FDA Briefing Document

Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee

January 16, 2019

BLA 761062
Romosozumab
Amgen, Inc

Proposed Indication:
Treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

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Disclaimer Statement

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Table of Contents

Table of Figures

Table of Tables

Executive Summary

The Division of Bone, Reproductive and Urologic Products has convened this advisory committee meeting to discuss romosozumab for the treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. The romosozumab dose is 210 mg given subcutaneously (SC) once monthly. The effect on bone mineral density (BMD) wanes by 12 months of therapy; therefore, the treatment duration is limited to one year. The dose requires two injections of 105 mg each, administered by a healthcare provider. Romosozumab functions predominantly as a bone anabolic agent.

This is the second review cycle for romosozumab. In the first review cycle, the applicant submitted trial 20070337, a placebo-controlled fracture trial in women with postmenopausal osteoporosis, to support approval of the biologics license application (BLA). This trial did not show an increase in cardiovascular risk with romosozumab compared to placebo. During the first cycle review, the applicant completed two additional studies, trial 20110142, an alendronate-controlled fracture trial in postmenopausal women with osteoporosis, and trial 20110174, a placebo-controlled BMD study in men with osteoporosis. Trials 20110142 and 20110174 demonstrated effectiveness of romosozumab on their primary efficacy endpoints. However, there was a higher incidence of positively adjudicated cardiovascular serious adverse events during the year of romosozumab therapy in both studies. The applicant notified and met with the FDA to discuss the cardiovascular safety findings. Consequently, FDA issued a complete response letter on July 13, 2017 requiring the applicant to evaluate the newly emerged cardiovascular findings. In the initial BLA submission, the applicant proposed the indication of treatment of osteoporosis in postmenopausal women. Due to the cardiovascular safety signal, in this application resubmission, the applicant now proposes to narrow the indication to treatment of osteoporosis in postmenopausal women at high risk of fracture. The applicant is also proposing a Boxed Warning as well as a Warning and Precaution for cardiovascular risk.

FDA agrees that the applicant has established the effectiveness of romosozumab for the treatment of postmenopausal osteoporosis. In the placebo-controlled trial 20070337, the new morphometric (radiographic) vertebral fracture absolute risk reduction was 1.3% (95% CI: 0.8, 1.8) and the relative risk reduction was 73% (95% CI: 53, 84) at 12 months with romosozumab compared to placebo. Romosozumab or placebo was given for the first year, and for the second year of the trial all subjects were switched to the antiresorptive agent denosumab. At 24 months, the new morphometric vertebral fracture incidence was 2.5% in the placebo then denosumab group and 0.6% in the romosozumab then denosumab group with an absolute risk reduction of 1.9% (95% CI: 1.3, 2.5) and relative risk reduction of 75% (95% CI: 60, 84). In the alendronate-controlled trial 20110142, which enrolled a population at higher fracture risk than trial 20070337, romosozumab or alendronate was given for the first year, and for the second year of the trial all subjects received alendronate. The incidence of new morphometric vertebral fracture at month 24 was 8.0% in the alendronate group compared to 4.1% in the romosozumab then alendronate group with an absolute risk reduction of 4.0% (95% CI: 2.5, 5.6) and a relative risk reduction of 50% (95% CI: 34, 62).

In trial 20110142, romosozumab also significantly reduced the incidence of nonvertebral fracture compared to alendronate. Trials 20070337 and 20110142 were not prospectively designed to show a reduction in hip fracture.

Aside from the cardiovascular safety signal, romosozumab was generally well tolerated. The overall safety events in postmenopausal women were balanced between the treatment groups in both the placebo-controlled trial and the alendronate-controlled trial. Injection site reactions occurred in approximately 5% of subjects receiving romosozumab. Both osteonecrosis of the jaw (ONJ) and atypical femoral fractures occurred infrequently with romosozumab therapy. These findings are surprising based on romosozumab's predominant function as a bone anabolic agent. The mechanism is not clear but may be related to romosozumab's additional antiresorptive effects. Currently, it remains unclear if romosozumab therapy increases the risk of ONJ or atypical femoral fracture during follow-on antiresorptive therapy.

The adverse cardiovascular finding seen in romosozumab phase 3 trials 20110142 and 20110174 is FDA's main concern and the reason for convening this advisory committee meeting. The applicant adjudicated cardiovascular serious adverse events in all three phase 3 trials. For some of the events, information was inadequate for adjudication. There were too few events in the small trial in men to draw definitive conclusions. Based on a meta-analysis of major adverse cardiovascular events (MACE, a composite endpoint of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) during the 12-month double-blind treatment period of the two fracture trials 20070337 and 20110142 in postmenopausal women, there were 51 (0.9%) subjects with MACE in the control group and 71 (1.3%) subjects with MACE in the romosozumab group, with a hazard ratio (95% CI) of 1.38 (0.96, 1.99).

The applicant conducted a thorough review and subgroup analyses to identify potential differences in baseline cardiovascular risk between the two trials. However, these were not cardiovascular outcome trials and not all known cardiovascular risk factors, including fasting lipid levels and high sensitivity C-reactive protein levels, were available. This limits the use of cardiovascular risk calculators. Using the information available, cardiovascular risk appeared similar between the populations enrolled in the two fracture trials. Further nonclinical evaluations did not demonstrate a potential mechanism for cardiovascular adverse effects with romosozumab.

One main difference between trial 20070337 and 20110142 is the control group. In the active-controlled trial 20110142, alendronate was used as control. This raises the question of whether alendronate may confer a cardioprotective effect in the first year of therapy. The mechanism of action of bisphosphonates at bone is through binding to hydroxyapatite and promoting osteoclast apoptosis through inhibition of the mevalonate pathway. Inhibition of the mevalonate pathway is also the mechanism of action of statin products for the treatment of hyperlipidemia. While it may be biologically plausible that alendronate and other bisphosphonates could have a cardioprotective effect, their very high specificity to bone and osteoclasts would not suggest that such a benefit occurs. To date, studies evaluating this question have yielded mixed results.

A question remains regarding whether the cardiovascular safety outcomes seen in both trial 20070337 and 2010142 are generalizable to the US population and US medical practice given

that cardiovascular risk varies among nations that enrolled subjects in these fracture trials. Enrolled subjects from the US accounted for 1.8% of subjects in trial 20070337 and 1.4% subjects in trial 20110142.

When considering the benefits and risks of romosozumab, the outcome of osteoporosis that confers the highest morbidity and mortality is hip fracture. Approximately 300,000 hip fractures occur each year in the US. Mortality in the year following hip fracture ranges from 10 – 58% in published reports and increases with age. While the romosozumab fracture studies were not powered to adequately assess hip fracture, a positive trend in hip fracture risk reduction was seen. Conversely, the occurrence of a cardiac ischemic event in postmenopausal women also confers the risk of considerable morbidity and mortality (with 1-year mortality estimates ranging from approximately 5-20% for myocardial infarction and 20-30% for ischemic stroke). Cardiovascular disease is the leading cause of death in women and cardiovascular risk increases after menopause.

With a hazard ratio for MACE of 1.38 (95% CI: 0.96, 1.99) in the meta-analysis of trials 20070337 and 20110142 and discrepant cardiovascular findings between trials, we are seeking the advisory committee's input on whether the benefits of romosozumab outweigh its cardiovascular risks, whether additional cardiovascular data are needed, and if such data are necessary, whether these data should be obtained pre- or post-approval and whether these data should come from a randomized, controlled trial or an observational study.

We look forward to hearing the committee's discussion and recommendations on this application. Thank you in advance for participating in this meeting and helping FDA fulfill its mission of protecting and promoting public health by helping ensure human drugs are safe and effective for their intended use.

Draft Points to Consider

Discuss whether the cardiovascular safety of romosozumab is adequately characterized. If additional safety data are needed, discuss the type(s) of data that are needed and whether these data should be obtained pre-approval or whether these data can be obtained post-approval.

Is the overall benefit/risk profile of romosozumab acceptable to support approval of romosozumab for the treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy?

If romosozumab were to be approved, discuss whether the indicated population for romosozumab should be further narrowed to a population at low cardiovascular and cerebrovascular risk. If the indication should be narrowed, discuss how to define a population that is at sufficiently low cardiovascular and cerebrovascular risk.

If romosozumab were to be approved, discuss whether romosozumab should be contraindicated in patients at high risk of a cardiovascular or cerebrovascular disease. If a contraindication is needed, discuss how to identify patients for whom romosozumab should be contraindicated.

1. Introduction

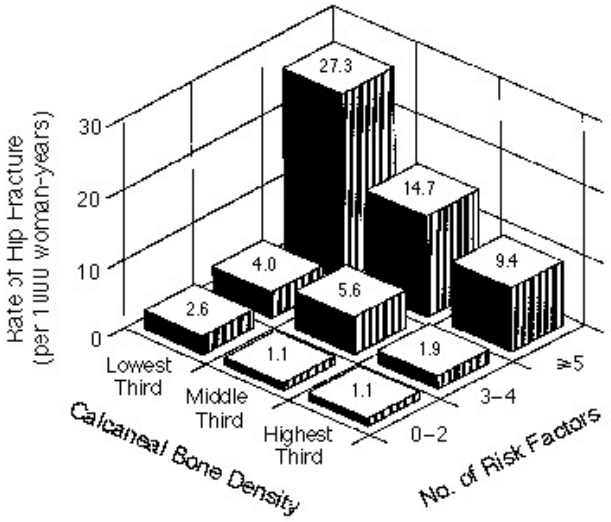
Romosozumab is an IgG2 humanized monoclonal antibody that binds and inhibits sclerostin. Sclerostin inhibitors are a new therapeutic class of osteoporosis therapies and romosozumab is first in the class. Sclerostin is the protein product of the SOST gene and is secreted by the osteocyte. Sclerostin is thought to act by binding to low-density lipoprotein receptor-related proteins 4, 5, and 6 (LRP4, LRP5, and LRP6). At bone, this is thought to inhibit Wingless-related integration (Wnt) signaling and reduce osteoblast-mediated bone formation. Inhibition of sclerostin leads to a transient stimulation of bone formation and inhibition of bone resorption. Romosozumab functions predominantly as an anabolic bone agent.

Osteoporosis is a skeletal disorder characterized by low bone mass and structural deterioration of bone, which leads to bone fragility and increased fracture risk. Osteoporosis is generally defined using World Health Organization (WHO) criteria which are based on standard deviations from a mean cohort of young healthy adults (T-score). Fracture risk increases as T-score decreases and current guidelines recommend initiation of treatment if an osteoporotic fracture has occurred, if T-score is ≤ 2.5, or if T-score is less than -1.0 with additional risk factors present.

Osteoporotic fractures can significantly impact an individual's quality of life, morbidity and mortality. Data reported by the National Osteoporosis Foundation indicate that 10 million people in the United States have osteoporosis and an additional 44 million have low bone mass (T-score <-1.0). Approximately 1.5 million osteoporotic fractures occur each year. Hip fracture is associated with the highest morbidity and mortality. In a study of recovery following hip fracture in Baltimore, investigators estimated a mortality rate as high as 24% one year after hip fracture with only 40% of patients able to perform activities of daily living independently[1]. The risk factors for fracture include age, bone mineral density, maternal history of hip fracture, and history of prior fracture. Figure 1 below graphically displays the importance of both BMD and risk factors with increasing hip fracture rates with low bone mass and a greater number of risk factors. The mortality associated with hip fracture also increases with age.

[1] Magaziner, et.al. J Gerontol. 1990; 45:M101-107

Figure 1: Annual Risk of Hip Fracture According to the Number of Risk Factors and Age-Specific Calcaneal Bone Density (source[2])



The goal of therapy for osteoporosis is to reduce the risk of fracture. For treatment of osteoporosis, there are currently five classes of products approved in the United States. Approved anabolic agents include teriparatide, a parathyroid hormone analog and abaloparatide, a parathyroid hormone related peptide analog. Approved antiresorptive agents include bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid), estrogen agonist/antagonist agents (raloxifene), a RANK ligand antagonist (denosumab), and salmon calcitonin products.

This is the second review cycle for romosozumab. In the first review cycle, trial 20070337, the placebo-controlled fracture trial, was submitted to support approval of the licensing application. During the first cycle review, the applicant completed two additional trials, 20110142 and 20110174, that also demonstrated the effectiveness of romosozumab but showed a higher incidence of positively adjudicated cardiovascular serious adverse events during the year of romosozumab therapy. The applicant notified and met with the FDA to discuss the cardiovascular safety findings. Consequently, FDA issued a complete response letter on July 13, 2017 requiring the applicant to evaluate the newly emerged cardiovascular safety signal.

2. Romosozumab Clinical Development Program

The romosozumab clinical development program for postmenopausal osteoporosis includes the phase 2 dose-finding study 20060326, the phase 3 placebo-controlled fracture trial 20070337, and the phase 3 alendronate-controlled trial 20110142. The applicant also conducted a smaller BMD trial to assess the effects of romosozumab on bone mass in men with osteoporosis. Cardiovascular safety data from the male osteoporosis trial are also included in the application.

[2] Cummings SR, et.al, Risk Factors for Hip Fracture in White Women. N Engl J Med 1995; 332:767-774

2.1. Trial 20060326

Trial 20060326 (NCT 00896532) is a randomized, placebo and active-controlled 24-month dose finding study that evaluated 5 different doses of romosozumab. The study has been extended several times. The first extension (months 24 to 36) is for a 12-month phase where subjects were randomized to either placebo or denosumab 60 mg administered SC every 6 months. All subjects were to take at least 1000 mg calcium and at least 800 IU Vitamin D daily. The enrolled postmenopausal population included 419 women, age 55 – 85 years, with low bone mass. Subjects with a positive osteoporotic fracture history were excluded from enrollment. The mean age of the enrolled population was 67 years, 86% of the population was white, and the mean lumbar spine T score was -2.3.

2.2. Trial 20070337

Trial 20070337 (NCT 01575834) is a 24-month, multicenter, double-blind, randomized, placebo-controlled study evaluating romosozumab 210 mg monthly (given SC by healthcare providers as three 1 mL prefilled syringes containing 70 mg/mL) for the treatment of postmenopausal osteoporosis. Because of the waning bone effect of romosozumab after 1 year, the applicant chose to limit the duration of romosozumab exposure to one year. Therefore, this 24-month study was designed as double-blind in the first year during which subjects received either healthcare provider administered romosozumab or placebo, and then all subjects were switched to healthcare provider administered open-label denosumab 60 mg every 6 months in the second year while still remaining blinded to their initial treatment assignment (romosozumab or placebo). Subjects were to receive daily calcium (500 to 1000 mg) and vitamin D (600 to 800 IU) supplementation.

Randomization was stratified by age (< 75 years, ≥ 75 years) and prevalent vertebral fracture (yes, no), as determined by site staff at randomization based on local reading of the spine X-ray.

Multiple substudies were included in this trial: a pharmacokinetic (PK) substudy; a bone turnover marker and biomarker substudy; an imaging substudy I that evaluated forearm dual X-ray absorptiometry (DXA), total body DXA, and high resolution peripheral quantitative computed tomography (HR-pQCT); an imaging substudy II that evaluated lumbar spine and proximal femur DXA; a bone biopsy substudy; a calcium substudy; an audiology substudy; an osteoarthritis substudy; a pharmacogenetics substudy; and mineral substudy that evaluated serum intact parathyroid hormone (iPTH) and urinary calcium.

