigilance activity for the following issues: hypocalcaemia, cardiovascular events, and safety of romosozumab therapy in patients with renal impairment (onset of hypocalcaemia).

PMDA considers that the focusing issues and the additional pharmacovigilance activity plan are appropriate. The details will be finalized taking into account the comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. There was an unfavorable finding. A staff member of the sponsor had revised or corrected some data in case reports. However, some of these revised or corrected data were not able to be identified at the investigator. This was an error to be corrected, but the final data recorded in the case reports were checked and confirmed by the investigator. Therefore, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1, 5.3.5.1-3, and 5.3.5.1-6) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, it was confirmed that the study was generally conducted in compliance with GCP, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding requiring corrective action at some of the study sites. Although it did not substantially affect the evaluation of the entire study, the issue was notified to the head of the study sites as a finding requiring corrective action:

Finding requiring corrective action

Study site

- Prior to an X-ray re-examination performed in some subjects, they were informed of the continuation of the study and provided consent. However, the study site failed to document these processes.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that romosozumab has efficacy in the treatment of osteoporosis, and that romosozumab has acceptable safety in view of its benefits. Romosozumab is clinically meaningful because it offers a new treatment option in the treatment of osteoporosis. Issues including hypocalcaemia, cardiovascular events, and safety of romosozumab therapy in patients with renal impairment should be further evaluated in post-marketing surveillance.

PMDA has concluded that romosozumab may be approved if romosozumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 15, 2018

Product Submitted for Approval

Brand Name	Evenity Subcutaneous Injection 105 mg Syringe
Non-proprietary Name	Romosozumab (Genetical Recombination)
Applicant	Amgen Astellas BioPharma K.K.
Date of Application	December 19, 2016

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's view:

In a global phase III study (Study 20070337) in postmenopausal women with osteoporosis, romosozumab was shown to be superior to placebo in terms of the incidence of new vertebral fracture, the primary endpoint, demonstrating that romosozumab is effective in reducing the risk of fracture in postmenopausal women with osteoporosis. Furthermore, a global phase III study (Study 20110174) in men with osteoporosis showed the superiority of romosozumab to placebo in the primary endpoint, namely, the percentage change from baseline in BMD at the lumbar vertebrae at Month 12, indicating that romosozumab increased BMD in men with osteoporosis. The results show that romosozumab is expected to have efficacy to a certain extent in reducing the risk of fracture in men with osteoporosis as well. The data of the Japanese subpopulation and the entire study population from these studies indicate that romosozumab has promising efficacy in Japanese patients as well.

This conclusion was supported by the expert advisors at the Expert Discussion.

1.2 Safety

1.2.1 Hypocalcaemia

PMDA's view:

In Japanese and foreign clinical studies, only a few romosozumab-treated subjects experienced hypocalcaemia. None of them were serious or severe. However, patients who had already been diagnosed to have hypocalcaemia at the screening office visit were excluded from the clinical studies, and calcium and vitamin D were co-administered as base treatment drugs throughout the study period. These factors may have contributed to maintaining serum calcium concentration. Transient decreases in albumin-corrected serum calcium level and compensatory increases in iPTH occurred at the beginning of treatment with romosozumab in the studies. In the pharmacokinetic study in patients with renal impairment, hypocalcaemia occurred in a certain proportion of subjects with severe renal impairment or ESRD. Given these, the possible hypocalcaemia following administration of romosozumab should be carefully monitored. Accordingly, romosozumab should be contraindicated in patients with hypocalcaemia, and patients with severe renal impairment or those with renal impairment on dialysis are subject to careful administration, which should be highlighted in the package insert. The package insert should also advise that patients who have hypocalcaemia, etc. should be treated for the symptom before starting romosozumab therapy and that appropriate levels of calcium and vitamin D supplementation should be performed during romosozumab therapy and change in albumin-corrected serum calcium level should be closely monitored particularly at the beginning of treatment.

This conclusion was supported by the expert advisors at the Expert Discussion.

PMDA requested the applicant to include the cautionary statements in the package insert, and the applicant took appropriate measures.

