CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761062Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA Resubmission
Application Number(s)	761062
Priority or Standard	Standard
Submit Date(s)	July 9, 2018
Received Date(s)	July 9, 2018
PDUFA Goal Date	April 9, 2019
Division/Office	Division of Bone, Reproductive, and Urologic Products Office of Drug Evaluation III
Review Completion Date	(electronic stamp)
Established Name	romosozumab
(Proposed) Trade Name	Evenity
Pharmacologic Class	Sclerostin inhibitor
Code name	
Applicant	Amgen
Formulation(s)	90 mg/mL solution (1.17 mL) in each single-use (b) (4) (b) (4) prefilled syringe (PFS); 2 injections per dose (210 mg)
Dosing Regimen	210 mg subcutaneously once a month administered by a healthcare professional
Applicant Proposed Indication(s)/Population(s)	Treatment of osteoporosis in postmenopausal women at high risk for fracture
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	102447009 Postmenopausal osteoporosis (disorder)
Recommendation on Regulatory Action	APPROVE
Recommended Indication(s)/Population(s) (if applicable)	Treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	102447009 Postmenopausal osteoporosis (disorder)

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OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DB7=Division of Biostatistics 7
DSAT=Division Support and Analysis
CDRH= Center for Device s and Radiologic Health, Office of Device Evaluation
DPMH=Division of Pediatric and Maternal Health
DMPP=Division of Medical Policy Programs

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
ECG	electrocardiogram
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event

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1 Executive Summary

1.1. Product Introduction

The applicant, Amgen, Inc. has submitted this Biologics License Application (BLA) under section 351 of the Public Health Services Act for romosozumab, proposed tradename Evenity, seeking an indication for the treatment of postmenopausal women with osteoporosis at high risk of fracture. The proposed dose is 210 mg once monthly for one year. Romosozumab 210 mg is administered by a healthcare provider and requires 2 separate subcutaneous injections utilizing two single-use prefilled syringes. Romosozumab, also referred to as AMG785 in the application, is an IgG2 humanized monoclonal antibody that binds and inhibits sclerostin. The pharmacologic class proposed by the applicant in labeling is "sclerostin inhibitor". 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), inhibiting Wingless-related integration (Wnt) signaling and reducing osteoblast-mediated bone formation. Inhibition of sclerostin leads to a transient stimulation of bone formation and inhibition of bone resorption. Romosozumab is first in class with sclerostin inhibitors being a new therapeutic class of osteoporosis treatments.

This is the second review cycle for romosozumab. Late in the first review cycle of this BLA, data from an active-controlled, phase 3 fracture study in women with postmenopausal osteoporosis at increased risk for fracture, Study 20110142 (Study 142), became available and demonstrated an imbalance in positively adjudicated serious cardiovascular events for romosozumab vs. the active control alendronate. In response to the concerning cardiovascular safety findings, FDA issued a Complete Response Letter. This submission addresses the deficiencies outlined.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness to support approval of romosozumab for the treatment of osteoporosis in postmenopausal women at high risk of fracture. The evidence of effectiveness derives from the placebo-controlled fracture trial 20070337 (Study 337) and the active-controlled fracture trial 20110142 (Study 142). These studies evaluated whether 12 months of treatment with romosozumab followed by continued therapy with an anti-resorptive agent provided fracture risk reduction in postmenopausal women.

Study 337 (N = 7180), reviewed in the first BLA cycle, was a phase 3, randomized, double-blind, placebo-controlled, parallel-group study that assessed the efficacy and safety of romosozumab 210 mg administered subcutaneously (SC) every month (QM) for a duration of 12 months followed by denosumab 60 mg every 6 months for 12 months compared to 12 months of placebo followed by 12 months of denosumab in women with postmenopausal osteoporosis.

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The study demonstrated a statistically significant reduction with romosozumab compared to placebo for both co-primary endpoints, which were 1) the subject incidence of new vertebral fractures at 12 months and 2) the subject incidence of new vertebral fractures at 24 months. During the 12-month double-blind period, the subject incidence of new vertebral fracture with romosozumab was 0.5% compared to 1.8% with placebo, with a significant absolute risk reduction of 1.3% (95% confidence interval [CI]: 0.8, 1.8; $p < 0.001$) and relative risk reduction of 73% (95% CI: 53, 84; $p < 0.001$). At 24 months, the subject incidence of new vertebral fracture with romosozumab followed by denosumab was 0.6% compared to 2.5% with placebo followed by denosumab, with a significant absolute risk reduction of 1.9% (95% confidence interval [CI]: 1.3, 2.5; $p < 0.001$). and relative risk reduction of 75% (95% CI: 60, 84; $p < 0.001$). Romosozumab also significantly increased bone mineral density (BMD) at all sites. At month 12, compared with placebo, romosozumab increased mean BMD by 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 all sites at month 24.

Study 142 (N = 4093) was a phase 3, randomized, double-blind, alendronate-controlled study that assessed the efficacy and safety of romosozumab 210 mg SC monthly for a duration of 12 months followed by alendronate 70 mg weekly compared with alendronate 70 mg weekly alone in women with postmenopausal osteoporosis with a history of fracture. Compared with Study 337, Study 142 enrolled a population at higher risk of osteoporosis-related fracture. The two primary endpoints were 1) time to first clinical fracture (including nonvertebral and symptomatic vertebral fracture, the applicant pre-specified this endpoint as “subject incidence of clinical fractures”, which is not appropriate, see details in 8.1.1) through the primary analysis period and 2) the subject incidence of new vertebral fracture through month 24. The primary analysis period ended after clinical fracture events had been confirmed for at least 330 subjects and all subjects had completed the month 24 visit. At 24 months, the subject incidence of new vertebral fracture with romosozumab followed by alendronate was 4.1% compared to 8.0% with alendronate alone, with a significant absolute risk reduction of 4.0% (95% CI: 2.5, 5.6) and relative risk reduction of 50% (95% CI: 34, 62; $p < 0.001$). Through the primary analysis period, the hazard ratio for clinical fractures was 0.73 (95% CI: 0.61, 0.88; $p < 0.001$) for romosozumab followed by alendronate compared to alendronate alone, based on 464 subjects with clinical fractures (9.7% in the romosozumab group and 13.0% in the alendronate alone group) with a median follow-up of 33 months. Regarding BMD, significantly higher increases were observed with romosozumab compared to alendronate at all sites assessed. At month 12, the mean BMD treatment difference was 8.7% at the lumbar spine, 3.3% at the total hip, and 3.2% at the femoral neck. Romosozumab followed by alendronate maintained the significantly higher increases in BMD at all sites at month 24.

The effect of romosozumab on the risk of vertebral fractures, clinical fractures and nonvertebral fractures in Study 337 and Study 142 is summarized in Table 1.

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Table 1. Effect of Romosozumab on the Risk of New Vertebral Fractures, Clinical Fractures, and Nonvertebral Fractures in Studies 337 and 142

Study 337: Romosozumab/Denosumab versus Placebo/Denosumab			
New Vertebral Fracture	**ARR (95% CI)**	**RRR (95% CI)**	**P-value**
Month 12	1.3% (0.8, 1.8)	73% (53, 84)	<0.001
Month 24	1.9% (1.3, 2.5)	75% (60, 84)	<0.001
Study 142: Romosozumab/Alendronate versus Alendronate/Alendronate			
New Vertebral Fracture	**ARR (95% CI)**	**RRR (95% CI)**	**P-value**
Month 24	4.0% (2.5, 5.6)	50% (34, 62)	<0.001
Through Primary Analysis Period*	**Hazard Ratio (95% CI)**		**P-value**
Clinical Fracture	0.73 (0.61, 0.88)		<0.001
Nonvertebral Fracture	0.81 (0.66, 0.99)		0.019
* Time-to-event analysis where follow-up time differed across subjects. Median follow-up was 33 months. ARR=absolute risk reduction; RRR=relative risk reduction			

Nonvertebral fractures were secondary endpoints in both studies. In Study 337, the risk reduction for nonvertebral fractures at 24 months observed with romosozumab followed by denosumab compared to placebo alone did not meet statistical significance when adjusted for multiplicity. In Study 142, romosozumab followed by alendronate significantly reduced the risk of nonvertebral fractures compared with alendronate alone through the primary analysis period, with a hazard ratio of 0.81 (95% CI: 0.66, 0.99; $p < 0.019$), based on 395 subjects with nonvertebral fractures with a median follow-up of 33 months.

The data suggested a potential reduction in hip fractures, however, Studies 337 and 142 were not designed adequately to demonstrate romosozumab's efficacy for reduction in hip fractures.

Additional analyses of the primary endpoints of Studies 337 and 142 (new vertebral fracture and clinical fracture in Study 142 and new vertebral fracture in Study 337) conducted in postmenopausal women did not identify differences in efficacy across subgroups defined by the following baseline characteristics: age, race, geographic region, baseline lumbar spine BMD T-score, baseline total hip/femoral neck BMD T-score, baseline body mass index (BMI), fracture history, and Fracture Risk Assessment Tool (FRAX) score. Likewise, subgroup analyses of

percent change in BMD at the lumbar spine and total hip in Study 142 and Study 337 showed that romosozumab increased BMD over a wide range of baseline BMD T-scores and in subgroups defined by age and geographic region. The effects of romosozumab across these subgroups indicate that romosozumab can be effective in increasing BMD and reducing the risk for vertebral and nonvertebral fracture across a broad population of postmenopausal women with osteoporosis at high risk for fracture.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Romosozumab, trade name Evenity, is a sclerostin inhibitor proposed for the treatment of osteoporosis in postmenopausal women at high risk of fracture. The dosing regimen is 210 mg administered by a healthcare professional once monthly for one year. The FDA has concluded that the benefits outweigh the risks and is granting approval.

Osteoporosis is a skeletal disorder characterized by low bone mass and structural deterioration of bone, which leads to bone fragility and increased fracture risk. Postmenopausal osteoporosis occurs due to the hormonal changes beginning at menopause which leads to increased bone loss. In the United States, about 8 million women aged 50 years or older have postmenopausal osteoporosis and approximately 1.5 million suffer osteoporosis-related fractures annually. The risk of fracture increases with age and a history of a prior osteoporosis-related fracture. Osteoporotic fractures can be associated with significant morbidity and mortality. Hip fractures are the most serious type of fractures and can impair the ability to walk and to live independently. Hip fractures are also associated with increased mortality.

Multiple effective treatments for postmenopausal osteoporosis are currently available. However, postmenopausal osteoporosis remains both underdiagnosed and undertreated in the United States. Approved therapies for postmenopausal osteoporosis include anti-resorptive agents (bisphosphonates, denosumab, calcitonin and raloxifene) as well as bone-forming (anabolic) agents (teriparatide and abaloparatide). These therapies with the exception of calcitonin, have been shown to reduce fracture. However, compliance, side effects, and some limitations on duration of use may be obstacles to treatment with these approved drugs.

The efficacy of romosozumab for the treatment of postmenopausal women with osteoporosis at high risk of fracture was established in two fracture studies, Study 337 and Study 142

Study 337 (N = 7180) was a 24-month randomized, multicenter, double-blind, placebo-controlled clinical trial in postmenopausal women with osteoporosis aged 50 to 90 years (mean age of 71 years). Patients were randomized to receive one year of romosozumab 210 mg (N = 3589) or placebo (N = 3591) once monthly by subcutaneous injection administered by a healthcare professional. During the second year of the trial, all patients received denosumab 60 mg every 6

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months. Patients also received daily supplemental calcium (500 to 1000 mg) and vitamin D (600 to 800 IU). At baseline, the mean T-score was -2.7 at the lumbar spine and 18% of patients had at least one prevalent vertebral fracture.

The co-primary endpoints of study 337 were the incidence of new vertebral fractures in patients treated with romosozumab compared to placebo at 12 months and the incidence of new vertebral fractures in patients treated with romosozumab then denosumab compared to placebo then denosumab at 24 months. During the 12-month double-blind romosozumab treatment period, the subject incidence of new vertebral fracture with romosozumab was 0.5% compared to 1.8% with placebo, with an absolute risk reduction of 1.3% (95% confidence interval [CI]: 0.8, 1.8; $p < 0.001$) and a relative risk reduction of 73% (95% CI: 53, 84; $p < 0.001$). At 24 months, the subject incidence of new vertebral fracture with romosozumab followed by denosumab was 0.6% compared to 2.5% with placebo followed by denosumab, with an absolute risk reduction of 1.9% (95% CI: 1.3, 2.5; $p < 0.001$) and a relative risk reduction of 75% (95% CI: 60, 84; $p < 0.001$).

Study 142 (N = 4093) was a multicenter, randomized, double-blind, alendronate-controlled clinical trial in postmenopausal women with osteoporosis and a history of a fracture aged 50 to 90 years (mean age of 74 years). Patients were randomized to receive one year of romosozumab 210 mg once monthly by subcutaneous injection administered by a healthcare professional or oral alendronate 70 mg once weekly. During the second year of the trial, all patients received oral alendronate 70 mg once weekly. Patients also received daily supplemental calcium (500 to 1000 mg) and vitamin D (600 to 800 IU). At baseline, the mean T-score was -3.0 at the lumbar spine and 96% of patients had at least one prevalent vertebral fracture. Compared with Study 337, Study 142 enrolled a population at higher risk of osteoporosis-related fracture.

The coprimary endpoints of study 142 were the incidence of new morphometric vertebral fractures at month 24 and time to first clinical fracture (a composite of nonvertebral fracture and symptomatic vertebral fracture). The clinical fracture endpoint was event-driven and the primary analysis occurred when all subjects had reached 24 months of study participation and clinical fracture was confirmed in at least 330 subjects. At 24 months, the subject incidence of new vertebral fracture with romosozumab followed by alendronate was 4.1% compared to 8.0% with alendronate alone, with an absolute risk reduction of 4.0% (95% confidence interval [CI]: 2.5, 5.6; $p < 0.001$) and a relative risk reduction of 50% (95% CI: 34, 62; $p < 0.001$). Through the primary analysis period the hazard ratio for clinical fracture was 0.73 (95% CI: 0.61, 0.88; $p < 0.001$) for romosozumab followed by alendronate compared to alendronate alone, based on 464 subjects with clinical fractures (9.7% in the romosozumab group and 13.0% in the alendronate alone group) with a median follow-up of 33 months. Additionally, romosozumab followed by alendronate significantly reduced the risk of nonvertebral fractures compared with alendronate alone through the primary analysis period, with a hazard ratio of 0.81 (95% CI: 0.66, 0.99; $p < 0.019$), based on 395 subjects with nonvertebral fractures with a median follow-up of 33 months.

When considering the risks and benefits of romosozumab, hip fracture is associated with the highest morbidity and mortality. Hip fractures were recorded in both Studies 337 and 142. While

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the data suggest a reduction in hip fractures, neither study was adequately designed to assess romosozumab for hip fracture reduction.

Romosozumab demonstrated statistically significant gains in BMD at the lumbar spine, total hip and femoral neck. Results for BMD increases were consistent across the phase 2 and phase 3 placebo- and active-controlled studies. For both Study 142 and Study 337, the treatment effects were consistent (relative risks favored romosozumab) in all subgroups of baseline characteristics examined, including age, race, geographic region, a range of baseline BMD T-scores, and subjects with a history of prior vertebral, nonvertebral, or fragility fracture. Although only a very small percentage of patients were from the United States in both studies (1.8% in Study 337 and 1.4% in Study 142), the consistent efficacy results among all subgroups support applicability of romosozumab effects on fracture risk reduction and extrapolation of efficacy results to the US population.

The safety profile of romosozumab is mainly derived from the two fracture clinical trials (studies 337 and 142). Important adverse events that occurred in the placebo-controlled fracture trial (Study 337) included hypersensitivity reactions, injection site reactions, hypocalcemia, osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). Safety data from Study 142 confirmed the previously established risks of romosozumab. However, Study 142 also raised a new safety concern. In Study 142, there was an imbalance in serious cardiovascular events for romosozumab vs. the active control alendronate (2.5% romosozumab vs. 1.9% alendronate) during the 12-month double-blind period of the study.

This cardiovascular risk imbalance prompted additional analyses that focused on major adverse cardiac events (MACE), a composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke that is commonly used to assess cardiovascular risk or benefit. Across the two fracture trials, 51 (0.9%) subjects in the control group and 71 (1.3%) subjects in the romosozumab group experienced MACE, yielding a hazard ratio of 1.38 (95% CI: 0.96, 1.99). However, when each fracture trial is considered separately, the results diverged. In the placebo-controlled Study 337, MACE:29 (0.8%) subjects in the control group and 30 (0.8%) subjects in the romosozumab group experienced MACE, with a hazard ratio of 1.03 (95% CI: 0.62, 1.72). In contrast, in the active controlled Study 142 where subjects were slightly older, 22 (1.1%) subjects in the control group and 41 (2.0%) subjects in the romosozumab group experienced MACE yielding a hazard ratio of 1.87 (95% CI: 1.11, 3.14).

It is unclear whether romosozumab truly increases cardiovascular risk, as there are several factors that make the interpretation of the signal difficult. The fracture studies were not specifically designed to assess cardiovascular safety outcomes. Data regarding these events may not have been collected as rigorously as was necessary during the conduct of the studies to accurately capture all events. In addition, most of the analyses of the cardiovascular safety findings were conducted post-hoc after the imbalance in serious cardiovascular events in Study 142 was identified. Another limitation is the low number of MACE during the 12-month double-blind period of the fracture studies (approximately 60 events in each trial). Additionally, there is

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uncertainty regarding the applicability of the cardiovascular findings to the US population. Only 1.8% of the study population of Study 337 and 1.4% of the study population of Study 142 were from the US, raising questions about the generalizability of the cardiovascular safety findings to the US population. Lastly, we are unable to rule out a cardioprotective effect of alendronate in Study 142 or that the findings were due to chance.

A definitive mechanistic cause to explain romosozumab's effect on the cardiovascular system has not been found. An alternate explanation for the cardiovascular findings has also not been found. Therefore, given the totality of the available data, and the uncertainty surrounding these data, major adverse cardiac events are considered potential risks of romosozumab therapy.

Other important safety risks of romosozumab include the following:

1. Hypersensitivity reactions: Like other monoclonal antibodies, romosozumab is associated with hypersensitivity reactions. Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria, occurred in romosozumab-treated subjects in the clinical studies, but the incidence was low.
2. Hypocalcemia: Inhibition of sclerostin by romosozumab leads to rapid bone mass accrual at initiation of treatment and an increased demand for bone-building substrates such as calcium. Based on the clinical study data, hypocalcemia is an important identified risk. Mild and transitory decreases in albumin-corrected calcium and a compensatory increase in intact parathyroid hormone (iPTH) were observed after initiation of romosozumab. Based on the totality of data, the risk of hypocalcemia is manageable, with adequate calcium and vitamin D intake recommended for all romosozumab-treated patients and monitoring of serum calcium in patients with stage 5 chronic kidney disease (CKD).
3. Osteonecrosis of Jaw (ONJ): ONJ is an important risk of romosozumab due to its antiresorptive activity. There was one case of ONJ during treatment with romosozumab and two cases after romosozumab-treated subjects had transitioned to antiresorptive therapy.
4. Atypical Femur Fracture (AFF): AFF is an important risk of romosozumab due to its antiresorptive activity. Three cases of AFF were reported after romosozumab-treated subjects had transitioned to alendronate therapy.
5. Injection Site Reactions: There was a higher incidence of injection site reactions during the double-blind period in the romosozumab group than in the control groups in all phase 2 and 3 studies, with an incidence of about 5%.

When all data are considered, the benefits outweigh the risks for one year of romosozumab therapy in postmenopausal women with osteoporosis who are at high risk of fracture and who have not had a recent myocardial infarction or stroke. Romosozumab reduces the risk of vertebral and nonvertebral fracture. Although the fracture studies were not designed adequately to assess hip fracture, the outcome with the most associated morbidity and mortality, there were favorable point estimates in both studies for the romosozumab group compared to the control group, suggesting the potential for reduction in the risk of hip fractures on romosozumab. The evidence was not sufficient (b) (4) but the plausibility of an effect

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was considered in the benefit-risk assessment. Because of the different cardiovascular findings in the two large trials of romosozumab, it is not possible to exclude cardiovascular risk with romosozumab use. Given this potential risk, and the high risk of subsequent cardiac events in the year following a myocardial infarction or stroke, patients who are candidates for romosozumab therapy who have had a myocardial infarction or stroke within the prior year should not initiate romosozumab, as outlined in product labeling, including a Boxed Warning for prescribers and a Medication Guide for patients. Romosozumab's other risks are also adequately mitigated with labeling.

In addition to routine pharmacovigilance, a postmarketing study will be required to assess the impact of the boxed warning on romosozumab's prescribing patterns and potential for channeling bias. Depending on the findings of this study, a comparative safety study or trial may also be required to rule out an unacceptable increase in risk of MI, stroke, and cardiovascular death among users of romosozumab compared to users of an appropriate comparator(s).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Postmenopausal osteoporosis is a bone disease characterized by loss of bone mass, leading to an increased risk for fractures. • Postmenopausal women are the most common patient group to have osteoporosis. About 50% of postmenopausal women over age 50 will fracture bone due to osteoporosis • The risk of fracture increases with age. The risk also increases with a history of a previous osteoporosis-related fracture • In older patients, hip fracture is associated with increased loss of independence and increased mortality	Osteoporosis increases the risk of fracture in postmenopausal women. The risk of fracture increases with age and a history of a prior osteoporosis-related fracture. In older patients, fracture, predominantly hip fracture, is associated with increased morbidity and mortality.
Current Treatment Options	• Current treatment options for postmenopausal osteoporosis include medications that inhibit bone loss (bisphosphonates, RANK ligand inhibitors, estrogen agonists/antagonists, and	Multiple therapies are available for the treatment of osteoporosis in postmenopausal women. Rare but serious side effects have decreased the usage of some of the currently available therapies and many patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	calcitonin) and medications that stimulate bone formation (parathyroid hormone (PTH) and parathyroid hormone related peptide (PTHrP) analogs) • Bisphosphonates are the most widely prescribed medications for osteoporosis. Rare but serious side effects with bisphosphonates (osteonecrosis of the jaw and atypical femoral fractures) have reduced the use of these medications. • Denosumab is a potent antiresorptive therapy that also is associated with osteonecrosis of the jaw and atypical femoral fractures. Denosumab is also associated with an increased risk of fracture after discontinuation. • Teriparatide and abaloparatide are the only approved bone anabolic therapies. Their use is limited to two years because of the potential risk of osteosarcoma, which was noted in animal studies. • Raloxifene is associated with deep venous thrombosis and an increase in fatal strokes.	with osteoporosis who would benefit from therapy remain untreated. Additional therapies in a new class such as romosozumab, will expand the treatment options.
Benefit	• Vertebral Fracture: In the placebo-controlled trial, romosozumab reduced the risk of vertebral fractures with an absolute risk reduction of 1.3% and a relative risk reduction of 73% at month 12. Romosozumab followed by denosumab reduced the risk of vertebral fractures with an	Treatment with romosozumab 210 mg monthly for one year followed by antiresorptive therapy significantly increases bone mineral density at the lumbar spine and hip with accompanying significant vertebral fracture risk reduction (as demonstrated in the placebo and active-controlled trials) and nonvertebral fracture risk reduction

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	absolute risk reduction of 1.9% and a relative risk reduction of 75% at month 24 compared to placebo followed by denosumab. In the active controlled trial in postmenopausal women at high risk of fracture, romosozumab followed by alendronate was superior to alendronate alone, reducing the risk of vertebral fractures with an absolute risk reduction of 4.0% and a relative risk reduction of 50% at month 24. • Nonvertebral Fracture: In the placebo-controlled trial, romosozumab was not significantly different from placebo in reducing the risk of nonvertebral fracture. In the active controlled trial in postmenopausal women at high risk of fracture, romosozumab followed by alendronate was superior to alendronate alone in reducing the risk of nonvertebral fractures after a median follow-up of 33 months, with a hazard ratio of 0.81. • Bone Mineral Density (BMD): Romosozumab demonstrated consistent and significant increases in BMD at the lumbar spine, total hip and femoral neck in the fracture studies. Compared to placebo, romosozumab increased bone mineral density at the lumbar spine 13%, total hip 6% and femoral neck 5% after 12 months of therapy.	(as demonstrated in the active-controlled trial) in postmenopausal women with osteoporosis

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety data from the two large fracture trials for romosozumab include 5621 postmenopausal women who received romosozumab 210 mg once monthly for one year. • Safety concerns with romosozumab use include major adverse cardiac events, injection site reactions, hypersensitivity reactions, hypocalcemia, osteonecrosis of the jaw and atypical femoral fractures. • Cardiovascular safety is an important potential concern with romosozumab use. The clinical fracture trials have discrepant results for major cardiac adverse event outcomes. Additionally, there are limited data on the role of sclerostin in the cardiovascular system. • The risks associated with romosozumab use can be managed with product labeling.	Product labeling will include a boxed warning about major adverse cardiac events, recommending that romosozumab not be initiated in patients who have had a myocardial infarction of stroke within the past year, and to consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. Product labeling will also include warnings and precautions for injection site reactions, hypersensitivity reactions, hypocalcemia, osteonecrosis of the jaw and atypical femoral fractures. A medication guide will inform patients about these important risks. A Risk Evaluation and Mitigation Strategy is not needed for this product. Postmarketing Required Studies include: • a study to assess the impact of the boxed warning on romosozumab's prescribing patterns and potential for channeling bias. • Depending on the findings of the first study, a comparative safety study or trial may also be required to rule out an unacceptable increase in risk of MI, stroke, and cardiovascular death among users of romosozumab compared to users of an appropriate comparator(s).

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1.4. Patient Experience Data

Table 2: Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 8.1.2 Study Results
			□	Observer reported outcome (ObsRO)	
			X	Clinician reported outcome (ClinRO)	Section 8.1.2 Study Results
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

2 Therapeutic Context

2.1. Analysis of Condition

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 results from imbalances between resorption of bone by osteoclasts and formation of new bone by osteoblasts during bone remodeling. The World Health Organization (WHO) defines osteoporosis by bone mineral density (BMD) criteria obtained using dual-energy X-ray absorptiometry (DXA). A T-score is generated by measurements of the BMD at the lumbar

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spine, total hip, and femoral neck. Osteoporosis is defined by T-score ≤ 2.5 standard deviations below the mean BMD of a young, healthy cohort of adults at the same location.

Osteoporosis is a common disorder, with the worldwide prevalence estimated to be around 200 million people according to the WHO. Postmenopausal osteoporosis (PMO), the most common type, is driven primarily by the hormonal changes beginning at menopause. In the US, an estimated 8.2 million women over age 50 years have postmenopausal osteoporosis and approximately 1.5 million sustain osteoporosis-related fractures annually (NOF, 2018). The prevalence of PMO and hence the number of osteoporosis-related fractures are projected to increase substantially as the US population ages. Osteoporotic fractures, most notably hip fractures, are associated with decreased quality of life and increased morbidity and mortality.

Despite the morbidity and mortality associated with osteoporosis, and the availability of multiple treatments to reduce fracture risk (as discussed below), osteoporosis remains underdiagnosed and undertreated. Of postmenopausal women who have an osteoporosis-related fracture, only about 20% undergo DXA or receive a prescription for a drug to treat osteoporosis after a fracture (Balasubramanian et al, 2014; NOF, 2014).

2.2. Analysis of Current Treatment Options

Table 3 summarizes the currently approved pharmacologic therapies for PMO, which include several classes of antiresorptive therapies and two types of bone-forming (anabolic) agents that act through the PTH receptor. Bisphosphonates, the main class of antiresorptive therapy, are currently the standard of care for first-line therapy. Denosumab, a RANKL antagonist, raloxifene, an estrogen receptor agonist/antagonist, and calcitonin are the other available antiresorptive therapies. Available bone-forming agents include teriparatide, a parathyroid hormone (PTH) analog and abaloparatide, a PTH related protein (PTHrp) analog.

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Table 3: **Summary of FDA-Approved Pharmacologic Treatment Options for Postmenopausal Osteoporosis**

Drug Class	Product Name	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues
Bisphosphonates	Fosamax (alendronate)	1995	70 mg PO weekly (tablet or solution) 10 mg PO daily (tablet)	Osteonecrosis of the jaw (ONJ) fractures (AFF) fractures (AFF) Hypocalcemia Not recommended or contraindicated in patients with severe renal impairment Upper gastrointestinal adverse events with oral formulations
	Fosamax Plus D (alendronate/ cholecalciferol)	2005	70 mg alendronate/2800 or 5600 IU cholecalciferol, 1 tablet weekly	
	Binosto (alendronate)	2012	70 mg PO weekly (effervescent tablet for oral solution)	
	Actonel (risedronate)	2000	Tablets: 5 mg PO daily 35 mg PO weekly 150 mg PO monthly	
	Atelvia (risedronate)	2010	35 mg PO weekly (delayed release tablet)	
	Boniva (ibandronate)	2003	150 mg PO monthly (tablet)	
	Boniva (ibandronate)	2006	3 mg IV q3 months	ONJ, AFF, hypocalcemia
	Reclast (zoledronic acid)	2007	5 mg IV yearly	ONJ, AFF, hypocalcemia, renal toxicity, acute phase reactions
RANKL antagonist	Prolia* (denosumab)	2010	60 mg SC q6 months	ONJ, AFF, hypocalcemia
Estrogen agonist/antagonist	Evista (raloxifene)	1997	60 mg PO daily (tablet)	Venous thromboembolism Death due to stroke
PTH analog/ PTHrP analog	Forteo* (teriparatide)	2002	20 mcg SC daily	Osteosarcoma risk (animal data) limiting use duration to 2 years, hypercalcemia
	Tymlos* (abaloparatide)	2017	80 mcg SC daily	Osteosarcoma risk (animal data) limiting use duration to 2 years, hypercalcemia
Calcitonin-salmon	Miacalcin**	1986	SC or IM injection, 100 IU every other day	Hypersensitivity, hypocalcemia, malignancy
	Miacalcin**	1995	Nasal spray, 200 IU daily	
	Fortical**	2005	Nasal spray, 200 IU daily	

*approved only for osteoporotic patients at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

**approved only for osteoporotic patients for whom alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies). Fracture efficacy for calcitonin-salmon has not been established.