Study population: Trial 20070337 enrolled 7180 postmenopausal women with osteoporosis aged 55 to 90 years. Osteoporosis was defined as a BMD T-score at the total hip or femoral neck of ≤ -2.5. Subjects with a BMD T-score of ≤ -3.5 at the total hip or femoral neck, history of hip fracture, severe vertebral fracture, or more than 2 moderate vertebral fractures were excluded from the study. Subjects with metabolic bone disease, significant laboratory abnormalities, or use of drugs known to affect bone were also excluded. Prior use of osteoporosis therapies was allowed with appropriate wash out. The original study enrollment targeted 6000 subjects. The

sample size was increased to 6600 subjects after blinded review of the pooled nonvertebral fracture incidence was 12.5% lower than the original assumptions.

The mean age of the enrolled population was 71 years. Approximately 57% of subjects were white. The geographic distribution of enrolled subjects was Western Europe/Australia/New Zealand (14%), Central Europe/Eastern Europe (29%), Central/Latin America (43%), North America (3%,), and Asia Pacific (11%). Overall, 132 subjects (1.8%) from the United States participated in the study.

Efficacy measures: The coprimary endpoints of trial 20070337 were the incidence of new morphometric vertebral fractures at month 12 and month 24. Spine radiographs were obtained at screening, month 6, month 12, and month 24. Morphometric vertebral fractures were determined using the semiquantitative method of Genant. Nonvertebral fractures were confirmed using radiographs, CT, or MRI. If these were not available, a medical report was acceptable. Bone mineral density of the hip and lumbar spine by DXA was obtained at baseline, month 12 and month 24. DXA and fracture outcomes were assessed using a central read facility.

Safety measures: Specific safety evaluations for romosozumab included assessment of immunogenicity and local tolerance evaluations for injection site reactions. Specific substudies of trial 20070337 included evaluation of bone histomorphometry, calcium and mineral metabolism, audiology, and osteoarthritis. Specific adverse event adjudication committees were established to evaluate osteonecrosis of the jaw, atypical femoral fractures, and cardiovascular events.

2.3. Trial 20110142

Trial 20110142 (NCT 01631214) is a double-blind, randomized, active-controlled, event-driven trial evaluating romosozumab 210 mg monthly administered SC by healthcare providers for 12 months compared to oral alendronate 70 mg once weekly for 12 months. The dose of 210 mg required three 1 mL prefilled syringes of 70 mg/mL romosozumab.

This study was designed as double-blind in the first year, then romosozumab was stopped and all subjects received alendronate in the second year while remaining blinded to their initial treatment group. Subjects were to receive daily calcium (500 to 1000 mg) and vitamin D (600 to 800 IU) supplementation.

Randomization was stratified by age (< 75 years, ≥ 75 years).

Study population: Trial 20110142 enrolled 4093 postmenopausal women aged 55 to 90 years with osteoporosis or low bone mass assessed by BMD and a history of a prevalent osteoporotic fracture.

The mean age of the enrolled population was 74 years. Approximately 70% of subjects were white. The geographic distribution of enrolled subjects was Western Europe/Australia/New Zealand (13%), Central Europe/Eastern Europe and the Middle East (40%), Central/Latin

America (34%), North America (2%), Asia Pacific (7%), and South Africa (4%). Overall, 57 subjects (1.4%) from the United States participated in the study.

Efficacy measures: The coprimary endpoints of trial 20110142 were the incidence of new morphometric vertebral fractures at month 24 and incidence of clinical fracture (defined by the applicant as nonvertebral fracture or clinical vertebral fracture). The clinical fracture endpoint was event-driven. The primary analysis would occur when all subjects had reached 24 months of study participation and clinical fracture was confirmed in at least 330 subjects. Upon completion of the primary analysis period, the study was to continue until at least 440 subjects experienced a nonvertebral fracture or if the superiority of romosozumab was proven for nonvertebral fractures at the primary analysis. Spine radiographs were obtained at screening, month 6, month 12, and month 24. Morphometric vertebral fractures were determined using the semiquantitative method of Genant. Nonvertebral fractures were confirmed using radiographs, CT, or MRI. If these were not available, a medical report was acceptable. BMD of the hip and lumbar spine by DXA was obtained at baseline, month 12 and month 24. DXA and fracture outcomes were assessed using a central read facility.

Safety measures: Specific safety evaluations for romosozumab included assessment of immunogenicity and local tolerance evaluations for injection site reactions. Specific adverse event adjudication committees were established for osteonecrosis of the jaw, atypical femoral fractures, and cardiovascular events.

2.4. Trial 20110174

Trial 20110174 (NCT 02186171) is a 15-month, randomized, double-blind, placebo-controlled study evaluating 12 months of romosozumab treatment in men with osteoporosis. Subjects received healthcare provider administered romosozumab 210 mg (3 injections of 70 mg each) or matching placebo for 12 months and were followed for an additional 3 months to assess immunogenicity. This study was included in the resubmission application due to the findings pertaining to cardiovascular safety. A complete review of this study was not conducted.

Study population: Trial 20110174 enrolled 245 men with osteoporosis aged 55 – 90 years old. Osteoporosis was defined as a T-score of $\leq$ -2.5 at the lumbar spine, total hip or femoral neck, or a T-score of $\leq$ -1.5 with a history of a fragility fracture. Subjects were excluded from the study if the T-score was <-3.5 at the hip or if they had a history of a hip fracture.

The mean age of the enrolled population was 72 years. Approximately 74% of subjects were white. The geographic distribution of enrolled subjects was Europe (66%), Japan (11%), Latin America (14%) and North America (9%).

Safety measures: Safety analyses included assessments of treatment-emergent adverse events, clinical laboratory assessments, vital signs, and anti-romosozumab antibodies. Specific adverse event adjudication committees were established for osteonecrosis of the jaw, atypical femoral fractures, and cardiovascular events.

3. Clinical Pharmacology of Romosozumab

3.1. General pharmacokinetics of romosozumab

Romosozumab exhibits nonlinear pharmacokinetics following subcutaneous (SC) administration of doses ranging from 0.1 to 10 mg/kg or following intravenous (IV) administration of doses ranging from 1 to 5 mg/kg. The clearance of romosozumab decreases as dose increases; and romosozumab exposure increases in a greater than dose-proportional manner. The systemic clearance (CL/F) is 0.38 mL/hr/kg following a single SC administration of 3 mg/kg. The mean effective half-life is 13 days after 3 monthly SC doses of 3 mg/kg.

Following a single SC administration of 210 mg romosozumab in healthy male and female subjects, the mean (±SD) maximum serum concentration (Cmax) is 22.2±5.8 mcg/mL and the mean (±SD) area-under-the-concentration-time curve (AUC) is 389 (±127) mcg*day/mL. The estimated bioavailability is 81%. The median time to achieve Cmax is 5 days. Following multiple SC administrations of 210 mg romosozumab monthly in postmenopausal women, steady-state concentrations were achieved by month 3 and the mean trough serum romosozumab concentrations at months 3, 6, 9, and 12 ranged from 8 to 13 mcg/mL.

3.2. Intrinsic factors and specific populations

Romosozumab exposure is higher in subjects with lower body weight, in subjects with severe renal impairment, and in male subjects; however, no dose adjustment is needed based on body weight, renal function or sex. Population PK analysis indicated that other factors including age, race, disease state (low bone mass or osteoporosis), or prior exposure to alendronate do not have meaningful influence on the PK of romosozumab.

4. Clinical Effectiveness of Romosozumab

The Division agrees that the applicant has established substantial evidence of effectiveness for romosozumab. Romosozumab is effective in increasing bone mineral density and decreasing the risk of fracture in postmenopausal women. The efficacy findings from the key trials are briefly outlined in this section.

4.1. Trial 20060326

In trial 20060326, the Phase 2 dose-finding study, the primary endpoint was lumbar spine BMD at month 12. Results of this BMD analysis are outlined in the table below. Treatment with romosozumab demonstrated a dose-related increase in BMD with a waning of BMD increases after the first year of therapy. Romosozumab increased BMD of the hip with larger increases achieved in the monthly dosing groups. The treatment difference compared to placebo with romosozumab 210 mg monthly was 4.9% (95% CI: 4.0, 5.8) at the total hip and 4.8% (95% CI: 3.7, 6.0) at the femoral neck. At the mid-third radius, a site of predominantly cortical bone, small decreases in BMD were seen in all romosozumab dose groups, similar to placebo.

Table 1: Trial 20060326: Percent Change in Lumbar Spine BMD at Month 12, Linear Mixed Effect Model

	placebo	Romosozumab				
		70 mg Every Month	140 mg Every 3 Months	140 mg Every Month	210 mg Every 3 months	210 mg Every Month
Randomized, N	50	49	52	48	53	50
Analysis Dataset, n	47	44	49	46	51	49
LS Mean, %	-0.1	5.4	5.4	9.1	5.5	11.3
Treatment Difference, %		5.5	5.6	9.2	5.6	11.5
95% CI		4.0, 7.0	4.1, 7.0	7.8, 10.7	4.2, 7.2	10.0, 12.9

The 210 mg once monthly dose was chosen for further development and used in the Phase 3 fracture trials. Dosing with romosozumab is proposed for one year of therapy. The Division requires 2 years of data for phase 3 fracture trials. Therefore, in the Phase 3 fracture trials, romosozumab was dosed for 1 year followed by dosing with an antiresorptive agent in the second year of the trials.

4.2. Trial 20070337

In trial 20070337, the placebo-controlled Phase 3 trial, the coprimary endpoints were the incidence of new morphometric (radiographic) vertebral fractures at month 12 and at month 24. To control the overall type I error, the primary and secondary efficacy endpoints were tested sequentially at the 2-sided 5% significance level, as listed:

1. Incidence of new vertebral fracture through months 12 and 24
2. Incidence of clinical fracture through month 12
3. Incidence of non-vertebral fracture through months 12 and 24 (testing for months 12 and 24 were controlled by Hochberg procedure at 0.05 level within the step)
4. Incidence of clinical fracture through month 24
5. Incidence of major non-vertebral fracture through months 12 and 24 (testing for months 12 and 24 were controlled by Hochberg procedure at 0.05 level within the step)
6. Incidence of new or worsening vertebral fracture through months 12 and 24 (testing for months 12 and 24 were controlled by Hochberg procedure at 0.05 level within the step)
7. Incidence of hip fracture through months 12 and 24 (testing for months 12 and 24 were controlled by Hochberg procedure at 0.05 levels within the step)

Fracture: As outlined in the Table 2, the primary efficacy endpoints were met, with an absolute risk reduction in morphometric vertebral fractures of 1.3% (95% CI: 0.8, 1.8) at month 12 and 1.9% (95% CI: 1.3, 2.5) at month 24. The first secondary endpoint is clinical fracture at month 12. The applicant defined clinical fracture as all nonvertebral fractures plus all symptomatic vertebral fractures. Of the 148 clinical fractures in the first 12 months, 131 (88%) were nonvertebral fractures. While treatment with romosozumab resulted in a significant decrease in clinical fractures at month 12, the reduction in nonvertebral fractures was not significant at month 12. Regardless of the statistical outcome, it is clear that romosozumab is efficacious with at least a positive trend in fracture reduction at nonvertebral sites.

Table 2: Trial 20070337: Fracture Endpoints

	Placebo/ Denosumab	Romosozumab/ Denosumab	Absolute Risk Reduction (95% CI)	Relative Risk Reduction (95% CI)	p-value
Primary Endpoints					
Vertebral Fracture, month 12, %	1.8	0.5	1.3 (0.8, 1.8)	73 (53, 84)	<0.001
Vertebral Fracture, month 24, %	2.5	0.6	1.9 (1.3, 2.5)	75 (60, 84)	<0.001
Secondary Endpoints					
Clinical Fracture, month 12, %	2.5	1.6	1.2 (0.4, 1.9)	36 (11, 54)	0.008
Nonvertebral Fracture, month 12, %	2.1	1.6	0.8 (0.1, 1.4)	25 (-5, 47)	0.096
Nonvertebral Fracture, month 24, %	3.6	2.7	1.0 (0.2, 1.9)	25 (3, 43)	Testing stopped
Clinical Fracture, month 24, %	4.1	2.8	1.4 (0.5, 2.4)	33 (13, 48)	
Hip Fracture, month 12, %	0.4	0.2	0.9 (0.0, 0.6)	46 (-35, 78)	-
Hip Fracture, month 24, %	0.6	0.3	0.4 (0.0, 0.7)	50 (-4, 76)	-

Bone Mineral Density: As outlined in the table below, romosozumab significantly increased bone mineral density (BMD) at all sites. At month 12, compared with placebo, romosozumab increased BMD 12.7% at the lumbar spine, 5.8% at the total hip, and 5.2% at the femoral neck. Romosozumab followed by denosumab maintained the increases in BMD at the lumbar spine, total hip and femoral neck at month 24.

Table 3: Trial 20070337: Bone Mineral Density, Mean Percent Change, LOCF, ANCOVA

	Placebo/ Denosumab	**Romosozumab/ Denosumab**	**LS Mean Difference (95% CI)**
Lumbar Spine			
Month 12, mean, %	0.4	13.1	12.7 (12.4, 12.9)
Month 24, mean, &	5.5	16.6	11.1 (10.8, 11.4)
Total Hip			
Month 12, mean, %	0.3	6.0	5.8 (5.6, 6.0)
Month 24, mean, %	3.2	8.5	5.3 (5.1, 5.5)
Femoral Neck			
Month 12, mean, %	0.3	5.5	5.2 (4.9, 5.4)
Month 24, mean, %	2.3	7.3	4.9 (4.7, 5.2)
LOCF=last observation carried forward, ANCOVA= analysis of covariance			

4.3. Trial 20110142

In trial 20110142, the alendronate-controlled Phase 3 trial, the two coprimary endpoints were incidence of new morphometric (radiographic) vertebral fractures at month 24 and new clinical (nonvertebral plus clinical vertebral) fractures at the primary analysis point, which was event and time driven (330 events and all patients reached 24 months). The final analysis (end-of-study) point occurred when nonvertebral fracture events were confirmed for at least 440 subjects, or earlier if the primary analysis demonstrated superiority of romosozumab treatment for nonvertebral fracture risk reduction.

To control the overall type I error, if both primary endpoints were significant at the 0.05 level (2-sided), each of the following secondary BMD and fracture endpoints were tested hierarchically at the 2-sided 5% significance level, as listed:

1. BMD at lumbar spine, month 24
2. BMD at total hip, month 24
3. BMD at femoral neck, month 24
4. BMD at lumbar spine, month 12
5. BMD at total hip, month 12
6. BMD at femoral neck, month 12
7. Nonvertebral fracture at primary analysis point and at final analysis point

The incidence of new vertebral fracture at month 24 was 8.0% in the alendronate group compared to 4.1% in the romosozumab group with an absolute risk reduction of 4.0% (95% CI: 2.5, 5.6) and a relative risk reduction of 50% (95% CI: 34, 62). For the clinical fracture endpoint, the cumulative incidence of fractures was summarized using the Kaplan-Meier estimates and a stratified Cox proportional hazards model was used for analyses. At the time of the primary analysis, 464 subjects had experienced a clinical fracture and all subjects had completed the 24-month visit. The median follow-up time was 33 months. Through the primary analysis period, the incidence of clinical fracture was 13.0% in the alendronate group and 9.7% in the romosozumab group, yielding a hazard ratio of 0.73 (95% CI: 0.61, 0.88).