1.2.2 Cardiovascular events

PMDA's view:

In a foreign phase III alendronate-controlled study in postmenopausal women with osteoporosis (Study 20110142), serious cardiovascular events occurred more frequently in the romosozumab group than in the alendronate group. In contrast, in the pivotal phase III study (Study 20070337) in which postmenopausal Japanese women also participated, the incidence of cardiovascular events was similar between the placebo group and romosozumab group. Studies 20070337 and 20110142 both demonstrated the superiority of romosozumab to placebo or alendronate in reducing fractures. Based on these clinical study data, the safety profiles of romosozumab related to cardiovascular events are clinically acceptable from the benefit-risk balance standpoint. Nevertheless, the results of serious cardiovascular events in Study 20110142 are important particularly in terms of drug selection for osteoporosis. The package insert should present the results of Study 20110142 and advise to decide the use of romosozumab for patients at high risk of cardiac ischemic disease or cerebrovascular disorder with due consideration of benefit-risk balance so that physicians select drugs based on the data from Study 20110142. Post-marketing data on cardiovascular events following administration of romosozumab should also be gathered for comparison with other osteoporotic drugs and for further evaluation.

In response to the PMDA's conclusion, the expert advisors made the following comments at the Expert Discussion. The expert advisors supported PMDA's conclusion, i.e., the acceptance of safety of romosozumab, with appropriate written advice and any other safety measures taken.

- While the cardiovascular events reported in Study 20110142 are not likely to pose clinically significant problems in Japan, the difference in the incidence of serious cardiovascular events between the alendronate and romosozumab groups in the study is not insignificant. Since the incidence of serious cardiovascular events is higher in older patients and patients with a medical history of hypertension, cardiovascular diseases or cerebrovascular disorders (Table 71), these results are unlikely to be incidental variation. Therefore, it is appropriate to give advice so that physicians can select a drug based on the study results.
- Given that sclerostin is a mineralization inhibitor, the possibility cannot be denied that romosozumab promotes vascular calcification. In the heart, Wnt signaling increases during heart failure. Therefore, the possibility that romosozumab may pose adverse effects on the heart cannot be ruled out in theory.
- Fracture events affect the prognosis of patients with osteoporosis significantly. Therefore, the benefit-risk balance of romosozumab therapy should be carefully considered. In Study 20110142, the incidence of fracture was significantly lower in the romosozumab group than the alendronate group,[64] and the difference in the incidence of serious cardiovascular events between the romosozumab and alendronate groups at Month 24 was smaller than that at Month 12 (Table 70). These results do not necessarily deny the benefits of romosozumab.
- As concluded by PMDA, the applicant should communicate the importance of benefit-risk consideration for decision making on the use of romosozumab for patients with a high risk of cardiac ischemic disease or cerebrovascular disorder.

PMDA requested the applicant to provide relevant cautionary statements in the package insert, and the applicant took an appropriate action.

1.3 Clinical positioning of romosozumab and indication

PMDA's view:

The global phase III study (Study 20070337) in postmenopausal women with osteoporosis demonstrated the effect of romosozumab in reducing new vertebral fracture, and romosozumab is expected to be effective in men with osteoporosis to a certain extent. Romosozumab has acceptable safety in men and in postmenopausal women with osteoporosis where used according to appropriate cautionary advice, and therefore romosozumab can be a new treatment option for patients with osteoporosis.

The proposed indication of romosozumab was "osteoporosis with a high risk of fracture." It is important to increase bone volume and reduce the risk of fracture as early as possible particularly in patients with a high

[64] The incidence of new vertebral fracture at Month 24, the primary endpoint, was 8.0% (147 of 1834 subjects) in the alendronate group, and 4.1% (74 of 2046 subjects) in the romosozumab/alendronate group (12-month romosozumab therapy was followed by 12-month alendronate treatment), with the risk ratio [95% CI] being 0.50 [0.38, 0.66].

risk of fracture, and the safety profiles related to cardiovascular events in romosozumab-treated patients are clinically acceptable. However, given the results on serious cardiovascular events in an alendronate-controlled, foreign phase III study (Study 20110142) in postmenopausal women with osteoporosis, the applicant's explanation about romosozumab's greater benefit in patients with relatively higher risk of fracture is fairly reasonable. Study 20070337, a pivotal confirmatory study, was conducted in postmenopausal women without taking into account the extent of risk of fracture. The results showed similar trends towards an increase in BMD and a decrease in the incidence of fracture between the subgroup with a high risk of fracture and the rest of study population, and safety profiles did not differ significantly between the groups. When focusing on the results in the subgroup and of the above confirmatory study, it is possible to define the indication without the phrase "with a high risk of fracture."