Excluding the calcitonin products (which were approved based on total body calcium and/or BMD data), the pharmacologic therapies listed in the above table were approved for treatment of PMO based on reduction of morphometric vertebral fractures, consistent with 1994 FDA guidance on osteoporosis drug development. Such fractures are defined solely by radiographic criteria and may be asymptomatic. Although the clinical effects of such fractures vary, as discussed above they are associated with increased morbidity and mortality and are a strong predictor of subsequent fractures (vertebral and nonvertebral). Additionally, vertebral fractures are the most common osteoporosis-related fractures in postmenopausal women (Khosla, 2003).

Table 4 lists the absolute and relative risk reductions (ARR and RRR, respectively) compared to placebo in new morphometric vertebral fractures (the primary endpoint) in the PMO trials of approved drugs. Risk reductions were generally apparent within 1 or 2 years and maintained through 3 years. Because the trial populations had different baseline fracture risks, ARR is highly variable between drugs and trials, while RRR is more consistent. For example, the FIT-1 trial of Fosamax enrolled a high-risk population (women with baseline vertebral fractures) whereas FIT-2 enrolled a lower risk population (no baseline fractures); fracture rates in both treatment groups were much higher in FIT-1, but relative reduction in fracture risk was nearly identical in the two studies.

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Table 4. PMO Fracture Trials: New Morphometric Vertebral Fractures, Risk Reductions by Year (Compared to Placebo)

Drug	12 Months		24 Months		36 Months	
	ARR (%)	RRR (%)	ARR (%)	RRR (%)	ARR (%)	RRR (%)
Teriparatide (Forteo)			9.3*	65*		
Abaloparatide (Tymlos)			3.9**	87**		
Denosumab (Prolia)	1.4	61	3.5	71	4.8	68
Zoledronic acid (Reclast)	2.2	60	5.5	71	7.6	70
Alendronate (Fosamax-FIT 1)					7.1	47
Alendronate (Fosamax-FIT-2)					2.3***	48***
Risedronate (Actonel-NA)	4.0	65	5.9	55	5.0	41
Risedronate (Actonel-MN)	7.7	61	13.1	59	10.9	49
Ibandronate (Boniva PO)					4.9	52
Raloxifene (Evista) ≥1 baseline fracture					6.1	30
Raloxifene (Evista) no baseline fracture					2.4	55

ARR = Absolute Risk Reduction; RRR= Relative Risk Reduction
*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
MN=multinational
NA=North America
Sources: Unites States Prescribing Information

Nonvertebral fracture is not a required endpoint for regulatory approval. Table 5 lists the ARR and RRR compared to placebo in the PMO trials of approved drugs that demonstrated statistically significant reductions in nonvertebral fracture risk.

Table 5 PMO Fracture Trials: Nonvertebral Fractures, Risk Reductions by Year (compared to placebo)

Drug	12 Months		24 Months		36 Months	
	ARR (%)	RRR (%)	ARR (%)	RRR (%)	ARR (%)	RRR (%)
Teriparatide (Forteo)			2.9*	53*		
Abaloparatide (Tymlos)			2.9**	52**		
Denosumab (Prolia)					1.5	20
Zoledronic acid (Reclast)					2.7	25
Risedronate (Actonel-NA)					3	39
Risedronate (Actonel-MN)					5	31
ARR = Absolute Risk Reduction; RRR= Relative Risk Reduction *Forteo trial: 19 months median exposure **Tymlos trial: risks at 25 months ***Fosamax FIT-2 trial: 48-month assessment Sources: Unites States Prescribing Information						

In summary, there are a number of pharmacologic therapies available for the treatment of PMO. However, there are limitations with the different treatment options as detailed in Table 3 above. Given that PMO is a disease that is reportedly undertreated and a disease that carries with it a risk of morbidity and mortality associated with osteoporotic fracture, additional treatment options that offer advantages over the current options are needed.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Romosozumab is a new molecular entity and currently not marketed in the US or anywhere else in the world. The FDA took a Complete Response action for the original BLA submission in July 2017 as described above in Section 1.1. There are currently no other marketing applications for romosozumab under review in other divisions of the FDA.

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3.2. Summary of Presubmission/Submission Regulatory Activity

The romosozumab IND (100391) was opened in November 2006. For a detailed listing of presubmission regulatory activity, refer to the review of the original BLA submission (signed in DARRTS May 3, 2017). An End of Phase 2 meeting was held in 2011. The applicant proposed to conduct a 12-month placebo-controlled phase 3 fracture trial. After discussion, the Division advised that the duration of the study should be a minimum of 2 years. It was acceptable that romosozumab treatment be limited to one year with all enrolled subjects (placebo and romosozumab treated subjects) receiving the same active control product for the second year. It was agreed that new vertebral fracture at 12 months and at 24 months could be coprimary efficacy endpoints.

The BLA was first submitted on July 19, 2016, with evidence of efficacy and safety from the 24-month primary analysis of the phase 3 placebo-controlled fracture study in women with PMO, Study 2007337 (Study 337). Late in the first review cycle, data from an active-controlled, phase 3 fracture study in women with PMO at increased risk for fracture, Study 20110142 (Study 142), became available and demonstrated an imbalance in positively adjudicated serious cardiovascular events for romosozumab vs. the active control alendronate during the 12-month double-blind period of the study. Additionally, data from the recently completed 12-month placebo-controlled phase 3 BMD study in men with osteoporosis, Study 20110174 (Study 174), also indicated an imbalance in positively adjudicated serious cardiovascular events. The applicant requested a meeting with FDA to discuss these findings, which took place on May 19, 2017.

In response to the concerning cardiovascular safety findings of Study 142 and Study 174, the FDA issued a Complete Response Letter on July 13, 2017, which outlined the following:

> *DEFICIENCY:*
> *Preliminary findings from Study 20110142 show a higher incidence of cardiovascular serious adverse events with romosozumab compared to alendronate in women with postmenopausal osteoporosis. A similar signal was seen in Study 20110174, a smaller study comparing romosozumab to placebo in men with osteoporosis. These findings raise concerns that romosozumab may increase cardiovascular risk. Although Study 20070337 did not appear to have a cardiovascular safety signal, these disparate findings across studies require detailed review once the completed final analyses have been submitted. These additional data, including the efficacy data from the head-to-head comparison of romosozumab to alendronate, are needed before we can complete the benefit/risk assessment and determine whether the benefits of romosozumab outweigh its risks.*
>
> *TO ADDRESS THIS DEFICIENCY:*
> *Complete analyses of Studies 20110142 and 20110174. Submit the individual clinical study reports together with an integrated assessment of cardiovascular risk that takes*

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> *into account the totality of the data. This should include the basis for your conclusion that the benefits of romosozumab outweigh the identified cardiovascular risks. Provide all pertinent narratives and datasets. We recommend that you request a meeting to discuss the details of your proposal for responding to the deficiency before you resubmit the application.*

An End of Review meeting was held with the applicant on October 26, 2017. FDA requested an analysis of Major Adverse Cardiovascular Events (MACE), a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, as well as analyses of each of these individual components. Additionally, because of the early separation of events in the treatment groups (by Month 2), FDA recommended that the cardiovascular safety analyses include demonstration that romosozumab does not have off-target effects on platelet aggregation (e.g., via an in vitro platelet aggregation study), vasoconstriction, and systolic and diastolic blood pressure. FDA also requested an analysis of non-serious cardiac ischemic events (e.g., angina).

The BLA was resubmitted on July 9, 2018. The resubmission addressed the requirements put forth in the Complete Response letter and the recommendations communicated to the applicant at the End of Review meeting.

On January 4, 2019, the applicant submitted a clinical information amendment outlining all changes that resulted from additional data available through the end of the final analysis periods of Studies 337 and 142 (as compared to what was initially reported in the clinical study reports, which covered the primary analysis periods of the studies). This constituted a major amendment to the application. On January 7, 2019, FDA notified the applicant that the PDUFA goal date would therefore be extended by three months to allow time for a thorough review of this amendment.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Inspections of clinical sites participating in Study 2011142 were deemed not necessary. Many of the clinical sites in Study 142 were the same as those participating in Study 337. During the initial BLA submission, four clinical sites participating in Study 337 were audited. The rationale for selection of these sites and final inspection results are as follows:

- Site 1-678YLY, Jose Fernando Molina Restrepo, M.D., Medellin, Columbia: two investigators with the same last name in the same location appeared unusual, high enrollment (752 total between the two sites), new investigator(s). A Form 483 was issued for failure to conduct an investigation in accordance with the signed statement of investigator and the investigational plan. This site was classified as voluntary action indicated (VAI). This VAI did not impact data integrity from this site.
- Site 1-64PLTY, Jaime Restrepo, M.D., Medellin, Columbia: two investigators with same last name in same location appeared unusual, high enrollment (752 total between the two sites), new investigator(s). This site was classified as no action indicated (NAI).
- Site 1-52SFOU, Magda Dabrowska, M.D., Poland: high enrollment (264), high site efficacy effect (- 2.04), relative high number of outliers, no prior inspection in the past 3 years. This site was classified as NAI.
- Site 1-3RA0SB (Recknor, US): US site for comparison. This site was classified as NAI.

4.2. Product Quality

The review team from the Office of Biotechnology Products recommends approval of this BLA. The supplement does not include any changes related to product quality. Please see the Office of Biotechnology Product's BLA 761062 Resubmission Executive Summary and Memorandum of Review.

Drug Substance: Romosozumab is produced from a recombinant DNA-derived Chinese Hamster Ovary (CHO) cell line using standard cell culture techniques. The master cell bank (MCB) and working cell bank (WCB) have been adequately characterized and tested. Tables 1 and 2, pages 7 – 19 of the Integrated Quality Assessment from the first review cycle outline the critical quality attributes of the romosozumab drug substance. The data provided in the BLA supports a shelf life of (b) (4) months for the romosozumab drug substance when stored at (b) (4).

Drug Product Manufacturing: Drug product manufacturing process steps include (b) (4)
(b) (4)

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(b) (4) (b) (4). Table 3 and 4, pages 23 – 26 of the Integrated Quality Assessment from the first review cycle outline the critical quality attributes of the romosozumab drug product.

Drug Product: Evenity (romosozumab) is a combination product with the drug product presented in single-use prefilled syringes with a romosozumab concentration of 90 mg/mL. Each prefilled syringe contains 105 mg romosozumab in 1.17 mL volume. Other excipients in the 1.17 mL volume include calcium (0.61 mg), acetate (3.8 (b) (4) mg), sucrose (70 mg), polysorbate 20 (0.07 mg), sodium hydroxide (b) (4), and Water for Injection. Evenity is a sterile, preservative-free, clear to opalescent, colorless to light yellow solution for subcutaneous injection. The pH of the solution is 5.2. The dose of romosozumab, 210 mg, requires injection of two prefilled syringes. Evenity is packaged as a carton containing two single use prefilled syringes. The stability data in the BLA support a shelf life of 36 months for Evenity when stored at the recommended storage condition of 2 - 8°C.

Microbiology: Both the drug substance and drug product quality microbiology parts of this BLA are recommended for approval. Refer to reviews from the first review cycle for complete details.

Facilities: No new facilities are proposed in this BLA resubmission. All facilities were recommended for approval in the first review cycle.

Environmental Assessment: A claim for a categorical exclusion under 21 CFR 25.31 (c) is found acceptable.

Device considerations: During the first review cycle, the device constituent was found acceptable for approval by the General Hospital Devices Branch (GHDB)/ Office of Device Evaluation/Center for Devices and Radiological Health (CDRH). In this resubmission, the applicant includes the addition of breakloose and extrusion (BLE) testing for use in stability and lot release at the Amgen Dun Laoghaire (ADL) site. The information provided is adequate to support transfer of drug product syringe break loose and extrusion testing from Amgen Manufacturing Limited (AML) to ADL.

Labeling: Product labeling has been reviewed by the Office of Biotechnology Products and changes have been agreed upon with the applicant

Postmarketing studies: During the original review cycle, a postmarketing commitment study (b) (4) (b) (4) had been discussed with the applicant. The requested data are included in the BLA resubmission, have been reviewed, and are acceptable.

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4.3. Clinical Microbiology

Romosozumab is not an antimicrobial agent. Clinical microbiology studies are not applicable to this BLA. The microbiology product quality of the romosozumab drug substance and combination drug/device product were reviewed by the Product Quality team.

4.4. Devices and Companion Diagnostic Issues

Drug product manufacturing processes were modified to manufacture prefilled syringes (PFS) in three presentations: 70 mg/mL and 120 mg/mL in 1 mL Long glass syringes, and 90 mg/mL in 1 mL (b) (4) syringes. Only the 90 mg/mL (b) (4) syringe presentation is intended for commercial registration and production. Refer to the Center for Devices and Radiological Health (CDRH) review for details.

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant carried out a comprehensive nonclinical program for the original BLA submission that included pharmacology, pharmacokinetics/ADME and toxicology studies.

Prompted by the adverse cardiovascular findings in Study 142, the sponsor conducted five additional nonclinical studies to examine the potential risk of sclerostin inhibition for acute ischemic cardiovascular events. A study to assess the risk for osteonecrosis of the jaw (ONJ) was also conducted.

The new studies showed (A) in an in vitro study: no activation of human platelets by romosozumab; (B) in the ovariectomized (OVX) ApoE knockout (KO) mouse atherosclerosis model: no effects of sclerostin antibody on systemic markers of inflammation or endothelial activation, no meaningful qualitative or quantitative effects of sclerostin antibody treatment on aortic atherosclerotic lesions except for a decrease in plaque volume at end of study, and no effects of sclerostin antibody on gene transcription that would be consistent with an atherogenic effect; (C) in human artery atherosclerotic plaques: no expression of sclerostin in vulnerable plaque areas, and generally no association between sclerostin expression and plaque features or cardiovascular events observed in the plaque donors; (D) in a genome-wide association study (GWAS) database: no genetic association between risk of osteoporosis or fracture and risk of MI or stroke; and (E) in human coronary artery rings: no vasoconstrictive effect of romosozumab or human sclerostin. An additional nonclinical study showed lack of induction of ONJ-like lesions by sclerostin antibody in OVX rats with experimental periodontitis.

The Applicant discussed the concerns about cardiovascular safety, particularly the potential for ischemic events, from a nonclinical perspective based on the available nonclinical data and current literature. The concerns included potential roles of sclerostin in vascular calcification and atherosclerosis-associated pathology. The data from previously conducted nonclinical studies suggested that sclerostin inhibition does not induce or exacerbate vascular calcification. The data from the newly conducted study in the mouse atherosclerosis model showing lack of an effect of sclerostin antibody on mineralized plaque volume appeared to confirm this conclusion. Additionally, the fact that the inverse relationship between sclerostin expression and dystrophic calcification in human carotid arterial plaques was unlikely to reflect a direct relationship also strengthened this conclusion.

The atherosclerosis study in the ApoE KO mice was the most elaborate new nonclinical study conducted. The results of this 16-week study did not suggest exacerbation of atherosclerosis or significant transcriptional changes in aortic plaques as a result of antibody-mediated sclerostin inhibition. Accordingly, the reduced expression of sclerostin in human and mouse atherosclerotic plaques does not appear to be causally related to atherosclerosis or its

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progression. However, there was an increase in the incidence of atherosclerotic plaques with necrosis in sclerostin antibody treated mice compared to control animals at the end of the 16-week study, signaling a potential overall increase in plaque vulnerability. Some concern about the relation between sclerostin and atherosclerosis also remains based on the results from a recently published study (Krishna et al, 2017) suggesting a protective effect of sclerostin in the Angiotensin-II treated ApoE KO mice, a mouse model for atherosclerosis and aneurysm. Further evaluation of the effects of sclerostin or its inhibition in the ApoE KO and the Angiotensin-II ApoE KO model, respectively, could provide additional nonclinical information. However, the data are unlikely to change the clinical concern about serious cardiovascular events based on inconsistent data from different trials.

No association was found between sclerostin inhibition and plaque rupture or erosion through reduced extracellular matrix, mechanical instability (via calcification or hemorrhage), endothelial apoptosis/dysfunction or thrombogenesis, which are known mechanisms or pathways that can lead to ischemic/thrombotic events. Also, no association was identified between sclerostin inhibition and vascular tone, blood pressure or hemostasis. In addition, human genetics data did not clearly indicate an association between lower sclerostin expression, which was linked to a lower risk of osteoporosis and fracture, and myocardial infarction or stroke.

In conclusion, the nonclinical data did not definitively show a causal relationship between sclerostin inhibition and adverse cardiovascular structural or functional effects. However, the increase in necrotic plaques in the ApoE KO mice upon treatment with sclerostin antibody may signal an increase in plaque vulnerability and an increased risk of plaque rupture. Based on the remaining uncertainty about the clinical relevance of the nonclinical data, the concern about the cardiovascular safety of romosozumab should not be dismissed.

5.2. Pharmacology/Toxicology Overview

Introduction

The resubmission included five new nonclinical studies to further investigate the effects of sclerostin antibody on cardiovascular endpoints and identify a potential biological mechanism for the adverse cardiovascular effects.

Summary of previous studies

Sclerostin is an extracellular inhibitor of the canonical Wnt signaling pathway and is produced mainly by the osteocyte. A comprehensive nonclinical study program was conducted to support the original BLA submission.

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Romosozumab blocks the interaction of sclerostin with low density lipoprotein receptor-related protein (LRP)5 and LRP6, two co-receptors involved in Wnt signaling, thereby activating the Wnt pathway in osteoblastic cells.

In humans, romosozumab transiently stimulates bone formation and inhibits bone resorption, based on evaluation of bone turnover markers. In 12-month bone quality studies in ovariectomized (OVX) rats and monkeys, at doses equivalent to 1-19x and 1-22x the human AUC(0-τ) of 12888 μg.h/mL at the monthly subcutaneous dose of 210 mg, respectively, romosozumab increased bone mass and strength of the lumbar spine, tibia, femur, and radius in a dose- and time-dependent manner. Bone formation and resorption markers were rapidly and transiently increased. The bone changes consisted of increases in trabecular thickness in vertebrae and long bone metaphyses and increases in cortical thickness in long bone metaphyses and diaphyses. These effects were due to stimulation of bone formation concomitant with suppression of bone resorption, mostly at trabecular and endosteal bone surfaces, as observed by histomorphometry. An improvement in bone quality was observed in the vertebrae of rats and monkeys at 19-22x human exposure multiples. Bone quality was maintained at all other evaluated sites.

Toxicity studies of up to 6-month duration were conducted in rats and monkeys. The main findings were related to the pharmacologic effect of romosozumab and included red blood cell, white blood cell and platelet decreases, serum calcium and phosphorus decreases, and extramedullary hematopoiesis. The effects were associated with hyperostosis and increases in bone formation and densitometric parameters. Exposure multiples in the 6-month studies ranged from 1-38x and 1-93x human exposure, in rats and monkeys, respectively. Assessments of local tolerance did not reveal significant concerns.

A carcinogenicity study was conducted in Sprague Dawley rats. The rats were dosed for up to 98 weeks with 0, 3, 10, 50 mg/kg/week, equivalent to 1-19x human exposure. Romosozumab did not affect mortality and caused a dose-dependent increase in bone mass with trabecular and cortical bone thickening at all doses. Romosozumab did not cause significant increases in tumor incidences in males or females. A low incidence of osteosarcoma (2/54) was observed in high dose males at 19x human exposure. However, the lack of statistical significance of this finding and the large exposure multiple suggests that romosozumab is unlikely to increase the human risk of osteosarcoma.

Reproductive toxicity was evaluated in rat fertility and early embryonic development (FEED), embryofetal development (EFD) and pre- and postnatal development (PPND) studies. Findings in the definitive FEED and EFD studies included reduced ventral processes of the 6th cervical vertebrae at doses of 100 and 300 mg/kg (17-56x human exposure). However, this anatomical structure is not present in humans and the finding is not considered clinically relevant. Fetal poly- and syndactyly were observed in the definitive EFD study at 32x human exposure, consistent with the syndactyly that has been observed in sclerosteosis patients and SOST knockout mice. Although it may have been treatment-related, the finding is considered of low

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clinical relevance based on the exposure multiple and the timing of digit formation in the first trimester in humans when placental transfer of immunoglobulins is limited. In the PPND study, there were small decreases in femoral bone density and/or thickness in the F1 offspring at 1.5-56x human exposure of unclear biological significance. None of these findings are considered relevant for the postmenopausal indication.

In the original BLA submission, the sponsor evaluated multiple potential safety concerns based on the weight of evidence from nonclinical studies, clinical studies and published literature. There was no indication that romosozumab would increase the risks for vascular calcification, but potential effects on processes underlying cardiovascular ischemic events were not considered at the time. Increased risks for osteoarthritis, altered longitudinal bone growth, hyperostosis, hypercementosis, altered hematopoiesis or glucose metabolism, sarcopenia, and exacerbation of TNFα-mediated inflammation were also considered unlikely. The risk of vascular calcification is further discussed in the general discussion of concerns about cardiovascular effects of sclerostin at the end of this section.

5.3. Nonclinical Evaluation of Sclerostin and Cardiovascular Disease

To further address the imbalance in serious cardiovascular (CV) events observed in clinical studies and to assess the plausibility of a treatment related effect, the sponsor conducted five new non-GLP nonclinical pharmacology studies with romosozumab or a rat surrogate sclerostin-antibody (r13C7), which is romosozumab engineered with rat Fc. A study of the effects of r13C7 in a rodent model of ONJ was also conducted (Table 6).

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Table 6: New Nonclinical Pharmacology Studies

Reviewer's Study #	Amgen Study Nr.	Study Type	Study Title
Study #1	**125269**	**Secondary Pharmacology**	**Platelet Activation Assay for AMG785**
Study #2	**124609**	**Secondary Pharmacology**	**r13C7: Atherosclerotic and Transcriptional Changes in Aortas from High Fat Diet-fed Ovariectomized Wild Type and ApoE KO Mice Administered Scl-Ab**
Study #3	**150498**	**Secondary Pharmacology**	**Immunohistochemical assessment of sclerostin expression in human atherosclerotic plaques**
Study #4	**150655**	**Secondary Pharmacology**	**Analysis of BMD-Associated SNPs at the SOST Locus for Association With Stroke and Myocardial Infarction in the UK Biobank**
Study #5	**150483**	**Safety Pharmacology**	**Study to Assess the Effects of Recombinant Human Sclerostin and AMG 785 on Isolated Healthy Human Coronary Arteries**
Study #6	**122002**	**Secondary Pharmacology**	**r13C7: Differences of Antiresorptives on Osteonecrosis of the Jaw (ONJ) Initiation and Resolution**
AMG785 = romosozumab; r13C7 = rat sclerostin antibody; KO = knock out; BMD = bone mineral density; SNP = single nucleotide polymorphism			

STUDY #1

Platelet Activation Assay for AMG785

(Amgen Study #125269, Sponsor Amgen; non-GLP)

AMG 785 (romosozumab) was tested for platelet activation in order to evaluate its potential for pro-thrombotic effects. Flow cytometry (expression of CD62P and P-selectin on CD41a+ cells) showed that there was no activation of platelets in human whole blood at concentrations of 1, 3, 10, 30, 100 and 300 ug/mL romosozumab. The highest concentration (300 ug/mL) represented an approximate 10-fold multiple of Cmax (28.1 ug/mL) at the monthly subcutaneous clinical romosozumab dose of 210 mg.

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STUDY #2

r13C7: Atherosclerotic and Transcriptional Changes in Aortas from High Fat Diet-fed Ovariectomized Wild Type and ApoE KO Mice Administered Scl-Ab

(Amgen Study No. 124609; Test Facility: (b) (4) (b) (4), non-GLP)

Introduction

The objective of this study was to evaluate the potential effects of sclerostin antibody r13C7 on potential transcriptional and morphologic changes in atherosclerotic plaques in aortas from high fat diet-fed ovariectomized (OVX) Apolipoprotein E (ApoE) knockout (KO) mice (ApoE KO-OVX mice) compared with high fat diet-fed OVX Wild Type (WT) mice (WT-OVX mice). The effects of alendronate for 16 weeks were also evaluated.

The ApoE KO mouse model is a well-known model of atherogenesis. ApoE plays a key protective role in atherosclerosis. First, plasma ApoE maintains plasma cholesterol homeostasis by facilitating hepatic uptake of lipoprotein remnants. Second, in atherosclerotic lesions ApoE together with ApoA-I facilitates cholesterol efflux from macrophage foam cells within the affected intimal layer. ApoE present in the atherosclerotic lesion also modifies macrophage- and T lymphocyte-mediated immune responses that contribute to this chronic inflammatory disease.

Methods

Female WT or ApoE KO mice (C57Bl/6) were placed on a high-fat (42% from fat) diet at 5-6 weeks of age. After 2 weeks, the mice were ovariectomized (OVX). Two weeks after ovariectomy, at age 9-10 weeks, mice were dosed by subcutaneous injection once weekly with 10 mg/kg of the rat sclerostin antibody r13C7 for 3, 8, or 16 weeks, or twice weekly with alendronate (ALN) (0.02 mg/kg) for 16 weeks. Control mice were treated with reference item A or B (placebo solution or saline), respectively (Table 7). 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 (measured by microCT). A defined region of the aortic arch was used for RNA sequencing.

Anticipated exposure (AUC) to sclerostin-antibody r13C7 (10 mg/kg) was approximately 4-fold greater than clinical exposure to romosozumab 210 mg monthly based on AUC comparison. It is unclear how this exposure was calculated but it may have been based on data from a 1-year rat bone quality study (107899), in which the 10 mg/kg dose yielded a 4.3-fold animal vs. human AUC exposure multiple, the bone formation marker osteocalcin was increased by approximately 30% at 3 months, and vertebral BMD was increased by up to 35% after 1 year. The 0.02 mg/kg alendronate dose was 4-fold greater than the human equivalent oral weekly dose of 70 mg assuming 1% bioavailability (5 µg/kg, twice weekly, S.C). Effects of alendronate in WT mice were not described or discussed in the main section of the report.

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Table 7: Experimental Design of Amgen Study No. 124609 (Study #2)

Text Table 1
Experimental Design

	Group No.	Test Material	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Main Females	Number of Satellite Females
Reference Item A	1	Wild Type – OVX – Reference Item A	0	9.62	0	42[a]	30[b]
	2	ApoE KO – OVX – Reference Item A	0	9.62	0	42[a]	30[b]
Test Item A	3	Wild Type – OVX – r13C7	10	9.62	1.04	42[a]	30[b]
	4	ApoE KO – OVX – r13C7	10	9.62	1.04	42[a]	30[b]
Reference Item B	5[d]	Wild Type – OVX – Reference Item B	0	9.62	0	14[c]	10[c]
	6	ApoE KO – OVX – Reference Item B	0	9.62	0	14[c]	10[c]
Test Item B	7[d]	Wild Type – OVX – Alendronate	0.02	9.62	0.002	14[c]	10[c]
	8	ApoE KO – OVX – Alendronate	0.02	9.62	0.002	14[c]	10[c]

[a] Fourteen (14) females/group, designated for fluorochrome labeling, micro-CT and histology were euthanized after 3, 8, and 16 weeks.
[b] Ten (10) females/group, designated for RNA, biochemical markers of bone turnover and cytokine/chemokine analysis were euthanized after 3, 8, and 16 weeks.
[c] Animals were euthanized after 16 weeks.
[d] Individual in life and clinical pathology data collected from animals in Groups 5 and 7 are presented in Appendices to the report, but no Summary Tables and no further interpretation of the data are reported.

Results

Clinical signs and body weight;

Mortality, clinical observations and body weight were not affected by r13C7 or alendronate treatment.

Bioanalysis (TK)

In general, all animals dosed with r13C7 had detectable r13C7 serum levels on Days 22, 57 and 113, confirming exposure. However, levels were quite variable.

Clinical chemistry

Lipids: ApoE KO-OVX mice showed the expected increases in serum cholesterol, HDL, LDL, cholesterol/HDL ratio, and triglycerides as compared to WT-OVX mice. Treatment with r13C7 or ALN did not have an effect on clinical chemistry parameters in either WT-OVX or ApoE KO-OVX mice.

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Bone turnover markers (PINP, OPG, TRACP 5b):
Levels of PINP (bone formation marker) were similar in WT-OVX and ApoE KO-OVX control mice. R13C7 significantly increased PINP in both WT-OVX and ApoE KO-OVX mice at all time points, indicating the expected bone formation effect. The increase in PINP was variable and averaged approximately 50%, at all time points. ALN for 16 weeks led to a significant reduction in serum PINP in ApoE KO OVX mice, as expected for an antiresorptive drug.