Bone mineral density endpoints were evaluated first in the hierarchy of secondary endpoints. The treatment comparisons of the BMD at the lumbar spine, total hip and femoral neck at months 12 and 24 were analyzed using an analysis of covariance (ANCOVA) model including treatment, age (stratification factor), presence or absence of severe vertebral fracture at baseline, machine type, machine type-by-baseline value interaction and baseline value of the endpoint. Missing data were imputed using last-observation-carried-forward. As outlined in the Table 4, romosozumab significantly increased BMD by 8.7%, 3.3%, and 3.2% compared with alendronate at month 12 at the lumbar spine, total hip and femoral neck, respectively. At month 24, romosozumab for 12 months followed by alendronate for 12 months significantly increased BMD by 8.1%, 3.8%, and 3.8%, compared with alendronate alone for 24 months, at the lumbar spine, total hip, and femoral neck, respectively.

Table 4: Trial 20110142: Percent Change in Bone Mineral Density

	Alendronate/ Alendronate	Romosozumab/ Alendronate	LS Mean Difference (95% CI)
Lumbar Spine			
Month 12, mean, %	5.0	13.7	8.7 (8.3, 9.1)
Month 24, mean, %	7.2	15.3	8.1 (7.6, 8.6)
Total Hip			
Month 12, mean, %	2.8	6.2	3.3 (3.0, 3.6)
Month 24, mean, %	3.5	7.2	3.8 (3.4, 4.1)
Femoral Neck			
Month 12, mean, %	1.7	4.9	3.2 (2.9, 3.5)
Month 24, mean, %	2.3	6.0	3.8 (3.4, 4.1)

Nonvertebral fracture was evaluated next in the hierarchy of secondary endpoints. Through the primary analysis period, a total of 395 subjects experienced a nonvertebral fracture. The incidence of nonvertebral fracture was 10.6% in the alendronate group and 8.7% in the romosozumab group, yielding a hazard ratio of 0.81 (95% CI: 0.66, 0.99). This was statistically significant with a 1-sided nominal p-value of 0.019 below the alpha level of 0.0233 at primary analysis using the Lan-DeMets alpha spending function.

Other pre-specified analyses not included in the statistical testing sequence included the evaluation of nonvertebral and hip fracture at month 12 and month 24. Results are shown in the Table 5.

Table 5: Trial 20110142: Secondary Fracture Endpoints

	Alendronate Alendronate	Romosozumab Alendronate	Risk Difference* (95% CI)	Hazard Ratio (95% CI)
Nonvertebral Fracture, month 12, %	4.6	3.4	1.4 (0.1, 2.6)	0.74 (0.54, 1.01)
Nonvertebral Fracture, month 24, %	7.8	6.3	1.6 (-0.1, 3.3)	0.81 (0.64, 1.02)
Hip Fracture, month 12, %	1.1	0.7	0.3 (-0.3, 0.9)	0.64 (0.33, 1.26)
Hip Fracture, month 24, %	2.3	1.6	0.6 (-0.2, 1.4)	0.72 (0.46, 1.15)
*based on Kaplan Meier estimate				

4.4. Applicability of Efficacy Findings to U.S. Patients and U.S. Medical Practice

Only a very small number of subjects in trials 20070337 (132/7180, 1.8%) and 20110142 (57/4093, 1.4%) were enrolled in the United States. Analyses conducted in both trials demonstrated that there was no treatment-by-region interaction for the primary endpoints. Additionally, the lumbar spine and total hip BMD changes were consistent across all geographic areas. Given these consistent findings across all geographic regions, the fracture and BMD can be considered applicable to the U.S. population and U.S. medical practice.

4.5. Conclusions on Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness to support one year of romosozumab therapy for the treatment of osteoporosis in postmenopausal women.

Romosozumab 210 mg SC administered by a healthcare provider once a month reduced morphometric vertebral fractures compared to placebo in trial 20070337. At 12 months, the new morphometric vertebral fracture absolute risk reduction was 1.3% (95% CI: 0.8, 1.8) and the relative risk reduction was 73% (95% CI: 53, 84) with romosozumab compared to placebo. Romosozumab or placebo was given for the first year of this trial, and for the second year of the trial all subjects were switched to denosumab, an antiresorptive agent. At 24 months, the new morphometric vertebral fracture incidence was 2.5% in the placebo then denosumab group and 0.6% in the romosozumab then denosumab group with an absolute risk reduction of 1.9% (95% CI: 53, 84) and a relative risk reduction of 75% (95% CI: 60, 84).

In trial 20110142, which enrolled a population at higher risk of fracture, the incidence of new vertebral fracture at month 24 was 8.0% in the alendronate alone group compared to 4.1% in the group that received romosozumab for one year then alendronate for the second year, with an absolute risk reduction of 4.0% (95% CI: 2.5, 5.6) and a relative risk reduction of 50% (95% CI: 34, 62).

Although trial 20070337 demonstrated a significant reduction in clinical fractures (defined by the applicant as a composite of nonvertebral fractures and symptomatic vertebral fractures) at month 12 with romosozumab compared to placebo (with an absolute risk reduction of 1.2% and a relative risk reduction of 36% [p=0.008]), this trial did not demonstrate a significant reduction in nonvertebral fractures alone (which accounted for 88% of the fractures in this composite endpoint). The applicant has attributed the failure of romosozumab to show a statistically significant reduction on nonvertebral fracture risk to unexpectedly low nonvertebral fracture rates in Central/Latin America, the region with the highest enrollment (43%).

Conversely, trial 20110142, which had clinical and nonvertebral fractures as event-driven endpoints, demonstrated that romosozumab was efficacious in decreasing the risk of clinical fractures and nonvertebral fractures compared to alendronate. At the time of the primary analysis, 464 subjects had experienced a clinical fracture and 395 subjects had experienced a nonvertebral fracture and the median follow-up time was 33 months. The incidence of clinical fracture was 13.0% in the alendronate group and 9.7% in the romosozumab group, yielding a hazard ratio of 0.73 (95% CI: 0.61, 0.88). The incidence of nonvertebral fracture was 10.6% in the alendronate group and 8.7% in the romosozumab group, yielding a hazard ratio of 0.81 (95% CI: 0.66, 0.99). These findings were statistically significant with a 1-sided nominal p-value of 0.019 that was smaller than the alpha level of 0.0233.

BMD increases were consistent across the three postmenopausal osteoporosis trials. At 12 months, the increase in lumbar spine BMD with romosozumab 210 mg monthly was 11.6% in Phase 2 trial 20060326, 13.1% in trial 20070337, and 13.7% in trial 20110142. Increases in hip BMD were also consistently observed with romosozumab therapy.

Because of the cardiovascular safety concerns raised with romosozumab, it is important to evaluate romosozumab in the context of other osteoporosis therapies. Clearly, in the short term, romosozumab, as an anabolic agent, increases BMD and decreases fracture risk compared to alendronate. This is not surprising, given the different mechanisms of action of the two drug products. Table 6 below outlines the primary efficacy findings for approved osteoporosis therapies. Due to ethical concerns related to placebo-controlled fracture trials, more recent trials have enrolled a lower risk population, which has yielded a lower rate of fracture. Few trials report month 12 results, as this has not been a requirement for fracture studies.

Table 6: Postmenopausal Osteoporosis Fracture Trials: New Morphometric Vertebral Fractures, Risk Reductions

Drug		12 Months		24 Months		36 Months	
	Year	Absolute Risk Reduction (%)	Relative Risk Reduction (%)	Absolute Risk Reduction (%)	Relative Risk Reduction (%)	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
Romosozumab		1.3	73				
Abaloparatide	2017			3.9**	87**		
Denosumab	2010	1.4	61	3.5	71	4.8	68
Zoledronic acid	2007	2.2	60	5.5	71	7.6	70
Ibandronate (oral)	2003					4.9	52
Teriparatide	2002			9.3*	65*		
Risedronate (North America)	1998	4.0	65	5.9	55	5.0	41
Risedronate (Multinational)	1998	7.7	61	13.1	59	10.9	49
Raloxifene (≥1 baseline fracture)	1997					6.1	30
Raloxifene (no baseline fracture)	1997					2.4	55
Alendronate (FIT 1)	1995					7.1	47
Alendronate (FIT-2)	1995					2.3***	48***

*Forteo trial: 19 months median exposure
**Tymlos trial: risks at 25 months (18 months exposure to Tymlos or placebo, 1 month of no treatment, followed by 6 months of alendronate therapy)
***Fosamax FIT-2 trial: 48-month assessment
Sources: Unites States Prescribing Information

5. General Safety of Romosozumab

5.1. Overall Safety Outcomes

The general safety of romosozumab is predominantly derived from the 12-month romosozumab treatment periods in the placebo-controlled fracture trial 20070337 and the alendronate-controlled fracture trial 20110142. Event classifications were coded using the medical dictionary for regulatory activities (MedDRA) 20.0 for all trials. The overall incidence of reported adverse events are listed in Table 7 below and are consistent between treatment groups and across trials.

Table 7: Safety Events in Trials 20070337 and 20110142

Trial	**20070337**		**20110142**	
	Placebo	**Romosozumab**	**Alendronate**	**Romosozumab**
N	**3591**	**3589**	**2047**	**2046**
n, safety analysis	3576	3581	2014	2040
Age, years, mean (SD)	71 (6.9)	71 (7.0)	74 (7.5)	74 (7.5)
Death, n (%)	24 (0.7)	29 (0.8)	22 (1)	30 (2)
Serious Adverse Event	314 (9)	344 (10)	278 (14)	262 (13)
Adverse Event, Study Withdrawal	50 (1)	45 (1)	27 (1)	28 (1)
Adverse Event, Drug Withdrawal	96 (3)	106 (3)	66 (3)	71 (4)
Adverse Event	2863 (80)	2812 (79)	1584 (79)	1543 (76)

5.2. Deaths

In the two phase 3 fracture trials, a total of 105 deaths occurred during the double-blind 12-month study periods. In trial 20070337, 24 (0.7%) placebo subjects and 29 (0.8%) romosozumab subjects had a fatal adverse event. In trial 20110142, the population was slightly older and 22(1%) alendronate subjects and 30 (2%) romosozumab subjects died during the double-blind study period. Deaths by system/organ/class are outlined in Table 8. The events were generally well balanced between the treatment groups with two exceptions. In trial 20070337, an imbalance in deaths due to neoplasms was noted, occurring in 3 (<0.1%) subjects in the placebo group and 8 (0.2) subjects in the romosozumab group. This imbalance in deaths was predominantly due to malignant lung neoplasm, which occurred in no subjects in the placebo group and 4 subjects in the romosozumab group. A thorough review was conducted and is discussed in the adverse events of interest section below. All affected subjects were current or former smokers, the time to onset was short (47-132 days after first treatment of romosozumab), and the overall incidence of fatal and nonfatal lung neoplasms was balanced between treatment groups. In trial 20110142, an imbalance in deaths was noted in fatal cardiac disorders, which occurred in 3 (0.1%) alendronate-treated subjects and 9 (0.4%) romosozumab-treated subjects. A thorough evaluation of cardiac disorders was conducted and is discussed in section 6.1.

Table 8: Fatal Adverse Events in Trials 20070337 and 20110142

Trial	20070337		20110142	
	Placebo	**Romosozumab**	**Alendronate**	**Romosozumab**
N	**3591**	**3589**	**2047**	**2046**
n, safety analysis	3576	3581	2014	2040
Death, n (%)	24 (0.7)	29 (0.8)	22 (1)	30 (2)
Neoplasms	3 (<0.1)	8 (0.2)	3 (0.1)	4 (0.2)
Cardiac Disorders	5 (0.1)	7 (0.2)	3 (0.1)	9 (0.4)
General Disorders	7 (0.2)	6 (0.2)	5 (0.2)	2 (<0.1)
Injury, Poisoning, Procedural	1 (<0.1)	3 (<0.1)	0	2 (<0.1)
Nervous System	3 (<0.1)	1 (<0.1)	2 (<0.1)	3 (0.1)
Vascular Disorders	1 (<0.1)	2 (<0.1)	0	3 (0.1)
Gastrointestinal Disorders	1 (<0.1)	1 (<0.1)	0	0
Reproductive and Breast Disorders	0	1 (<0.1)	0	0
Hepatobiliary Disorders	1 (<0.1)	0	1 (<0.1)	0
Infections and Infestations	1 (<0.1)	0	6 (0.3)	5 (0.2)
Respiratory Disorders	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Psychiatric Disorders	0	0	0	1 (<0.1)
Renal Disorders	0	0	0	0

5.3. Serious Adverse Events

In trial 20070337, 314 (9%) subjects in the placebo group and 352 (10%) subjects in the romosozumab group reported a serious adverse event during the double-blind 12-month study period. In trial 20110142, the incidence of serious adverse events was slightly higher, occurring in 278 (14%) subjects in the alendronate group and 262 (13%) subjects in the romosozumab group during the double-blind 12-month study period. Serious adverse events by system/organ/class are outlined in Table 9. The most common serious adverse events in the romosozumab treatment group were pneumonia (10 subjects (0.3%) on placebo, 19 subjects (0.5%) on romosozumab); hypertension (5 subjects (0.1%) on placebo, 8 subjects (0.2%) on romosozumab); unstable angina (3 subjects (<0.1%) on placebo, 7 subjects (0.2%) on romosozumab); and congestive heart failure (4 subjects (0.1%) on placebo, 7 subjects (0.2%) on romosozumab) in trial 20070337. In the alendronate-controlled trial 20110142, there were no imbalances between the treatment groups in serious adverse events by preferred term.