Based on the above discussion, PMDA asked the expert advisors for opinions on whether the indication is appropriate, and the following comments were made by the expert advisors.

- The indication should be defined based on the design and results of the pivotal confirmatory study. Study 20070337 demonstrated similar efficacy and safety between the subgroup with a high risk of fracture and the rest of the study population. Based on the results of the pivotal study, the indication of romosozumab should simply be "osteoporosis."
- It is also important that concerns still remain about serious cardiovascular events. From the standpoint of describing the patient population that will better benefit from romosozumab, "osteoporosis with a high risk of fracture" is also a reasonable indication.

PMDA's conclusion:
The global phase III study (Study 20070337) in postmenopausal women with osteoporosis, etc. demonstrated the efficacy of romosozumab, and there were no significant differences in efficacy between the subgroup with a high risk of fracture and the rest of study population in Study 20070337. Thus, romosozumab is effective regardless of the risk level of fracture. The safety profiles related to cardiovascular events are clinically acceptable. However, romosozumab is an agent with a new mechanism of action. The risk of cardiovascular events and other potential risks attributable to the action mechanism of romosozumab are anticipated as described in Section "7.R.2 Safety." Considering all the circumstances, including the discussion in Section "1.2.2 Cardiovascular events" as well as the comments made by the expert advisors, the use of romosozumab should be clearly limited to patients at relatively high risk of fracture, taking into account the risks associated with romosozumab therapy. However, when deciding whether romosozumab is suitable for a patient, healthcare professionals should check through the efficacy and safety data carefully, particularly on cardiovascular events comparing romosozumab with a control drug or placebo, such as the results of Studies 20070337 and 20110142. This must be clearly communicated to healthcare professionals along with relevant information. Accordingly, PMDA requested the applicant to take appropriate actions for the indication.

The applicant's explanation:

In general, patients with osteoporosis are relatively old and thus a certain proportion of patients already have factors that may be related to the onset of cardiovascular diseases. It is therefore appropriate to decide whether to use romosozumab for a patient in light of the incidence of cardiovascular events in Study 20110142. In addition, romosozumab has a new mechanism of action that inhibits sclerostin; therefore, its safety should be carefully verified in the post-marketing setting, where romosozumab is available for more patients than in the clinical studies. If romosozumab needs to be used again during other osteoporotic drug therapy following the completion of initial romosozumab therapy, for a new fracture or for other reasons, the total duration of treatment with romosozumab will be longer. Safety data of romosozumab in long-term use are limited. Recently, the report of the Working Group on Goal-Directed Treatment for Osteoporosis, established by the American Society for Bone and Mineral Research (ASBMR) and the United States National Osteoporosis Foundation (NOF) proposed that, for patients with recent fractures or patients with a T-score substantially below −2.5, sequential therapy, in which a bone anabolic agent is used at the beginning of treatment followed by antiresorptive agent therapy, is the optimal treatment sequence (*J Bone Miner Res*. 2017;32:3-10). Conventional osteoporotic drugs usually require 2 to 3 years to exhibit a fracture reduction effect. In contrast, romosozumab reduced the incidence of new vertebral fracture by Month 12, suggesting that romosozumab can play a role as a bone anabolic agent. Taking into consideration the potential risks of romosozumab and the patient population that best benefits from romosozumab, the indication of romosozumab should be "osteoporosis with a high risk of fracture." In routine medical practice, for patients with osteoporosis who are not considered at high risk of fracture by the physician, other conventional osteoporotic drugs will be preferentially selected before use of romosozumab. After market launch, the applicant plans to prepare information materials on the efficacy and safety of romosozumab including the results of Study 20110142, to ensure that healthcare professionals are well informed so that romosozumab is used for eligible patients.