Levels of OPG (osteoprotegerin) (inhibitor of osteoclast formation/maturation and also a known Wnt target gene and negative regulator of vascular calcification) were lower in ApoE KO-OVX mice than in WT mice on Days 57 and 113. OPG levels were not affected by either r13C7 or alendronate treatment for either genotype at any time point.

Levels of TRACP 5b (osteoclast marker) decreased over time in ApoE KO-OVX mice and were significantly lower than in WT mice on D113. TRACP 5b levels were not affected by either r13C7 or ALN in either genotype.

Systemic markers of inflammation or endothelial activation
Markers evaluated included:

- Chemokines that attract and/or recruit activated blood immune cells to sites of inflammation (MCP1, RANTES, IL-16, MIP-1α, MIP-2, CXCL16, MCP2, SDF1α and KC/GRO)
- CD40L and biomarkers released by endothelial cells in response to vascular injury (Endocan-1, Follistatin, ICAM1, P-selectin and E-selectin)
- Major pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α)
- Biomarkers of vascular calcification (OPN) and cell proliferation (TIMP1 and M-CSF)

Small increases in only a couple of markers (OPN and TIMP1) were observed in ApoE KO vs. WT mice on Day 22. There were also a few transient changes, usually decreases on Day 57 only, in a couple of markers in r13C7-treated but not vehicle-treated WT or ApoE KO animals, e.g. a decrease in E-Selectin in r13C7-treated ApoE KO mice. However, in general, r13C7 did not significantly alter these markers in either WT or ApoE KO OVX mice. Based on the lack of an effect of r13C7 on P-selectin and CD40L in both genotypes, sclerostin inhibition had no effect on platelet activation.

Alendronate significantly increased (approximately 10-fold) monocyte/neutrophil-derived KC/GRO (neutrophil chemoattractant and activator) in ApoE KO mice after 16 weeks, indicating an enhancement of the pro-inflammatory immune response.

Histopathology (aorta)
Atherosclerotic lesions (plaques) occurred only in the ApoE KO-OVX and not in WT-OVX mice. Atherosclerotic plaques observed in three different aorta segments (ascending aorta, aortic arch, and descending aorta) were categorized according to Stary-derived types 1 through 5. Incidence was determined in groups of 14 animals per time point.

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At Week 3, type 1 and 2 plaques (containing macrophage foam cells) were noted in all ApoE KO mice with incidence unaffected by r13C7 treatment. At later time points (Weeks 8 and 16), type 3, 4 and 5 plaques, containing extracellular lipid pools (type 3) or confluent lipid cores (type 4) or fibromuscular tissue (type 5), were also observed. Some type 2-5 plaques had necrotic areas, while type 3-5 plaques contained variable numbers of mesenchymal or macrophage cells as well as lipid deposits and sometimes fibro-cartilaginous tissue ('metaplasia'), occasionally with tinctorial changes consistent with mineralization. All microscopic features were consistent with changes expected in ApoE KO-OVX mice on a high fat diet.

At Week 8, an increase in the combined incidence of atherosclerotic plaques in ApoE KO-OVX mice treated with r13C7 was observed, due to a higher incidence of type 2 atherosclerotic plaque. This was considered of low significance because the incidence of type 1 and type 3, 4 or 5 plaques at both Week 8 and Week 16 was not affected by r13C7. Also, at Week 16, the total incidence of plaques was similar in ApoE KO-OVX control and r13C7-treated animals. This suggests that r13C7 did not promote atheroprogression.

At Week 16, the only effect in the ApoE KO-OVX mice appeared to be a r13C7-related increase in the incidence of plaques of all types (2-5) with necrosis (combined incidence [#plaques with necrosis/#aorta-segments]: 32/39 vs. 24/39 in treated vs controls). This finding signals a potential concern about a sclerostin-antibody induced increase in plaque instability. At Week 16, there was no effect of r13c7 on the incidence of plaques with fibro-cartilaginous tissue.

Alendronate, at Week 16, had no meaningful effects on the various types of atherosclerotic plaques (types 1-5) in ApoE KO-OVX mice. However, there was a slight increase in incidence of intra-plaque fibro-cartilaginous tissue with matrix tinctorial change, consistent with ongoing mineralization, in type 3-5 plaques in these ALN-treated animals.

There was no evidence of hemorrhage or thrombosis associated with atherosclerotic plaques in either r13C7- or alendronate-treated ApoE KO-OVX animals.

RNA-sequencing analyses

Atherosclerosis associated genes

A large number of genes were differentially expressed in the aorta of ApoE KO-OVX vs. WT-OVX mice and the statistical significance of the changes increased over time with atherosclerosis progression. Increases of up to 12-fold were observed at all time points for some genes in the ApoE KO-OVX vs. WT-OVX mice. Upregulation of Spp1 (osteopontin) and several MMP (matrix metalloproteinase) genes was observed in ApoE KO aortas, consistent with extracellular remodeling in the plaque, and with gene expression changes in humans, supporting the relevance of the model.

The most significant differentially expressed pathways in ApoE KO vs. WT aorta were related to inflammation. They included granulocyte and agranulocyte adhesion and diapedesis genes, dendritic cell maturation genes, genes involved in communication between innate and adaptive

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immune cells, leukocyte extravasation signaling genes, and TREM1 signaling genes. These results were also consistent with data on altered gene expression in human plaques. A genotype effect on extracellular matrix (ECM) and prostaglandin metabolism gene expression was also observed, as expected. Wnt target genes were not significantly differently expressed in ApoE KO-OVX vs. WT mice. There was also a genotype effect on the expression of ossification and bone mineralization related genes, but only at Week 16.

Effects of r13C7 in WT-OVX and ApoE KO-OVX mice
Gene expression changes following r13C7 treatment were limited in number and the change was much smaller and less significant than the genotype-related changes. Expression changes (≥2-fold) were not consistently present at each time point in the study or between genotypes (WT-OVX vs. ApoE KO-OVX mice).

In WT-OVX mice, a limited number of Wnt target genes, or genes known to be regulated by sclerostin antibody related to ossification and bone mineralization, were differentially expressed in the aorta of r13C7-treated animals at Week 3 (only), and an acute response pre-Week 3 cannot be excluded. Some genes involved in ECM organization were also differentially expressed at Week 3 in r13C7 vs. vehicle treated WT mice.

In ApoE KO-OVX mice, r13C7 treatment led to a significant gene expression change in 3 pathways at Week 8, but the enrichment of these pathways was driven by only a small number of genes. The pathways did not intersect with the atherosclerosis-related pathways identified by genotype (ApoE KO-OVX vs. WT-OVX) comparison and are therefore unlikely to play a role in atherosclerosis progression. Two of these pathways were related to triglyceride synthesis and vascular calcification, respectively, possibly playing a role in arterial disease. However, this is weak evidence for a significant vascular effect of sclerostin antibody. At week 16, only 4 genes changed expression, and no pathways were significantly enriched.

In the ApoE KO-OVX mice, no Wnt target genes or sclerostin antibody responsive bone genes significantly changed expression due to r13C7 treatment at any time point. However, Dkk2, a known Wnt antagonist, was upregulated (about 2-fold) with r13C7 treatment at week 3. In ApoE KO-OVX mice, there was no clear evidence of upregulation by r13C7 of genes involved in ECM structure, bone mineralization, and cell cycle. Sclerostin antibody had no effect on prostaglandin signaling genes in ApoE KO-OVX mice, suggesting a lack of related prothrombotic effects.

Thus, RNA sequencing did not identify a typical gene expression signature attributable to r13C7 treatment that would be associated with the development or progression of atherosclerosis.

SOST and Dkk1
In bone, expression of Wnt antagonists Dkk1 and SOST is upregulated in response to sclerostin antibody treatment, possibly explaining the attenuation of the bone effect over time. In the current study, the Dkk1 gene was not expressed in mouse aorta in any of the conditions

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examined. SOST expression was downregulated in ApoE KO-OVX vs. WT-OVX mouse aortas at Weeks 8 and 16, suggesting atherosclerosis might be associated with Wnt pathway inhibition and feedback SOST decrease. However, the lack of changes in Wnt pathway genes in ApoE KO-OVX vs. WT-OVX mice, described above, contradicts this hypothesis. SOST expression was not affected by r13C7 treatment in either WT-OVX or ApoE KO-OVX mice at any time point, which is different from the increase in SOST expression in bone upon sclerostin antibody treatment and osteoblastic Wnt activation.

To understand the SOST downregulation in ApoE KO-OVX mouse aorta, an analysis was performed on relevant genes differentially expressed in ApoE KO-OVX vs. WT-OVX mice. The data showed that upstream regulators compatible with both upregulation and downregulation of SOST expression were enriched in ApoE KO-OVX vs. WT-OVX mouse aorta. However, it is unclear which of these regulators is a major modulator of SOST expression in the vasculature.

While systemic markers of inflammation or endothelial activation were not affected by r13C7 (above), several genes related to inflammation, e.g. MCP-1, IL-6, and ICAM1, were locally upregulated in the aorta of ApoE KO-OVX mice, consistent with the local upregulation of inflammation signaling pathways. The expression of these genes was not affected by r13C7 in either genotype. There was no evidence of in vivo platelet activation in WT or ApoE KO-OVX mice by sclerostin antibody, since P-selectin and CD40L were unaltered.

Thus, the data indicate that Scl-Ab r13C7 does not affect atherosclerosis-related gene expression in aortic arch tissue.

Micro-CT evaluation of atherosclerotic plaques

In the ApoE KO-OVX mice, atherosclerotic total plaque volume (mm^3) (absolute and relative to aorta volume) increased over time, as expected, and consistent with the histology data. Treatment with r13C7 led to a statistically significant decrease in plaque volume of approximately 30% at Week 16, a finding dismissed in the sponsor's report as not biologically relevant. The relatively small mineralized plaque volume was increased in ApoE KO-OVX mice vs. WT-OVX mice (from <1% to 3%) at Week 16 but not at Week 3 and 8. However, mineralized plaque volume was not affected by r13C7. The increase in mineralized plaque volume in untreated ApoE KO-OVX vs. WT-OVX mice was consistent with the observed decrease in serum OPG, which has been reported to be a negative regulator of vascular calcification.

Alendronate caused a slight decrease in total plaque volume but had no effect on mineralized plaque volume at Week 16.

In a published study by Krishna et al (2017) conducted in ApoE KO male mice on high fat diet and dosed with Angiotensin II (Ang II) for 28 days, a model in which atherosclerosis and aortic aneurysm develop, excess systemic levels of sclerostin reduced several measures of atherosclerosis, aneurysm, and markers of inflammation. Atherosclerotic plaque area (Sudan IV stain) after 4 weeks (22%) was much larger than that in the Sponsor's ApoE KO model after 16

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weeks (22%) and was significantly reduced by SOST excess to approximately 5%. The contrasting results of this study and the sponsor's study are discussed further in Section 5.4.

Conclusions

The action of sclerostin antibody r13C7 was investigated in the high fat diet-fed ApoE KO-OVX mouse, an established mouse model for atherosclerosis, following ovariectomy. Administration of r13C7 by subcutaneous injection once weekly at a dose of 10 mg/kg (predicted to be 4-fold greater than the clinical exposure of romosozumab of 210 mg once monthly) for 3, 8, or 16 weeks was well tolerated in ovariectomized (OVX) ApoE KO and WT mice. There was no genotype effect on the levels of systemic markers of inflammation or endothelial/platelet activation (cytokines/chemokines). Sclerostin inhibition by r13C7 also had no significant effects on these markers in either WT-OVX or ApoE KO-OVX mice. Sclerostin antibody had no meaningful effects on the incidence of atherosclerotic plaques in ApoE KO-OVX mice. There was an increase in the incidence of plaques with necrosis at Week 16, but no effect on plaque fibro-cartilaginous metaplasia at any time point in ApoE KO-OVX mice. The increase in plaque necrosis may signal a concern about increased plaque instability. Sclerostin antibody decreased aortic total plaque volume at Week 16, but the significance of this finding is unclear in the context of the other study results. Sclerostin antibody had no effect on the mineralized plaque volume in ApoE KO-OVX mice. Sclerostin antibody did not result in gene transcriptional changes in aorta tissue that would be expected to affect 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 r13C7 administration 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 generally support the concept that inhibition of sclerostin by r13C7 does not promote atheroprogression in the OVX ApoE KO mouse model. However, the data on plaque necrosis suggest a potential concern about increased plaque instability.

STUDY #3

Immunohistochemical assessment of sclerostin expression in human atherosclerotic plaques

(Amgen Study #150498; Sponsor UCB, (b) (4) (b) (4); non-GLP)

Introduction

The expression pattern of sclerostin was examined using immunohistochemistry in sections of human atherosclerotic plaques classified as stable or unstable based on morphological features (i.e. fibrotic vs. classical atheromatous plaques) derived from the carotid and femoral arteries of patients undergoing an endarterectomy procedure. The association between sclerostin expression and factors known to predispose to plaque rupture, i.e., lipid content, macrophage content, smooth muscle cell content, collagen content, calcification, and intraplaque hemorrhage was also determined.

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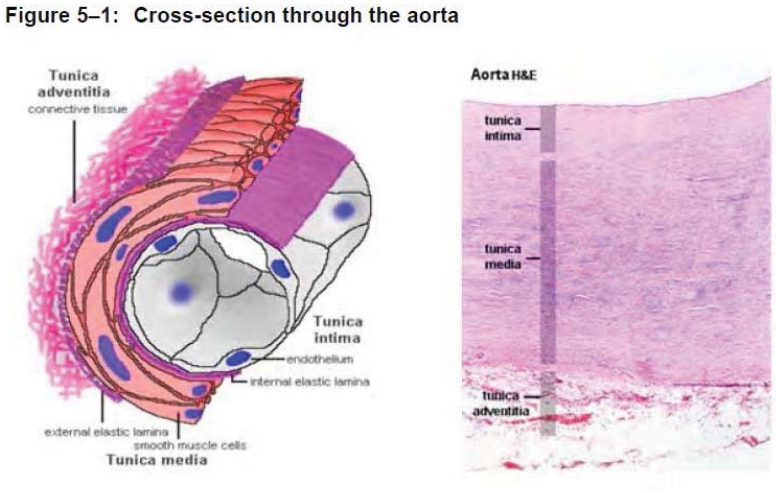
Methods

A retrospective analysis was performed on 94 carotid artery plaques and 50 femoral/iliac artery plaques collected from women. Samples were accessed from the AtheroExpress biobank of embedded atherosclerotic plaque samples that had been collected during surgical endarterectomy. Serial sections were stained for expression of alpha-smooth muscle actin (aSMA) and human sclerostin, and a third section was stained with hematoxylin and eosin (H&E). Sections were scored to reflect the extent and location of sclerostin staining and the results were combined with pre-existing AtheroExpress data pertaining to the plaques selected and the clinical characteristics of the patients. Two control formalin fixed paraffin embedded (FFPE) aorta specimens were also stained for sclerostin. The types of plaques assessed in this study were considered representative of those found in post-menopausal women.

Results

The aorta consists of three layers, the Tunica Adventitia (T.adventitia), Tunica media (T.media), and Tunica intima (T.intima) (Figure 1). Sclerostin staining revealed generally low expression in the T.media of the arterial plaques examined, with the majority (78%) showing no expression. Strong staining was observed in the vessel wall of a limited number of early atherosclerotic plaque samples with only minimal to slight expansion of the T. intima, as well as in control FFPE aorta. Staining was already decreased in intensity in the region immediately deep to the intimal expansion, indicating sclerostin expression decreases early in plaque formation. Advanced lesions typically showed low or absent staining. Where present, sclerostin expression was restricted to deeper parts of the plaque/vessel wall, i.e., the T. media and adjacent sub-intimal region, where it was of decreased intensity compared to control aorta. Expression of sclerostin was never seen in the superficial plaque region closest to the vessel lumen (fibrous cap and endothelium) which are relevant to plaque stability.

Figure 1: Cross-section showing microscopic structure of the aorta

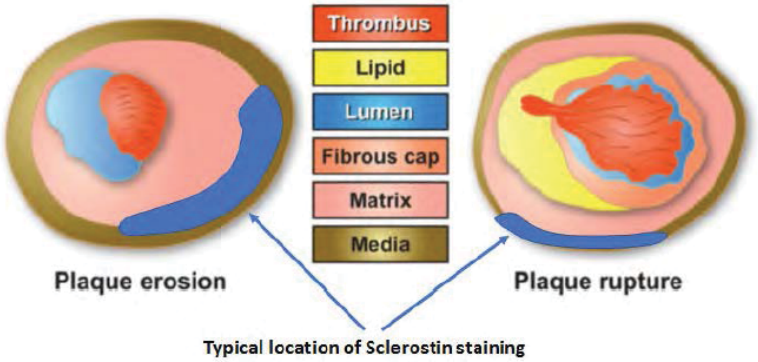


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Figure 2: Diagram of typical sclerostin location in human atherosclerotic plaques

Figure 5–2: Diagrammatic representation of a fibrous and atheromatous plaque showing typical location of sclerostin expression within the T. media and adjacent region of T. intima.



Left hand image shows approximately 30% of the circumference of the plaque wall expressing sclerostin within the T. media and deep layer of T. intima. Right hand image shows more restricted expression primarily within the T. media. Both images were typical of the pattern and extent of sclerostin expression within the subset of positively staining plaques. (Diagram modified from Libby and Pasterkamp, 2015.)

Absence of sclerostin expression was not associated with age at endarterectomy, history of artery disease or cardiac outcomes during the patient follow up period of at least 3 years. Absence of sclerostin was also not associated with plaque pro-inflammatory cytokine expression (MCP1, IL6, TNFα, and osteopontin), and was not associated with most of the plaque features assessed including lipid content, macrophage content, collagen content, and hemorrhage.

Absence of sclerostin expression was associated with two plaque features. One feature was moderate/heavy dystrophic calcification in the T. intima and T. media of the carotid (not femoral) artery, which is a feature of advanced plaques. The report's authors concluded that given the common absence of sclerostin from plaques in the study and given that down-regulation of sclerostin appears to occur during plaque progression, the absence of sclerostin expression in plaques with dystrophic calcification most likely reflects the advanced nature of the atherosclerosis in these plaques rather than a direct association with calcification per se. There was also an association between the absence of sclerostin and moderate/heavy smooth muscle cell (SMC) content in the T. intima but not the T. media in the femoral (not carotid) artery, but this was not further discussed.

Elevated sclerostin has been shown to reduce circulating levels of the pro-inflammatory cytokines MCP1, IL6 and TNFα in a mouse model of atherosclerosis (Krishna et al, 2017). However, the current study showed no relationship between sclerostin expression and the presence of any of these cytokines in atherosclerotic plaques.

Conclusions

Sclerostin staining of human atherosclerotic plaques showed decreased expression of sclerostin in plaques relative to control aorta. No evidence was found to suggest that sclerostin is expressed in areas relevant to plaque stability. The absence of sclerostin expression was not associated with any of the plaque features assessed, except dystrophic calcification in the carotid artery. This inverse association was likely related to downregulation of sclerostin expression in late stage plaques. There was no association between sclerostin expression and cardiovascular events prior to or following endarterectomy.

STUDY #4

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

(Amgen Study #150655; Sponsor Amgen; non-GLP)

Introduction

According to published literature, common single nucleotide polymorphisms (SNPs) near SOST are associated with levels of SOST RNA expression and BMD. None of these SNPs have so far been reported to be significantly associated with risk of stroke or MI by genome-wide association studies (GWAS). Public databases of GWAS results from the UK Biobank were examined to test for an association of these SNPs with stroke or myocardial infarction.

Methods

In a search using the Global Biobank Engine three BMD-associated SNPs from the GWAS literature were found in the UK Biobank dataset. The SNP rs2741856 was selected for this study, because it has been genotyped in UK Biobank participants, and is strongly linked to the most significant BMD association at the SOST locus reported in the literature. Values reported are from the Global Biobank Engine (Stanford).

Results

Both alleles of rs2741856, C and G, are common in the UK Biobank participants of European descent, and the frequency of the minor allele G is approximately 9%. In the GTEx Portal.org database, the major allele C is associated with lower expression of SOST, with the most statistically significant effect in tibial artery ($p = 4.5 \times 10^{-6}$; normalized expression score -0.29; n = 388). A statistically significant effect was also observed in aorta ($p = 4.9 \times 10^{-4}$; normalized expression score -0.30; n = 267), and in coronary artery, thyroid, brain and nerve-tibial ($p<0.05$ for all). The level of expression in these tissues varied also between -0.2 and -0.32.

Among the 337,208 participants of European descent, there is an imbalance in osteoporosis and fracture risk between the carriers of the 2 alleles. The major allele C with lower SOST expression is associated with a decreased risk of osteoporosis ($p = 1.32 \times 10^{-9}$; odds ratio (OR) = 0.84 [95% CI 0.79, 0.89]; n = 9,135 cases) and a decreased occurrence of fracture in the past 5 years ($p = 3.88 \times 10^{-7}$; OR = 0.93 [95% CI 0.90, 0.95]; n = 33,636 cases). It is likely that this allele mirrors the pharmacologic effects of romosozumab 210 mg once monthly (a non-saturating

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dose expected to bind only part of sclerostin) more closely than loss-of-function mutations resulting in complete absence of sclerostin. In the UK Biobank, event rates available for myocardial infarction (n = 12,138 cases) and stroke (n = 5,783 cases) were of the same order of magnitude. Results from the Global Biobank Engine showed that the major allele C of SNP rs2741856 associated with lower SOST expression, higher BMD, and lower risk of osteoporosis and fracture, did not have a detectable effect on the risk of MI or stroke ($p > 0.10$ for both). Results were similar in 2 other publicly available databases (GeneAtlas and Rapid GWAS), except that 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.

Conclusion

In the database examined, no statistically significant genetic association was identified between risk of osteoporosis and fracture and risk of MI or stroke.

STUDY #5

Study to Assess the Effects of Recombinant Human Sclerostin and AMG 785 on Isolated Healthy Human Coronary Arteries

(Amgen Study #150483; Test Facility (b) (4) ; non-GLP)

Introduction

Coronary circulation (vasoconstriction) is a factor affecting risk of acute ischemia (MI/stroke). Thus, a potential effect of romosozumab on vascular tone could be an underlying factor in the observed MI/stroke imbalance. Therefore, the sponsor conducted an in vitro vasoconstriction assay.

Methods

Human coronary artery rings were prepared from healthy human donors and mounted on an isometric test apparatus to allow for direct measurement of contraction or relaxation of the coronary rings in myograph baths containing physiological saline solution. The effects of romosozumab (1, 3, 10, 30, 10, 300 ug/mL) and human recombinant sclerostin (MW 21498 Da) (1, 3, 10, 30, 100, 300 pmol/L) (stock solutions prepared in a vehicle of sodium acetate buffer) on vascular tone were evaluated. Sumatriptan was used as a positive control.

Results

Romosozumab did not induce vasoconstriction at concentrations up to 300 ug/mL, which is equivalent to approximately 10-fold the human Cmax with 210 mg once monthly (28.1 µg/mL). Recombinant human sclerostin also did not induce vasoconstriction at concentrations up to 300 pmol/L, a concentration approximately 10-fold the reported serum values in postmenopausal women. The responses to both sclerostin-antibody and sclerostin were similar to those of the vehicle control. The positive control, sumatriptan, caused the expected concentration dependent constriction of the isolated human coronary artery rings.

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Conclusions
Romosozumab or human sclerostin did not induce vasoconstriction of healthy human heart coronary artery rings in physiological salt solution.

STUDY #6
r13C7: Differences of Antiresorptives on Osteonecrosis of the Jaw (ONJ) Initiation and Resolution
(Amgen Study #122002, Sponsor Amgen; Testing Facility (b) (4) (b) (4); non-GLP)

Introduction
Since romosozumab is an inhibitor of bone resorption, it may be associated with a rare side effect, osteonecrosis of the jaw (ONJ). Therefore, this study was conducted in aged OVX rats with ligature-induced experimental periodontitis to examine the potential for sclerostin inhibition to increase the risk for ONJ.

Methods
Female Sprague Dawley rats were ovariectomized at 6 months of age followed by a 2-month bone depletion period. Rats were then administered either weekly intraperitoneal injections of vehicle, 200 µg/kg zoledronic acid (ZA), or 5 mg/kg sclerostin antibody (r13C7). The dose of sclerostin antibody was predicted to provide a similar systemic exposure as the 210 mg once monthly clinical dose of romosozumab, based on AUC. After 12 weeks of treatment, periodontitis was induced with a ligature around the left maxillary second molar. Animals were necropsied after an additional 10-week treatment period. Study endpoints included evaluation of serum bone formation marker PINP at pre-dose, weeks 6, 12, and 22, ex-vivo micro-CT of dissected maxillae and vertebrae, histopathologic evaluation of the maxillae, and histomorphometry of vertebral cancellous bone.

Results
Sclerostin antibody r13C7 transiently increased serum PINP and increased mineralizing surface (MS/BS) and bone volume in vertebral cancellous bone, consistent with the expected stimulation of bone formation by sclerostin inhibition. In vertebral bone, ZA decreased bone formation (MS/BS), and sclerostin antibody suppressed bone resorption (ES/BS). Vehicle-treated animals showed extensive alveolar bone loss and inflammatory infiltrate in areas of experimental periodontitis. By contrast, ZA-treated animals showed minimal alveolar bone loss and a reduced number of osteoclasts. In sclerostin antibody treated rats, bone loss was also markedly reduced compared to vehicle controls, but osteoclastic bone resorption did not appear suppressed. ZA-treated but not sclerostin antibody treated rats developed radiographic and histologic features of ONJ, evidenced by a marked increase in the relative area of osteonecrotic bone containing empty osteocytic lacunae and by increased bone exposure. Features of ONJ were not observed in sclerostin antibody treated animals. The alveolar bone of sclerostin antibody and vehicle treated animals had a similar appearance, with minimal

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osteonecrosis (relative area approximately 1%) and histologic evidence of active bone resorption.

Conclusion
In OVX rats with experimental periodontitis, sclerostin antibody enhanced bone formation and prevented alveolar bone loss, but did not induce ONJ-like lesions in contrast to the bisphosphonate ZA.

5.4. Discussion of concerns (nonclinical perspective)

In the attempt to clarify the observed imbalance in serious CV events observed in the alendronate-controlled Study 142 and in Study 174, the sponsor discussed the concerns regarding potential cardiovascular effects of sclerostin inhibition based on nonclinical studies and published literature. The issues addressed included: (1) medial vascular calcification, (2) potential effects on pathophysiological mechanisms underlying thrombotic/ischemic events such as MI and stroke (plaque rupture, plaque erosion, and vasospasm), and (3) potential association between genetic variability in sclerostin expression and MI or stroke based on human genetics data.

Vascular calcification
Sclerostin is expressed in the aorta of several species (mouse, monkey, human). Since 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 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 AUC (Study 107426), and no vascular mineralization in aged OVX monkeys dosed for 1 year with romosozumab at 22-fold clinical AUC exposure (Study 107903). Vascular lesions were also not observed in a 6-month rat study with romosozumab at up to 39-fold clinical AUC exposure.

Although sclerostin expression is absent or low in rat aorta (Study 119937), 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 is not promoted in the total absence of sclerostin in SOST 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 the clinical AUC exposure (Study 107895).

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Thus, sclerostin inhibition does not appear to cause initiation of vascular calcification or exacerbation of pre-existing medial calcification in animals.

Mechanisms underlying MI and stroke

Atherosclerosis is a chronic inflammatory disease and most commonly underlies thrombotic/ischemic events such as MI and stroke. Specific mechanisms that can lead to these events include plaque rupture, plaque erosion and vasospasm.

Atherosclerosis

In Amgen Study #2 (124609) in the ApoE KO OVX mouse atherosclerosis model, it was shown that treatment with sclerostin antibody r13C7 had no significant effects on systemic inflammation markers or on atherosclerosis or aortic transcriptional changes.

The results were 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 (in SOST-transgenic ApoE KO mouse, or in ApoE KO mice injected with SOST) inhibited Ang II–induced aortic aneurysm and atherosclerosis, and was associated with reductions in circulating proinflammatory cytokines (MCP-1, IL-6 and TNF-α) and reduced aortic extracellular matrix degradation and macrophage infiltration. The sponsor commented that the contrasting findings between the two studies suggest that the consequence of overexpression of SOST or excess sclerostin does not predict the effects of inhibition of sclerostin with sclerostin antibody administered at 'non-saturating' doses.

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 (Krishna et al., 2017) may specifically contribute to atherosclerosis and/or aneurysm through activation of sclerostin-sensitive Wnt signaling. In fact, the study showed that Wnt signaling was activated in Ang II-treated ApoE KO mice that developed aortic aneurysms vs. those that did not, and that SOST expression in human aortic aneurysm samples was decreased possibly through epigenetic silencing. In the sponsor's study in ApoE KO mice not treated with Ang II, there was no difference in Wnt target gene expression between control and ApoE KO mice. Therefore, atherosclerosis in this model appears to be Wnt-independent, which may explain the lack of effect of sclerostin antibody. It is unlikely that the sclerostin antibody dose selection 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, TGF-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.