Table 9: Serious Adverse Events in Trials 20070337 and 20110142

Serious Adverse Events				
Trial	**20070337**		**20110142**	
	Placebo	**Romosozumab**	**Alendronate**	**Romosozumab**
N	**3591**	**3589**	**2047**	**2046**
n, safety analysis	3576	3581	2014	2040
Serious Adverse Reaction, n (%)	314 (9)	344 (10)	278 (14)	262 (13)
Infections and Infestations	46 (1)	67 (2)	48 (2)	47 (2)
Neoplasms	47 (1)	51 (1)	23 (1)	29 (1)
Cardiac Disorders	39 (1)	48 (1)	34 (2)	40 (2)
Injury, Poisoning, Procedural	43 (1)	35 (1)	61 (3)	44 (2)
Nervous System	29 (1)	34 (1)	34 (2)	37 (2)
Gastrointestinal Disorders	31 (1)	32 (1)	23 (1)	31 (2)
Vascular Disorders	14 (0.4)	18 (0.5)	23 (1)	13 (1)
General Disorders	11 (0.3)	16 (0.4)	10 (0.5)	9 (0.4)
Musculoskeletal Disorders	31 (1)	16 (0.4)	32 (2)	17 (1)
Respiratory Disorders	26 (1)	15 (0.4)	25 (1)	13 (1)
Hepatobiliary Disorders	13 (0.4)	11 (0.3)	7 (0.3)	10 (0.5)
Reproductive and Breast Disorders	5 (0.1)	11 (0.3)	2 (<0.1)	6 (0.3)
Metabolism and Nutrition Disorders	5 (0.1)	10 (0.3)	11 (0.5)	4 (0.2)
Renal Disorders	7 (0.2)	7 (0.2)	4 (0.2)	8 (0.4)
Blood and Lymphatic Disorders	7 (0.2)	5 (0.1)	7 (0.3)	5 (0.2)
Eye Disorders	5 (0.1)	5 (0.1)	7 (0.3)	5 (0.2)
Psychiatric Disorders	5 (0.1)	5 (0.1)	3 (0.1)	3 (0.1)
Endocrine Disorders	2 (<0.1)	3 (<0.1)	3 (0.1)	2 (<0.1)
Ear	4 (0.1)	3 (,0.1)	2 (<0.1)	2 (<0.1)
Immune Disorders	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Investigations	4 (0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Product Issues	0	0	1 (<0.1)	1 (<0.1)
Skin Disorders	2 (<0.1)	5 (0.1)	1 (<0.1)	1 (<0.1)
Surgical and Medical Procedures	0	3 (<0.1)	0	1 (<0.1)
Social Circumstances	1 (<0.1)	0	0	0

5.4. Adverse Events Leading to Study Withdrawal

In trial 20070337, 50 (1%) placebo-treated subjects and 45 (1%) romosozumab-treated subjects withdrew from the study due to adverse events during the double-blind first year of the study. The events were evenly distributed across the treatment groups. The system/organ classes with the highest number of adverse events leading to withdrawal were musculoskeletal disorders, neoplasms, gastrointestinal disorders and nervous system disorders. In trial 20110142, 27 (1%) alendronate-treated subjects and 28 (1%) romosozumab-treated subjects withdrew from the study due to adverse events during the double-blind first year of the study. Similar to the placebo-controlled trial, events were evenly distributed between treatment groups and the system/organ classes with the highest number of adverse events leading to withdrawal were neoplasms, gastrointestinal disorders, nervous system disorders, and musculoskeletal disorders.

5.5. Adverse Events Leading to Study Drug Discontinuation

In trial 20070337, 96 (3%) subjects in the placebo group and 106 (3%) subjects in the romosozumab group discontinued study drug due to an adverse event during the double-blind 12-month treatment period. The most common reasons for study drug discontinuation were pain in extremity (1 placebo, 8 romosozumab); arthralgia (5 placebo, 5 romosozumab); nausea (0 placebo, 4 romosozumab); bone pain (1 placebo, 3 romosozumab); allergic dermatitis (1 placebo, 3 romosozumab); dizziness (5 placebo, 3 romosozumab); fatigue (3 placebo, 3 romosozumab); and musculoskeletal pain (7 placebo, 3 romosozumab). In trial 20110142, 66 (3%) subjects in the alendronate group and 71 (4%) subjects in the romosozumab group discontinued study drug due to an adverse event during the double blind 12-month treatment period. The adverse event pattern was similar to the placebo-controlled trial.

5.6. Common Adverse Events

During the double-blind treatment period of trial 20070337, 2863 (80%) placebo subjects and 2812 (79%) romosozumab-treated subjects reported an adverse event. As outlined in Table 10, the most common adverse events were viral upper respiratory tract infection, arthralgia, and back pain. A similar pattern of adverse events for romosozumab was reported in the alendronate-controlled trial 20110142.

Table 10: Common Adverse Events in Trials 20070337 and 20110142

Common Adverse Events				
Trial	**20070337**		**20110142**	
	Placebo	**Romosozumab**	**Alendronate**	**Romosozumab**
N	**3591**	**3589**	**2047**	**2046**
n, safety analysis	3576	3581	2014	2040
Adverse Events, n (%)	2863 (80)	2812 (79)	1584 (79)	1543 (76)
Viral upper respiratory infection	580 (16)	573 (16)	233 (12)	217 (11)
Arthralgia	434 (12)	468 (13)	194 (10)	166 (8)
Back pain	381 (11)	375 (11)	228 (11)	185 (9)
Pain in extremity	299 (8)	278 (8)	131 (7)	121 (6)
Fall	320 (9)	255 (7)	154 (8)	129 (6)
Headache	208 (6)	235 (7)	110 (6)	106 (5)
Hypertension	265 (7)	265 (6)	132 (7)	114 (6)

5.7. Adverse Events of Interest

Injection Site Reactions: In trial 20070337, injection site reactions occurred in 104 (3%) subjects in the placebo group and 188 (5%) subjects in the romosozumab group. There were no serious adverse events related to injection site reactions. Discontinuation from the trial due to injection site reactions occurred in 2 subjects in each treatment group. Discontinuation of study drug due

to injection site reactions occurred in 2 (<0.1%) subjects in the placebo group and 5 (0.1%) subjects in the romosozumab group.

During the double-blind treatment period of trial 20110142, adverse events of injection site reactions were reported for 53 (3%) subjects in the alendronate group and 90 (4%) subjects in the romosozumab group and none were reported as serious. The most common preferred terms for injection site reactions were injection site pain and injection site erythema.

Hypocalcemia*:* Hypocalcemia has been reported with osteoporosis therapies that inhibit bone resorption. Romosozumab predominantly functions as a bone anabolic agent but also has some function as an antiresorptive agent. The nadir in serum calcium appears to be 1 month following romosozumab injection. In trial 20070337, no serious adverse events of hypocalcemia were reported during the first year. One adverse event of Grade 2 hypocalcemia (albumin-corrected serum calcium 7.0 to 8.0 mg/dL, 1.75 to 2.0 mmol/L) was reported in a romosozumab-treated subject. In trial 20110142, 1 (< 0.1%) adverse event of hypocalcemia was reported in each treatment group. No hypocalcemia event was reported as serious. Both adverse events of hypocalcemia were grade 1 or grade 2 in severity and did not result in discontinuation of investigational product or discontinuation from the study.

Hypersensitivity: The applicant used the narrow standardized MedDRA query (SMQ) for hypersensitivity reactions. In trial 20070337, this query identified potential hypersensitivity reactions in 247 (7%) subjects in the placebo group and 242 (7%) subjects in the romosozumab group during the double-blind 12-month study period. The most common preferred terms were rash, dermatitis allergic, and eczema. When the search was narrowed to events occurring within 2 days of study drug administration, events were reported in 30 (1%) placebo subjects and 47 (1%) romosozumab subjects, and the most common preferred terms were injection site rash and rash. One fatality due to circulatory collapse occurred on study day 345, 9 days after romosozumab administration. The investigator did not attribute this event to study drug as there were no reports of flushing, pruritus, or urticaria preceding the event. Serious adverse events related to hypersensitivity reactions occurred in 0 subjects in the placebo group and 6 (0.2) subjects in the romosozumab group. Discontinuation from the trial due to hypersensitivity reactions occurred in 2 (<0.1%) subjects in the placebo group and 3 (<0.1%) subjects in the romosozumab group. Discontinuation of study drug due to potential hypersensitivity reactions occurred in 6 (0.2%) subjects in the placebo group and 11 (0.3%) subjects in the romosozumab group.

In trial 20070337, the applicant assessed whether the presence of antidrug antibody status impacted the development of hypersensitivity reactions. During the 12-month double-blind treatment period, potential hypersensitivity reactions occurred in 7% of placebo-treated subjects, 7% of romosozumab-treated subjects who were antibody negative and 7% of romosozumab-treated subjects who were antibody positive. When evaluated in terms of neutralizing antibody status, potential hypersensitivity reactions occurred in 7% of placebo-treated subjects, 7% of romosozumab-treated subjects who did not develop neutralizing antibodies and 3% of romosozumab-treated subjects who developed neutralizing antibodies. These data do not support an association between antidrug antibody status and hypersensitivity reactions.

In trial 20110142, potential hypersensitivity reactions were reported for 118 (6%) subjects in the alendronate group and 122 (6%) subjects in the romosozumab group during the 12-month double-blind period. The most common preferred terms were rash, rash pruritic, dermatitis allergic, and eczema. Serious adverse events related to potential hypersensitivity were reported for 2 (< 0.1%) subjects in the alendronate group and 3 (0.1%) subjects in the romosozumab group. Discontinuation from the trial due to hypersensitivity reactions occurred in no subjects in the alendronate group and 1 (<0.1%) subject in the romosozumab group. Discontinuation of study drug due to potential hypersensitivity reactions occurred in 3 (0.1%) subjects in the alendronate group and 4 (0.2%) in the romosozumab group.

Malignant or unspecified tumors: The Wnt-beta-catenin pathway plays a role in sclerostin signaling. Wnt-beta catenin is also thought to play a role in some tumor suppressor signals. Therefore, the applicant evaluated whether inhibition of sclerostin by romosozumab increases the incidence of malignant tumors using the narrow SMQ for malignancies and unspecified tumors. As discussed previously, in trial 20070337, an imbalance in deaths was noted in the system/organ/class neoplasms. The imbalance was predominantly due to malignant lung neoplasm, which occurred in no subjects in the placebo group and 4 subjects in the romosozumab group. A thorough case review was conducted. All affected subjects were current or former smokers, the time to diagnosis/onset was short (47-132 days after first treatment of romosozumab), and the overall incidence of fatal and nonfatal lung neoplasm was balanced between treatment groups. Overall, adverse events of malignant or unspecified tumors were reported in 55 (2%) subjects in the placebo group and 50 (1%) subjects in the romosozumab group during the 12-month double-blind portion of the trial. Serious adverse events of malignant or unspecified tumors were reported in 41 (1%) subjects in the placebo group and 35 (1%) subjects in the romosozumab group. Basal cell carcinoma was the most common malignancy reported, occurring in 16 (0.4%) subjects in the placebo group and 8 (0.2%) subjects in the romosozumab group.

In trial 20110142, there were no imbalances in neoplasm events during the 12-month double-blind period. Fatal adverse events due to neoplasm occurred in 3 (0.1%) subjects in the alendronate group and 4 (0.2%) subjects in the romosozumab group. Serious adverse events of malignant or unspecified tumors were reported in 20 (1%) subjects in the alendronate group and 25 (1%) subjects in the romosozumab group. Adverse events of malignant or unspecified tumors were reported in 28 (1%) subjects in the alendronate group and 32 (2%) subjects in the romosozumab group. The most common malignancy reported was basal cell carcinoma occurring in 4 (0.2%) subjects in the alendronate group and 4 (0.2%) subjects in the romosozumab group.

When evaluated in totality, FDA does not believe that there is a safety signal for neoplasms.

Table 11: Neoplasm Events in Trials 20070337 and 20110142

Neoplasm* Adverse Events				
Trial	**20070337**		**20110142**	
	Placebo	**Romosozumab**	**Alendronate**	**Romosozumab**
N	3591	3589	2047	2046
n, safety analysis	3576	3581	2014	2040
Death, n (%)	3 (<0.1)	8 (0.2)	3 (0.1)	4 (0.2)
Lung neoplasm, malignant	0	4 (0.1)	0	0
Lung adenocarcinoma	0	0	0	1 (<0.1)
Serious Adverse Event	47 (1)	51 (1)	23 (1)	29 (1)
MedDRA SMQ**	41 (1)	35 (1)	20 (1)	25 (1)
Adverse Event	101 (3)	113 (3)	58 (3)	64 (3)
MedDRA SMQ**	55 (2)	50 (1)	28 (1)	32 (2)
Basal cell carcinoma	16 (0.4)	8 (0.2)	4 (0.2)	4 (0.2)
*Neoplasms SOC = neoplasms benign, malignant and unspecified (including cysts and polyps) **MedDRA SMQ = standardized MedDRA Query (SMQ) for Malignancy and Unspecified Tumors				

Inflammatory Conditions: Some literature suggests that sclerostin inhibition promotes tumor necrosis factor (TNF)-mediated inflammatory joint disease. The applicant constructed a MedDRA search strategy to identify events related to TNF-mediated inflammation during the 12-month double-blind portion of the two fracture trials. In trial 20070337, in subjects with a prior history of TNF-mediated inflammatory disease, TNF-mediated inflammatory adverse events occurred in 8 (14%) subjects in the placebo group and 6 (9%) subjects in the romosozumab group. In subjects without a prior history, TNF-mediated inflammatory adverse events occurred in 5 (0.1%) subjects in the placebo group and 2 (<0.1%) subjects in the romosozumab group. In trial 20110142, in subjects with a prior history of TNF-mediated inflammatory disease, TNF mediated inflammatory adverse events occurred in 6/69 (9%) subjects in the alendronate group and 5/54 (9%) subjects in the romosozumab group. In subjects with no prior history, TNF-mediated inflammatory adverse events occurred in 8/1945 (0.4%) subjects in the alendronate group and 6/1986 (0.3%) subjects in the romosozumab group.

Osteoarthritis: Sclerostin is expressed in articular cartilage, raising concerns that sclerostin inhibition may negatively affect articular cartilage. In trial 20070337, adverse events of osteoarthritis were reported in 318 (9%) subjects in the placebo group and 285 (8%) subjects in the romosozumab group during the 12-month double-blind period. Serious adverse events of osteoarthritis were reported in 17 (1%) subjects in the placebo group and 7 (0.2%) subjects in the romosozumab group. In trial 20110142, during the 12-month double-blind period, 148 (7.3%) subjects in the alendronate group and 138 (6.8%) subjects in the romosozumab group were reported to have adverse events of osteoarthritis. The most frequently reported adverse events were osteoarthritis, spinal osteoarthritis, and exostosis. Serious adverse events of osteoarthritis events were reported for 6 (0.3%) subjects in the alendronate group and 8 (0.4%) subjects in the romosozumab group.

The applicant also conducted an osteoarthritis substudy in trial 20070337. This substudy enrolled 343 (175 placebo, 168 romosozumab) subjects. During the 12-month double-blind

period, 38 subjects (25 subjects (14%) on placebo, 13 subjects (8%) on romosozumab) discontinued the study. The endpoint was change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score analyzed with ANCOVA using treatment, baseline WOMAC score, baseline body mass index (BMI), and baseline age as independent variables. The baseline WOMAC total score was 36.7 in the placebo group and 39.4 in the romosozumab group. The LS mean change in total WOMAC score was -1.3 in the placebo group and -2.2 in the romosozumab group. Progressive worsening of knee osteoarthritis was reported in 25 (21%) placebo subjects and 21 (17%) romosozumab subjects. Osteoarthritis adverse events were reported in 12% of placebo subjects and 8% of romosozumab subjects in this substudy.

Hyperostosis: Hyperostosis with adverse neurologic consequences is a feature of diseases of sclerostin under-expression (sclerosteosis and van Buchem disease). The applicant constructed a MedDRA search strategy to identify events related to hyperostosis. In trial 20070337, adverse events of hyperostosis were reported in 28 (1%) subjects in the placebo group and 18 (1%) subjects in the romosozumab group during the 12-month double-blind period. Most preferred terms were related to spinal stenosis. Serious adverse events of hyperostosis were reported in 5 (0.1%) subjects in the placebo group and 1 (<0.1%) subject in the romosozumab group. In trial 20110142, adverse events of hyperostosis were reported in 12 (1%) subjects in the alendronate group and 2 (< 0.1%) subjects in the romosozumab group during the one-year double-blind period. The most common preferred terms were exostosis and spinal stenosis. Serious adverse events of hyperostosis were reported in 2 (<0.1%) subjects in the alendronate group and no subjects in the romosozumab group.