PMDA requested the applicant to define the indication and precautions for indication to be presented in the package insert as shown below and to ensure that healthcare professionals are well informed of the proper way to select patients at high risk of fracture via written materials so that romosozumab is used for eligible patients. The applicant agreed and took appropriate actions.

Indication

Osteoporosis with a high risk of fracture

Precautions for Indication

(1) Patients are eligible for the treatment with romosozumab if they have risk factors such as low bone mineral density, pre-existing fractures, older age, and family history of femoral neck fracture.

(2) In an alendronate sodium-controlled comparative study conducted overseas, the incidence of cardiovascular events (cardiac ischemic diseases or cerebrovascular disorders) tended to be higher in the romosozumab group than alendronate sodium group. Eligible patients should be selected only with

a thorough understanding of the benefits and risks of romosozumab (see “Important Precautions,” “Other Precautions,” and “CLINICAL STUDIES”).

1.4 Dosage and administration

1.4.1 Dosage and administration and treatment duration

PMDA’s view:

Based on the results of a foreign phase II study (Study 20060326), global phase III study (Study 20070337) in postmenopausal women with osteoporosis, and global phase III study (Study 20110174) in men with osteoporosis, a 210-mg subcutaneous dose administered once a month for 12 months is the appropriate dosage regimen of romosozumab.

In the foreign phase II study (Study 20060326), patients treated with romosozumab followed by placebo experienced decreases in BMD at the lumbar vertebrae, proximal femur, and femoral neck during placebo treatment that had been once increased by romosozumab. Furthermore, bone resorption markers increased before treatment with romosozumab. The package insert should communicate the necessity of appropriate osteoporotic drug therapy after the completion of romosozumab therapy.

This conclusion was supported by the expert advisors at the Expert Discussion.

PMDA requested the applicant to present the cautionary statement for the package insert as shown below, and the applicant took the appropriate action.

Dosage and Administration

The usual adult dosage is 210 mg of romosozumab (genetical recombination) administered as a subcutaneous injection once a month for 12 months.

Precautions for Dosage and Administration

The effect of romosozumab to reduce the risk of fracture was demonstrated in 12-month treatment and has yet to be evaluated in treatment longer than 12 months. As a rule, an appropriate osteoporotic drug therapy should follow the completion of treatment with romosozumab.

1.4.2 Retreatment

PMDA’s view:

The foreign phase II study (Study 20060326) did not raise any particular concerns regarding the efficacy and safety of romosozumab when patients were retreated with romosozumab. Thus there is no evidence compelling the restriction of retreatment with romosozumab for patients requiring it despite previous romosozumab therapy with a subsequent appropriate osteoporotic therapy.

In response, an expert advisor pointed out the limited availability of efficacy and safety data on retreatment with romosozumab that should be kept in mind. Nevertheless, the expert advisors supported the PMDA's conclusion that there is no need to restrict retreatment with romosozumab.

1.4.3 Initial loading of high dose vitamin D

PMDA's view:

In the clinical studies of romosozumab, the extent of decrease in albumin-corrected serum calcium level was small after administration of romosozumab, even without initial loading of high-dose vitamin D, and there was no hypocalcaemia causative of clinical problems. However, after the administration of romosozumab, a compensatory increase in serum iPTH level occurred, and it may have inhibited decreases in serum calcium. Therefore, the package insert should advise that patients be treated for hypocalcaemia or bone/mineral metabolism disorders such as magnesium and iPTH, if any, before starting romosozumab therapy.

This conclusion was supported by the expert advisors at the Expert Discussion.

1.5 Patient groups with special patient characteristics (renal impairment)

PMDA's view:

The action mechanism of romosozumab, low calcium absorption in patients with renal impairment, increased exposure to romosozumab in patients with deteriorated renal function, and pharmacokinetic studies in patients with renal impairment indicate that hypocalcaemia occurred at a certain incidence in subjects with severe renal impairment or ESRD. Therefore, patients with severe renal impairment and those on dialysis are subject to careful administration of romosozumab. Further, it is necessary to gather information about the safety of romosozumab in patients with renal impairment (particularly the incidence of hypocalcaemia) in the post-marketing setting.