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A study in the ApoE KO mouse similar to the study by Krishna et al. (2017) could be done 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 sclerostin antibody in the Ang II-treated mouse could be conducted to identify a potentially atherosclerosis-enhancing effect.

Regardless, a positive result in any model would not negate the lack of an imbalance on serious cardiovascular events observed in clinical Study 337. Similarly, the negative result of the completed study in the ApoE KO OVX mouse does not refute the cardiovascular safety signal in clinical Studies 142 and 174. Ultimately the role of sclerostin and its inhibition in these cardiovascular events remains unclear.

Plaque rupture

Plaque rupture can be induced by inflammation and altered immunity via a reduction in extracellular matrix, particularly the plaque's fibrous cap. However, the study in the ApoE KO-OVX mice (Study 124609) did not show an effect of sclerostin antibody r13C7 on inflammatory markers or on the transcription of genes that play a role in inflammation, adaptive immunity, or ECM homeostasis, even though the latter genes were differentially regulated in ApoE KO-OVX vs. WT mice. In this context, the relevance of the slight decrease in plaque volume in the r13C7-treated ApoE KO-OVX mice at Week 16, 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 previously conducted rat and monkey toxicity studies, and sclerostin inhibition did not cause aortic calcification in CKD rodents. Also, sclerostin antibody r13C7 did not affect mineralized plaque volume in Study 124609, and sclerostin was not expressed in human atherosclerotic plaques' fibrous caps, a location that is important for the plaque's stability (Study 150498). In addition, plaque hemorrhage was not observed in ApoE KO-OVX mice (Study 124609) and sclerostin expression was not correlated with human arterial plaque hemorrhage. Plaque necrosis is an additional feature potentially associated with increased plaque instability. The increase in the incidence of plaques with necrosis upon dosing of ApoE KO-OVX mice with sclerostin antibody may suggest a possible role for sclerostin in plaque rupture.

Plaque erosion

Plaque erosion due to endothelial apoptosis/dysfunction in combination with platelet adhesion and activation, neutrophil activation, and local oxidative stress is believed to enhance thrombogenesis and precipitate cardiovascular ischemic events. In ApoE KO-OVX mice, transcriptional pathways related to apoptosis, innate immunity, neutrophil recruitment/signaling and oxidative stress were upregulated, but these pathways were not affected by sclerostin antibody administration. Furthermore, sclerostin antibody treatment did not affect circulating markers of endothelial activation and their aortic mRNA expression (Study 124609). In addition, based on the lack of sclerostin expression in the T. intima and endothelium in human atherosclerotic plaques, sclerostin inhibition seems to be an unlikely factor in plaque erosion.

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Both plaque rupture and erosion can be complicated by enhanced thrombogenesis triggered by an imbalance in vasodilators (e.g. the prostanoids prostacyclin, PGI2) and vasoconstrictors (e.g. platelet thromboxane A2, TXA2). However, in the aorta of ApoE KO-OVX mice, gene transcription related to the prostanoid pathway, while differentially regulated than in WT mice, was not affected by sclerostin antibody. Circulating markers of endothelial/platelet activation were also not changed by sclerostin antibody treatment (Study 124609). In addition, romosozumab did not enhance in vitro platelet activation at up to 10-fold the clinical Cmax achieved with 210 mg once monthly (Study 125269). Moreover, in rat and monkey repeat dose toxicity studies, intrinsic and extrinsic coagulation was not affected by romosozumab, altogether suggesting a lack of effect of sclerostin inhibition on thrombogenesis.

Vasospasm

Vasospasm may cause acute ischemia both in the presence and absence of atherosclerosis. It may be precipitated by hyperreactivity of vascular smooth muscle cells or by endothelial dysfunction in response to blood flow changes that can reduce nitric oxide, which has a regulatory function in vasodilation. Neither romosozumab at up to 10-fold human Cmax with 210 mg once monthly, nor human recombinant sclerostin at up to 10-fold the serum concentration in postmenopausal women induced vasoconstriction (a key mediator of vasospasm) in an in vitro assay using isolated healthy human coronary artery rings (Study 150483).

Romosozumab is unlikely to cause acute changes in blood flow through effects on blood pressure since blood pressure and electrocardiograms were unaffected in instrumented monkeys following single intravenous dose of romosozumab at approximately 32- and 21-fold clinical exposure with 210 mg once monthly based on AUC and Cmax, respectively, or in 1-month and 6-month repeat dose toxicity study in monkeys. Additionally, although nitric oxide signaling pathways were differentially regulated in the ApoE KO-OVX mouse, these pathways were unchanged in response to sclerostin antibody treatment (Study 124609). Also, no clinically important effects on blood pressure or electrocardiograms have been observed in clinical trials with romosozumab.

Human genetics

In sclerosteosis subjects, clinical or radiographic evidence of involvement of the central or peripheral cardiovascular system has not been reported in the literature. However, the size of this population is small. Using public databases of GWAS, a statistically more robust analysis of common SNPs at the SOST locus showed that genetically reduced SOST expression in aorta and tibial artery by a common SNP in the European population has a significant effect on BMD, osteoporosis and bone fracture, but no detectable effect on risk of myocardial infarction or stroke (Study 150655).

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6 Clinical Pharmacology

6.1. Executive summary

The original BLA included a total of 17 clinical studies (7 clinical pharmacology studies, 5 biopharmaceutical studies and 5 efficacy and safety studies) to support the romosozumab clinical development program. The BLA resubmission included two additional studies: Study 20110142 (phase 3) in postmenopausal women who are at high risk for fractures and Study 20110174 (phase 3) in men with osteoporosis. Note that the Office of Clinical Pharmacology review for the original BLA determined that the clinical pharmacology information was acceptable to support approval. Refer to Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) of the original BLA submission for additional information.

The Clinical Pharmacology section of this multi-disciplinary review assesses whether there is a potential exposure-response relationship of romosozumab for MACE. Although the data are limited, the available data do not support evidence of a clear exposure-response relationship for MACE.

6.1.1. Recommendations

The review team recommends approval of this BLA from the clinical pharmacology's perspective.

6.1.2. Post-Marketing Requirement and Commitments

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Refer to Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) for the original BLA submission. Appendices to this multi-disciplinary review (Section 14.3) provide updated immunogenicity and population PK analysis results.

6.2.2. General Dosing and Therapeutic Individualization

The recommended romosozumab dosage regimen is 210 mg administered by subcutaneous injection monthly for 12 months. Therapeutic individualization is not recommended based on the available data. Refer to Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) for the original BLA submission for detailed information.

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6.2.3. Outstanding issues

There are no outstanding issues that preclude approval from Clinical Pharmacology's perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

This section provides a brief summary of romosozumab's pharmacokinetic (PK) characteristics to facilitate interpretation of the data presented in Section 6.3.2 below.

Romosozumab exhibits nonlinear PK 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 $t_{1/2}$ is 13 days after 3 monthly SC doses of 3 mg/kg.

Following a single SC administration of romosozumab 210 mg 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.

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.

Impact of immunogenicity on PK
Among 5914 postmenopausal women treated with the romosozumab 210 mg SC monthly dosage regimen, approximately 18.1% (1072/5914) developed antibodies to romosozumab. Of the subjects who developed antibodies to romosozumab, approximately 4.6% (50/1072) had antibodies that were classified as neutralizing. Development of anti-drug antibodies (ADA) was associated with reduced serum romosozumab concentrations.

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6.3.2. Clinical Pharmacology Questions

6.3.2.1. Do PK results in romosozumab clinical trials suggest a potential exposure-response relationship for MACE?

No, the available PK data do not support a clear exposure-response relationship for MACE.

Among the 77 romosozumab-treated subjects who had MACE in Studies 20070337, 20110142 and 20110174, 8 subjects had PK data available. The patient profiles for these 8 subjects are summarized in Table 8. The romosozumab concentrations in these 8 subjects and in the overall study population are shown in Figure . The PK data show that the romosozumab concentrations in subjects who had MACE were generally within the range of the overall observed concentrations in Phase 3 trials. The limited data did not demonstrate a correlation between systemic romosozumab exposure and MACE. It should be noted that samples for assessment of plasma concentrations were collected at various times post-dose in all subjects and are not necessarily reflective of concentrations at the time of MACE.

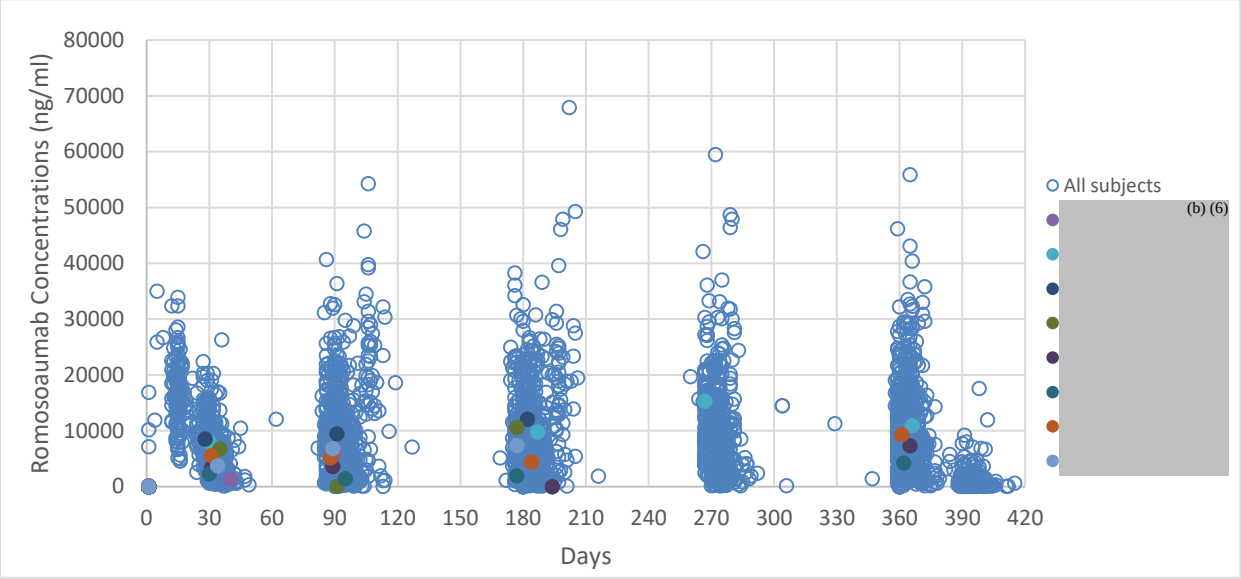
Table 8 Patient Profile for Subjects Who Experienced MACE and Had PK Data Available in Studies 20070337, 20110142 and 20110174

Subject ID	Body Weight (kg)	Age (year)	Sex	Race	Dose (mg)	eGFR Category	CV-related Death?	MACE from the first dose (days)	MACE from the last dose (days)
(b) (6)	41	64	F	White	210	Mild	Yes	106	17
	42	85	F	White	210	Mild	No	70	10
	82	79	M	White	210	Normal	No	96	6
	64	72	M	White	210	Normal	No	98	10
	75	72	M	White	210	Mild	No	138	16
	72	82	M	White	210	Mild	No	348	19
	70	79	M	Other	210	Moderate	No	324	23
	61	80	M	Other	210	Mild	Yes	317	16

Source of data: FDA Reviewer's analysis based on clinical study report for Studies 20070337, 20110142, 20100174 and the comprehensive cardiovascular report

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Figure 3 Serum Romosozumab Concentrations in Subjects Who Experienced MACE and Had PK Data Available in Studies 20070337, 20110142 and 20110174



Source of data: FDA Reviewer's analysis and plot based on clinical study report for Study 20070337, 20110142, 20100174 and the comprehensive cardiovascular report. d, cardiovascular-related death

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 9 lists the studies that are relevant to the review of the BLA resubmission. For a listing of all clinical studies performed in the romosozumab development program, refer to the clinical review of the original submission.

Table 9. Listing of Clinical Trials Relevant to this Supplemental BLA

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Primary Endpoint	Treatment Duration/ Follow Up	No. of Pts.	Study Population	No. of Centers/ Count-ries
	Controlled Studies to Support Efficacy and Safety						
20070337/ 01575834	Randomized, double-blind, placebo-controlled	Romosozumab 210 mg SC QM or placebo SC QM for 12 months followed by denosumab 60mg SC Q6M for 12 months	Incidence of new vertebral fracture at month 12 and month 24 (co-primary)	24 months with 12 month extension period with open-label denosumab	7180	Post-menopausal osteoporosis	222 centers countries
20110142/ 01631214	Randomized, double-blind, active-controlled	Romosozumab 210 mg SC QM or alendronate 70 mg po QW for 12 months followed by alendronate 70 mg po QW	Subject incidence of clinical fracture and new vertebral fracture	Event driven median follow-up 33 months; minimum 24 months	4093	Post-menopausal osteoporosis	270 centers 41 countries
	Studies to Support Safety						
20110174/ 02186171	Randomized, double-blind, placebo-controlled	Romosozumab 210 mg SC QM or placebo SC QM	Percent change from baseline in lumbar spine BMD at 12 months	12 month treatment period 15 months total follow-up	245	Men with osteoporosis	31 centers 10 countries
SC = subcutaneous; QM = once monthly; po = orally							

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7.2. Review Strategy

The efficacy evaluation is based on efficacy results from Study 337 and 142. Efficacy results from Study 142 are thoroughly reviewed in Section 8.1.2. Since efficacy results from Study 337 were previously reviewed with the original submission, this review only provides a summary of the efficacy results from Study 337 (in Section 8.1.5). Efficacy results from Study 174 are not addressed in this review, as the study population is not one for which an indication is currently sought.

The safety evaluation is based on safety results from Study 337, Study 142 and Study 174. All safety results from Study 142 are thoroughly reviewed in Section 8.2. Since the safety results of Study 337 were previously reviewed in detail with the original submission, this review will only summarize key safety results of Study 337 in Section 8.2. General safety results from Study 174 are not addressed in this review, as the study population is not one for which an indication is currently sought. The cardiovascular safety results from Study 337 and Study 174, however, are included in this review alongside those of Study 142 (in Section 8.2.5, *Analysis of Cardiovascular Safety*).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 20110142: Design

Study Title: *A Multicenter, International, Randomized, Double-blind, Alendronate-controlled Study to Determine the Efficacy and Safety of Romosozumab in the Treatment of Postmenopausal Women With Osteoporosis*

Investigators and Study Centers: The study was conducted at 270 centers in 41 countries (89 centers in Western Europe and Australia/New Zealand, 88 centers in Central and Eastern Europe and the Middle East, 49 centers in Central/Latin America, 26 centers in North America, and 18 centers in Asia Pacific and South Africa).

Objectives

The primary objective of this study was to assess the effect of romosozumab treatment for 12 months followed by alendronate (ALN) treatment compared with ALN treatment alone on the subject incidence of the following during the primary analysis period:

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- clinical fracture (nonvertebral fracture and symptomatic vertebral fracture) in postmenopausal women with osteoporosis; and
- new vertebral fracture in postmenopausal women with osteoporosis

The secondary objectives of the study included the following:

- to assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on the following during the primary analysis period:
    - The subject incidence of fracture (all fractures [nonvertebral fracture and new or worsening vertebral fracture], new or worsening vertebral fracture, nonvertebral fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], hip fracture, multiple new or worsening vertebral fracture, and clinical vertebral fracture); and
    - Percent changes in DXA BMD at the lumbar spine, total hip, and femoral neck.
- to assess the effect of romosozumab treatment for 12 months compared with ALN treatment on the following during the 12-month double-blind ALN-controlled study period:
    - The subject incidence of fracture (clinical fracture [nonvertebral fracture and clinical vertebral fracture], new vertebral fracture, all fractures [nonvertebral fracture and new or worsening vertebral fracture], nonvertebral fracture, hip fracture, clinical vertebral fracture, and major osteoporotic fracture [hip, forearm, humerus, and clinical vertebral]); and
    - Percent changes in DXA BMD at the lumbar spine, total hip and femoral neck
- to assess the effect of romosozumab treatment for 12 months followed by ALN treatment compared with ALN treatment alone on subject incidence of hip fracture, major nonvertebral fracture [pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip], and nonvertebral fractures during the overall study period.

The term “clinical” vertebral fracture refers to those vertebral fractures that are symptomatic. Many vertebral fractures are asymptomatic and are detected incidentally on radiographic imaging.

The use of an active control in Study 142 enabled a direct comparison of romosozumab efficacy to a currently approved therapy. The active control, alendronate, an oral bisphosphonate that reduces fracture risk by decreasing bone resorption and subsequently increasing bone density, represented a different mechanism of action from the bone-forming agent teriparatide that was used in Study 289, the other active-controlled study in the romosozumab clinical program (discussed in review of the original BLA).

Methodology

Study 142 was a phase 3, multicenter, international, randomized, double-blind, double-dummy, alendronate-controlled study of romosozumab in postmenopausal women with osteoporosis.

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The study was designed to evaluate whether romosozumab treatment for 12 months followed by alendronate, compared with alendronate treatment alone, is effective in reducing the incidence of clinical fracture and new vertebral fracture.

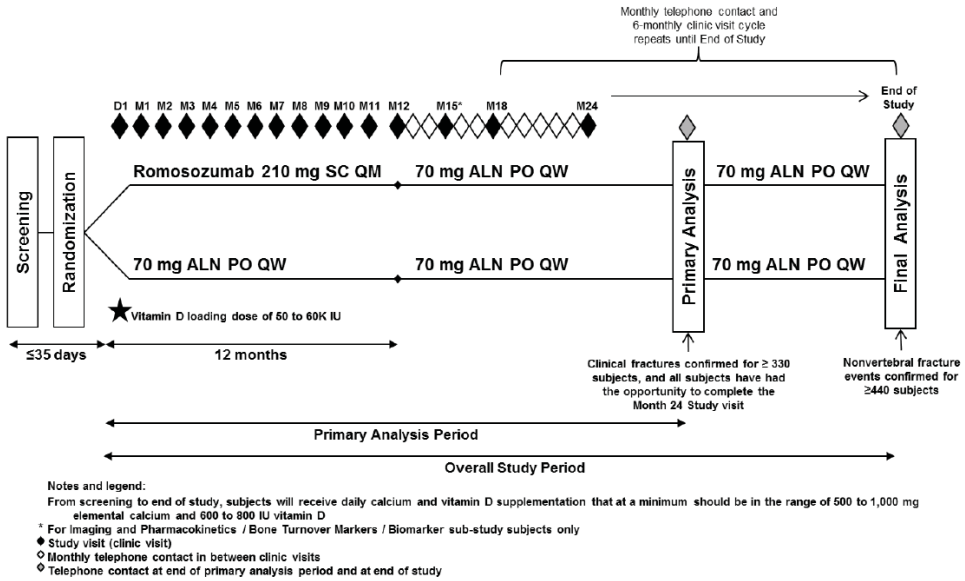
Subjects were randomized in a 1:1 ratio (stratified by age [< 75 years, ≥ 75 years]) to receive either romosozumab 210 mg subcutaneously (SC) every month (QM) or alendronate 70 mg orally every week (QW) in a blinded fashion for the duration of the 12–month double-blind alendronate-controlled study period. All subjects also received matched placebo for either alendronate or romosozumab. After the initial 12-month study period, subjects received alendronate for the remainder of the study while remaining blinded to their initial treatment assignment (romosozumab or alendronate).

The primary analyses were to be performed at the end of the primary analysis period, which was defined as when clinical fracture events were confirmed for at least 330 subjects and all subjects completed the month 24 study visit. Upon completion of the primary analysis period, the study was to continue until at least 440 subjects experienced a nonvertebral fracture (unless the superiority of romosozumab was already proven for nonvertebral fractures at the primary analysis).

Approximately 200 subjects at participating centers were also enrolled in an Imaging and pharmacokinetic/bone turnover marker (PK/BTM)/Biomarker substudy. Within this substudy, a subset of approximately 100 subjects were planned to participate in the imaging (DXA, QCT) portion of the substudy.

The study schema is presented in **Figure** .

Figure 4: Study 20110142 Schema



Source: Figure 8-1 of CSR

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Number of Subjects Planned: Approximately 4000 subjects (2000 subjects per treatment group)

Key Enrollment Criteria

Subjects included ambulatory postmenopausal women age 55 to 90 years with at least 1 of the following BMD and fracture criteria:

- BMD T-score at the total hip or femoral neck of ≤ -2.50 and EITHER:
  - at least 1 moderate (SQ2) or severe (SQ3) vertebral fracture OR
  - at least 2 mild (SQ1) vertebral fractures

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

In addition, at least 1 hip must have been evaluable by DXA. Key exclusion criteria included a history of metabolic or bone diseases, severe and significant lab abnormalities, organ or bone marrow transplants, or possible diagnosis of multiple myeloma or related lymphoproliferative disorder. The use of agents affecting bone metabolism was also exclusionary; however, for selected therapies permissible off-treatment periods prior to randomization were allowed as outlined in Section 4.2 of the study protocol. Detailed inclusion and exclusion criteria for the main study are provided in Section 4 of the study protocol.

Subjects participating in the imaging component of the Imaging and PK/BTM/Biomarker Substudy were to be excluded if they had the following: a non-evaluable vertebra in the region of interest for spine QCT scans as assessed by the central imaging vendor at the time of screening, based on lateral spine x-rays; a nonvertebral fracture or clinical vertebral fracture within 6 months prior to enrollment; or were unavailable for protocol-required substudy procedures.

The eligibility criteria were appropriate to ensure that the population only included subjects at high risk for fracture (which is acceptable for an active-controlled trial) and were adequate to ensure reliable interpretation of efficacy results. The participants in Study 142 were at higher risk for subsequent fracture than the participants in the placebo-controlled Study 337. Study 337 had exclusionary criteria based on severity of prior fracture (including hip fracture) and low BMD T-scores.

Methods for Treatment Assignment and Blinding

Treatment assignments were obtained through an interactive voice response system (IVRS). Eligible subjects were randomized in a 1:1 ratio in a double-blind manner to either the romosozumab or the alendronate treatment group. Randomization was stratified by age (< 75

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years, ≥ 75 years).

Following the end of the primary analysis period, subjects and site personnel remained blinded to a subject's original treatment assignment.

These randomization and blinding methods are acceptable.

Investigational Products, Dose and Mode of Administration

Romosozumab was supplied as a single-use 1 mL prefilled syringe (PFS) containing 70 mg of romosozumab per mL. During the 12-month double-blind alendronate-controlled study period, subjects received 3 SC prefilled syringe injections of romosozumab (i.e., 210 mg) or matched placebo at each dosing visit (i.e., day 1 study visit, and monthly study visits thereafter to month 11). Injections were administered by a healthcare professional into different sites on the subject's anterior abdominal wall, upper thigh, or upper arm.

The study protocol and the clinical study report specified that the active control alendronate was considered an investigational product; neither document specified whether the alendronate used in the study was US-approved. Blinded and open-label alendronate was "commercially manufactured and labeled." Therefore, specific alendronate dosing instructions (as detailed in marketed labeling) were to be provided to all subjects. Although the protocol and clinical study report (CSR) did not describe the specific alendronate dosing instructions, both the protocol and CSR did specifically state that alendronate labeling was to be followed when alendronate was dispensed. Placebo to alendronate was presented in identical containers. During the 12-month double-blind study period, subjects were dispensed a 2-month supply of alendronate or matched placebo on day 1 of the month 2, 4, 6, 8, and 10 visits. One 70 mg tablet was self-administered orally by the subjects once each week. Following the 12-month double-blind study period, subjects were dispensed a 6-month supply at the month 12 visit and every 6 months thereafter through the end of study. Subjects were asked to bring in all used and unused packages to study visits to assess compliance. The investigational site staff counted the number of returned tablets and captured this information on drug accountability forms and in the eCRF.

Dose Adjustments and Modifications

No dosing adjustments for romosozumab/placebo were permitted. Romosozumab/placebo could be administered +/- 2 weeks of the target visit date; if the dose could not be administered +/- 2 weeks of the target visit date, the dose was considered missed.

No dosing adjustments for alendronate/placebo or alendronate were permitted. If a subject missed a scheduled dose of the investigational product, the dose was to be taken as soon as possible as long as it was before the next scheduled dose. Dosing was to be resumed at the same dose (70 mg QW). Double or extra doses were not permitted.

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Other Protocol-required Therapies:

From screening to end-of-study, subjects were to receive daily calcium and vitamin D supplementation at a minimum of 500 to 1,000 mg elemental calcium and 600 to 800 IU vitamin D. In addition, subjects with a serum 25-hydroxy (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening received an initial loading dose of 50,000 to 60,000 IU vitamin D after randomization. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may have received the vitamin D loading dose at the principal investigator's discretion.

If a subject developed hypercalcemia or hypocalcemia during the study, the calcium and/or vitamin D supplementation could be adjusted to maintain serum calcium concentration within the normal range.

Concomitant Therapy

Investigators were permitted to prescribe any concomitant medications or treatments deemed necessary to provide adequate care, except for those listed as excluded concomitant medications in the protocol (which included all medications known or suspected to affect bone metabolism). If a subject received any IV bisphosphonate therapy or oral bisphosphonate therapy equivalent to > 1 month of therapy (except alendronate as study medication) while on-study, investigational product was discontinued.

Study Assessments

Following the initial screening visit and the Day 1 visit, study visits occurred monthly during the 12-month double-blind period of the study. For the remainder of the study, visits occurred at Month 15, Month 18 and Month 24, and every 6 months thereafter (for subjects who were in the study for more than 24 months); phone contacts were performed during the months with no study visits (for continuous monthly monitoring of adverse events and concomitant medications).

Lateral spine X-rays were performed at screening, Month 12, Month 24 and at the end of study. DXA of the lumbar spine was performed on Day 1, Month 12, Month 24 and at the end of study. Serum laboratory assessments (including serum chemistry and hematology and antiromosozumab antibodies) were performed at most study visits. The detailed schedule of assessments is provided in the CSR (Table 8-3).

Fracture Analysis and Definitions

At baseline/screening, a single, central imaging center radiologist determined prevalent vertebral fractures on lateral-spine X-rays using the following Genant visual semiquantitative grading (SQ) scale:

- SQ grade 0 (SQ0) = no fracture
- SQ grade 1 (SQ1) = mild fracture, 20 to 25% reduction in vertebral height (anterior,

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middle, or posterior)
- SQ grade 2 (SQ2) = moderate fracture, 25 to 40% reduction in height
- SQ grade 3 (SQ3) = severe fracture, greater than 40% reduction in height

For assessment of incident vertebral fracture, x-rays were scored at the central imaging center blinded to treatment and using the SQ scale. Investigators were alerted by the central imaging vendor when a new or worsening vertebral fracture was identified.

If a subject presented with acute back pain at a time point other than when a scheduled lateral spine x-ray was obtained during the primary analysis period, unscheduled lateral spinal x-rays were obtained for submission to the central imaging facility for evaluation. The central imaging vendor informed the sites if a new or worsening vertebral fracture was identified. Worsening was defined as an increase of at least 1 grade on the SQ scale.

For incident fractures, the following listing defines each fracture type:

New vertebral fractures occurred when there was ≥ 1 grade increase from the previous grade of 0 in any vertebra from T4 to L4 on the Genant SQ Scoring scale. A primary reader reviewed radiographs as received. If a new vertebral fracture was identified, the second reader assessed the results blinded to the first reader's findings. A third reader adjudicated if the primary and secondary readers disagreed.

Clinical fractures included clinical vertebral and nonvertebral fractures (excluding skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges) that were associated with signs and/or symptoms indicative of a fracture. Clinical vertebral fractures were included regardless of trauma severity or pathologic fractures; nonvertebral fractures associated with high trauma severity or pathologic fractures were excluded. A single, central imaging center radiologist confirmed clinical fractures from either local radiology reports or from local radiographs sent to the central imaging center.

Nonvertebral fracture was defined as a fracture present on a copy of radiographs or other diagnostic images such as computerized tomography (CT) or magnetic resonance imaging confirming the fracture within 14 days of a reported fracture, excluding skull, facial, mandible, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, metacarpus, finger phalanges, and toe phalanges. In addition, fractures associated with high trauma severity or pathologic fractures were excluded.

Major nonvertebral fracture was a subset of nonvertebral fractures limited to pelvis, distal femur (i.e., femur excluding hip), proximal tibia (i.e., tibia excluding ankle), ribs, proximal humerus (i.e., humerus excluding elbow), forearm, and hip.

Hip fracture was a subset of nonvertebral fractures limited to femur neck, femur intertrochanter, and femur subtrochanter.

Major osteoporotic fractures included hip, forearm or humerus fractures that were not

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associated with a pathologic fracture regardless of trauma severity, and clinical vertebral fractures.

Study Endpoints

The co-primary endpoints were the following:

- Time to first clinical fracture through the primary analysis period
- Subject incidence of new vertebral fracture through Month 24

For time to first clinical fracture through the primary analysis period, with differing follow-up time for subjects, the pre-defined statistical analysis method was a Cox proportional hazards model. Therefore, the Applicant's description of the clinical fracture endpoint as "subject incidence of clinical fracture through the primary analysis period" does not appear to be consistent with the analysis method, which describes the relation between the time to first clinical fracture incidence and treatment (adjusting for other potential covariates), with varying follow-up time as opposed to fixed follow-up time across subjects. Results for the clinical fracture endpoint will be described in labeling as risk reduction based on a time to event analysis for the above endpoint.