One potential neurologic consequence of hyperostosis is hearing loss. The applicant conducted an audiology substudy of trial 20070337 that enrolled 498 (243 placebo, 255 romosozumab) subjects. During the 12-month double-blind period, 34 subjects (18 subjects (7%) on placebo, 16 (6%) subjects on romosozumab) discontinued the substudy. The protocol defined hearing changes using American Speech-Language-Hearing Association (ASHA) criteria. Hearing loss was defined as an increase in hearing threshold $\geq$ 20 dB at any single frequency, or loss of $\geq$ 10 dB at any 2 adjacent frequencies, or loss of response at 3 consecutive frequencies where responses were previously obtained. Hearing gain was defined as a decrease hearing threshold $\geq$ 20 dB at any single frequency, or gain of $\geq$ 10 dB at any 2 adjacent frequencies, or loss of response at baseline but a response obtained post-baseline at 3 consecutive frequencies. Through month 12, protocol-defined hearing loss was reported in 43/184 (23%) subjects in the placebo group and 54/209 (26%) subjects in the romosozumab group. Protocol-defined hearing gain was reported in 24/184 (19%) subjects in the placebo group and 40/209 (19%) subjects in the romosozumab group. The LS mean change in air conduction was 0.3 in the placebo group and 1.0 in the romosozumab group.

Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ) is a rare adverse reaction associated with potent antiresorptive medications. The applicant defined ONJ as an event of interest and all potential events of ONJ identified through a predefined search of MedDRA terms were submitted to an independent external adjudication committee for review and adjudication. In trial 20070337, no placebo subjects and one romosozumab subject had a positively adjudicated case of ONJ during the 12-month double-blind period. One additional subject who had received

romosozumab had positively adjudicated ONJ while undergoing denosumab therapy in the second year of the trial. In trial 20110142, no cases of ONJ occurred in the 12-month double-blind treatment period. In the second year of the trial when all subjects were on alendronate, two cases of ONJ occurred. One subject was in the alendronate alone group and the other subject was in the romosozumab then alendronate group.

While ONJ has been reported with potent antiresorptive agents such as denosumab and alendronate, the occurrence of ONJ with romosozumab therapy was not anticipated, given the predominant anabolic action of the drug. The mechanism is unclear at this time and ONJ will continue to be followed closely.

To further inform the ONJ risk the applicant conducted a study in a rat model of ONJ. Osteoporotic rats were treated with vehicle, zoledronic acid or sclerostin antibody (Scl-Ab) for 12 weeks, after which experimental periodontitis was induced by molar ligature. Animals were necropsied after an additional treatment period of 10 weeks. Evaluations included bone formation assessment, histology of maxillae, microCT of maxillae and vertebra, and vertebral histomorphometry. The data showed a transient increase in systemic bone formation by Scl-Ab. Vertebral bone formation was markedly increased by Scl-Ab and decreased by zoledronic acid. Vehicle-treated animals showed extensive alveolar bone loss and inflammatory infiltrate in areas of experimental periodontitis. Bone loss was markedly reduced compared to vehicle controls in zoledronic acid -treated animals and osteoclast number was decreased. Bone loss was also reduced in Scl-Ab treated animals. Zoledronic acid-treated rats developed radiographic and histologic features of ONJ, evidenced by a marked increase in relative area of osteonecrotic bone containing empty osteocytic lacunae and by increased bone exposure. Features of ONJ were not observed in Scl-Ab treated animals. It was concluded that in ovariectomized rats with experimental periodontitis, Scl-Ab enhanced bone formation and prevented bone loss but did not induce ONJ-like lesions in contrast to the bisphosphonate zoledronic acid.

Atypical femoral fractures: Atypical femoral fracture is a rare adverse reaction associated with potent antiresorptive medications. The applicant defined atypical femoral fracture as an event of interest and all potential events of femoral fracture identified through a predefined search of MedDRA terms were submitted to an independent external adjudication committee for review and adjudication. In trial 20070337, no placebo subjects and one romosozumab subject had a positively adjudicated case of atypical femoral fracture. In trial 20110142, no cases of atypical femoral fracture occurred in the 12-month double-blind treatment period. In the second year of the trial when all subjects were on alendronate, 6 cases of atypical femoral fracture were positively adjudicated (four in the alendronate alone group and 2 in the romosozumab then alendronate group). An additional subject from the romosozumab then alendronate group experienced an atypical femoral fracture after withdrawing from the study. She had received romosozumab for 12 months and alendronate for 2.5 years.

5.8. Immunogenicity

Romosozumab is a large humanized monoclonal antibody that could trigger an immune response. The applicant developed and validated two assays to detect the presence of anti-

romosozumab antibodies in human serum: an electrochemiluminescence (ECL)-based bridging immunoassay to detect binding antibodies to romosozumab and an ECL-based competitive binding assay to determine the neutralizing potential of anti-drug antibodies (ADA). Data on antibody titer are not available. The applicant used signal to noise values to evaluate the magnitude of the antibody response.

In trial 20070337, among subjects who received romosozumab, 22 (0.6%) subjects tested positive for pre-existing binding antibodies at baseline; none had pre-existing neutralizing antibodies. For subjects with postbaseline results at any time during the study (n = 3575), 637 (17.8%) subjects developed binding anti-romosozumab antibodies and 5 (0.1%) subjects developed neutralizing antibodies.

In trial 20110142, among subjects who received romosozumab, 6 (0.3%) subjects tested positive for pre-existing binding antibodies at baseline; none had pre-existing neutralizing antibodies. For subjects with postbaseline results during the 12-month double blind treatment period and through month 18 (n = 1955), 310 (15%) subjects developed binding anti-romosozumab antibodies (transient in 177 subjects [9%]) and 12 (0.6%) subjects developed neutralizing antibodies.

Effects of anti-drug antibody development on romosozumab exposure: Among 5914 postmenopausal women treated with the romosozumab SC 210 mg monthly dosage regimen in both fracture trials, approximately 18% developed antibodies to romosozumab. Of the subjects who developed antibodies to romosozumab, approximately 5% had antibodies that were classified as neutralizing. Development of ADA was associated with reduced serum romosozumab concentrations. At month 12, exposures were approximately 10% decreased in antibody positive subjects compared to antibody negative subjects.

Effects of anti-drug antibody development on efficacy parameters: Exploratory analyses were conducted to evaluate the effect of romosozumab antibody on BMD. In trial 20070337, the month 15 antibody status was used for evaluation. As outlined in the Table 12, at months 12 and 24, subjects who developed antibodies experienced similar BMD increases to subjects without antibodies to romosozumab. Additionally, the assay signal-to-noise ratio did not appear to affect the BMD results. Similar results were seen for trial 20110142.

Table 12: Efficacy Parameters Based on Antibody Status

Efficacy Parameters Based on Antibody Status			
	ADA negative	ADA binding Antibody positive	ADA neutralizing Antibody positive
Trial 20070337			
Bone Mineral Density at 12 months			
Lumbar Spine, mean % (SD)	13.1 (6.0)	13.1 (5.9)	11.6 (5.0)
Total Hip, mean % (SD)	6.0 (4.2)	6.1 (4.2)	7.4 (4.6)
Femoral Neck, mean % (SD)	5.5 (4.6)	5.7 (4.7)	7.3 (6.4)
Bone Mineral Density at 24 months			
Lumbar Spine, mean % (SD)	16.7 (7.0)	16.7 (7.2)	15.1 (7.7)
Total Hip, mean % (SD)	8.5 (4.8)	8.8 (5.1)	9.0 (7.6)
Femoral Neck, mean % (SD)	7.5 (5.1)	7.7 (5.6)	9.3 (8.9)
Trial 20110142			
Bone Mineral Density at 12 months			
Lumbar Spine, mean % (SD)	13.7 (7.2)	13.8 (7.1)	13.8 (8.5)
Total Hip, mean % (SD)	6.2 (5.2)	6.3 (5.0)	6.3 (4.5)
Femoral Neck, mean % (SD)	5.3 (5.5)	5.3 (5.4)	7.9 (6.4)
Bone Mineral Density at 24 months			
Lumbar Spine, mean % (SD)	15.4 (8.4)	14.8 (8.7)	14 (7.6)
Total Hip, mean % (SD)	7.2 (5.8)	7.5 (5.7)	6.9 (4.8)
Femoral Neck, mean % (SD)	6.3 (6.1)	6.6 (5.4)	7.5 (4.2)
ADA=anti-drug antibody			

Effects of anti-drug antibody development on safety parameters: When evaluated based on antibody status, there were no differences in overall adverse event reporting in antibody positive subjects compared to antibody negative subjects. Specific evaluations were performed for hypersensitivity reactions, injection site reactions, and autoimmune disorders. There were no differences in potential hypersensitivity reaction and autoimmune disorder adverse event reporting in antibody positive subjects compared to antibody negative subjects. Injection site reaction adverse events were reported in 3% of placebo subjects, 5% of romosozumab antibody negative subjects, and 6% of romosozumab antibody positive subjects.

6. Cardiovascular Safety of Romosozumab

Sclerostin gene SOST mRNA is expressed in the heart, aorta, liver, and kidney. Therefore, there is a concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification. The applicant identified cardiovascular adverse events as an event of interest and adjudicated all deaths and cardiovascular serious adverse events in their two postmenopausal osteoporosis phase 3 trials and in their male osteoporosis phase 3 trial. The placebo-controlled fracture trial 20070337 did not show a cardiovascular safety signal. However, the alendronate-controlled fracture trial 20110142 and the smaller BMD trial 20110174 in men with osteoporosis did show a cardiovascular safety signal. These findings are explained in more detail in the sections below.

6.1. Clinical Cardiovascular Evaluation

Two large, pivotal, controlled studies were conducted to establish the efficacy and safety of romosozumab for the treatment of postmenopausal women with osteoporosis. A smaller study in men with osteoporosis was also conducted to support a future indication in that population.

The outcomes of interests to evaluate cardiovascular risk were major adverse cardiovascular events (MACE) and cardiovascular serious adverse events (CV SAEs) that occurred during the double-blind period of each trial. MACE was defined as a composite endpoint of cardiovascular death, nonfatal myocardial infarction (MI) or nonfatal stroke, and CV SAEs included death, cardiac ischemic events (MI, angina, coronary revascularization), cerebrovascular events (stroke, transient ischemic attack), noncoronary revascularization, hospitalization for heart failure, and peripheral vascular events not requiring revascularization. Cardiovascular death included deaths of undetermined cause.

The applicant performed a comprehensive evaluation of cardiovascular safety that included two adjudications of potential cardiovascular adverse events reported in the pivotal phase 3 trials (20070337, 20110142 and 20110174). The initial cardiovascular adjudication was performed by the Duke Clinical Research Institute (DCRI). All deaths and serious adverse events that were indeterminate or deemed by the investigator to be of potential cardiovascular origin or etiology, were submitted to this independent committee for adjudication. SAEs with terms mapping to a pre-defined preferred term list potentially indicative of cardiovascular etiology were also adjudicated. The initial adjudication process focused on cardiovascular SAEs. Once a signal was seen, the applicant felt it was necessary to perform a comprehensive review of all available data from trials 20070337, 20110142 and 20110174. Therefore, the Thrombolysis in Myocardial Infarction (TIMI) Study Group conducted a second adjudication. The TIMI assessment was performed as an independent, post-hoc, blinded review of all adverse event data (serious and non-serious) from Trials 20070337, 20110142, and 20110174 and included re-adjudication of all deaths and other serious adverse events previously adjudicated by DCRI, blinded to treatment and DCRI adjudication result. The external independent adjudication committees were comprised of physicians with expertise in cardiology, osteoporosis, internal medicine, or neurology. The DCRI and TIMI adjudications yielded similar results. Therefore, the results below focus on the original DCRI-adjudication rather than the post-hoc TIMI-adjudication.

For each osteoporosis fracture trial, the applicant analyzed the time to MACE and CV SAE and estimated the hazard ratios (HR) for romosozumab compared to placebo (Trials 20070337, 20110174) or alendronate (Trial 20110142). The applicant also conducted a meta-analysis using data from all three trials that combined placebo and alendronate into one comparator group. The statistical population for these analyses was the safety population, defined as all randomized subjects who received at least one dose of study medication in the 12-month double-blind study period.

The FDA conducted a similar meta-analysis using Trials 20070337 and 20110142, studies conducted in postmenopausal women with osteoporosis, the indicated population. The FDA evaluated the MACE results from the male osteoporosis trial separately because that trial

included a different patient population and was much smaller than the fracture outcomes trials in postmenopausal osteoporosis.

Additionally, the FDA conducted a network meta-analysis using the two postmenopausal osteoporosis fracture trials to compare multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of randomized controlled trials. This analysis compared the hazard of MACE in the romosozumab arm to the placebo arm in trial 20070337 and compared the hazard of MACE in the alendronate arm from trial 20110142 to the placebo arm in trial 20070337. The FDA conducted two network meta-analyses based on a fixed-effects model, one that used univariate analysis with treatment group adjusted only and another that used multivariate analysis with treatment group and age adjusted and stratified by countries.

Findings**:**

The following information relevant to the assessment of cardiovascular risk was collected during routine patient screening and at study visits: age, blood pressure, medical history which could be queried for prior myocardial infarction, prior stroke, hypertension, diabetes mellitus, hypercholesterolemia, smoking history, and concomitant medications. Fasting lipids and high sensitivity C-reactive protein levels were not evaluated. As outlined in Table 13, cardiovascular medical history and baseline cardiovascular risk characteristics for trials 20070337 and 20110142 were reasonably balanced across treatment groups within each study.

Table 13: Baseline Cardiovascular Risk Characteristics (Trials 20070337 and 20110142)

Trial	**20070337**		**20110142**	
	Placebo	**Romosozumab**	**Alendronate**	**Romosozumab**
n, safety analysis	3576	3581	2014	2040
Age (mean, standard deviation)	71 (6.9)	71 (7.0)	74 (7.5)	74 (7.5)
Any cardiovascular related disease, n (%)	2703 (76)	2649 (74)	1603 (80)	1618 (79)
Hyperlipidemia, n (%)	1408 (39)	1379 (39)	675 (34)	709 (35)
Hypertension, n (%)	1919 (54)	1890 (53)	1227 (61)	1248 (61)
Diabetes, n (%)	472 (13)	452 (13)	276 (14)	245 (12)
Cardiovascular Disease, n (%)	2331 (65)	2327 (65)	1456 (72)	1497 (73)
Ischemic Heart Disease, n (%)	343 (10)	318 (9)	257 (13)	295 (15)
Myocardial Infarction, n (%)	77 (2)	76 (2)	50 (3)	71 (4)
Revascularization, n (%)	48 (1)	51 (1)	42 (2)	40 (2)
Afib/Aflutter, n (%)	76 (2)	58 (2)	76 (4)	93 (5)
Cerebrovascular Disease, n (%)	198 (6)	179 (5)	186 (9)	149 (7)
Ischemic CVA/TIA, n (%)	185 (5)	169 (5)	176 (9)	140 (7)
Stroke, n (%)	95 (3)	83 (2)	81 (4)	58 (3)

Afib=atrial fibrillation; Aflutter=atrial flutter; CVA=cerebrovascular accident; TIA=transient ischemic attack

In the placebo-controlled trial 20070337, there was no evidence of an imbalance in MACE or CV SAEs. As outlined in the table below, the incidence of MACE, CV SAE, and cardiovascular death was similar between treatment groups during the first year of the trial. In contrast, during

the first year of Trial 20110142, imbalances were seen in MACE (22 (1.1%) in the alendronate group and 41 (2.0%) in the romosozumab group) with a hazard ratio of 1.87 (95% CI: 1.11, 3.14) and the components of MACE, cardiovascular death (12 (0.6%) in the alendronate group and 17 (0.8%) in the romosozumab group) with a hazard ratio of 1.42 (95% CI: 0.68, 2.97), myocardial infarction (5 (0.2%) in the alendronate group and 16 (0.8%) in the romosozumab group) with a hazard ratio of 3.21 (95% CI: 1.18, 8.77) and stroke (7 (0.3%) in the alendronate group and 13 (0.6%) in the romosozumab group) with a hazard ratio of 1.86 (95% CI: 0.74, 4.67).