This conclusion was supported by the expert advisors at the Expert Discussion. An expert advisor pointed out that patients with renal impairment who are on dialysis are particularly prone to cardiovascular events, and that information about cardiovascular events in patients with renal impairment should be gathered in the post-marketing setting.

Based on the above, PMDA requested the applicant to gather post-marketing data on cardiovascular events in patients with renal impairment, and the applicant took appropriate actions.

1.6 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for romosozumab should include the safety specifications presented in Table 93, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 94.

Table 93. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypersensitivity • Hypocalcaemia	• Serious cardiovascular events • Osteonecrosis of jaw • Atypical femoral fracture • Hyperostosis • Fetal risk • Effects of antibody development • Safety after the completion or discontinuation of treatment	• Safety in patients with renal impairment
Efficacy specification		
None		

Table 94. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database survey (hypocalcaemia, safety in patients with renal impairment) • Post-marketing database survey (serious cardiovascular events, safety in patients with renal impairment)	• Disseminate data gathered during early post-marketing phase vigilance • Patient card (osteonecrosis of jaw)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration statements as shown below, with the following conditions for approval. Since romosozumab is a drug with a new active ingredient, the re-examination period is 8 years. Romosozumab is classified as a biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Osteoporosis with a high risk of fracture

Dosage and Administration

The usual adult dosage is 210 mg of romosozumab (genetical recombination) administered as a subcutaneous injection once a month for 12 months.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ADCC	antibody dependent cellular cytotoxicity
ADCP	Antibody dependent cellular phagocytosis
Adverse reaction	Adverse event for which a causal relationship to the study drug cannot be ruled out
ALP	Alkaline phosphatase
AUC	Area under the Concentration Time Curve
BAP	bone alkaline phosphatase
BMI	Body mass index
CAL	Cells at the limit of *in vitro* cell age used for production
CDC	Complement Dependent Cytotoxicity
CHO	Chinese hamster ovary
CL	clearance
C_{max}	Maximum plasma concentration
CQA	Critical quality attribute
CTCAE	Common Terminology Criteria for Adverse Events
CTX	type I collagen cross-linked C-telopeptide
Denosumab	Denosumab (Genetical Recombination)
DPD	Deoxypyridinoline
DXA	dual-energy X-ray absorptiometry
ECL	Electrochemiluminescence
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ESRD	end stage renal disease
HCP	Host cell protein
hPTH	human parathyroid hormone
HRpQCT	high-resolution peripheral quantitative computed tomography
IgG	Immunoglobulin G
iPTH	intact parathyroid hormone
Kd	equilibrium dissociation constant
LCM	laser capture microdissection
LRP	low-density lipoprotein receptor-related protein
MACE	Meta-analysis of Positively Adjudicated Cardiovascular Adverse Events
MBF	Modeling-based bone formation
MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
m13C7	a mouse anti-sclerostin antibody
NTX	type I collagen cross-linked N-telopeptide
OC	Osteocalcin
OVX	ovariectomized
PFS	prefilled syringe
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
pQCT	peripheral quantitative computed tomography
PTH	parathyroid hormone
P1NP	type I procollagen-N-propeptide
QbD	Quality by design
Q1M	every month

Q3M	every 3 months
Q2W	every 2 weeks
Q4W	every 4 weeks
RANKL	Receptor activator of nuclear factor kappa-B ligand
RBF	Remodeling-based bone formation
rhPTH (1-34)	recombinant human parathyroid hormone (1-34)
r13C7	a rat anti-sclerostin antibody
SMI	Structure Model Index
SNP	single nucleotide polymorphism
Teriparatide	Teriparatide (Genetical Recombination)
TRACP5b	tartrate-resistant acid phosphatase 5b
vBMC	Volumetric bone mineral content
vBMD	Volumetric bone mineral density
V_2	volume of distribution of the central compartment
WCB	Working cell bank