The secondary endpoints controlled for overall type I error were the following:

- Percent change from baseline in BMD at the lumbar spine, total hip and femoral neck at month 12 and month 24
- Nonvertebral fracture through the primary analysis period

Additional secondary endpoints that were not controlled for type I error were the following:

- During the primary analysis period:
    - nonvertebral fracture (key secondary endpoint)
    - all fractures (nonvertebral fractures and new or worsening vertebral fractures)
    - major nonvertebral fracture
    - hip fracture
- Through month 24:
    - new or worsening vertebral fracture
    - multiple new or worsening vertebral fractures
    - clinical fracture
    - nonvertebral fracture
    - hip fracture
    - clinical vertebral fracture
- Through month 12:
    - clinical fracture
    - new vertebral fracture
    - all fractures
    - nonvertebral fracture

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    - hip fracture
    - major osteoporotic fracture
    - clinical vertebral fracture
- At the final analysis:
    - nonvertebral fracture
    - major nonvertebral fracture
    - hip fracture
- Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at month 36

The primary and key secondary endpoints were appropriate as clinically relevant endpoints. Currently the most widely used endpoint in clinical trials for new osteoporosis drugs is new morphometric (radiographically identified) vertebral fracture (which may or may not be symptomatic), which is the most common osteoporosis-related fracture in postmenopausal women (Khosla, 2003). Clinical fractures, which encompass all symptomatic fractures (i.e., nonvertebral fractures and vertebral fractures that are symptomatic and come to clinical attention), account for most of the morbidity and mortality associated with osteoporosis. Of note, for the clinical fracture endpoint, symptomatic vertebral fractures were included regardless of trauma severity or pathologic fractures. Historically, high-trauma fractures and pathologic fractures have been excluded in the assessment of fracture endpoints.

As discussed above in Section 2.1, nonvertebral fractures (the key secondary endpoint in this study) at virtually any site increase the risk of subsequent fracture and are associated with increased mortality.

There were multiple exploratory endpoints, including the following measuring PRO (patient-reported outcomes) and ClinRO (clinician-reported outcomes):

- PRO and ClinRO measures (Osteoporosis Assessment Questionnaire Short Version [OPAQ SV], EQ-5D-5L [EuroQoL-5 Dimensions-5 Levels Health Survey], Limited Activity Days survey [LAD], and Brief Pain Inventory [BPI] worst pain) at months 6,12, 18, 24, 30, and 36
- Change from baseline in PRO and ClinRO measures (OPAQ SV, EQ-5D-5L, LAD, and BPI worst pain) at months 6, 12, 18, 24, 30, and 36

Safety endpoints included the following (assessed during the 12-month double-blind alendronate-controlled study period and the primary analysis period):

- Subject incidence of adverse events by system organ class and preferred term
- Changes from baseline in laboratory assessments (serum chemistry and hematology) and the shifts from baseline to the worst value
- Changes from baseline in vital signs
- Subject incidence of antiromosozumab antibodies

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These safety endpoints were adequate to assess general safety and the previously identified risks of romosozumab. However, as discussed in Section 8.2.5, safety measures were not adequate for a comprehensive assessment of cardiovascular risk (e.g., electrocardiograms and serum lipid values were not performed).

Statistical Analysis Plan

Sample size considerations

The study planned to enroll 4000 subjects (2000:2000 equally allocated between the treatment groups) based on the anticipated number of clinical fracture and new vertebral fracture endpoints using a simulation study. The dropout rate was assumed 10% for the first year and 8% per year thereafter. Endpoints were to be tested 2-sided with alpha level at 0.05. The assumptions and the corresponding study power with 2000 subjects per group are presented in the table below based on simulation results.

Table 10: Study 142 Sample Size Considerations

Endpoint	Assumptions	Power
New Vertebral Fracture	One-year incidence if untreated: 5.5% ALN decreases this incidence by 60% Romosozumab decreases this incidence by 80%	95%
Clinical Fracture	Romosozumab will reduce the risk by 30% compared to ALN	Need 330 events to achieve 90%
BMD endpoints	See Table 1 and Table 2 in the SAP	>99%

Source: study 20110142 SAP.

Study Time Intervals

The Applicant pre-specified different analysis time intervals as follows.

On-Study Period: The time period from the randomization date to the end of study date, inclusive.

Double-blind Period: The time period from the randomization date to the end of double-blind period date, inclusive.

Open-label ALN Period: The time period from the end of double-blind period date to the end of study date, inclusive.

Month 12 to Month 24 ALN Study Period: For subjects entering the ALN open-label period, the time period from the end of double-blind period date to the Month 24 visit date, study day 761, or end of study date, whichever is the earliest, inclusive. The Month 24 visit date is defined as the latest assessment collected at Month 24.

24-month ALN Study Period: The time period from the randomization date to the Month 24 visit date, study day 761, or end of study date, whichever is the earliest, inclusive

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Primary Analysis Period: The time period from the randomization date to the end of primary analysis period date, inclusive.

Overall Study Period: If the study will continue to the final analysis, the overall study period is defined as the time period from the randomization date to the end of final analysis period date, inclusive.

Analysis Populations

The Applicant pre-defined the following analysis sets. In all efficacy analysis sets, subjects were analyzed according to their randomized treatment assignment, regardless of treatment received. In the safety analysis set, subjects were analyzed according to their actual received treatment.

Full Analysis Set: All randomized subjects. Used as the primary analysis set for the following endpoints: nonvertebral fracture, clinical fracture, clinical vertebral fracture, all fracture, major nonvertebral fracture, major osteoporotic fracture, and hip fracture. These fractures were identified from adverse event reporting.

Primary Efficacy Analysis Set For Vertebral Fractures: All randomized subjects who had a baseline and at least 1 post-baseline evaluation of vertebral fracture by lateral spine X-ray (as planned in the study's schedule of assesments), at or before the time point under consideration. Subjects who had vertebrae with missing Genant semiquantitative scores at baseline and whose first post-baseline spinal radiograph showed no fracture on the same vertebrae were also included in this analysis set. This analysis set was used as the primary analysis set for new, new or worsening, and multiple new or worsening vertebral fractures.

Primary Efficacy Analysis Set for BMD Endpoints for the Double-blind ALN-controlled Study Period and Primary Analysis Period: All randomized subjects who had a baseline and at least 1 post-baseline evaluation at or before the time point under consideration. Note that this subset could potentially be different from endpoint to endpoint due to missing data.

Safety Analysis Set: All randomized subjects who received at least 1 active dose of investigational product in the 12-month double-blind ALN-controlled study period. Used to analyze safety data for the double-blind study period, primary analysis period, and overall study period.

Handling of Missing Data

For vertebral fracture assessment, any missing post-baseline vertebral fracture status due to missing spinal x-ray assessment was imputed using the status from the last nonmissing post-baseline visit (i.e., last observation carried forward [LOCF]). For other type of fractures, no imputation was used unless specified.

For endpoints evaluated by DXA or QCT at any anatomical site, missing post-baseline values were imputed using LOCF approach (by carrying forward the last nonmissing post-baseline

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value prior to the missing value from the same anatomical site). For the open-label period endpoints, only the open-label period value was used for imputation, the values in the double-blind period were not carried forward into the open-label period. The LOCF imputation was done up to Month 36. Missing post-baseline data were NOT imputed when a repeated measures
model was used as a sensitivity analysis.

Handling of Multiplicity

If both the co-primary endpoints were significant at the 0.05 level (2-sided), each of the following secondary DXA BMD endpoints were tested hierarchically at 0.05 (2-sided) according to the following sequence:

1) percent change from baseline in BMD at lumbar spine at Month 24
2) percent change from baseline in BMD at total hip at Month 24
3) percent change from baseline in BMD at femoral neck at Month 24
4) percent change from baseline in BMD at lumbar spine at Month 12
5) percent change from baseline in BMD at total hip at Month 12
6) percent change from baseline in BMD at femoral neck at Month 12.

If all preceding endpoints were significant,

7) the nonvertebral fracture endpoint would be tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test (alpha=0.025). The Lan-DeMets alpha spending function (Lan and DeMets,1983) that approximates a Pocock boundary (Pocock, 1977), (0.025*LN(1+(EXP(1) -1)*information fraction)), was to be used to determine the significance level at the time of the primary analysis. Based on the number of subjects with nonvertebral fractures at the time of the primary analysis out of the total 440 planned, which represents the information fraction in the alpha spending function, the significance level would be calculated at the time of primary analysis. For example, if the information fraction is 80% at time of the primary analysis, the significance level is 0.0216.

If the significance of nonvertebral fracture is not demonstrated at the time of the primary analysis, the nonvertebral fracture endpoint will be tested again using a 1-sided test at the time of the final analysis. Based on the alpha level spent at the primary analysis, the significance level at final will be determined.

Analysis of Co-Primary Efficacy Endpoints

The number and percentage of subjects with at least 1 new vertebral fracture through Month 24 were summarized by randomized treatment group. Point estimates of absolute risk reduction (difference in proportions, control – treatment) and the relative risk reduction (100*(1-risk ratio)) (risk ratio was the ratio of proportions, treatment over control) as well as the corresponding 95% confidence intervals were also calculated via the Mantel-Haenszel method, adjusting for age strata, baseline total hip BMD T-score strata (≤ -2.5, > -2.5) and presence or absence of vertebral fracture at baseline. The subject incidence of new vertebral

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fractures through Month 24 was tested using a logistic regression model and the primary efficacy analysis set for vertebral fractures. The model included the treatment as the main effect, age strata, baseline total hip BMD T-score, and presence or absence of severe vertebral fracture at baseline as covariates.

Time to first clinical fracture through the primary analysis period was analyzed using a stratified Cox proportional hazards model controlling for age strata with presence or absence of severe vertebral fracture at baseline, baseline total hip BMD T-score, and treatment as the independent variable based on the full analysis set. The estimated hazard ratio, corresponding 95% confidence interval, and the p-value from the model were provided. The cumulative incidence of fractures was summarized using the Kaplan-Meier estimates.

Analysis of Secondary Efficacy Endpoints

The primary efficacy subset for BMD was used for analysis of percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at months 12, 24 and 36.

The treatment comparisons of the BMD in lumbar spine, total hip and femoral neck at months 12 and 24 were analyzed using the ANCOVA LOCF 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. The least-squares mean of the treatment difference (treatment – control) and the corresponding 95% confidence interval were summarized by time points of interest, where each time point was estimated using a separate ANCOVA model.

The primary efficacy analysis set for vertebral fracture was used for analysis of subject incidence of new vertebral fracture through Month 12.

The full analysis set was used for analysis of the following endpoints:

- Subject incidence of nonvertebral fracture through Month 12, through Month 24, and through the primary analysis period;
- Subject incidence of hip fracture through Month 12 and through Month 24.

The cumulative incidence of each type of fracture was summarized using the Kaplan-Meier estimates at the time point(s) of interest. The point estimate of the adjusted risk difference (difference in Kaplan-Meier estimates at the time point of interest, control arm - treatment arm) and the corresponding 95% confidence interval were provided using the inverse variance-weighted method. Stratified Cox proportional hazards model controlling for age strata with presence or absence of severe vertebral fracture at baseline, baseline total hip BMD T-score, and treatment as the independent variable was also used. The significance of the treatment effect between treatment arm and control arm (for the secondary endpoints in the testing sequence) was assessed based on the Cox proportional hazards model. The estimated hazard ratio and corresponding 95% confidence interval from the model were also provided.

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Subgroup analysis

The co-primary efficacy endpoints (incidence of new vertebral fractures through Month 24 and clinical fractures through the primary analysis period), and nonvertebral fractures through the primary analysis period, were also evaluated by subgroups defined below.

- Age (< 75 years, ≥ 75 years)
- Presence or absence of severe vertebral fracture at baseline (based on most severe Genant semiquantitative grade at baseline on screening spinal radiograph)
- Number of prevalent vertebral fractures at baseline (0-1, 2, ≥3; based on screening spinal radiograph)
- Race (White and non-White)
- Geographic region
  - Western Europe and New Zealand/Australia
  - Central and Eastern Europe and Middle East
  - Asia Pacific and South Africa
  - North America
  - Central/Latin America
- Central/Latin America and all regions excluding Central/Latin America
- Baseline lumbar spine BMD T-score (≤ -3, > -3 and ≤ -2.5, > -2.5)
- Baseline total hip or femoral neck BMD T-score ≤ -3 vs. both total hip and femoral BMD T-score > -3
- Baseline body mass index (BMI; tertiles)
- Fracture Risk Assessment tool (FRAX) score for major osteoporotic fracture (tertiles)
- History of nonvertebral fracture at age ≥ 55 years (yes, no)

The percent changes from baseline in lumbar spine BMD and total hip BMD at Month 12 and Month 24 were analyzed for the following subgroups:

- Age (< 75 years, ≥ 75 years; < 65 years, ≥ 65 years)
- Geographic region
- Baseline lumbar spine BMD T-score (≤ -3, > -3 and ≤ -2.5, > -2.5; for lumbar spine BMD analysis only)
- Baseline total hip BMD T-score (≤ -3, > -3 and ≤ -2.5, > -2.5; for total hip BMD analysis only)

For each category of a subgroup, these endpoints were summarized and analyzed using the same approach as the primary analysis described above. The treatment-by-subgroup interaction was tested using the same statistical model (i.e. logistic regression for new vertebral fractures, Cox proportional hazard model for clinical fractures, and nonvertebral fractures and ANCOVA-LOCF model for percent change in BMD endpoints) including individual subgroup and treatment-by-subgroup interaction. If the p-value of the interaction was > 0.05, the treatment-by-subgroup interaction was considered not significant. Otherwise, a 2-sided Gail and Simon test was used to test whether there was qualitative interaction.

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Protocol Amendments

The original protocol for this study was approved on December 15, 2011 and was amended 5 times. All amendments occurred before unblinding. Major changes to the study protocol in these 5 amendments are summarized as follows:

Amendment 1 (April 27, 2012):

- Subjects with a reported history of hearing loss associated with cranial nerve VIII compression due to excessive bone growth were excluded from study participation.
- A physician was to be available during administration of investigational product, and all subjects were closely observed for approximately 30 minutes after dosing.
- The investigator was to be alerted if a subject experienced a BMD loss from baseline of ≥ 7% at the total hip and/or at the lumbar spine at any time during the study and was required to discuss implications for individual fracture risk, alternative treatment options, and options for continuing in the study with the subject.

Amendment 2 (November 14, 2012):

- Amended exclusion criteria to ensure that pre-existing disorders and/or the administration of medications did not confound the benefit/risk assessment for romosozumab.
- Amended proscribed treatments during the study to ensure those did not confound the benefit/risk assessment for romosozumab.
- Provided more detail on the adjudication of possible events of osteonecrosis of the jaw, atypical femoral fractures, and cardiovascular events.
- Clarified that worsening vertebral fractures were considered for endpoints evaluating the incidence of all fractures.
- For endpoints evaluating the incidence of major osteoporotic fractures, corrected the definition to include forearm instead of wrist fractures.
- Baseline total hip BMD T-score was aligned with the Statistical Analysis Plan as an adjustment factor for the evaluation of new vertebral fracture incidence.
- Specified that serious adverse events must be reported within 24 hours after the investigator's knowledge of the event and clarified the point of reference for evaluation of expectedness of serious adverse events (i.e., clarified the appropriate reference safety information per local regulatory reporting requirements).
- Clarified the day 1 lumbar spine DXA scan may have been taken together with the screening proximal femur DXA scan for subject convenience.
- Replaced the Month 21 clinic visit with a telephone call.
- For subjects participating in the Imaging and PK/BTM /Biomarker Substudy, the spine QCT assessments at Month 36 and the end-of-study visits were eliminated.

Amendment 3 (June 21, 2013)

- Lowered the minimum age from 60 to 55 years and allowed 3 additional qualifying BMD

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and fracture history combinations.
- The protocol-mandated off-treatment times for exclusionary medications were revised.
- Rescreening was allowed for subjects who previously failed screening if in the opinion of the investigator the reason for the initial screen failure has resolved or was no longer applicable.
- Assessments for formation of antiromosozumab antibodies were added at the Month 1 and Month 3 study visits to allow a more comprehensive characterization of the antibody response.
- Retesting of serum calcium would be permitted within the screening window if the initial test indicated an elevated level of serum calcium within 1.1 x the upper limit of normal.

Amendment 4 (July 8, 2015)

- Upon completion of the primary analysis period, subjects were followed for nonvertebral fractures. Subjects and site personnel remained blinded to initial treatment assignments and the study proceeded in an event-driven manner. The final analysis (end-of-study) 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. The duration of participation for subjects was changed from 25 to 59 months if study completion was achieved at primary analysis, or from 37 to 71 months if study completion was achieved when 440 subjects experienced a nonvertebral fracture.
- Approximately 200 subjects were planned to be enrolled in the Imaging and PK/BTM/Biomarker Substudy, with a subset of approximately 100 subjects participating in the imaging (DXA, QCT) portion of the substudy.
- The exclusion criteria for hyper-/hypothyroidism and hyper-/hypoparathyroidism were clarified.
- The Month 15 study visit was eliminated for all but the substudy participants, and sampling for antibody testing was added to the Month 18 visit. The end of primary analysis and end-of-study visits were replaced by telephone contact.

Amendment 5 (September 14, 2016)

- Moved the following Month-12 exploratory endpoints to secondary endpoints: nonvertebral fracture, hip fracture, major osteoporotic fracture (hip, forearm, humerus, and clinical vertebral).
- Added clinical vertebral fracture as a new Month-12 secondary endpoint.
- Added new endpoints to the overall study period and the Month 12 to 24 open-label alendronate period.
- Added the following new secondary endpoints through Month 24 during the primary analysis period: clinical fracture, nonvertebral fracture, hip fracture, and clinical vertebral fracture.
- DXA BMD endpoints were added to the testing sequence for multiplicity adjustment.

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The majority of these changes were made in response to FDA requests. All of these changes were acceptable.

Data Quality and Integrity

Study Monitoring
The study centers were monitored by the applicant. Monitors were responsible for reviewing adherence to the protocol, compliance with Good Clinical Practices, and the completeness, accuracy, and consistency of the data.

The applicant used multiple Contract Research Organizations (CROs) for this study. The CROs used and their respective roles are listed in Table 11.

Table 11 Contract Research Organizations and Responsibilities



*Source: Table 8-1 of CSR

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From study start until primary analysis, an external, independent Data Monitoring Committee (DMC) monitored the unblinded safety data and considered efficacy data to assess the benefit/risk profile of romosozumab. The DMC members had access to individual treatment assignments if knowledge of this was necessary to evaluate safety. To minimize the potential for bias, the DMC members did not have direct contact with study site personnel or subjects.

Standardization of Laboratory and Radiographic Procedures

Central laboratories were used to analyze all screening and on-study samples for serum chemistry, hematology, biomarker and BTMs (P1NP, osteocalcin [OC], bone-specific alkaline phosphatase [BSAP], serum Type I collagen C-telopeptide [sCTX], tartrate-resistant acid phosphatase 5b [TRAP 5b]), 25 (OH) vitamin D, PK, and antiromosozumab antibodies as well as X-rays, DXA data, and High Resolution peripheral QCT (HR-pQCT) data. Regarding local laboratories, study monitors evaluated their internal and external quality control, quality assurance, and accreditation schemes.

The central laboratories used in this study and their respective responsibilities are listed in Table 12.

Table 12 Central Laboratories and Responsibilities

(b) (4)

* Source: Table 8-2 of CSR.

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Lateral spine X-rays, DXA images, and HR-pQCT images were acquired according to specific instructions provided by the central imaging vendor and all images were analyzed by the central imaging center, Bioclinica Inc. Adequate quality control measures were in place as detailed in the charter for the central imaging vendor.

In summary, it appears that adequate measures were in place to ensure data quality and integrity.

8.1.2. Study 20110142: Efficacy Results

Compliance with Good Clinical Practices

The applicant attested that the study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable FDA or local regulations/guidelines.

Subject Enrollment and Disposition

Subject disposition during the full analysis period is presented in Table 133. A total of 4093 subjects were randomized; 2046 subjects were randomized to the romosozumab 210 mg QM treatment group and 2047 subjects were randomized to the alendronate 70 mg QW treatment group. Subjects were stratified by age; 48% of subjects were < 75 years and 52% were ≥ 75 years.

Eighty nine percent of enrolled subjects completed the 12-month double-blind period (romosozumab: 90%; alendronate: 89%) and 77% of subjects completed the primary analysis period (romosozumab/alendronate: 77%; alendronate/ alendronate: 77%). During the 12-month double blind period, withdrawn consent, death and adverse events were the most frequently reported reasons for discontinuation from study in both treatment groups (6%, 1% and 1%, respectively, in the romosozumab group and 7%, 1% and 1%, respectively, in the alendronate group). Throughout the primary analysis period, withdrawn consent and death were the most frequently reported reasons for discontinuation from study in both treatment groups (13% and 5%, respectively, in the romosozumab/alendronate group and 12% and 5%, respectively, in the alendronate/alendronate group).)

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Table 13 Subject Disposition (Full Analysis Set) (Primary Analysis)

	Alendronate 70 mg QW/ Alendronate 70 mg QW n (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW n (%)	All n (%)
Randomized	2047	2046	4093
12-Month Double-blind Period			
Discontinued during double-blind period	224 (10.9)	215 (10.5)	439 (10.7)
Consent withdrawn	139 (6.8)	129 (6.3)	268 (6.5)
Death	24 (1.2)	27 (1.3)	51 (1.2)
Adverse event	25 (1.2)	25 (1.2)	50 (1.2)
Lost to follow-up	16 (0.8)	13 (0.6)	29 (0.7)
Other	6 (0.3)	9 (0.4)	15 (0.4)
Noncompliance	4 (0.2)	7 (0.3)	11 (0.3)
Ineligibility determined	5 (0.2)	2 (<0.1)	7 (0.2)
Protocol deviation	3 (0.1)	3 (0.1)	6 (0.1)
Administrative decision	1 (<0.1)	0 (0)	1 (<0.1)
Requirement for alternative therapy	1 (<0.1)	0 (0)	1 (<0.1)
Completed double-blind period	1823 (89.1)	1831 (89.5)	3654 (89.3)
Primary Analysis (PA) Period			
Discontinued during PA period	471 (23)	472 (23.1)	943 (23)
Consent withdrawn	251 (12.3)	263 (12.9)	514 (12.6)
Death	97 (4.7)	95 (4.6)	192 (4.7)
Adverse event	43 (2.1)	45 (2.2)	88 (2.2)
Lost to follow-up	35 (1.7)	32 (1.6)	67 (1.6)
Other	16 (0.8)	16 (0.8)	32 (0.8)
Noncompliance	12 (0.6)	14 (0.7)	26 (0.6)
Requirement for alternative therapy	7 (0.3)	2 (<0.1)	9 (0.2)
Protocol deviation	4 (0.2)	3 (0.1)	7 (0.2)
Ineligibility determined	5 (0.2)	2 (<0.1)	7 (0.2)
Administrative decision	1 (<0.1)	0 (0)	1 (<0.1)
Safety analysis	2014 (98)	2040 (99.7)	4054 (99.0)
Primary analysis	1576 (77.0)	1574 (76.9)	3150 (77.0)
Overall study analysis	1576 (76.9)	1574 (76.9)	3150 (76.9)
*Source: adapted from Table 14-1.1 of CSR			

The study had a somewhat high overall discontinuation rate through the end of primary analysis period (23%). However, this rate was the same in each treatment group, and reasons for discontinuation were also generally balanced between the treatment groups. Disposition results are similar to Study 337, with the exception that the overall discontinuation rate was lower in Study 337 (16%).

In the 12-month double-blind period, 85% of randomized subjects completed investigational product (romosozumab: 86%; alendronate: 85%). Eight (0.4%) subjects in the romosozumab group never received investigational product, all due to withdrawn consent after randomization. Seven (0.3%) subjects in the alendronate group never received investigational

product, 4 due to withdrawn consent, 2 due to ineligibility, and 1 subject was mistakenly randomized. Forty-nine (1%) subjects completed double-blind investigational product, but never received open-label alendronate (romosozumab: 1%; alendronate 1%).

Overall for the primary analysis period, 70% of subjects completed investigational product administration (romosozumab/alendronate: 70%; alendronate/alendronate, 70%). During the primary analysis period, the most frequently reported reasons for discontinuation of investigational product were withdrawn consent (romosozumab/alendronate: 7%; alendronate/alendronate: 6%), adverse event (3% and 3%), and death (2% and 3%).

Overall the study had an acceptable level of investigational product completion, and rates of investigational product discontinuation were balanced between treatment groups for both the double-blind and overall primary analysis period. Results are similar to Study 337.

Protocol Deviations

Important protocol deviation (IPD) categories were defined prior to the first subject visit and updated during the IPD reviews throughout the study prior to database lock.

12-Month Double-blind Period

A total of 227 (6%) subjects had at least 1 IPD during the double-blind period (Table 14). The most frequently reported IPDs pertained to subjects who received < 75% or >125% of planned weekly alendronate or matching placebo tablets (2% in the romosozumab group; 3% in the alendronate group) and those who missed more than 3 scheduled monthly injections of romosozumab or matching placebo during the double-blind period (1%; 2%, respectively).

During the double-blind treatment period, 6 subjects who were randomized to alendronate received either romosozumab or matching placebo to romosozumab. Two of these subjects received active doses of romosozumab. These 2 subjects were included in the alendronate group for efficacy analyses, but in the romosozumab group for safety analyses, as described in SAP. The other 4 subjects received all SC placebo injections and active alendronate tablets as planned in the double-blind period.

Similarly, during the double-blind period, 2 subjects who were randomized to romosozumab received alendronate or matching placebo tablets. One of these subjects received and took 4 active alendronate tablets. Both of these subjects were included in the romosozumab group for efficacy and safety analyses.

Other important protocol deviations during the 12-month double-blind treatment period included the following: entered study even though entry criteria were not satisfied (53 subjects, 1%); received an excluded concomitant medication (7 subjects; 0.2%); other deviations (2 subjects, < 0.1%); and developed withdrawal criteria but was not withdrawn (1 subject; < 0.1%).

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Primary Analysis Period

Over the primary analysis period, 345 (8%) subjects had at least 1 IPD (Table 144). The most frequently reported important protocol deviations pertained to subjects who received < 75% or >125% of planned weekly alendronate or matching placebo tablets during the double-blind period (romosozumab/alendronate: 3%; alendronate/alendronate: 3%), subjects who missed > 3 scheduled monthly injections of romosozumab or matching placebo during the double-blind period (1%; 2%), and subjects who received < 75% or >125% of planned open-label alendronate doses (2%; 2%). Other IPDs during the primary analysis period included: received an excluded concomitant medication (24 subjects; 0.6%); other deviations (17 subjects, 0.4%); missing data (4 subjects, < 0.1%), and developed withdrawal criteria but was not withdrawn (1 subject; < 0.1%).

Table 14. Important Protocol Deviations (Full Analysis Set) (Primary Analysis)

	Alendronate 70 mg QW/ Alendronate 70 mg QW (N=2047) n (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N=2046) n (%)	All (N=4093) n (%)
12-Month Double-blind Study Period			
Subjects with at least one IPD	124 (6.1)	103 (5.0)	227 (5.5)
Received the wrong treatment or incorrect dose	95 (4.6)	75 (3.7)	170 (4.2)
Received < 75% or > 125% of planned ALN/placebo doses	60 (2.9)	42 (2.1)	102 (2.5)
Missed > 3 doses of romosozumab/placebo	32 (1.6)	29 (1.4)	61 (1.5)
Entered study even though entry criterion was not satisfied	25 (1.2)	28 (1.4)	53 (1.3)
Received an excluded concomitant treatment	4 (0.2)	3 (0.1)	7 (0.2)
Other Deviations	0 (0)	2 (<0.1)	2 (<0.1)
Developed withdrawal criteria but was not withdrawn	1 (<0.1)	0 (0)	1 (<0.1)
Primary Analysis Period			
Subjects with at least one IPD	183 (8.9)	162 (7.9)	345 (8.4)
Received the wrong treatment or incorrect dose	139 (6.8)	119 (5.8)	258 (6.3)
Received < 75% or >125% of planned ALN/placebo doses	67 (3.3)	52 (2.5)	119 (2.9)
Received < 75% or >125% of planned open-label ALN doses	42 (2.1)	33 (1.6)	75 (1.8)
Missed > 3 doses of	33 (1.6)	29 (1.4)	62 (1.5)

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	Alendronate 70 mg QW/ Alendronate 70 mg QW (N=2047) n (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N=2046) n (%)	All (N=4093) n (%)
romosozumab/placebo			
Entered study even though entry criterion was not satisfied	25 (1.2)	28 (1.4)	53 (1.3)
Received an excluded concomitant treatment	16 (0.8)	8 (0.4)	24 (0.6)
Other Deviations	5 (0.2)	12 (0.6)	17 (0.4)
Missing data (Month 24 or ET Lateral spine x-ray not available)	2 (<0.1)	2 (<0.1)	4 (<0.1)
Developed withdrawal criteria but was not withdrawn	1 (<0.1)	0 (0)	1 (<0.1)
*Source: adapted from Table 14-3.1 of CSR			

The number of protocol deviations was low and overall balanced between treatment groups. Based on their nature and low, balanced incidences, the important deviations identified in this study were unlikely to have affected the interpretation of the study results.