Table 14: Adjudicated Major Adverse Cardiovascular Events (MACE), Cardiovascular (CV) Serious Adverse Events (SAEs) and Cardiovascular Deaths

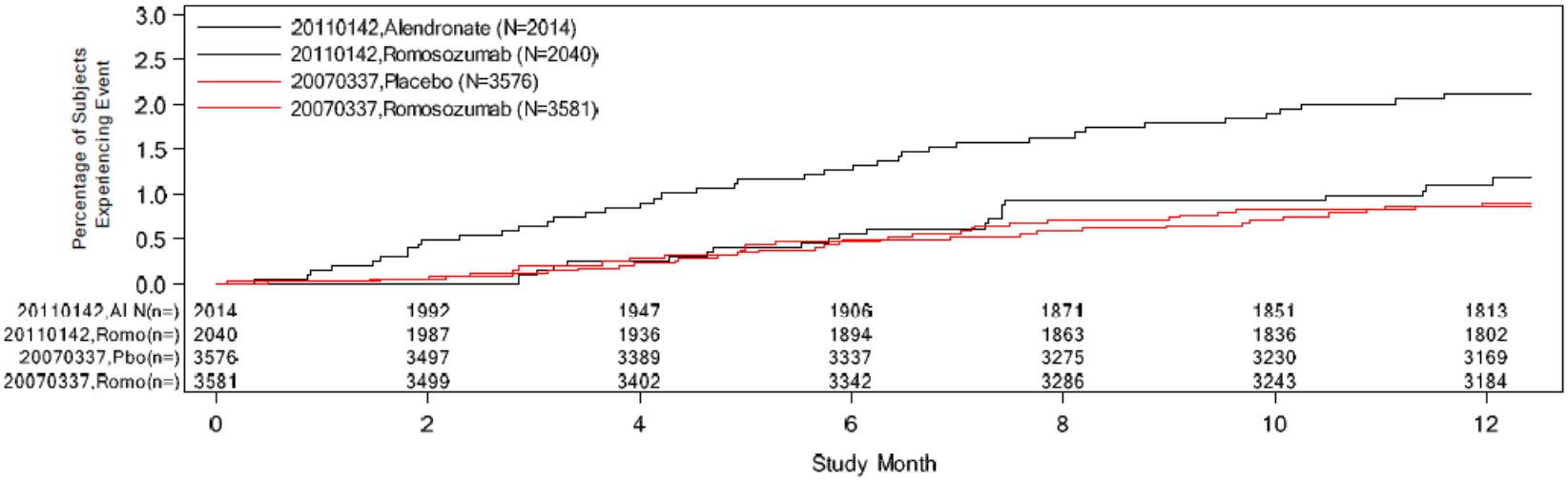
Trial	**20070337**		**20110142**	
	Placebo	**Romosozumab**	**Alendronate**	**Romosozumab**
n, safety analysis	3576	3581	2014	2040
MACE, n (%)	29 (0.8)	30 (0.8)	22 (1.1)	41 (2.0)
Hazard Ratio (95% CI)	1.03 (0.62, 1.72)		1.87 (1.11, 3.14)	
CV Death, n (%)	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.8)
Hazard Ratio (95% CI)	1.13 (0.56, 2.26)		1.42 (0.68, 2.97)	
Myocardial Infarction, n (%)	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Hazard Ratio (95% CI)	1.12 (0.43, 2.91)		3.21 (1.18, 8.77)	
Stroke, n (%)	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)
Hazard Ratio (95% CI)	0.80 (0.32, 2.02)		1.86 (0.74, 4.67)	
Any cardiovascular SAE, n (%)	46 (1.3)	46 (1.3)	38 (1.9)	50 (2.5)
Hazard Ratio (95% CI)	1.00 (0.66, 1.50)		1.32 (0.87, 2.01)	
Cardiac ischemic event, n (%)	16 (0.4)	16 (0.4)	6 (0.3)	16 (0.8)
Hazard Ratio (95% CI)	1.00 (0.50, 2.00)		2.68 (1.05, 6.84)	
Heart failure, n (%)	5 (0.1)	7 (0.2)	8 (0.4)	4 (0.2)
Hazard Ratio (95% CI)	1.40 (0.44, 4.40)		0.50 (0.15, 1.66)	
Non-coronary revascularization, n (%)	2 (<0.1)	1 (<0.1)	5 (0.2)	3 (0.1)
Hazard Ratio (95% CI)	0.50 (0.05, 5.49)		0.60 (0.14, 2.52)	
Cerebrovascular event, n (%)	11 (0.3)	10 (0.3)	7 (0.3)	16 (0.8)
Hazard Ratio (95% CI)	0.91 (0.39, 2.14)		2.30 (0.94, 5.58)	
Periph vascular, no revascular, n (%)	1 (<0.1)	4 (0.1)	2 (<0.1)	0 (0.0)
Hazard Ratio (95% CI)	3.99 (0.45, 35.72)		Not Estimable	
CI = Confidence interval				

Trial 20110174 is the 12-month, placebo-controlled, bone mineral density study in men with osteoporosis that enrolled 244 men aged 55 to 90 years with a mean age of 72 years. In Trial 20110174, there was one subject in each treatment group with a positively adjudicated cardiovascular fatal adverse event. CV SAE occurred in 2 (2.5%) subjects in the placebo group and 8 (4.9%) subjects in the romosozumab group. MACE occurred in 2 (2.5%) in the placebo group and 6 (3.7%) subjects in the romosozumab group.

The figure below displays the time to first MACE through the 12-month double-blind romosozumab treatment period for Trials 20070337 and 20110142.

Figure 2: Time to First Occurrence of Adjudicated MACE

Figure 14-6.2.1.9. Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Event Leading to Death, Serious Myocardial Infarction or Stroke Through Month 12
(Safety Analysis Set)
(DCRI Adjudication of 20070337 and 20110142)



N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period
n = Number of subjects at risk for event at time point of interest
Study 20070337 used 1:1 randomization allocation ratio between romosozumab and placebo.
Study 20110142 used 1:1 randomization allocation ratio between romosozumab and alendronate.
The timepoint for study month 12 is set at study day 359 (study day 366 - 7 days).
Death events include fatal events adjudicated as cardiovascular-related or undetermined.

Top black line = romosozumab arm in Trial 20110142
Bottom black line = alendronate arm in Trial 20110142

Across the three phase 3 trials, there was a total of 53 subjects (0.9%) who received placebo or alendronate and 77 subjects (1.3%) who received romosozumab who experienced MACE in the 12-month double-blind period. A meta-analysis of time to first MACE using data from all three trials and comparing romosozumab to placebo and alendronate combined, resulted in a HR of 1.40 (95% CI: 0.99, 1.99).

When limiting the meta-analysis to the two studies in postmenopausal women, Trials 20070337 and 20110142, 51 (0.9%) subjects in the control group and 71 (1.3%) subjects in the romosozumab group experienced MACE, yielding a HR of 1.38 (95% CI: 0.96, 1.99).

Evaluating Potential Explanations for the Cardiovascular Findings

Romosozumab did not appear to have effects on blood pressure in the phase 3 trials and as noted previously, other cardiovascular risk factors, such as lipid parameters were not assessed. In addition, there were no apparent imbalances in cardiovascular risk factors between treatment groups that could explain the cardiovascular findings. After conducting additional exploratory analyses, some of which are summarized below, neither the applicant nor the FDA has been able to conclusively determine the cause(s) for the discrepant MACE results between the placebo-controlled postmenopausal osteoporosis trial and the other two phase 3 trials.

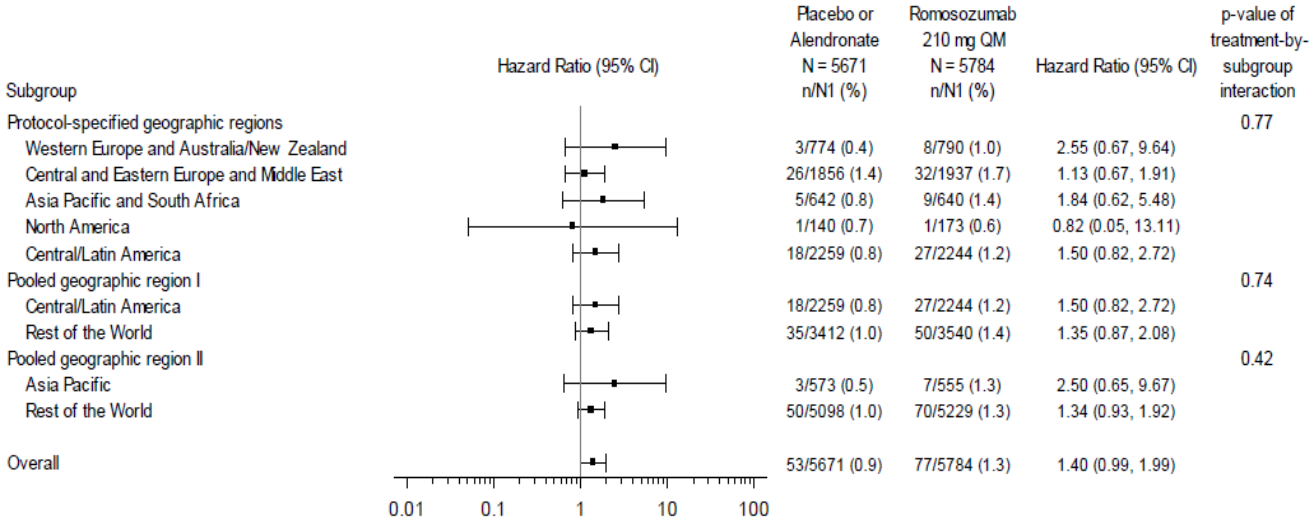
The FDA's univariate network meta-analysis yielded a HR of 1.03 (95% CI: 0.62, 1.72) when comparing the hazard of MACE in the romosozumab arm to the placebo arm. This HR was identical to the HR from Trial 20070337 because this study provided all the data for the comparison between romosozumab and placebo. In contrast, when comparing the hazard of MACE in the alendronate arm from Trial 20110142 to the placebo arm from Trial 20070337, the HR was 0.55 (95% CI: 0.27, 1.14), which represented a 45% risk reduction with alendronate compared to placebo. The multivariate network meta-analysis results, adjusted by treatment group and age, and stratified by country did not differ from the univariate analysis. This finding suggests that the rate of MACE with alendronate was lower than that with placebo, but is limited by cross-study comparisons and cannot definitively establish whether alendronate is cardioprotective.

The applicant used cardiovascular risk calculators post hoc to assess whether the cardiovascular findings with romosozumab differed depending on a subject's baseline cardiovascular risk in trials 20070337 and 20110142. However, the lack of fasting lipid levels impaired the ability to use the Raloxifene Use for the Heart (RUTH) or Framingham Risk Score as intended. Therefore, modified versions of these scores were used, with hyperlipidemia identified based on medical history (with narrow search of the hyperlipidemia SMQ), use of a statin at baseline, or with assumptions for total cholesterol and HDL cholesterol based on observed average values for age categories. In both studies, there were no significant differences in MACE among subgroups with different baseline risk categories (utilizing both modified RUTH and modified Framingham Risk Scores). This finding does not suggest an exacerbation of underlying cardiovascular disease with romosozumab, but the data are not conclusive.

Few subjects in these osteoporosis trials were enrolled from the United States. While the applicant has provided data that supports the generalizability of the efficacy findings to the US population and US medical practice, it is not clear that the cardiovascular findings are similarly generalizable. FDA generally requests that at least 25% of the enrolled population come from the US for cardiovascular outcome trials. The applicant conducted subgroup analyses based on geographic regions, as outlined in the figure below. Point estimates for hazard ratios of subgroups of the different geographic regions were consistent with the hazard ratios of the overall population.

Figure 3:Subgroup Analysis by Geographic Region

Figure 8. Subgroup Analysis by Geographic Region: Time to First MACE (Composite Endpoint) Through Month 12 (Safety Analysis Set) (DCRI Adjudication of Studies 20070337, 20110142, and 20110174)



N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period; N1 = Number of subjects in the subgroup
Hazard ratio and 95% CI are based on the Cox proportional hazard model comparing romosozumab versus 'control' (either placebo or alendronate).
Death events include fatal events adjudicated as cardiovascular-related or undetermined.

The applicant and FDA also evaluated the incidence rates of MI and stroke in the romosozumab phase 3 trials as compared to background rates reported in population-based studies for similarly aged cohorts of women and men. The FDA review identified 13 studies which revealed a wide range of incidence rate estimates (for MI: from 1.2 to 30.3 per 1,000 person-years (PYs) in osteoporosis patients and 5.8-10.4 per 1,000 PYs in the general population; for stroke, from 1.3 to 56.2 per 1,000 PYs in osteoporosis patients and 2.4 to 22.4 per 1,000 PYs in the general population). The FDA identified studies had a wider range of background incidence, likely due to population heterogeneity and outcome definitions, and may be subject to misclassification bias due to use of unadjudicated cases, which make them likely to overestimate the background incidence rates of MI and stroke in the osteoporosis population. Based on the literature review, FDA concludes that the background incidence rates of stroke and MI vary substantially in the

published literature; and the incidence rates of MI and stroke reported in patients ≥ 55 years old enrolled in the Phase 3 trials of romosozumab generally fall within the established background incidence rates from population-based studies for similarly aged cohorts of women and men.

Because of the early separation of the romosozumab treatment group in trial 20110142, FDA recommended that the applicant assess whether romosozumab has adverse effects that might contribute to the cardiovascular outcomes seen, such as platelet aggregation, vasoconstriction, and blood pressure. The results of these evaluations are discussed below in section 6.2.

6.2. Nonclinical and *in vitro* Cardiovascular Evaluation

Sclerostin inhibition and vascular calcification

The sclerostin (SOST) gene is expressed not only in bone, but also in other tissues including the aorta of several species (mouse, monkey, human). Because there have been reports of upregulation of sclerostin in foci of vascular calcification in mice, rats and humans, and sclerostin has been shown to inhibit mineralization by bone cells, it has been suggested that sclerostin may function as a negative regulator of vascular calcification. This raises the concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification, thus increasing the risk for serious cardiovascular events. However, conflicting data showing low expression of sclerostin in normal or calcified human vasculature indicate that the role of sclerostin in the aorta is unclear and its presence may simply be a marker of the calcification process.

Data from previously conducted nonclinical studies did not show evidence of adverse effects of sclerostin inhibition on the vasculature in the absence of vascular mineralization. There were no vascular effects in a 6-month repeat-dose monkey toxicity study conducted with romosozumab at up to 93-fold clinical exposure based on area under the concentration-time curve (AUC), and no vascular mineralization in aged ovariectomized monkeys dosed for 1 year with romosozumab at 22-fold clinical AUC exposure. Vascular lesions were also not observed in a 6-month rat toxicity study with romosozumab at up to 39-fold clinical AUC exposure.

Although sclerostin expression is absent or low in the normal rat aorta, aortic medial calcification has been observed in rats secondary to experimental chronic kidney disease (CKD), and sclerostin expression is upregulated in foci of vascular calcification. However, aortic calcification is not exacerbated when these rats are treated with sclerostin antibody and calcification is not promoted in the total absence of sclerostin in SOST knock out (KO) mice with CKD. In addition, romosozumab had no effect on the incidence or severity of spontaneous age-related arterial pathology characterized by focal medial vascular calcification or ectopic ossification in normal rats dosed for up to 98 weeks at up to 19-fold clinical AUC exposure. Thus, sclerostin inhibition does not appear to exacerbate pre-existing vascular medial calcification in animals.

Taken together, the available nonclinical data did not show evidence of adverse effects of sclerostin inhibition on the initiation or enhancement of vascular calcification.

Sclerostin inhibition and other cardiovascular concerns

To further address the potential for adverse effects of sclerostin inhibition on the cardiovascular system, the applicant conducted five additional nonclinical studies. The studies evaluated the effects of sclerostin inhibition on platelet activation, the effects of sclerostin inhibition on vasoconstriction, the effect of sclerostin inhibition on atherosclerosis in the ApoE knockout mouse model, the expression of sclerostin in human atherosclerotic plaques and the potential for a genetic association between sclerostin expression and MI or stroke.

Study 125269: *Platelet activation assay for romosozumab*

Romosozumab was tested for platelet activation in an in vitro assay to evaluate its potential for pro-thrombotic effects. Flow cytometry showed that romosozumab concentrations of 1, 3, 10, 30, 100 and 300 mcg/mL did not activate platelets in human whole blood. The highest concentration (300 mcg/mL) represents an approximate 10-fold multiple of the human Cmax (28.1 mcg/mL) at the monthly subcutaneous clinical dose of 210 mg. The in vitro data did not show a pro-thrombotic effect of romosozumab via platelet activation.

Study 150483: *Study to Assess the Effects of Recombinant Human Sclerostin and Romosozumab on Isolated Healthy Human Coronary Arteries*

Coronary vasoconstriction is a risk factor of acute ischemic events (MI/stroke) in subjects with acute coronary syndrome without thrombus, either in the presence or absence of atherosclerotic plaque. Therefore, the effects of romosozumab and human recombinant sclerostin on vascular tone were evaluated in vitro using healthy human coronary artery rings. Sumatriptan was used as a positive control.

Romosozumab (1, 3, 10, 30, 10, 300 mcg/mL) did not induce vasoconstriction at concentrations up to 300 mcg/mL, approximately 10-fold the clinical Cmax at the 210 mg monthly dose (28.1 mcg/mL). Recombinant human sclerostin (1, 3, 10, 30, 100, 300 pmol/L) also did not induce vasoconstriction at concentrations up to 300 pmol/L (approximately 10-fold greater than the reported serum values in postmenopausal women).

In addition, data from previously conducted nonclinical studies suggest that romosozumab is unlikely to cause acute changes in blood flow through effects on blood pressure. Blood pressure and electrocardiograms were unaffected in instrumented monkeys following a single intravenous dose of romosozumab at approximately 32- and 21-fold clinical exposure at the 210 mg monthly dose based on AUC and Cmax, respectively, and were also unaffected in 1-month and 6-month repeat-dose toxicity studies in monkeys at doses up to 200- and 93-fold clinical exposure based on AUC. Additionally, although nitric oxide signaling pathways, which have a regulatory function in vasodilation, were differentially regulated in the ovariectomized (OVX) Apolipoprotein E (ApoE) knockout (KO) mouse, these pathways were unchanged in response to sclerostin-antibody treatment (Study 124609, discussed below).

In summary, the data showed that romosozumab does not induce vasoconstriction in isolated human coronary arteries and does not have an effect on blood pressure or electrocardiograms in animals. Thus, romosozumab is unlikely to adversely affect the cardiovascular system through an unfavorable effect on vascular tone.

Study 124609*: r13C7: Atherosclerotic and Transcriptional Changes in Aortas from High Fat Diet-fed Ovariectomized Wild Type and ApoE KO Mice Administered Sclerostin-Antibody*

Atherosclerosis is a common background lesion in humans underlying acute thrombotic and ischemic events. This study was conducted to evaluate the potential effects of sclerostin antibody on atherosclerosis in the aortas from high fat, diet-fed ApoE KO-OVX mice. The effects of sclerostin antibody were also examined in high fat, diet-fed OVX Wild Type (WT) mice.

The ApoE KO mouse model is a well-known model of atherogenesis. ApoE plays a key protective role in atherosclerosis through stabilizing effects on plasma cholesterol homeostasis, facilitation of cholesterol efflux from macrophage foam cells in atherosclerotic lesions, and modification of macrophage- and T-lymphocyte-mediated immune responses contributing to this chronic inflammatory disease.

Female WT or ApoE KO mice were placed on a high fat diet, ovariectomized, and dosed with vehicle, sclerostin antibody (Scl-Ab) r13C7 (10 mg/kg) for 3, 8 or 16 weeks, or with alendronate (0.02 mg/kg) for 16 weeks. Evaluations included clinical signs, body weight, r13C7 serum concentrations, clinical chemistry, serum lipids, bone turnover markers, serum cytokine and chemokines, aorta histopathology, aorta gene (RNA) expression profiles, and aorta plaque volume and mineralization (via microCT). A defined region of the aortic arch was used for RNA sequencing. Anticipated exposure to sclerostin-antibody r13C7 was approximately 4-fold the clinical AUC exposure to romosozumab at the 210 mg monthly dose.

The administration of Scl-Ab r13C7 was well tolerated. Serum lipid levels were increased in ApoE KO-OVX mice compared to WT-OVX mice but were unaffected by treatment with Scl-Ab or alendronate. Scl-Ab significantly increased PINP (a bone formation marker) in both genotypes, indicating the expected bone formation effect. There was no difference between the two genotypes in the levels of systemic markers of inflammation or endothelial/platelet activation (cytokines/chemokines). Scl-Ab also had no significant effects on these markers in WT or ApoE KO OVX mice. Sclerostin inhibition had no meaningful effects on the incidence and morphology of the aorta atherosclerotic plaques in ApoE KO-OVX mice, including plaque fibro-cartilaginous metaplasia, at any time point. Aortic total plaque volume was decreased in Scl-Ab treated ApoE KO-OVX mice at only Week 16, but the significance of this finding is unclear. Scl-Ab had no effect on mineralized plaque volume in ApoE KO-OVX mice. Scl-Ab did not result in gene transcriptional changes in aorta tissue that would suggest an effect on the development or progression of atherosclerosis. Sclerostin (SOST) gene expression decreased with the progression of atherosclerosis in ApoE KO-OVX mice but was unaffected by Scl-Ab in both genotypes. Alendronate for 16 weeks did not alter total or mineralized plaque volume or plaque histologic features in ApoE KO-OVX mice. The findings support the concept that inhibition of sclerostin by Scl-Ab does not promote atheroprogression in the ovariectomized ApoE KO mouse model.

These results are in apparent contrast with those obtained by Krishna et al. (2017) in the ApoE KO male mouse treated with Angiotensin-II (Ang II) for 28 days, a model for atherosclerosis and aortic aneurysm (AA). Ang II plays a critical role in the induction of atherosclerosis and may accelerate the progression of atherosclerotic lesions to infarction. In that study, excess SOST (by injecting SOST or using a SOSTTg.ApoE-/- mouse genotype) inhibited Ang II-induced aortic aneurysm and atherosclerosis and was associated with decreases in circulating pro-inflammatory cytokines and reductions in aortic extracellular matrix degradation and macrophage infiltration.

The differences between the studies may be due to the different animal models used. The administration of Ang II in the mouse model used in the published study by Krishna et al. may specifically contribute to atherosclerosis and/or aneurysm through activation of sclerostin-sensitive Wnt signaling. In fact, the study by Krishna et al. (2017) showed that Wnt signaling was activated in the Ang II-treated Apo E KO mice that developed AA vs. those that did not, and that SOST expression in human AA samples was decreased likely through epigenetic silencing. In the applicant's study there was no genotype effect on Wnt target genes, therefore a potential effect of Scl-Ab on atherosclerosis via Wnt signaling may not have been detected. It is unlikely that the Scl-Ab dose selection in the applicant conducted studies was inadequate.

The role of Wnt signaling in cardiac and vascular disease has recently been reviewed (Foulqier et al., 2018). Interestingly, the article highlights the crosstalk between Wnt, transforming growth factor-β and Angiotensin II signaling. The authors concluded that, despite conflicting experimental data, a general picture is emerging that excessive stimulation of Wnt signaling adversely affects cardiovascular pathology.

A study in the ApoE KO mouse similar to the study by Krishna et al. (2017) could be carried out to test for a potential reduction in atherosclerosis by SOST addition or use of the SOST-Tg genotype. Conversely, an evaluation of the effect of Scl-Ab in the Ang II-treated mouse could be conducted to identify a potentially atherosclerosis-enhancing effect. However, a positive result in any model would not negate the lack of an imbalance on serious cardiovascular events in Study 20070337. Similarly, the negative result of the study in the ApoE KO OVX mouse does not refute the cardiovascular safety signal in Study 20110142 (and 20110174).

Study 150498: *Immunohistochemical assessment of sclerostin expression in human atherosclerotic plaques*

To obtain information on the presence, location and role of sclerostin in atherosclerotic plaques, the expression pattern of sclerostin was examined using immunohistochemistry in sections of human atherosclerotic plaques from carotid or femoral/iliac arteries of female (mostly post-menopausal) patients that underwent an endarterectomy procedure. The associations between sclerostin expression and plaque features, i.e., lipid content, macrophage burden, smooth muscle cell content, collagen content and calcification, cytokine expression, and patient cohort characteristics were also determined.

Strong staining for sclerostin was observed in the vessel wall of control aorta and a limited number of early atherosclerotic plaque samples with minimal to slight expansion of the tunica

intima. Decreased expression of sclerostin was observed in the arterial plaques, with the majority (approximately 80%) showing no expression. In early plaques, staining was already decreased in the region immediately beneath the intimal expansion. More advanced lesions typically showed low or absent staining. Where present, expression was restricted to deeper parts of the plaque/vessel wall, i.e., the tunica media and adjacent sub-intimal region. Expression of sclerostin was never seen in the superficial plaque region closest to the vessel lumen (fibrous cap and endothelium), an area most relevant to plaque stability.

There was no significant association between the absence of sclerostin and the various plaque features, except for an inverse association between sclerostin expression and dystrophic calcification in the carotid artery in both the medial and intimal layer. Given the apparent down-regulation of sclerostin during plaque progression, this association was considered to reflect the advanced nature of the atherosclerosis in these plaques rather than indicate a direct association. Absence of sclerostin was also not associated with plaque pro-inflammatory cytokine expression (MCP1, IL6, TNFα, and osteopontin). In addition, there was no association between sclerostin expression and the patients' cardiovascular events prior to, or following, endarterectomy.

The data showed that in human atherosclerotic plaques sclerostin expression is downregulated compared to normal aorta, restricted to deeper parts of the vessel wall, and not expressed in superficial areas relevant to plaque stability. The absence of sclerostin expression was not significantly associated with any of the plaque features assessed. There was no association between sclerostin expression and cardiovascular events in the patients. The downregulation of sclerostin expression in the plaques is unlikely to play a causal role in atherosclerosis based on the data from the ApoE KO-OVX mouse study showing that antibody-mediated sclerostin inhibition did not affect atherosclerosis and atherosclerotic plaque features (Study 124609).

Sclerostin inhibition and potential mechanisms underlying cardiovascular ischemic events

Myocardial infarction and stroke can be triggered by rupture or erosion of atherosclerotic plaques. Plaque rupture can be induced by inflammation via a reduction in extracellular matrix, particularly the plaque's fibrous cap. However, the study in ApoE KO-OVX mice (Study 124609) did not show an effect of Scl-Ab on inflammatory markers or on the transcription of genes that play a role in inflammation or extracellular matrix homeostasis. The relevance of the Scl-Ab induced decrease in plaque volume at Week 16 in ApoE KO-OVX animals, e.g., for plaque rupture, is unclear. Plaque rupture can also be caused by mechanical instability due to calcification or hemorrhage. However, romosozumab did not promote vascular calcification in the rat and monkey toxicity studies, and sclerostin inhibition did not cause aortic calcification in CKD rodents. Also, Scl-Ab had no effect on mineralized plaque volume in Study 124609, and sclerostin was not expressed in human atherosclerotic plaques' fibrous caps, an area important for plaque stability (Study 150498). In addition, plaque hemorrhage was not observed in ApoE KO-OVX mice (Study 124609) and sclerostin expression was not associated with human arterial plaque hemorrhage.

Plaque erosion due to endothelial dysfunction in combination with platelet and neutrophil activation and oxidative stress is believed to enhance thrombogenesis and precipitate cardiovascular ischemic events. In ApoE KO-OVX mice, some transcriptional pathways that are

likely to be involved in plaque erosion were upregulated, but they were not affected by Scl-Ab administration (Study 124609). Moreover, Scl-Ab treatment did not affect circulating markers of endothelial activation and their aortic mRNA expression. In addition, based on the lack of sclerostin expression in the tunica intima and endothelium in human arterial plaques, sclerostin inhibition seems to be an unlikely factor in plaque erosion.

Both plaque rupture and erosion can be complicated by enhanced thrombogenesis triggered by an imbalance in vasodilators (e.g., endothelial prostacyclin) and vasoconstrictors (e.g., platelet thromboxane A2). However, circulating markers of endothelial/platelet activation and aortic gene transcription related to the prostanoid pathway were not affected by Scl-Ab in the ApoE KO-OVX mice (Study 124609). In addition, romosozumab did not enhance in vitro platelet activation (Study 125269). Also, intrinsic and extrinsic coagulation was not affected by romosozumab in repeat dose rat and monkey toxicity studies. Altogether, this suggests a lack of effect of sclerostin inhibition on thrombogenesis.

Human genetic data

Study 150655*: Analysis of BMD-Associated SNPs at the SOST Locus for Association with Stroke and Myocardial Infarction in the UK Biobank*

To further investigate the role of sclerostin in cardiovascular events, human genetic data were evaluated. Public databases of results from genome-wide association studies (GWAS) from the UK Biobank were examined to test for association of single nucleotide polymorphisms (SNPs) near SOST, associated with SOST RNA expression levels and BMD, with stroke or myocardial infarction. The SNP rs2741856 was chosen for this study because it has been reported to be strongly linked to the most significant BMD association at the SOST locus.