Demographic Characteristics

Demographic and disease characteristics were generally balanced between the 2 treatment groups (Table 155). As required by the inclusion criteria, all enrolled subjects were women. The mean age of all subjects was 74.3 years (range: 55 to 90 years), and 52% of subjects were ≥ 75 years of age at enrollment. Approximately 70% of subjects were white and 70% were non-Hispanic/Latino. Body composition of the subjects included mean (SD) weight of 59 (11) kg, mean (SD) height of 152 (8) cm, and mean (SD) body mass index (BMI) of 25.4 (4.4) kg/m^2. The mean number of years since menopause was 26.9 years.

Subjects were from the following geographic regions: Western Europe and Australia/New Zealand (13% of randomized subjects), Central and Eastern Europe and the Middle East (40% of randomized subjects), Central/Latin America (34% of randomized subjects), North America (2% of randomized subjects), and Asia Pacific and South Africa (11% of randomized subjects). Countries that randomized more than 10% of subjects included Colombia (16%), and Poland (17%)

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Table 15. Demographic Characteristics (Full Analysis Set) (Primary Analysis)

	Alendronate 70 mg QW/ Alendronate 70 mg QW (N=2047)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N=2046)	All (N=4093)
Age (years)			
Mean (SD)	74.2 (7.5)	74.4 (7.5)	74.3 (7.5)
Median (min., max.)	75.0 (55, 90)	75.0 (55, 90)	75.0 (55, 90)
Geriatric Group – n (%)			
<65 years	240 (11.7)	239 (11.7)	479 (11.7)
<75 years	976 (47.7)	973 (47.6)	1949 (47.6)
≥75 years	1071 (52.3)	1073 (52.4)	2144 (52.4)
Sex - n (%)			
Women	2047 (100)	2046 (100)	4093 (100)
Ethnicity - n (%)			
Hispanic/Latino	662 (32.3)	631 (30.8)	1293 (31.6)
Not Hispanic/Latino	1385 (67.7)	1415 (69.2)	2800 (68.4)
Race – n (%)			
White	1415 (69.1)	1447 (70.7)	2862 (69.9)
Other	446 (21.8)	436 (21.3)	882 (21.5)
Asian	149 (7.3)	137 (6.7)	286 (7.0)
Black	23 (1.1)	19 (0.9)	42 (1.0)
American Indian or Alaska native	7 (0.3)	5 (0.2)	12 (0.3)
Native Hawaiian or Other Pacific Islander	2 (<0.1)	0 (0)	2 (<0.1)
Multiple	4 (0.2)	2 (<0.1)	6 (0.1)
Missing	1 (<0.1)	0 (0)	1 (<0.1)
Weight (kg)			
Mean (SD)	58.6 (11.4)	58.7 (11.4)	58.7 (11.4)
Median (min., max.)	57.5 (28, 113)	57.6 (27.7, 113)	57.5 (27.7, 113)
Height (cm)			
Mean (SD)	152 (7.9)	151.8 (7.9)	151.9 (7.9)
Median (min., max.)	152 (124, 179)	152 (122, 178)	152 (122, 179)
Body Mass Index (kg/m^2)			
Mean (SD)	25.4 (4.4)	25.5 (4.4)	25.4 (4.4)
Median (min., max.)	25.1 (13.5, 44.3)	25 (15.1, 47.4)	25 (13.5, 47.4)
Geographic Region - n(%)			
Central and Eastern Europe and Middle East	798 (39.0)	835 (40.8)	1633 (39.9)
Central/Latin America	727 (35.5)	674 (32.9)	1401 (34.2)
Western Europe and Australia/New Zealand	264 (12.9)	269 (13.1)	533 (13.0)
Asia Pacific and South Africa	216 (10.6)	213 (10.4)	429 (10.5)
North America	42 (2.1)	55 (2.7)	97 (2.4)
United States	24 (1.2)	33 (1.6)	57 (1.4)
Canada	18 (0.9)	22 (1.1)	40 (1.0)
Source: modified from Table 9-1 and Table 14-1.4 of CSR			

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Overall, the subject composition is very similar to Study 337, with the following exceptions:

- Subjects in Study 142 were 3.5 years older on average (mean age 74.3 years, with 52% of subjects ≥ 75 years) than subjects in Study 337 (mean age 70.9 years, with 31% of subjects ≥ 75 years).
- The highest enrollment was from Central and Eastern Europe and the Middle East (40%) in Study 142 and from Central/Latin America (43%) in Study 337.

The study population had a very low percentage of subjects from the US (1.4%). However, when compared by race, ethnicity, and individual geographical regions, each of the demographic groups demonstrated significant and similar efficacy for reducing fractures and increasing BMD at the lumbar spine, hip, and femoral neck with romosozumab compared to alendronate (as discussed in further detail below). Given this, and given that prior PMO trials with mostly non-US subjects have demonstrated applicability to the US population, the efficacy results of Study 142 are applicable to the US population. However, we are uncertain about the applicability of the cardiovascular safety findings to the US population (as discussed in Section 8.2.5).

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Other Baseline Characteristics

Baseline disease characteristics were generally balanced between the treatment groups (**Error! Reference source not found.**). Overall, 99% of subjects had a prior osteoporotic fracture on or after age 45. The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were -2.96, -2.80, and –2.90, respectively. Baseline spine radiographs evaluated by the central imaging vendor showed that 96% of subjects had a verified prevalent vertebral fracture at baseline.

Baseline clinical risk factors relevant to determination of the 10-year probability of a major osteoporotic fracture, according to the FRAX, were similar between treatment groups. The mean 10-year probabilities of major osteoporotic fractures calculated with femoral neck BMD were 20% for the romosozumab group and 20% for the alendronate group. For the subset of osteoporotic hip fractures, corresponding probabilities were 10% for the romosozumab group and 10% for the alendronate group.

Baseline cardiovascular risk factors were similar between the treatment groups. 52% of subjects were ≥ 75 years of age in each treatment group, 28% were current or former smokers (romosozumab: 26%, alendronate: 29%), and 79% of subjects in each treatment group reported a cardiovascular risk factor including history of hypercholesterolemia, hypertension, diabetes, or clinical cardiovascular disease. Of note, fasting serum lipid values were not assessed.

The use of prior osteoporosis medications was reported for 9% of subjects in each treatment group; oral bisphosphonates were the most frequently reported prior osteoporosis medication (6% in each treatment group), followed by PTH or PTH derivatives and calcitriol (both 1% in each treatment group).

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Nearly all subjects (98% in each treatment group) reported use of calcium and vitamin D at baseline. Based on screening values for 25(OH) vitamin D, 3032 (74%) subjects received an initial loading dose of 50000 to 60000 IU vitamin D within 1 week of randomization (romosozumab: 73%, alendronate: 75%).

In summary, as intended, the study enrolled a population of subjects at high risk for fracture, with 96% of subjects with at least 1 verified prevalent vertebral fracture at baseline and 38% of subjects with a history of nonvertebral fracture at or after age 45. This is in contrast to Study 337, with 18% of subjects enrolled with at least 1 verified prevalent vertebral fracture at baseline and 22% of subjects with a history of nonvertebral fracture at or after age 45. Baseline characteristics other than BMD and previous fracture history that contribute to the FRAX determination of fracture risk (e.g., BMI, smoking history, glucocorticoid use) were generally consistent with Study 337.

Baseline medical characteristics were similar to Study 337, with the exception of a higher percentage of subjects with a history of hypertension (61% versus 54%), cardiovascular disease (73% versus 65%), and cerebrovascular disease (8% versus 6%) in Study 142 versus Study 337. Within each study, however, cardiovascular medical history and baseline cardiovascular risk factors were balanced between treatment groups.

Treatment Compliance, Concomitant Medications

Treatment Compliance During 12-Month Double-blind Period

Eighty-six percent of subjects randomized to romosozumab continued investigational product throughout the double-blind treatment period. Of these subjects, 98% (1720/1749) received at least 75% of the scheduled romosozumab injections.

Eighty-five percent of subjects randomized to alendronate continued investigational product throughout the double-blind treatment period. Of these subjects, 97% (1678/1737) received at least 75% of the planned alendronate tablets.

Treatment Compliance During Open-label Period

Seventy percent of subjects randomized to romosozumab continued investigational product throughout the primary analysis period. Of these subjects, 98% (1401/1434) received at least 75% of the planned alendronate doses during the open-label period.

Seventy percent of subjects randomized to alendronate continued investigational product throughout the primary analysis period. Of these subjects, 97% (1379/1422) received at least 75% of the planned alendronate doses during the open-label period.

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Concomitant Treatments

Overall throughout the primary analysis period, 0.6% of subjects received an excluded concomitant treatment (0.8% in the alendronate group and 0.4% in the romosozumab group). Excluded concomitant treatments included systemic glucocorticoids (0.4% alendronate group and 0.2% romosozumab group), oral bisphosphonates (<0.1% alendronate group and 0% romosozumab) and systemic oral transdermal estrogen (<0.1% alendronate group and 0% romosozumab group).

The rates of treatment compliance and use of prohibited concomitant medications were acceptable and well-balanced between treatment groups.

Efficacy Results – Co-Primary Endpoints

New vertebral fractures through Month 24

Table 16 presents the primary efficacy results for new vertebral fractures through Month 24 for Study 20110142. The incidence of new vertebral fracture was 4.1% in the romosozumab group compared to 8.0% in the alendronate group (p-value: <0.001) through Month 24. The absolute risk reduction in new vertebral fracture was 4.03% in patients receiving romosozumab compared to alendronate and the corresponding relative risk reduction was 50%.

Table 16: Study 20110142 - Incidence of New Vertebral Fracture Through Month 24 – Primary analysis Set for Vertebral Fractures

Statistic	Alendronate 70 mg QW/ Alendronate 70 mg QW (N=2047)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)
Incidence, n/N1 (%)	147/1834 (8.0)	74/1825 (4.1)
Comparison vs. ALN/ALN		
Absolute risk reduction [a] (%) (95% CI)		4.03 (2.50, 5.57)
Relative risk reduction [b] (95% CI)		50% (34%, 62%)
p-value[c]		< 0.001

Source: Table 10-1 in study 20110142 report.
CI = confidence interval; N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures; QM = every month; QW = weekly; RRR = relative risk reduction
ALN/ALN is Alendronate 70 mg QW/Alendronate 70 mg QW
[a] Based on the Mantel-Haenszel method adjusted for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline
[b] Calculated from risk ratio as 100 x (1 – risk ratio)
[c] Based on logistic regression model adjusted for age strata, baseline total hip BMD T-score and presence of severe vertebral fracture at baseline; p-value based on score test

Reference ID: 4416253

Clinical fractures through primary analysis period

The study protocol pre-defined the clinical fractures as non-vertebral fractures and clinical (i.e. symptomatic) vertebral fractures. The primary analysis was event-driven based on the number of observed clinical fractures and occurred after a median follow-up time of 33 months. At the time of the primary analysis, 464 subjects had experienced a clinical fracture and all subjects had completed the 24-month visit. Clinical fracture occurred in 9.7% of subjects in the romosozumab group compared to 13.0% of subjects in the alendronate group through the primary analysis period. Romosozumab significantly reduced the risk of clinical fractures compared to alendronate alone with a hazard ratio of 0.73 (95% CI: 0.61-0.88, p-value: <0.001).

Table 17: Study 20110142 - Time to First Clinical Fracture Through Primary Analysis Period (Full Analysis Set)

Clinical fracture	**Alendronate 70 mg QW/ Alendronate 70 mg QW (N=2047)**	**Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)**
Through primary analysis period		
Subjects with fractures - n (%)	266 (13.0)	198 (9.7)
Comparison vs. ALN/ALN		
Hazard ratio [a] (95% CI)		0.73 (0.61, 0.88)
p-value		< 0.001

Source: Table 10-2 in study 20110142 report.
ALN/ALN is Alendronate 70 mg QW/Alendronate 70 mg QW; CI = confidence interval; N = Number of subjects randomized; QM = every month; QW = weekly;
a The hazard ratio estimate is based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5) , and presence of severe vertebral fracture at baseline.

Efficacy Results – Secondary endpoints controlled for type I error

The secondary efficacy endpoints that were controlled for type I error are presented in the order of testing sequence followed by other endpoints that were not included in the testing sequence.

BMD endpoints

With multiplicity adjustment, at Month 12, romosozumab significantly increased mean BMD by 8.7%, 3.3%, and 3.2% compared with alendronate at the lumbar spine, total hip and femoral neck respectively (p< 0.001 for all 3 sites). At Month 24, romosozumab for 12 months followed by alendronate for 12 months, significantly increased BMD with treatment differences of 8.1%, 3.8%, and 3.8%, compared with alendronate alone at the lumbar spine, total hip, and femoral neck (p < 0.001 for all 3 sites). Romosozumab followed by alendronate maintained increases in BMD at the lumbar spine, total hip, and femoral neck at all 3 sites at Month 36.

Reference ID: 4416253

Table 18. Study 20110142 - Percent Change From Baseline in BMD at Lumbar Spine at Months 12, 24, and 36 (ANCOVA LOCF, Primary Efficacy Analysis Set for BMD)

Time Point	Statistic	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 1757)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 1750)
Month 12	% Change from baseline (SE)	5.0 (0.1)	13.7 (0.2)
	LS mean diff. (SE)		8.7 (0.2)
	95% CI		(8.3, 9.1)
	P-value		<0.001
Month 24	% Change from baseline (SE)	7.2(0.2)	15.3 (0.2)
	LS mean diff. (SE)		8.1 (0.3)
	95% CI		(7.6, 8.6)
	P-value		<0.001
Month 36[a]	% Change from baseline (SE)	7.8 (0.2)	15.2 (0.2)
	LS mean diff. (SE)		7.4 (0.3)
	95% CI		(6.8, 7.9)

Source: Table 10-5 in study 20110142 study report.
N=Number of subjects with values at baseline and at least one post-baseline visit at or before month 36
LOCF=last-observation-carried-forward
a BMD endpoint at Month 36 was not under multiplicity control
Based on ANCOVA model adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction. Missing values are imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the treatment period.

Table 19. Study 20110142 - Percent Change From Baseline in BMD at Total Hip at Months 12, 24, and 36 (ANCOVA LOCF, Primary Efficacy Analysis Set for BMD)

Time Point	Statistic	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 1757)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 1750)
Month 12	% Change from baseline (SE)	2.8 (0.1)	6.2 (0.1)
	LS mean diff. (SE)		3.3 (0.1)
	95% CI		3.0, 3.6
	P-value		<0.001
Month 24	% Change from baseline (SE)	3.5 (0.1)	7.2 (0.1)
	LS mean diff. (SE)		3.8 (0.2)
	95% CI		3.4, 4.1
	P-value		<0.001
Month 36[a]	% Change from baseline (SE)	3.5(0.1)	7.2 (0.1)
	LS mean diff. (SE)		3.7 (0.2)
	95% CI		3.3, 4.0

Source: Table 10-5 in study 20110142 study report.
N=Number of subjects with values at baseline and at least one post-baseline visit at or before month 36.
LOCF=last-observation-carried-forward
a BMD endpoint at Month 36 was not under multiplicity control.
Based on ANCOVA model adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction. Missing values are imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the treatment period.

Table 20. Study 20110142 - Percent Change From Baseline in BMD at Femoral Neck at Months 12, 24, and 36 (ANCOVA LOCF, Primary Efficacy Analysis Set for BMD)

Time Point	Statistic	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 1757)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 1750)
Month 12	% Change from baseline (SE)	1.7 (0.1)	4.9 (0.1)
	LS mean diff. (SE)		3.2 (0.1)
	95% CI		2.9, 3.5
	P-value		<0.001
Month 24	% Change from baseline (SE)	2.3 (0.1)	6.0 (0.2)
	LS mean diff. (SE)		3.8 (0.2)
	95% CI		3.4, 4.1
	P-value		<0.001
Month 36[a]	% Change from baseline (SE)	2.4(0.2)	6.0 (0.2)
	LS mean diff. (SE)		3.6 (0.2)
	95% CI		3.2, 4.0

Source: Table 10-5 in study 20110142 study report.
N=Number of subjects with values at baseline and at least one post-baseline visit at or before month 36.
LOCF=last-observation-carried-forward
a BMD endpoint at Month 36 was not under multiplicity control.
Based on ANCOVA model adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction. Missing values are imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the treatment period.
Source: Table 10-5 in study 20110142 study report.

The positive gains in BMD were consistent with what was shown in Study 337 study, demonstrating that romosozumab is effective across populations at high risk for fracture.

Nonvertebral Fracture through Primary Analysis Period

Through the primary analysis period, a total of 395 subjects experienced nonvertebral fractures, 217 subjects in the romosozumab then alendronate group and 178 subjects in the alendronate alone group. Romosozumab followed by alendronate significantly reduced the risk of nonvertebral fracture (hazard ratio=0.81, 1-sided P-value=0.019, which was below the alpha level of 0.0233).

Table 21. Study 20110142 - Time to First Nonvertebral Fracture through Primary Analysis Period (Full Analysis Set)

Nonvertebral Fractures	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)	Romosozumab 210 mg QM/ Alendronate 70 mg QW vs. Alendronate 70 mg QW/ Alendronate 70 mg QW
Through Primary Analysis Period			
Subjects with fractures – n (%)	217 (10.6)	178 (8.7)	
Hazard ratio [a] (95% CI)			0.81 (0.66, 0.99)
Nominal p-value (1-sided)[b]			0.019

[a] The hazard ratio estimate is based on a Cox proportional hazards model adjusting for age strata and presence of severe vertebral fracture at baseline.
b. Under the group sequential design, with an information fraction of 90% (395/440), the significance level at primary analysis (Lan-DeMets alpha spending function that approximates a Pocock boundary) was determined to be 0.0233 (1-sided).
Source: Table 10-3 in Study 20110142 report.

Efficacy Results – Secondary endpoints not controlled for type I error

- New vertebral fractures through Month 12

Through Month 12, romosozumab demonstrated a relative risk reduction for new vertebral fracture of 36% (95% CI: 11% - 54%) compared with alendronate.

Table 22: Study 20110142 - Incidence of New Vertebral Fracture Through Month 12 – Primary Analysis Set for Vertebral Fractures

Statistic	**Alendronate 70 mg QW/ Alendronate 70 mg QW (N=2047)**	**Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)**
Incidence, n/N1 (%)	85/1703 (5.0)	55/1696 (3.2)
Comparison vs. ALN/ALN		
Absolute risk reduction[a] (%) (95% CI)		1.84 (0.51, 3.17)
Relative risk reduction[b] (95% CI)		36% (11%, 54%)
Odds ratio[c] (95% CI)		0.63 (0.44, 0.89)

N1 = Number of subjects in the primary analysis set for vertebral fractures with non-missing verified stratification values
[a] Based on the Mantel-Haenszel method adjusted for verified age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline status
[b] Calculated from risk ratio as 100 x (1 – risk ratio)
[c] Based on logistic regression model adjusted for verified age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline;
Source: Table 14-4.1.1 in study 20110142 report.

- Clinical Fracture through Month 12 and Month 24

A reduction in the percentage of subjects with clinical fractures was observed at the end of the 12-month double-blind treatment period (romosozumab: 3.9%; alendronate: 5.4%; hazard ratio: 0.72). Through Month 24, clinical fractures were reported for 7.1% of subjects in the romosozumab/alendronate group and 9.6% of subjects in the alendronate/alendronate group (hazard ratio: 0.74).

Table 23. Study 20110142 - Subject Incidence of Clinical Fracture through Month 12 and Month 24 (Full Analysis Set)

Nonvertebral Fractures	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)	Romosozumab 210 mg QM/ Alendronate 70 mg QW vs. Alendronate 70 mg QW/ Alendronate 70 mg QW
Through Month 12			
Subjects with fractures – n (%)	110 (5.4)	79 (3.9)	
KM estimate[a] (95% CI) - %	5.6 (4.7, 6.8)	3.9 (3.1, 4.9)	1.8 (0.5, 3.1)
Hazard ratio[b] (95% CI)			0.72 (0.54, 0.96)
Through Month 24			
Subjects with fractures – n (%)	197 (9.6)	146 (7.1)	
KM estimate[a] (95% CI) - %	10.2 (8.9, 11.7)	7.4 (6.3, 8.7)	2.7 (0.8, 4.5)
Hazard ratio[b] (95% CI)			0.74 (0.59, 0.91)

KM=Kaplan-Meier
[a]Absolute risk difference is based on inverse-weighted method adjusting for age strata, baseline total hip BMD Tscore (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.
[b]The hazard ratio estimate is based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Table 14-4.2.1 in study 20110142 report.

- Nonvertebral Fracture through Month 12 and Month 24

A reduction in the percentage of subjects with nonvertebral fractures was observed at the end of the double-blind treatment period through Month 12 (romosozumab: 3.4%; alendronate: 4.6%; hazard ratio: 0.74). Through Month 24, nonvertebral fractures were reported for 6.3% of subjects in the romosozumab/alendronate group and 7.8% of subjects in the alendronate/alendronate group (hazard ratio: 0.81).

Reference ID: 4416253

Table 24. Study 20110142 - Subject Incidence of Nonvertebral Fracture through Month 12 and Month 24 (Full Analysis Set)

Nonvertebral Fractures	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)	Romosozumab 210 mg QM/ Alendronate 70 mg QW vs. Alendronate 70 mg QW/ Alendronate 70 mg QW
Through Month 12			
Subjects with fractures – n (%)	95 (4.6)	70 (3.4)	
KM estimate[a] (95% CI) - %	4.9 (4.0, 6.0)	3.6 (2.9, 4.6)	1.4 (0.1, 2.6)
Hazard ratio[b] (95% CI)			0.74 (0.54, 1.01)
Through Month 24			
Subjects with fractures – n (%)	159 (7.8)	129 (6.3)	
KM estimate[a] (95% CI) - %	8.4 (7.2, 9.8)	6.8 (5.7, 8.0)	1.6 (-0.1, 3.3)
Hazard ratio[b] (95% CI)			0.81 (0.64, 1.02)

KM=Kaplan-Meier
[a]Absolute risk difference is based on inverse-weighted method adjusting for age strata, baseline total hip BMD Tscore (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.
[b]The hazard ratio estimate is based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Table 14-4.3.1 in study 20110142 report.

- Hip Fracture through Month 12, Month 24 and Primary Analysis Period

Through Month 12, hip fractures were reported for 0.7% of the subjects in the romosozumab group and 1.1% of subjects in the alendronate group (hazard ratio: 0.64). Through Month 24, hip fractures were reported for 1.5% of subjects in the romosozumab/alendronate group and 2.1% of subjects in the alendronate/alendronate group (hazard ratio: 0.72). Through the primary analysis period, hip fractures were reported for 2.0% of subjects in the romosozumab/alendronate group and 3.2% of subjects in the alendronate/alendronate group (hazard ratio: 0.62).

Table 25. Study 20110142 - Subject Incidence of Hip Fracture through Month 12, Month 24 and Primary Analysis (Full Analysis Set)

Hip Fractures	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2047)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046)	Romosozumab 210 mg QM/ Alendronate 70 mg QW vs. Alendronate 70 mg QW/ Alendronate 70 mg QW
Through Month 12			
Subjects with fractures – n (%)	22 (1.1)	14 (0.7)	
KM estimate[a] (95% CI) - % at month 12	1.1 (0.7, 1.7)	0.7 (0.4,1.2)	0.3 (-0.3, 0.9)
Hazard ratio[b] (95% CI)			0.64 (0.33, 1.26)
Through Month 24			
Subjects with fractures – n (%)	43 (2.1)	31 (1.5)	
KM estimate[a] (95% CI) - % at month 24	2.3 (1.7, 3.1)	1.6 (1.1, 2.3)	0.6 (-0.2, 1.4)
Hazard ratio[b] (95% CI)			0.72 (0.46, 1.15)
Through Primary Analysis Period			
Subjects with fractures – n (%)	66 (3.2)	41 (2.0)	
Hazard ratio[b] (95% CI)			0.62 (0.42, 0.92)

KM=Kaplan-Meier
[a]Absolute risk difference is based on inverse-weighted method adjusting for age strata, baseline total hip BMD Tscore (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline.
[b]The hazard ratio estimate is based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Table 14-4.4.7 in study 20110142 report.

Efficacy Results – Subgroup analyses

Romosozumab demonstrated a consistent treatment effect across the subgroups defined in section 8.1.1, as evident by estimates that favored romosozumab/alendronate over alendronate/alendronate in most of the subgroups of baseline characteristics examined with respect to new vertebral fractures, clinical fractures and non-vertebral fractures. In a few subgroups with small sample sizes, very minor numerical treatment effect estimates favoring alendronate/alendronate over romosozumab/alendronate were observed instead, but the confidence intervals for the treatment effect differences were wide. In summary, there was largely consistency of romosozumab's treatment effect on fracture risk reduction across subgroups (see forest plots presented in
Figure to **Figure** in Appendix 14.4).

At Month 12 and Month 24, romosozumab/alendronate appears to have a greater BMD increase at the lumbar spine, total hip and femoral neck compared to alendronate/alendronate in all subgroups.

Effect of Antiromosozumab Antibodies on Efficacy

Reference ID: 4416253

Among subjects who received romosozumab, the overall incidence of antiromosozumab antibodies at any study visit through Month 18 was 16% for binding antibodies and 0.6% for neutralizing antibodies. The antibody status through Month 18 was selected for evaluation of efficacy and safety by antibody status, as the 6-month follow-up period after completion of the 12-month romosozumab treatment phase allowed for washout of romosozumab from serum and enabled the most accurate neutralizing antibody detection.

The presence of antiromosozumab binding and neutralizing antibodies did not affect the efficacy of romosozumab as assessed by BMD. For subjects who received romosozumab, the percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Month 12 and Month 24 was compared among subjects who developed binding or neutralizing antiromosozumab antibodies through Month 18 vs. those who were negative for antiromosozumab antibodies through Month 18. These results are summarized in Table 24.

Table 26. Study 20110142 - Bone Mineral Density Percent Change From Baseline by Antiromosozumab Antibody Status Through Month 18 (Romosozumab Arm in Primary Analysis Set for BMD: Descriptive Statistics, Observed Data) (20110142 Primary Analysis Period)

	Antiromosozumab Antibody Status through Month 18		
Percent change from baseline	Antibody Negative (N=1450)	Binding Antibody Positive (N=289)	Neutralizing Antibody Positive (N=11)
Lumbar Spine			
Month 12	14	14	14
Month 24	15	15	14
Total Hip			
Month 12	6	6	6
Month 24	7	8	7
Femoral neck			
Month 12	5	5	8
Month 24	6	7	8

At Month 12, the mean percent changes in BMD at the lumbar spine were 14% (negative antibody status), 14% (positive binding antiromosozumab antibody), and 14% (positive neutralizing antiromosozumab antibody). Corresponding values at Month 24 were 15%, 15%, and 14%, respectively.

At Month 12, the mean percent changes in BMD at the total hip were 6% (negative antibody status), 6% (positive binding antiromosozumab antibody), and 6% (positive neutralizing antiromosozumab antibody). Corresponding values at Month 24 were 7%, 8%, and 7%, respectively.

Reference ID: 4416253

At Month 12, the mean percent changes in BMD at the femoral neck were 5% (negative antibody status), 5% (positive binding antiromosozumab antibody), and 8% (positive neutralizing antiromosozumab antibody). Corresponding values at Month 24 were 6%, 7%, and 8%, respectively.

Imaging and Pharmacokinetics/Bone Turnover Marker/Biomarker Substudy

A total of 298 randomized subjects enrolled in the Imaging and PK/BTM/Biomarker Substudy, 157 subjects in the romosozumab/alendronate group and 141 subjects in the alendronate/alendronate group. Subjects from all geographic regions participated in the substudy. A total of 136 (87%) subjects in the romosozumab/alendronate group and 125 (89%) subjects in the alendronate/alendronate group continued investigational product through the end of the 12-month double-blind treatment period. Through the primary analysis period, 122 (78%) subjects in the romosozumab/alendronate group and 109 (77%) subjects in the alendronate/alendronate group continued investigational product; 130 (83%) subjects in the romosozumab/alendronate group and 123 (87%) subjects in the alendronate/alendronate group completed the primary analysis period.

Baseline values for BTMs were similar between the romosozumab and alendronate groups. The bone formation marker P1NP showed a rapid increase in the romosozumab group that peaked at Month 1 (time point of first assessment), returning to baseline by Month 6. As expected, during double-blind treatment, alendronate reduced P1NP through Month 12. The median percent change from baseline in P1NP was greater in the romosozumab group than in the alendronate group at all time points evaluated during double-blind treatment, and the difference between the romosozumab and alendronate groups was nominally statistically significant at each time point (nominal $p < 0.001$ at months 1, 3, 6, 9, and 12).

After Month 12 (i.e., when all subjects received open-label alendronate), the median P1NP value in the romosozumab/alendronate group decreased below baseline at Month 15 and remained consistently reduced through Month 36. The median P1NP values in the alendronate/alendronate group at Months 15, 18, 24, and 36 did not vary appreciably from the Month 12 value and were similar to the median P1NP values in the romosozumab/alendronate group (i.e., no significant differences between the romosozumab/alendronate group and alendronate/alendronate group after Month 12).

Similar to P1NP, serum concentrations of the other bone formation markers, BSAP and OC, peaked at Month 1 in romosozumab-treated subjects and declined through Month 12 (last assessment time point for these BTMs), returning to baseline by Month 9.

The bone resorption marker sCTX showed a decrease in the romosozumab group at Month 1 (time point of first assessment) and remained reduced but above the levels in the alendronate group through Month 12. After Month 12 (i.e., when all subjects received open-label alendronate), the median sCTX value in the romosozumab/alendronate group decreased at Months 15, 18, and 24 to levels that were similar to those in the alendronate/alendronate

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group. At Month 36, the median sCTX value in the romosozumab/alendronate group increased but remained below baseline (nominal p = 0.042 vs. alendronate/alendronate group).

In summary, the results of the BTM measures support the dual effect on bone and are consistent with those observed in the romosozumab group in the placebo-controlled studies.

Patient-reported and Clinician-reported Outcomes

PRO/ClinROs were evaluated as exploratory endpoints in Study 142 to describe subjects' experience of pain and its impact on subjects' activities and health-related quality of life at 6-month intervals for the overall 24-month study period and at 1-month intervals for the first 3 months post fracture using the OPAQ SV, EQ-5D-5L, LAD survey questionnaires, and 1 item extracted from the BPI assessing the worst pain experienced in the past 24 hours [BPI worst pain]).

No consistent or clinically meaningful differences in PRO/ClinRO endpoints (OPAQ SV, EQ-5D-5L, LAD, or BPI worst pain score) were identified between the romosozumab and alendronate groups during the 12-month double-blind period or between the romosozumab/alendronate and alendronate/alendronate groups during the primary analysis period. A summary of results for these endpoints is provided in Table 11-1 of the CSR.

Post fracture data were obtained at months 1, 2, and 3 for subjects who had a clinical fracture on study using the prefracture baseline for comparison. No consistent or clinically meaningful differences in PRO/ClinRO endpoints (OPAQ SV, EQ-5D-5L, LAD, or BPI worst pain score) were identified between the romosozumab and alendronate groups 1, 2, or 3 months postfracture. A summary of results for these endpoints is provided in Table 11-2 of the CSR.

8.1.3. Study 20110174

This section summarizes the key design elements of Study 174. Although the clinical study report was submitted with this BLA, this review does not include a review of efficacy and general safety results of Study 174, as the study population is not one for which an indication is currently sought with this BLA. Cardiovascular safety data from Study 174, however, are included in the review of this BLA (and are discussed alongside those of Study 337 and Study 142 in Section 8.2.5, *Analysis of Cardiovascular Safety*).

Study 174 was a 15-month randomized, double-blind, placebo-controlled study evaluating the effect of 12 months of romosozumab treatment on lumbar spine BMD in men with osteoporosis. Subjects were randomized 2:1 to receive either 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.

The population included men 55 to 90 years old with osteoporosis, defined as a T-score of ≤ -2.5 at the lumbar spine, total hip or femoral neck, or a T-score of ≤ -1.5 with a history of a

Reference ID: 4416253

fragility nonvertebral or vertebral fracture. Subjects were excluded from the study if T-score was <-3.5 at the hip or 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 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.

8.1.4. Study 20070337: Design

This section summarizes the key design elements of Study 337, which was previously reviewed during the first review cycle.

Study 337 was a 24-month, multicenter, double-blind, randomized, placebo-controlled study in postmenopausal women with osteoporosis age 55 to 90 years 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. 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 washout periods.

Subjects were randomized 1:1 to receive either romosozumab 210 mg or matching placebo by subcutaneous (SC) injection every month for the first 12 months of the study. After the 12-month double-blind treatment period, all subjects received denosumab 60 mg SC every 6 months in an open-label fashion while still remaining blinded to their initial treatment assignment. 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.

The coprimary endpoints of the study were incidence of new vertebral fractures at 12 and 24 months. Secondary endpoints included clinical fracture and nonvertebral fracture. To control the overall type I error, the primary and secondary efficacy endpoints were tested sequentially at the 2-sided 5% significance level, as follows:

1. Incidence of new vertebral fracture through Months 12 and 24
2. Incidence of clinical fracture through Month 12

Reference ID: 4416253

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)

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.

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

8.1.5. Study 20070337: Efficacy Results

Study population: The study enrolled 7180 subjects. The mean age of the enrolled population was 71 years. Approximately 57% of subjects were white. The geographic distribution of enrolled subjects was as follows: Western Europe and Australia/New Zealand (14%), Central and Eastern Europe (29%), Central/Latin America (43%), North America (3%), and Asia Pacific (12%). Overall, 132 subjects (1.8%) from the United States participated in the study.

Fracture: As outlined in the table below, 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 was 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 reduction in clinical fractures at Month 12, the reduction in nonvertebral fractures was not significant at Month 12.

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Table 27: 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 was not included in the hierarchy of secondary endpoints. It is an important metric for osteoporosis therapies and therefore, included in this efficacy discussion. As outlined in the table below, romosozumab significantly increased BMD at all sites. At Month 12, compared with placebo, romosozumab increased BMD 12.7% at the lumbar spine, 5.8% at 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.

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Table 28: 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			

Subgroup analyses demonstrated consistent results for the coprimary endpoints in all subgroups of baseline characteristics examined, including age, race, geographic region, a range of baseline BMD T-scores, and subjects with a history of prior vertebral, nonvertebral, or fragility fracture. Similar estimates of treatment effect were obtained in sensitivity analyses based on stratification variables, the full analysis set, and per protocol analysis set. After controlling for baseline covariates individually and simultaneously in the primary analysis model, romosozumab (Month 12) and romosozumab/denosumab (Month 24) continued to demonstrate a treatment effect compared with placebo (Month 12) and placebo/denosumab (Month 24) for the coprimary endpoint at Month 12 and Month 24.

8.1.6. Study 20060326

This section summarizes the key features of supportive Study 326, the dose-finding study reviewed with the original BLA.

Study 326 was a multiple dose study in 419 postmenopausal women with low BMD that primarily evaluated the effect of romosozumab versus placebo on lumbar spine BMD. During the 24-month romosozumab treatment phase of the study, subjects were randomized to 1 of 5 double-blind dosing regimens of romosozumab (70 mg monthly, 140 mg every 3 months, 210 mg every 3 months or 210 mg monthly), placebo, open-label alendronate or teriparatide for the first 12 months. During the second 12 months of the treatment phase of the study, the romosozumab and placebo groups continued their assigned treatment. The primary endpoint was percent change from baseline in lumbar spine BMD at Month 12.

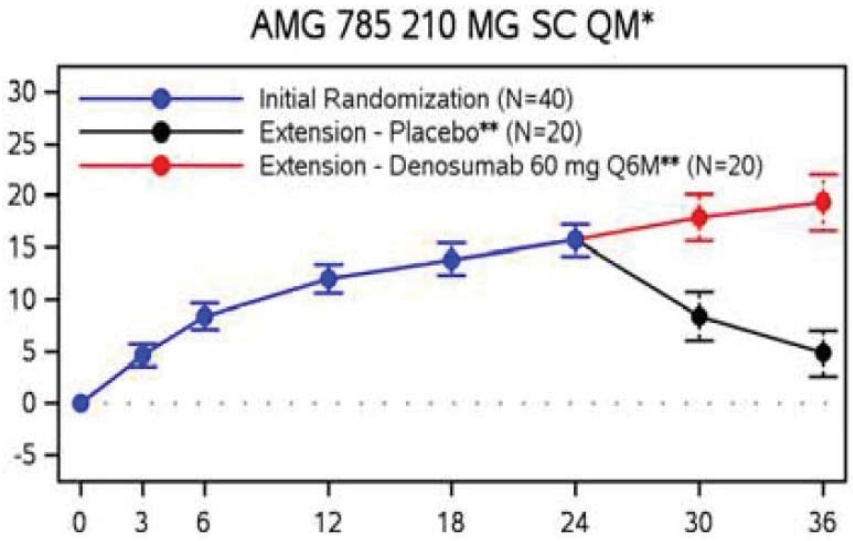
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Treatment with romosozumab demonstrated a dose-related increase in BMD with a waning of BMD increases after the first year of therapy. At Month 12, the mean percent chance in lumbar spine BMD in the romosozumab groups ranged from 5% for 70 mg monthly to 11% for 210 mg monthly, compared with -0.1% in the placebo group. The 210 mg monthly dosage regimen was chosen for further development in the Phase 3 studies.

All subjects in the placebo and romosozumab dose groups continued on their blinded therapy for the second year of the study. BMD in the romosozumab arms did continue to increase in the second year of therapy although the increases were not as robust as those achieved in the first year of therapy. Figure 6 below depicts the BMD response for the 210 mg dose group and shows waning BMD increases after 12 months of therapy. Figure 6 also shows the BMD response once romosozumab is discontinued and patients are transitioned to no therapy (placebo). BMD approaches baseline within one year off therapy.

Based on the results of this trial, the applicant chose to limit the duration of exposure to 12 months of romosozumab the fracture trials. These data therefore support limiting the duration of romosozumab therapy to 12 months.

Figure 5 Lumbar Spine BMD Percent Change from Baseline (Study 326 Months 0-36)



*Source: modified from Figure 10-11 of Study 326 Clinical Study Report

8.1.7. Integrated Assessment of Efficacy

The evidence of effectiveness of romosozumab for the treatment of PMO derives from Study 142, the phase 3 study covered in this review, as well as phase 3 Study 337 and four additional supportive studies (326, 291, 156, and 289), which were all reviewed with the original BLA.

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This section focuses on the efficacy results from the primary analyses of Study 142 and Study 337, which together comprise the majority of the efficacy data and are the only studies with fracture endpoints. Efficacy data from these studies are presented side by side and are not integrated with each other due to the differences in the control group (placebo in 337 versus active control in 142) and patient populations (i.e., higher fracture risk in Study 142).

Fracture Efficacy Results

New Vertebral Fracture

Morphometric vertebral fracture was a primary endpoint for both Study 337 (at 12 months and 24 months) and Study 142 (at 24 months).

In the placebo-controlled Study 337, the subject incidence of morphometric vertebral fracture at Month 12 was 1.8% in the placebo group and 0.5% in the romosozumab group, yielding an absolute risk reduction of 1.3% (95% CI: 0.8, 1.8) and a relative risk reduction of 73% (95% CI: 53, 84). At Month 24 during treatment with denosumab, the subject incidence of morphometric vertebral fracture was 2.5% in the placebo/denosumab group and 0.6% in the romosozumab/denosumab group with an absolute risk reduction of 1.9% (95% CI: 1.3, 2.5) and a relative risk reduction of 75% (95% CI: 60, 84).

In the active-controlled Study 142, the subject incidence of morphometric vertebral fracture at Month 24 was 8.0% in the alendronate alone group compared to 4.1% in the romosozumab followed by 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). The higher fracture incidence in Study 142 was expected given the high fracture risk of the enrolled population.

Clinical Fracture

Clinical fracture incidence at Month 12 was the first secondary endpoint in the testing sequence in Study 337 and time to first clinical fracture through the primary analysis period was a co-primary endpoint in Study 142. Clinical fracture is a composite endpoint including symptomatic vertebral fractures and nonvertebral fractures.

In Study 337, romosozumab significantly reduced the risk of clinical fracture through Month 12, with an absolute risk reduction of 1.2% (95% CI: 0.4, 1.9) and a relative risk reduction of 36% (95% CI: 11%, 54%; $p = 0.008$) compared with placebo. However, the reduction in clinical fractures at 24 months did not reach statistical significance when adjusted for multiplicity.

In Study 142, a significant reduction in clinical fracture risk for subjects who received 12 months of romosozumab followed by alendronate was seen when compared with subjects who received alendronate alone for the duration of the primary analysis period. The hazard ratio for romosozumab followed by alendronate was 0.73 (95% CI: 0.61, 0.88; $p < 0.001$) compared to

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alendronate alone, based on 464 subjects with clinical fractures with a median follow-up of 33 months. The clinical fracture risk reduction at Month 12 did not meet statistical significance when adjusted for multiplicity.

Nonvertebral Fracture

Nonvertebral fracture was a secondary endpoint included in the testing hierarchy for both Study 337 and Study 142.

In Study 337, nonvertebral fracture risk reduction with romosozumab was not statistically significant. The applicant attributes this finding to a lower than expected nonvertebral fracture incidence in the placebo group in Central/Latin America in the first 12 months of 1.2% (expected rate 3.5%) compared to a 1.2% fracture incidence in the romosozumab group. Central/Latin America was the highest enrolling region, accounting for 43% of the randomized study population. Overall baseline characteristics were similar across all of the geographic regions. However, the applicant notes that a lower prevalence of historical nonvertebral fracture and a lower FRAX 10-year probability of major osteoporotic and hip fracture was observed for subjects in the Central/Latin America region relative to most other regions.

In Study 142, nonvertebral fracture assessed through the primary analysis period was a secondary endpoint included in the sequential testing procedure. Through the primary analysis period, there was an estimated hazard ratio of 0.81 (95% CI: 0.66, 0.99; $p < 0.019$) for romosozumab followed by alendronate compared to alendronate alone, based on 395 subjects with nonvertebral fractures and a median follow-up of 33 months. The multiplicity adjusted 1-sided p-value (adjusting for the fixed sequence and the group sequential testing) was significant ($p = 0.019$) for this endpoint, indicating a significant benefit with romosozumab followed by alendronate compared with alendronate alone.

Hip Fracture

Hip fracture outcomes were not included in the hierarchal testing procedures for Studies 337 and 142. Additionally, neither study was designed to demonstrate a difference in hip fractures. In Study 337 a statistically significant reduction in hip fractures compared to placebo was not demonstrated although a trend in reduction at both 12 and 24 months was seen.

In Study 142, through the primary analysis period, romosozumab followed by alendronate showed a reduced risk of hip fracture compared with alendronate alone, with a hazard ratio of 0.62 (95% CI: 0.42, 0.92), based on 107 subjects with hip fractures. However, this endpoint was not part of the planned statistical testing sequence and was not adjusted for multiplicity.

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Summary of Fracture Endpoint Results with Follow-on Therapy

Both Study 337 and Study 142 demonstrated that romosozumab provides ongoing vertebral and nonvertebral fracture risk reduction with follow-on antiresorptive therapy after the end of the 12-month treatment period.

BMD Results

Romosozumab demonstrated significantly higher BMD increases at the lumbar spine, total hip and femoral neck, compared to both placebo and alendronate.

BMD percent change from baseline at Month 12 in Study 337 and Study 142 is summarized in Table 298 below.

Table 29. Bone Mineral Density Percent Change From Baseline at Month 12 in the Pivotal Fracture Studies (ANCOVA Model) (Primary Efficacy Analysis Set for BMD, LOCF)

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

LOCF=last-observation-carried-forward
*Source: Table 15 of SCE

In both studies, subgroup analyses showed consistent percent BMD increases from baseline for romosozumab compared to control at the lumbar spine and total hip when analyzed by age,

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geographic region, and baseline BMD T-score. Of note, the percent change in BMD at the lumbar spine and total hip was similar between North America and all other regions.

Bone Turnover Markers Results

BTMs were assessed in Study 337, Study 142 and the supportive placebo-controlled studies. BTM results showed a similar pattern of increase in bone formation markers (P1NP, BSAP, and osteocalcin) and decrease in the bone resorption marker, sCTX. Bone formation markers peaked and returned to baseline by approximately month 6 to 9, while the bone resorption marker decreased within a month after the first dose and generally remained below levels seen with placebo at Month 12 (and slightly above levels seen with alendronate in Study 142). Across the studies, the maximum P1NP increase was observed at the Month 1 time point in all romosozumab groups and the maximum decrease in sCTX occurred at Month 1.

Although the BTM responses were reduced over subsequent doses, there remained a response after each dose, suggesting continued smaller effects of romosozumab after each dose over 12 months.

Additional Efficacy Considerations: Considerations on Benefit in the US Postmarket Setting

Only a very small number of subjects in Study 337 (132/7180, 1.8%) and Study 142 (57/4093, 1.4%) were enrolled in the United States. Analyses conducted in both studies demonstrated that there were no treatment-by-region interactions for the co-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 results can be considered applicable to the U.S. population and U.S. medical practice.

8.2. Review of Safety

8.2.1. Safety Review Approach

This section includes a comprehensive review of all safety results from Study 142. In addition, this section includes an evaluation of cardiovascular safety results from Studies 337 and 174 alongside those of Study 142.

Since the safety results of Study 337 were reviewed in detail with the first review cycle, this section does not include detailed general safety results from Study 337. Rather, this section references key safety findings from Study 337 alongside the safety results of Study 142 (where references or comparisons are necessary).

Additionally, since the population of Study 174 is one for which an indication is not currently sought (i.e., men with osteoporosis), the general safety results of this study are not included in this section.

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8.2.2. Review of the Safety Database

Overall Exposure

This BLA resubmission provides additional safety data from 4054 postmenopausal women with osteoporosis and a history of fracture in Study 142 as well as cardiovascular safety data from 244 men with osteoporosis in Study 174. The safety review during the first review cycle of this original BLA submission included data from 8274 postmenopausal women in the phase 2 and phase 3 studies, including 7157 women with osteoporosis in the placebo-controlled fracture study (Study 337), 218 subjects with osteoporosis who were transitioning from bisphosphonate therapy (Study 289), 353 subjects with low bone mass in the dose-finding study (Study 326), 252 Japanese subjects with osteoporosis in a dedicated study in Japan (Study 291), and 294 subjects with osteoporosis enrolled in a non-inferiority BMD study (Study 156).

With the additional data in this submission, the romosozumab safety database includes approximately 14000 subjects in 18 romosozumab clinical studies, of which 7518 subjects received at least 1 dose of romosozumab with 6180 women receiving romosozumab for at least 6 months and 5712 women receiving romosozumab for at least 12 months.

In addition, cardiovascular data from 244 men with osteoporosis who received romosozumab (n = 163) or placebo (n = 81) for 12 months (Study 174) are included in Section 8.2.5 (Analysis of Cardiovascular Safety) to provide an evaluation of cardiovascular safety across the pivotal phase 3 studies.

Relevant characteristics of the safety population

The study population in Study 142 was sufficiently diverse to represent the expected target population. Refer to the discussion in the demographic section of Section 8.1.2.

Adequacy of the safety database

The safety database for Study 142 was adequate in terms of size, duration, subject demographics, and disease characteristics. Refer to the demographics and baseline characteristics sections of Section 8.1.2.

Because of the large numbers of patients needed to show fracture risk reduction, the safety database for romosozumab also greatly exceeds ICH E1 guidelines, which recommend a minimum of 100 patients exposed for a minimum of one-year from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use (ICH Guideline: The Extent of Population Exposure to Assess Clinical Safety for Drugs

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Intended for Long-Term Treatment of Non-life-threatening Conditions, 1994).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Submission quality is adequate regarding overall organization, ease of finding information, proper location of information and data. There were no data quality or integrity issues identified.

Categorization of Adverse Events

The applicant's approach to the definition and categorization of adverse events was appropriate. Adverse event analyses were categorized using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

Routine Clinical Tests

The methodology and frequency of routine clinical testing (as described in Section 8.1.1) was adequate to monitor for known and potential safety risks of romosozumab in the study population.

8.2.4. Safety Results: Study 20110142

Results included in this section are based on the primary analyses of Studies 142 and 337, which are the analyses presented in the Clinical Study Reports (CSRs) of these studies. Of note, the Integrated Summary of Safety (ISS) includes results from the final analyses of both studies (which occurred after database lock). This led to small differences between the data in the study 337 study report from the first review cycle and the study 337 data submitted with integrated summary of safety in this resubmission. As requested in an IR during the review cycle, the applicant provided a detailed listing of every change that occurred when safety data were updated in the final analyses.

Exposure: In Study 142, the safety analyses included 2040 subjects in the romosozumab/alendronate group and 2014 subjects in the alendronate/alendronate group who received at least 1 dose of active investigational product. Of the 2046 subjects randomized to romosozumab in Study 142, 8 subjects did not receive investigational product during the 12-month double blind period and were therefore not included in the safety analysis group, and 2 subjects were added to the romosozumab safety analysis set group (subjects who were randomized to alendronate but mistakenly received active doses of romosozumab). Of the 2047 subjects randomized to alendronate in Study 142, 33 did not qualify for the safety analysis set. Seven subjects did not receive the subcutaneous placebo injection and oral alendronate was not dispensed, while 3 subjects received subcutaneous placebo but were not dispensed oral alendronate. The 2 subjects who mistakenly received at least one active dose of romosozumab

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were moved to the romosozumab treatment group for safety outcomes. The remaining 21 subjects who did not qualify for inclusion in the safety analysis set received at least one dose of subcutaneous placebo given in the clinic, however, boxes for the dispensed drug were never returned, and therefore reconciliation was unable to confirm exposure.

During the 12-month double-blind period, the median number of double-blind SC injections of romosozumab or matching placebo received was 12 (range: 1 to 12) in both groups. In the romosozumab group, 75% of subjects received 12 doses of SC romosozumab and, in the alendronate group, 75% received 12 SC injections of matching placebo. In the romosozumab treatment group, the median cumulative romosozumab exposure was 2520 mg (range: 70 mg to 2520 mg).

All Adverse Events

A summary of all adverse events is provided in Table 29.

Table 30 Summary of Subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set – 20110142 Primary Analysis)

	Double-blind Period		Primary Analysis Period	
	ALN 70 mg QW (N = 2014) n (%)	**Romo 210 mg QM (N = 2040) n (%)**	**ALN 70 mg QW/ ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM/ ALN 70 mg QW (N = 2040) n (%)**
All treatment-emergent adverse events	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Fatal adverse events	21 (1.0)	30 (1.5)	90 (4.5)	90 (4.4)
Serious adverse events	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Leading to discontinuation from study	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)
Leading to discontinuation of investigational product	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
ALN=alendronate; Romo=romosozumab *Source: modified from Table 12-2 of CSR				

Deaths

The incidence of fatal adverse events by system/organ/class (SOC) is provided in Table 29.

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During the 12-month double-blind treatment period, fatal adverse events occurred in 30 (1.5%) subjects in the romosozumab group and 21 (1.0%) subjects in the alendronate group. Adverse events (preferred terms) resulting in death, which occurred in 2 or more subjects in the romosozumab or alendronate groups, respectively, were acute myocardial infarction (3 subjects; 0 subjects), cardiac failure (2 subjects; 1 subject), urosepsis (2 subjects; 0 subjects), pneumonia (1 subject; 3 subjects), cerebrovascular accident (1 subject; 2 subjects), death (1 subject; 2 subjects), and sudden death (1 subject; 2 subjects).

During the primary analysis period, there was a cumulative total of 90 (4.4%) deaths in the romosozumab/alendronate group and 90 (4.5%) deaths in the alendronate/alendronate group. Adverse events (preferred terms) resulting in death, which occurred in ≥ 4 (0.2%) subjects in the romosozumab/alendronate or alendronate/alendronate treatment groups, respectively, were acute myocardial infarction (5 subjects; 4 subjects), cardiac failure (3 subjects; 4 subjects), cardiac failure congestive (2 subjects; 4 subjects), pneumonia (7 subjects; 8 subjects), cerebrovascular accident (4 subjects; 3 subjects), death (13 subjects; 17 subjects), and sudden death (4 subjects; 3 subjects).

Regarding the fatal adverse events that were termed “death,” review of the subject narratives revealed that one death was likely due to pulmonary sepsis (in the alendronate group), and the remaining deaths all had undetermined causes. Importantly, the incidence of death with an undetermined cause was similar in both treatment groups during both study periods (with a slightly higher incidence in the alendronate group).

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Table 31. Subject Incidence of Treatment-emergent Fatal Adverse Events by System Organ Class (Safety Analysis Set - 20110142 Primary Analysis)

	Double-blind Period		Primary Analysis Period	
SOC	**ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM (N = 2040) n (%)**	**ALN 70 mg QW/ ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM/ ALN 70 mg QW (N = 2040) n (%)**
No. of subjects reporting fatal TEAEs	21 (1.0)	30 (1.5)	90 (4.5)	90 (4.4)
Cardiac disorders	3 (0.1)	9 (0.4)	24 (1.2)	20 (1.0)
Infections and infestations	5 (0.2)	5 (0.2)	13 (0.6)	15 (0.7)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (0.1)	4 (0.2)	7 (0.3)	10 (0.5)
Nervous system disorders	2 (<0.1)	3 (0.1)	5 (0.2)	11 (0.2)
Vascular disorders	0	3 (0.1)	0	4 (0.2)
General disorders and administration site conditions	5 (0.2)	2 (<0.1)	23 (1.1)	19 (0.9)
Injury, poisoning and procedural complications	0	2 (<0.1)	3 (0.1)	3 (0.1)
Respiratory, thoracic and mediastinal disorders	2 (<0.1)	1 (<0.1)	9 (0.4)	6 (0.3)
Psychiatric disorders	0	1 (<0.1)	0	1 (<0.1)
Hepatobiliary disorders	1 (<0.1)	0	2 (<0.1)	0
Gastrointestinal disorders	0	0	2 (<0.1)	1 (<0.1)
Renal and urinary disorders	0	0	2 (<0.1)	0
Surgical and medical procedures	0	0	0	1 (<0.1)
ALN=alendronate; Romo=romosozumab *Source: modified from Table 12-6 of CSR				

In summary, the incidence of fatal adverse events (overall and by systems organ class) was similar between the two treatment groups in Study 142, with the exception of deaths due to cardiac disorders in the 12-month double-blind period, which occurred in 3 alendronate-treated subjects and in 9 romosozumab-treated subjects. Cardiac disorders are discussed further in

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Section 8.2.5.

Fatal adverse events were slightly more frequent in Study 142 (1.5% romosozumab; 1.1% alendronate) than in Study 337 (0.8% romosozumab; 0.7% placebo), likely a result of the older population enrolled in Study 142.

Of note, an imbalance in events of fatal malignant lung neoplasm was observed in Study 337 (4 subjects in the romosozumab group and 0 subjects in the placebo group). All subjects who had fatal malignant lung neoplasm events in Study 337 were current or former smokers, and all had a short time to diagnosis. In addition, the overall incidence of fatal and nonfatal lung neoplasm events was balanced between treatment groups. No imbalance in such events was observed in Study 142. Therefore, based on the totality of the data, there is no convincing safety concern for lung neoplasms. Malignant tumors are discussed further in the "Adverse Events of Interest" section below.

Serious Adverse Events

The subject incidence rate of serious adverse events was similar between treatment groups in the double-blind period and the primary analysis period. Serious adverse events reported for ≥ 0.5% of subjects in any treatment group are summarized in Table 31.

12-Month Double-blind Period

During the 12-month double-blind period, serious adverse events were reported for 262 (13%) subjects who received romosozumab and 278 (14%) subjects who received alendronate. The most frequently reported serious adverse events by preferred term (> 0.5% of subjects in either treatment group) were pneumonia (romosozumab: 0.8%; alendronate: 0.8%), femur fracture (0.5%; 0.6%), radius fracture (0.4%, 0.6%), chronic obstructive pulmonary disease (0.2%, 0.5%), and femoral neck fracture (0.2%, 0.6%).

Primary Analysis Period

During the primary analysis period, serious adverse events were reported for 586 (28%) subjects in the romosozumab/alendronate group and 605 (30%) subjects in the alendronate/alendronate group. The most frequently reported events by preferred term (> 1.0% of subjects) in the romosozumab/alendronate group were pneumonia (2%; alendronate/alendronate: 2%), femur fracture (2%; alendronate/alendronate: 2%), and chronic obstructive pulmonary disease (1%; alendronate/alendronate: 1%).