In the GTEx Portal database, the major allele C of rs2741856, as compared to minor allele G, is associated with lower expression of SOST, with the most statistically significant effect observed in tibial artery ($p = 4.5 \times 10\text{-}6$; normalized expression score -0.29). A statistically significant effect was also observed in aorta ($p = 4.9 \times 10\text{-}4$; normalized expression score -0.30; $n = 267$), and in coronary artery, thyroid, brain and tibial nerve ($p<0.05$ for all). The normalized expression score in these tissues also varied between -0.2 and -0.32.

Among the > 300,000 European participants, the major allele C (with lower SOST expression) is associated with higher BMD, a decreased risk of osteoporosis ($p = 1.32 \times 10\text{-}9$; odds ratio (OR) = 0.84) and decreased occurrence of fracture in the past 5 years ($p = 3.88 \times 10\text{-}7$; OR = 0.93) (values reported from the Global Biobank Engine database). This allele probably mirrors the pharmacologic effects of romosozumab at 210 mg monthly, a non-saturating dose expected to leave a reasonable fraction of sclerostin unbound. The major allele C did not have a detectable effect on the risk of MI or stroke ($p > 0.10$ for both). Results from the Gene Atlas and Rapid GWAS databases were similar as from the Global Biobank Engine database, although the Gene Atlas database showed one near-significant association of the C-allele with 'Illnesses of mother. Stroke" ($p=0.066$). However, the odds ratio was not mentioned.

The study of GWAS data allowed for a more robust analysis of the association between sclerostin expression and cardiovascular events than possible using data from the small sclerosteosis population in which involvement of the cardiovascular system has not been reported. The data showed that genetically reduced SOST expression is significantly associated with increased BMD, and decreased risk of osteoporosis and bone fracture, but is not associated with a detectable effect on the risk of myocardial infarction or stroke.

Nonclinical data summary

In summary, the nonclinical data did not show an association between sclerostin inhibition or reduction and adverse cardiovascular structural or functional effects. The data from previously conducted nonclinical studies suggested that the inhibition of sclerostin is unlikely to be associated with enhanced vascular calcification. Data from additional nonclinical studies in the OVX ApoE KO mouse model for atherosclerosis and isolated human arterial atherosclerotic plaques appeared to confirm this conclusion. The study in the OVX ApoE KO model did not provide evidence that sclerostin inhibition would increase inflammation, enhance atherosclerosis or activate atherosclerosis-related gene transcriptional events. Nonclinical information also suggested that sclerostin inhibition was unlikely to increase the susceptibility of atherosclerotic plaques to rupture or erosion, enhance thrombogenesis, or increase vasoconstriction. However, based on remaining uncertainty about the clinical relevance of these data, the clinical concern about the cardiovascular safety of romosozumab should not be completely dismissed.

6.3. Cardiovascular Summary

One of the two large safety and efficacy trials of romosozumab for the treatment of osteoporosis in postmenopausal women has yielded a concerning cardiovascular safety signal. A meta-analysis of time to first MACE using data from all three phase 3 trials, found a HR of 1.40 (95% CI: 0.99, 1.99) for the comparison of romosozumab to placebo and alendronate combined.

After extensive review, there were no findings that suggest differences in cardiovascular risk factors between the study populations that may have contributed to the discrepant results between the two large trials. However, it is also recognized that some important cardiovascular risk factors (e.g., lipid parameters) were not collected in these fracture trials.

Although it is recognized that sclerostin gene SOST mRNA is expressed in the heart, aorta, liver, and kidney, nonclinical and in vitro evaluations have not provided support for an association between sclerostin inhibition and adverse cardiovascular structural or functional effects.

One potential explanation for the discrepant results would be that the active control alendronate provided cardiovascular protection during the first year of the trial. This is plausible from a biologic perspective given the mineral binding capacity of bisphosphonates. However, the existing data have not convincingly demonstrated a cardioprotective effect of alendronate or other bisphosphonates. Also, this would not explain the MACE imbalance seen in the smaller male osteoporosis trial.

7. Further Evaluation of the Cardiovascular Signal

The cardiovascular signal in trials 20110142 and 20110174 cannot be ignored. The population for the osteoporosis indication is postmenopausal women, a generally older patient population that is already at increased risk of cardiovascular disease. FDA is requesting the committee's input on whether additional cardiovascular safety data are needed to better define a potential off-target cardiovascular effect of romosozumab, and whether such data should be obtained pre- or post-approval. When evaluating the need for additional safety data, there are two types of studies to consider: cardiovascular outcomes trials and observational studies.

7.1. Cardiovascular Outcomes Trials

Prospective, randomized, controlled cardiovascular outcomes trials could be considered the standard for assessing cardiovascular risk related to pharmacologic intervention. However, these trials can also raise challenges, such as generally requiring very large sample sizes, focusing enrollment on subjects at sufficiently high cardiovascular risk to ensure that an adequate number of events accrue (raising questions about generalizability of results to lower-risk subjects), and requiring long-term follow-up while needing to limit missing data. The one-year duration of therapy with romosozumab may present a challenge with conducting a cardiovascular outcomes trial, although it is noteworthy that the completed alendronate-controlled trial detected an increase in MACE over this time period.

7.2. Observational Studies

Nonrandomized (observational) studies can be conducted to complement the safety evidence generated from clinical trials by studying the real-world comparative safety of osteoporosis medications in large numbers of subjects. However, the suitability of observational data to inform a given safety signal should be evaluated weighing the strength of evidence required (or degree of imprecision tolerated) and the intended purpose of the study (e.g., hypothesis generation, signal strengthening, confirmation). These needs must be weighed against an assessment of the capability of the available data sources. This assessment consists of several domains including the ability to capture the population of interest, the exposure data for the drug of interest and the comparators, the safety outcomes of interest, important confounders, and an adequate sample size to generate sufficiently precise risk estimates.

Data sources

In the US, population-based healthcare databases that can be used to evaluate the romosozumab cardiovascular risk signal include administrative claims (e.g., CMS Medicare, Truven MarketScan), electronic medical records (EMR) (e.g., Kaiser Permanente, Department of Veterans Affairs), or registries.

Observational studies, particularly those using large administrative claims databases, have become increasingly popular sources of data for comparative safety research because they have several important strengths including large size, longitudinal data on prescription drug use, generalizability, and low cost. However, use of claims data is also criticized due to the lack of

important information not measured in claims data such as lifestyle factors, underlying disease severity, over-the-counter medication use, and laboratory or imaging test results.

One of the electronic healthcare data sources currently available to FDA and industry is the Sentinel Distributed Database (SDD).[3,4] The SDD comprises administrative medical and prescription drug insurance claims and demographic data, converted into a common data model.[5] As of early 2017, the distributed database contained information from 17 data partners with 223 million covered lives and 425 million person-years of observation time between 2000 and 2016. All data remain under the local control of each data partner site. Currently, the majority of the SDD are administrative claims with only a few small data partners that contribute EMR data.

EMR systems contain rich patient medical information (e.g., physician notes, laboratory results, and vital signs) and in some systems, health behavioral data, inpatient medication data, or medication filled out-of-plan and over-the-counter. However, because different EMR systems do not communicate with each other, information collected in one system may not transfer easily to another system using a different EMR system. Retrieval of medical information collected in EMR is usually not straightforward and often requires use of advanced techniques such as natural language processing (NLP), especially in unstructured data. Compared to claims data, the sample size may be an important concern for studies to assess serious but rare adverse events in EMRs (if data are from a single site).

Patient registries are organized systems that use observational methods to collect uniform data on a population defined by a particular disease or exposure. Strengths of patient registries include availability of information on disease severity, indication for drug use, prior medication history, family and personal history of illness. The weaknesses often include limited generalizability and sample size (due to voluntarily participation), and sometimes the lack of an internal comparison group.

No single existing data source is ideal. Whatever database is selected, it is important that the investigators understand its limitations (whether the database contains an appropriate population, captures key variables required to answer the study question, and the time to release the data is reasonable, etc.). Finally, an experienced study team with appropriate expertise in the selected database is crucial to the successful execution of the study.

Patient population

In trial 20070337, 21% of the participants were under the age of 65 (mean age: 70.9±7.0). In trial 20110142, the mean age of patients was 74.3 ± 7.5years and 12% were under age 65 years. Current guidelines recommend the start of screening for osteoporosis in women aged 65 years or

[3] Ball R, Robb M, Anderson SA, Dal Pan G. The FDA's sentinel initiative--A comprehensive approach to medical product surveillance. *Clin Pharmacol Ther.* 2016;99(3):265-268.

[4] Platt R, Carnahan RM, Brown JS, et al. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1:1-8.

5 Curtis LH, Weiner MG, Boudreau DM, et al. Design considerations, architecture, and use of the Mini-Sentinel distributed data system. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1:23-31.

older unless they have a prior history of fragility fracture.[6] Therefore, we anticipate that a substantial proportion of women who initiate treatment with romosozumab, denosumab or oral bisphosphonates would be captured in electronic healthcare data sources such as Medicare.

Exposures of interest

Patients receiving romosozumab as well as potential comparators such as denosumab or alendronate can be identified in claims data using the Healthcare Common Procedure Coding System (HCPS) codes or National Drug Codes (NDC).[7] Since these new injectable biologics have to be administered at a physician's office, we anticipate that the validity of using HCPS or NDC codes to capture these drugs in electronic healthcare data will be high.

As with any post-marketing study, the actual sample size of the study will be determined by the utilization of the study drugs of interest. Sample size also depends on reimbursement policy (e.g., formulary), especially for data sources that rely on insurance claims. For romosozumab, an additional concern is the speed of market uptake once the drug is approved. A feasibility study may be necessary to assess romosozumab's market uptake and the resulting sample size available for the post-marketing study.

Outcome of interest

In the clinical trials, imbalances were noted for cardiovascular adverse events which were driven primarily by MI and stroke. Thus, the primary outcome of interest for a post-marketing observational study could include a composite CV endpoint of hospitalization for MI or stroke during follow-up. The secondary outcome could include a composite of MI, stroke, heart failure (HF), coronary revascularization, based on hospital discharge diagnosis codes, and all-cause mortality. Cause-specific mortality, including cardiovascular mortality, is not available in administrative claims data. For the primary outcome, the claims-based coding algorithms have a positive predictive value (PPV) of $\geq$ 90%.[8,9] For the secondary outcome, the PPV of coding algorithms is > 80%.[10,11]

Covariates

[6] Kling JM, Clarke BL, Sandhu NP. Osteoporosis prevention, screening, and treatment: a review. *J Womens Health (Larchmt).* 2014;23(7):563-572.
[7] https://www.medicare.gov/coverage/prescription-drugs-outpatient
[8] Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J.* 2004;148(1):99-104.
[9] Kumamaru H, Judd SE, Curtis JR, et al. Validity of claims-based stroke algorithms in contemporary Medicare data: reasons for geographic and racial differences in stroke (REGARDS) study linked with medicare claims. *Circ Cardiovasc Qual Outcomes.* 2014;7(4):611-619.
[10] Zhang M, Solomon DH, Desai RJ, et al. Assessment of Cardiovascular Risk in Older Patients with Gout Initiating Febuxostat Versus Allopurinol. *Circulation.* 2018;138(11):1116-1126.
[11] Kim SC, Neogi T, Kang EH, et al. Cardiovascular Risks of Probenecid Versus Allopurinol in Older Patients With Gout. *J Am Coll Cardiol.* 2018;71(9):994-1004.

Well-conducted observational studies require understanding about the covariates (confounding variables) plausibly associated with both the exposure of interest and outcome of concern. The covariates of interest would include a broad range of demographic variables, medical comorbidities, and concomitant medications, and indicators of healthcare service utilization. Healthcare claims data can generally identify many, if not most, covariates relevant for the assessment of the safety signal considered here. Important exceptions are the lack of information on smoking history/status, body mass index, over-the-counter medication use, indication for use (prophylaxis vs. treatment) and severity of underlying bone disorder. Another limitation with respect to covariates is the incomplete capture of some comorbidity data because of the relatively short look-back periods (e.g., 365 days prior to the index date) commonly used in pharmacoepidemiology studies. EMRs or registries can have richer clinical and covariate information.

Limitation of research method

For this safety issue, the FDA has concerns with the potential for residual confounding and selection bias that may impact the interpretability of observational post-marketing studies.

Epidemiologic studies have shown that low BMD, history of fragility fracture, vitamin D deficiency and increased bone resorption are associated with higher risks of major cardiovascular events (MI, stroke, and cardiovascular death). Osteoporosis and cardiovascular disease also share some common risk factors (e.g., prolonged immobility, alcohol abuse) and there is a potential common pathophysiological mechanism between the two conditions.[12] Residual confounding due to failure to control for important covariates may bias the results to over or underestimate the CV risks.

Furthermore, when observational studies are used to study the safety issues of newly marketed drugs, patients prescribed the newer medication during the initial marketing-approval period may be substantially different from those receiving an existing comparator treatment. For example, patients prescribed the new biologic may be sicker due to more profound disease compared to initiators of the comparator drug. Further, in this specific scenario, postmenopausal women with osteoporosis are usually treated with bisphosphonates as first-line therapy because of the proven clinical effectiveness, long-term experience, and price consideration. Patients would likely switch from bisphosphonates to a new biologic due to poor clinical response or adverse events early in the course of the treatment. Hence, new users of romosozumab are more likely to have been previously exposed to drugs in the comparison groups or other drugs for the same indication (e.g., other approved antiresorptive medications) and this prior use may not be captured in a given data source. On the other hand, long-term users of osteoporosis drugs tend to be more adherent to therapy (which may lead to better health outcomes) than users of newly marketed drugs.[13] Failure to properly consider the influence of switching between

[12] Farhat GN, Cauley JA. The link between osteoporosis and cardiovascular disease. *Clin Cases Miner Bone Metab.* 2008;5(1):19-34.
[13] Gagne JJ, Bykov K, Willke RJ, Kahler KH, Subedi P, Schneeweiss S. Treatment dynamics of newly marketed drugs and implications for comparative effectiveness research. *Value Health.* 2013;16(6):1054-1062.

bisphosphonates and romosozumab may result in selection bias that will invalidate the treatment effect estimates.

Observational studies are vulnerable to various biases, particularly when conducted to evaluate safety outcomes of new drugs shortly after approval and when conducted in claims data where key potential confounders are not measurable. The recommended approaches to mitigate these biases include the avoidance of study designs that are prone to cause selection bias (because no analytic method can deal with these issues), careful selection of data sources that contain important study variables including key confounders, inclusion of incident users, and the application of propensity score methods (including high dimensional propensity score) to balance baseline covariates between initiators of different drugs.

Conclusions on Observational Safety Studies

Observational studies conducted in electronic health databases are powerful and appealing tools for providing critical data on the comparative cardiovascular risks of romosozumab compared to other established osteoporosis therapies. However, their use needs to be balanced against the context of the safety issue they are being used to examine. Finally, sound epidemiology studies need to properly address the important methodological issues such as channeling bias and residual confounding in addition to addressing the limitations of the chosen database and implement remedies to avoid these pitfalls.