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Table 32. Subject Incidence of Treatment-emergent Serious Adverse Events by SOC and Preferred Term (≥ 0.5% Subject Incidence in any Treatment Group) (Safety Analysis Set) (20110142 Primary Analysis)

	Double-blind Period		Primary Analysis Period	
SOC Preferred Term	**ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM (N = 2040) n (%)**	**ALN 70 mg QW/ ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM/ ALN 70 mg QW (N = 2040) n (%)**
Number of subjects reporting serious TEAEs	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Infections and infestations	48 (2.4)	47 (2.3)	114 (5.7)	130 (6.4)
Pneumonia	17 (0.8)	16 (0.8)	42 (2.1)	47 (2.3)
Urinary tract infection	8 (0.4)	8 (0.4)	20 (1.0)	19 (0.9)
Bronchitis	3 (0.1)	1 (<0.1)	4 (0.2)	11 (0.5)
Injury, poisoning and procedural complications	6 (3.0)	44 (2.2)	164 (8.1)	116 (5.7)
Femur fracture	12 (0.6)	11 (0.5)	47 (2.3)	38 (1.9)
Radius fracture	12 (0.6)	8 (0.4)	20 (1.0)	12 (0.6)
Femoral neck fracture	12 (0.6)	5 (0.2)	29 (1.4)	12 (0.6)
Humerus fracture	7 (0.3)	3 (0.1)	15 (0.7)	6 (0.3)
Ulna fracture	6 (0.3)	3 (0.1)	11 (0.5)	3 (0.1)
Fall	4 (0.2)	2 (<0.1)	11 (0.5)	11 (0.5)
Cardiac disorders	34 (1.7)	40 (2.0)	103 (5.1)	96 (4.7)
Acute myocardial infarction	2 (<0.1)	8 (0.4)	12 (0.6)	15 (0.7)
Cardiac failure	5 (0.2)	5 (0.2)	23 (1.1)	15 (0.7)
Atrial fibrillation	4 (0.2)	3 (0.1)	17 (0.8)	11 (0.5)
Cardiac failure congestive	5 (0.2)	2 (<0.1)	11 (0.5)	8 (0.4)
Nervous System disorders	34 (1.7)	37 (1.8)	80 (4.0)	103 (5.0)
Cerebrovascular accident	7 (0.3)	6 (0.3)	15 (0.7)	19 (0.9)
Transient ischemic attack	2 (<0.1)	6 (0.3)	5 (0.2)	11 (0.5)
Syncope	4 (0.2)	2 (<0.1)	10 (0.5)	5 (0.2)
Ischemic stroke	3 (0.1)	2 (<0.1)	10 (0.5)	10 (0.5)
Musculoskeletal and connective tissue disorders	32 (1.6)	17 (0.8)	60 (3.0)	49 (2.4)
Osteoarthritis	5 (0.2)	6 (0.3)	10 (0.5)	19 (0.9)
Back pain	9 (0.4)	2 (<0.1)	17 (0.8)	11 (0.5)
Respiratory, thoracic and mediastinal disorders	25 (1.2)	13 (0.6)	60 (3.0)	47 (2.3)
Chronic obstructive	10 (0.5)	5 (0.2)	29 (1.4)	22 (1.1)

	Double-blind Period		Primary Analysis Period	
SOC Preferred Term	**ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM (N = 2040) n (%)**	**ALN 70 mg QW/ ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM/ ALN 70 mg QW (N = 2040) n (%)**
Number of subjects reporting serious TEAEs	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
pulmonary disease				
General disorders and administration site conditions	10 (0.5)	9 (0.4)	43 (2.1)	33 (1.6)
Death	2 (<0.1)	1 (<0.1)	17 (0.8)	13 (0.6)
Blood and lymphatic system disorders	7 (0.3)	5 (0.2)	19 (0.9)	11 (0.5)
Anemia	3 (0.1)	1 (<0.1)	8 (0.4)	4 (0.2)
Eye disorders	6 (0.3)	5 (0.2)	11 (0.5)	20 (1.0)
Cataract	4 (0.2)	3 (0.1)	8 (0.4)	11 (0.5)
ALN=alendronate; Romo=romosozumab *Source: modified from Table 12-5 of CSR				

In general, the incidence of serious adverse events was fairly balanced between treatment groups. Of note, fractures occurred less commonly in the romosozumab arm, consistent with the superior fracture efficacy of romosozumab compared to alendronate. Myocardial infarction in the double-blind period occurred in 2 subjects in the alendronate arm and 8 subjects in the romosozumab arm.

Adjudicated Cardiovascular Serious Adverse Events

All deaths, as well as all serious adverse events deemed by the investigator to be of potential cardiovascular etiology were submitted to an independent committee for adjudication (the Duke Clinical Research Institute, or DCRI). In addition, all serious adverse events with terms mapping to a predefined preferred term list potentially indicative of cardiovascular etiology were also adjudicated. The positively adjudicated cardiovascular serious adverse events (CV SAEs) were summarized according to event classifications in the DCRI charters as follows: death, cardiac ischemic events (myocardial infarction, angina requiring hospitalization, coronary revascularization), cerebrovascular events (stroke, transient ischemic attack [TIA]), noncoronary revascularization, hospitalization for heart failure, and peripheral vascular event not requiring revascularization. Positively-adjudicated cardiovascular death included cardiovascular death and death of undetermined cause.

The subject incidence rate of all adjudicated positive CV SAEs was 2.5% in the romosozumab

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group (50 subjects) and 1.9% in the alendronate group (38 subjects) during the 12-month double-blind treatment period. This imbalance was driven by events of myocardial infarction, which occurred in 16 subjects (0.8%) in the romosozumab group and 5 subjects (0.2%) in the alendronate group, and stroke, which occurred in 13 subjects (0.6%) in the romosozumab group and 7 subjects (0.3%) in the alendronate group.

The following subject incidences were reported for various groupings of CV SAEs during the 12-month double-blind period: cardiovascular death (romosozumab: 0.8%; alendronate 0.6%), cardiac ischemic events (0.8%; 0.3%), cerebrovascular events (0.8%; 0.3%), hospitalization for heart failure (0.2%; 0.4%), non-coronary revascularization (0.1%; 0.2%), and peripheral vascular ischemic events not requiring revascularization (0.0%; 0.2%).

During the primary analysis period, the overall subject incidence of positively adjudicated CV SAEs was 6.5% in the romosozumab/alendronate group and 6.1% in the alendronate/alendronate group. Positively adjudicated cardiac ischemic events were reported for 1.5% and 1.0% of subjects, respectively; cerebrovascular events for 2.2% and 1.3%, respectively. Positively adjudicated cardiovascular deaths were reported for 2.8% of subjects in the romosozumab/alendronate group and 2.7% of subjects in the alendronate/alendronate group. Although there were small imbalances in certain CV SAEs during the primary analysis period, the imbalances were driven by events during the first 12 months of the study (that is, CV SAEs were balanced from Month 13 through the end of the study).

Refer to section 8.2.5 for discussion of the imbalance in CV SAEs observed in Study 142 as well as an overall analysis of cardiovascular safety.

Dropouts and/or Discontinuations Due to Adverse Effects

Withdrawal of Investigational Product (12-Month Double-blind Period)
The subject incidence rates of adverse events resulting in discontinuation of investigational product were similar between treatment groups in the double-blind period.

Adverse events led to discontinuation of investigational product for 70 (3%) subjects in the romosozumab group and 64 (3%) subjects in the alendronate group. The most frequently reported adverse events (≥ 0.2% in either treatment group) leading to discontinuation from investigational product were nausea (romosozumab: 0.2%; alendronate: < 0.1%), dyspepsia (0.2%, < 0.1%), abdominal pain upper (0.1%, 0.2%), and myalgia (0.2%, < 0.1%).

Withdrawal of Investigational Product (Primary Analysis Period)
The subject incidence rates of adverse events resulting in discontinuation of investigational product were similar between treatment groups in the primary analysis period as well.

Adverse events led to withdrawal of investigational product for 133 (7%) subjects who

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received romosozumab/alendronate and 146 (7%) subjects who received alendronate/ alendronate during the primary analysis period. Adverse events (preferred terms) that led to discontinuation of investigational product for > 0.2% of subjects in either treatment group were dyspepsia (romosozumab/alendronate: 0.4%; alendronate/alendronate: 0.2%), abdominal pain upper (0.3%; 0.3%), and myalgia (0.3%; < 0.1%).

Withdrawal From the Study (12-Month Double-blind Period)
The subject incidence rates of adverse events resulting in withdrawal from study were similar between treatment groups in the double-blind period. Adverse events led to withdrawal from the study for 30 (2%) subjects who received romosozumab and 27 (1%) subjects who received alendronate during the 12-month double-blind period. All adverse events (preferred terms) leading to withdrawal from the study were reported for < 0.1% of subjects in either treatment group.

Withdrawal From the Study (Primary Analysis Period)
The subject incidence rates of adverse events resulting in withdrawal from study were similar between treatment groups in the primary analysis period also.

Adverse events led to withdrawal from the study for 47 (2%) subjects who received romosozumab/alendronate and 43 (2%) subjects who received alendronate/alendronate during the primary analysis period. All adverse events (preferred terms) leading to withdrawal from the study were reported for < 0.1% of subjects in either treatment group.

In summary, the rates of discontinuations due to adverse events were acceptable. There was no substantial difference between the two treatment groups. Results for Study 142 were similar to those of Study 337 for adverse events leading to withdrawal.

Adverse Events of Interest

Events of interest for this study included hypocalcemia, injection site reactions, adverse events potentially related to hypersensitivity, malignant or unspecified tumor, hyperostosis, and osteoarthritis, as well as positively adjudicated atypical femoral fractures (AFF) and positively adjudicated osteonecrosis of the jaw (ONJ). These events represent those causally (i.e., hypocalcemia), potentially (i.e., hyperostosis), or theoretically (i.e., osteoarthritis, malignancy) associated with sclerostin inhibition; adverse events associated with injectable monoclonal antibodies (i.e., hypersensitivity events and injection site reactions); and positively adjudicated adverse events associated with antiresorptive therapies (osteonecrosis of the jaw [ONJ] and atypical femoral fracture [AFF]).

A summary of adverse events of interest is provided in Table 32. Subject incidences of these events in the romosozumab group were similar to the alendronate group, with the exception of injection site reactions. Search strategies using MedDRA SMQ-defined search terms to identify events associated with injection site reactions showed a slightly higher incidence of injection site reactions during the double-blind period in the romosozumab group than in the

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alendronate group (4% and 3%, respectively). There were 2 positively adjudicated cases of ONJ (1 in the romosozumab/alendronate group and 1 in the alendronate/alendronate group), both of which occurred in the alendronate open-label treatment phase. Six events of AFF occurred (2 in the romosozumab/alendronate group and 4 in the alendronate/alendronate group), all of which occurred in the alendronate open-label treatment phase.

Table 33. Summary of Subject Incidence of Treatment-emergent Adverse Events of Interest (Safety Analysis Set - 20110142 Primary Analysis)

	Double-blind Period		Primary Analysis Period	
Event of Interest	**ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM (N = 2040) n (%)**	**ALN 70 mg QW/ ALN 70 mg QW (N = 2014) n (%)**	**Romo 210 mg QM/ ALN 70 mg QW (N = 2040) n (%)**
Hypocalcemia				
Adverse events	1 (<0.1)	1 (<0.1)	1 (<0.1)	4 (0.2)
Serious adverse events	0	0	0	0
Hypersensitivity				
Adverse events	118 (5.9)	122 (6.0)	185 (9.2)	205 (10.0)
Serious adverse events	2 (<0.1)	3 (0.1)	4 (0.2)	7 (0.3)
Injection site reactions				
Adverse events	53 (2.6)	90 (4.4)	53 (2.6)	90 (4.4)
Serious adverse events	0	0	0	0
Tumors, malignant, unspecified				
Adverse events	28 (1.4)	31 (1.5)	85 (4.2)	84 (4.1)
Serious adverse events	20 (1.0)	25 (1.2)	59 (2.9)	61 (3.0)
TNF inflammatory events	14 (0.7)	11 (0.5)	25 (1.2)	19 (0.9)
Hyperostosis				
Adverse events	12 (0.6)	2 (<0.1)	27 (1.3)	23 (1.1)
Serious adverse events	2 (<0.1)	0	3 (0.1)	1 (<0.1)
Osteoarthritis				
Adverse events	146 (7.2)	138 (6.8)	268 (13.3)	247 (12.1)
Serious adverse events	6 (0.3)	8 (0.4)	11 (0.5)	24 (1.2)
Osteonecrosis of the jaw				
Adverse events	0	0	1 (<0.1)	1 (<0.1)
Serious adverse events	0	0	1 (<0.1)	0
Atypical femoral fracture				
Adverse events	0	0	4 (0.2)	2 (<0.1)
Serious adverse events	0	0	4 (0.2)	2 (<0.1)
ALN=alendronate; Romo=romosozumab *Source: modified from Table 12-7 of CSR				

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Adverse Events Potentially Related to Hypocalcemia

Hypocalcemia has been reported with osteoporosis therapies that inhibit bone resorption. Based on earlier studies, the nadir in serum calcium appears to occur between 2 weeks and 1 month following romosozumab injection. In this study, serum calcium was assessed at Month 1 and therefore, hypocalcemia defined by low laboratory values may have been missed.

Adverse Events of Hypocalcemia: During the 12-month double-blind period, 1 (< 0.1%) adverse event of hypocalcemia (preferred term) was reported in each treatment group. No hypocalcemia event was serious. Both adverse events of hypocalcemia were grade 1 (<lower limit of normal [LLN] to 8.0 mg/dL) or grade 2 (<8.0 – 7.0 mg/dL) in severity and neither resulted in discontinuation of investigational product or discontinuation from the study.

During the primary analysis period, adverse events of hypocalcemia were reported for 4 (0.2%) subjects in the romosozumab/alendronate group and 1 (< 0.1%) subject in the alendronate/alendronate group. No hypocalcemia event was serious. All 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

Adverse Events Potentially Related to Hypersensitivity

The applicant used a narrow standardized MedDRA query (SMQ) for hypersensitivity reactions. During the 12-month double-blind period, adverse events potentially related to hypersensitivity were reported for 122 (6%) subjects in the romosozumab group and 118 (6%) subjects in the alendronate group. Adverse events potentially related to hypersensitivity reported for ≥ 0.5% of subjects in either treatment group were rash (romosozumab: 1.1%; alendronate: 1.1%), dermatitis (0.8%, 0.6%), rash pruritic (0.6%, 0.3%), dermatitis allergic (0.6%, 0.7%), and eczema (0.4%, 0.6%). Serious adverse events potentially related to hypersensitivity were reported for 3 (0.1%) subjects in the romosozumab group and 2 (< 0.1%) subjects in the alendronate group. Adverse events potentially related to hypersensitivity led to discontinuation from investigational product and from the study for 4 (0.2%) and 1 (< 0.1%) subjects, respectively, in the romosozumab group and 3 (0.1%) and 0 (0.0%) subject in the alendronate group. Adverse events potentially related to hypersensitivity that occurred ≤ 2 days after administration of investigational product were reported for 4 (0.2%) subjects in the romosozumab group (3 subjects with injection site rash, 1 with mouth swelling) and no subject in the alendronate group. Adverse events potentially related to hypersensitivity that occurred from 2 days to ≤ 7 days after administration of investigational product were reported for 5 (0.2%) subjects in the romosozumab group (1 event each of dermatitis allergic, eye allergy, pruritus allergic, rash, rash maculopapular, and rash pruritic) and no subject in the alendronate group. Fifteen (0.7%) subjects in the romosozumab group and 7 (0.3%) subjects in the alendronate group reported concomitant (i.e., ≥ 1 type of hypersensitivity event on the same investigational product administration date with overlapping start and resolution dates) or recurrent (i.e., ≥ 1 type of hypersensitivity event at 2 or more different investigational product administration dates)

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adverse events potentially related to hypersensitivity. No concomitant event(s) was reported for more than 1 subject in either treatment group. Recurrent events reported for more than 1 subject in the romosozumab and alendronate groups, respectively, were rash (2 subjects, 3 subjects); eczema (2, 1); dermatitis allergic (2, 0); and injection site rash (2, 0).

For the overall primary analysis period, 205 (10%) subjects in the romosozumab/alendronate group and 185 (9%) subjects in the alendronate/alendronate group had adverse events potentially related to hypersensitivity; 7 (0.3%) and 4 (0.2%) subjects, respectively, had serious adverse events.

The potential hypersensitivity reactions reported in study 142 occurred using a drug product concentration of 70 mg/mL where patients required 3 injections of 1mL each to reach the 210 mg dose. The to-be-marketed formulation of romosozumab will be the 90 mg/mL concentration, where patients will need two injections of 1.17 mL each. Study 20120156 was a 6-month trial that compared bone density changes of the romosozumab 70 mg/mL formulation and the romosozumab 90 mg/mL formulation. Potential hypersensitivity reactions occurred in 3 (6%) subjects in the placebo group, 3 (3%) subjects in the 70 mg/mL romosozumab group and 14 (11%) subjects in the 90 mg/mL romosozumab group. The potential for hypersensitivity reactions may be more pronounced with the higher concentration of romosozumab.

Adverse Events of Injection Site Reactions

During the 12-month double-blind period, adverse events of injection site reactions were reported for 90 (4%) subjects in the romosozumab group and 53 (3%) subjects in the alendronate group; none were considered serious. The most frequently reported injection site reactions (≥1% of subjects in either treatment group) were injection site pain (romosozumab: 1.6%, alendronate: 1.2%) and injection site erythema (romosozumab: 1.3%, alendronate: 0.4%).

Injection site reactions reported in Study 142 occurred using a drug product concentration of 70 mg/mL where patients required 3 injections of 1 mL each to reach the 210 mg dose. In trial 20120156 comparing the 70 mg/mL and the 90 mg/mL formulations, injection site reactions occurred in no subjects in the placebo group, 11 (9%) subjects in the 70 mg/mL romosozumab group and 13 (11%) subjects in the 90 mg/mL romosozumab group, the to-be-marketed formulation. The potential for injection site reactions may be more pronounced with the higher concentration of romosozumab.

Adverse Events of Malignant or Unspecified Tumors

The Wnt-beta-catenin pathway plays a role in both sclerostin signaling and some tumor suppressor signaling. Therefore, the applicant evaluated romosozumab's potential to cause malignant tumors using a narrow standardized MedDRA query (SMQ) for malignancies and unspecified tumors.

During the 12-month double-blind period, 31 (1.5%) subjects in the romosozumab group and 28 (1.4%) subjects in the alendronate group were reported to have adverse events of malignancies

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or unspecified tumors. The most frequently reported adverse event (preferred terms) in the romosozumab and alendronate groups, respectively, was basal cell carcinoma (0.1%, 0.2%). All other events were reported for < 0.1% of subjects in either treatment group. Serious adverse events of malignancy were reported for 25 (1.2%) subjects in the romosozumab group and 20 (1.0%) subjects in the alendronate group.

During the 24-month study period, 84 (4%) subjects in the romosozumab/alendronate group and 85 (4%) subjects in the alendronate/alendronate group were reported to have adverse events of malignancies or unspecified tumors. The most frequently reported adverse events (preferred terms) in the romosozumab/alendronate and alendronate/alendronate groups, respectively, were basal cell carcinoma (0.7%, 0.8%), breast cancer (0.3%, 0.2%), squamous cell carcinoma (0.2%, < 0.1%), and lung neoplasm malignant (0.2%, < 0.1%). All other events were reported for < 0.2% of subjects in either treatment group. Serious malignancy events were reported for 61 (3%) subjects in the romosozumab/alendronate group and 59 (3%) subjects in the alendronate/alendronate group over the 24-month study period.

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 treatment period, TNF-mediated inflammatory events were reported for 0.5% of subjects in the romosozumab group and 0.7% in the alendronate group. The most frequently reported event (preferred term) was rheumatoid arthritis (romosozumab: 0.3%; alendronate: 0.4%). The incidence of TNF-mediated inflammatory events was similar between treatment groups for subjects with a prior history of these events (romosozumab: 9.3%; alendronate: 8.7%) and those with no prior history (0.3% and 0.4%, respectively). For subjects with a prior history of rheumatoid arthritis, the incidence of TNF-mediated inflammatory events was also similar between treatment groups (romosozumab: 11.1%; alendronate: 10.0%); all of these events had a preferred term of rheumatoid arthritis.

For the overall primary analysis period, TNF-mediated inflammatory events were reported for 0.9% of subjects in the romosozumab/alendronate group and 1.2% in the alendronate/alendronate group. The most frequently reported events (preferred terms) were rheumatoid arthritis (romosozumab/alendronate: 0.5%; alendronate/alendronate: 0.5%), and psoriasis (0.2%; 0.1%; Table 12-14). The incidence of TNF-mediated inflammatory events for subjects with a prior history of these events was 11.1% in the romosozumab/alendronate group and 17.4% in the alendronate/alendronate group, and 0.7% in each treatment group for those with no prior history. For subjects with a prior history of osteoarthritis, the incidence of TNF-mediated inflammatory events was similar between treatment groups (romosozumab/alendronate: 14.8%; alendronate/alendronate: 13.3%); all of these events had a preferred term of rheumatoid arthritis.

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Adverse Events of Hyperostosis

Hyperostosis with adverse neurologic consequences is a feature of diseases of sclerostin underexpression (sclerosteosis and van Buchem disease). The applicant constructed a MedDRA search strategy to identify events related to hyperostosis.

During the 12-month double-blind period, 2 (< 0.1%) subjects in the romosozumab group and 12 (0.6%) subjects in the alendronate group were reported to have adverse events of hyperostosis. Adverse events (preferred terms) reported by subjects in the romosozumab and alendronate groups, respectively, were exostosis (< 0.1%, 0.3%), lumbar spinal stenosis (0.0%, < 0.1%), spinal column stenosis (0.0%, < 0.1%), and cervical spinal stenosis (0.0%, < 0.1%). Adverse events of exostosis were primarily heel and calcaneal spurs. Serious hyperostosis events were reported for 2 (< 0.1%) subjects in the alendronate group and no subjects in the romosozumab group. Serious hyperostosis events occurring in the alendronate group were cervical spinal stenosis and lumbar spinal stenosis; both subjects were hospitalized and treated with medication.

During the primary analysis period, 23 (1.1%) subjects in the romosozumab/alendronate group and 27 (1.3%) subjects in the alendronate/alendronate group were reported to have adverse events of hyperostosis. Adverse events (preferred terms) reported by ≥ 0.1% of subjects in the romosozumab/alendronate and alendronate/alendronate groups, respectively, were exostosis (0.6%, 0.8%), lumbar spinal stenosis (< 0.1%, 0.2%), spinal column stenosis (0.2%, < 0.1%), and vertebral foraminal stenosis (0.1%, < 0.1%). Over the entire primary analysis period, serious hyperostosis events were reported for 1 (< 0.1%) subject in the romosozumab/alendronate group and 3 (0.1%) subjects in the alendronate/alendronate group. In addition to the 2 serious adverse events that occurred during the 12-month double-blind treatment period described above, during the open-label treatment period, 1 subject in the romosozumab/alendronate group had spinal column stenosis (grade 2, assessed by the investigator as not related), for which the subject was hospitalized, treated with medication and received surgical intervention 16 months later. Also during the open-label treatment period, 1 subject in the alendronate/alendronate group had extraskeletal ossification (ossification of maxillary sinus; grade 3, assessed by the investigator as related) in the setting of the serious adverse event of sinusitis, for which the subject was hospitalized and treated with medication. All 4 serious adverse events resolved, and none resulted in discontinuation from investigational product or from the study.

Adverse Events of Osteoarthritis

Sclerostin is expressed in articular cartilage, which raised the concern that sclerostin inhibition may negatively affect articular cartilage.

During the 12-month double-blind period, 138 (7%) subjects in the romosozumab group and 146 (7%) subjects in the alendronate group were reported to have adverse events of osteoarthritis. The most frequently reported adverse events (preferred terms) in the

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romosozumab and alendronate groups, respectively, were osteoarthritis (6%, 6%), spinal osteoarthritis (1.2%, 1.3%), and exostosis (< 0.1%, 0.3%). All other events were reported for < 0.1% of subjects in either treatment group. Serious osteoarthritis events were reported for 8 (0.4%) subjects in the romosozumab group and 6 (0.3%) subjects in the alendronate group.

During the primary analysis period, 247 (12%) subjects in the romosozumab/ alendronate group and 268 (13%) subjects in the alendronate/alendronate group were reported to have adverse events of osteoarthritis. The most frequently reported adverse events (preferred terms) in the romosozumab/alendronate and alendronate/alendronate groups, respectively, were osteoarthritis (10%, 10%), spinal osteoarthritis (2%, 3%), arthritis (0.7%, 0.4%), and exostosis (0.6%, 0.8%). All other events were reported for ≤ 0.2% of subjects in either treatment group. Serious osteoarthritis events were reported for 24 (1.2%) subjects in the romosozumab/ alendronate group and 11 (0.5%) subjects in the alendronate/alendronate group over the primary analysis period. Based on review of the subject narratives for these serious osteoarthritis events, these events are unlikely to be related to romosozumab therapy.

Adjudicated Events of Atypical Femoral Fracture

Atypical femoral fracture is a rare adverse reaction associated with potent anti-resorptive 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. No positively adjudicated adverse events of AFF were reported during the 12-month double-blind period.

Positively adjudicated atypical femoral fracture cases were identified during the open-label alendronate treatment period for a total of 3 subjects in the romosozumab/alendronate group and 4 subjects in the alendronate/alendronate group during the primary analysis period. All were considered serious adverse events.

Adjudicated Events of Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) is a rare adverse reaction associated with potent anti-resorptive 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. No positively adjudicated adverse events of ONJ occurred during the 12-month double-blind treatment period.

During the open-label alendronate treatment period, 1 adjudicated event of ONJ occurred in each treatment group, for a total of 2 adjudicated events of ONJ in the 24-month study period.

In summary, as was observed in Study 337, injection site reactions in Study 142 occurred at a higher incidence in the romosozumab group than in the control group. All other adverse events of interest occurred at a similar incidence in the romosozumab and control groups in each study. The conclusions regarding the adverse events of interest have not changed since the

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original BLA. Review of adverse events in these prespecified categories of interest did not reveal any clinically relevant findings in the two studies.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events (TEAEs) occurred at a similar incidence in both treatment groups. TEAEs (preferred terms) reported for ≥ 5% of subjects in either treatment group are summarized in Table 33.

12-Month Double-blind period

During the 12-month double-blind period, TEAEs occurred at a similar incidence in subjects who received romosozumab (76%) and subjects who received alendronate (79%). The system organ classes with the highest subject incidences of adverse events in both treatment groups were Infections and Infestations (romosozumab: 40%, alendronate: 43%), Musculoskeletal and Connective Tissue Disorders (34%, 38%), and Gastrointestinal Disorders (24%, 27%).

The most frequently reported TEAEs (preferred terms reported for ≥ 10% of subjects) during the 12-month double-blind period in the romosozumab or alendronate groups, respectively, were nasopharyngitis (10%, 11%) and back pain (9%, 11%). No TEAEs occurring in ≥ 2% of subjects in either treatment group had a ≥ 1% higher incidence in the romosozumab group than in the alendronate group.

Primary Analysis Period

During the primary analysis period, the percentages of subjects reporting TEAEs were similar between the romosozumab/alendronate group (87%) and the alendronate/alendronate group (89%). The system organ classes with the highest subject incidences of adverse events in both treatment groups were Infections and Infestations (romosozumab/alendronate: 55%, alendronate/alendronate: 59%), Musculoskeletal and Connective Tissue Disorders (49%, 54%), and Gastrointestinal Disorders (37%, 38%).

The most frequently reported TEAEs during the primary analysis period (preferred terms reported for ≥ 10% of subjects) in the romosozumab/alendronate and alendronate/ alendronate groups, respectively, were nasopharyngitis (18%, 19%), back pain (16%, 20%), arthralgia (16%, 18%), fall (14%, 17%), hypertension (11%, 11%), pain in extremity (11%, 12%), upper respiratory tract infection (10%, 11%), osteoarthritis (10%, 10%), and urinary tract infection (9%, 12%). The only TEAE occurring in ≥ 2% of subjects in either treatment group with a ≥ 1% higher incidence in the romosozumab/alendronate group than in the alendronate/alendronate group was cough (7%, 6%)

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Table 34. Subject Incidence of Treatment-emergent Adverse Events by Preferred Term (≥ 5% Subject Incidence in Either Treatment Group) (Safety Analysis Set) (20110142 Primary Analysis)

12-Month Double-blind Study Period		
	ALN 70 mg QW (N = 2014) n (%)	**Romo 210 mg QM (N = 2040) n (%)**
Number of subjects reporting TEAEs	1584 (78.6)	1544 (75.7)
Nasopharyngitis	218 (10.8)	213 (10.4)
Back pain	228 (11.3)	186 (9.1)
Arthralgia	193 (9.6)	166 (8.1)
Fall	152 (7.5)	131 (6.4)
Upper respiratory tract infection	132 (6.6)	130 (6.4)
Pain in extremity	131 (6.5)	121 (5.9)
Osteoarthritis	112 (5.6)	116 (5.7)
Hypertension	132 (6.6)	114 (5.6)
Headache	110 (5.5)	105 (5.1)
Urinary tract infection	134 (6.7)	104 (5.1)
Diarrhea	93 (4.6)	103 (5.0)
Bronchitis	101 (5.0)	89 (4.4)
Primary Analysis Period		
	ALN 70 mg QW/ ALN 70 mg QW (N = 2014) n (%)	**Romo 210 mg QM/ ALN 70 mg QW (N = 2040) n (%)**
Number of subjects reporting TEAEs	1784 (88.6)	1766 (86.6)
Nasopharyngitis	373 (18.5)	363 (17.8)
Back pain	393 (19.5)	329 (16.1)
Arthralgia	363 (18.0)	329 (16.1)
Fall	336 (16.7)	282 (13.8)
Hypertension	225 (11.2)	227 (11.1)
Pain in extremity	246 (12.2)	225 (11.0)
Upper respiratory tract infection	220 (10.9)	200 (9.8)
Osteoarthritis	203 (10.1)	195 (9.6)
Urinary tract infection	243 (12.1)	186 (9.1)
Bronchitis	180 (8.9)	177 (8.7)
Diarrhea	166 (8.2)	163 (8.0)
Headache	186 (9.2)	160 (7.8)
Dizziness	150 (7.4)	150 (7.4)
Cough	111 (5.5)	140 (6.9)
Musculoskeletal pain	151 (7.5)	138 (6.8)
Muscle spasms	125 (6.2)	119 (5.8)
Constipation	131 (6.5)	118 (5.8)

	ALN 70 mg QW/ ALN 70 mg QW (N = 2014) n (%)	Romo 210 mg QM/ ALN 70 mg QW (N = 2040) n (%)
Contusion	151 (7.5)	109 (5.3)
Cataract	97 (4.8)	109 (5.3)
Influenza	114 (5.7)	103 (5.0)
Abdominal pain upper	106 (5.3)	99 (4.9)
Gastritis	102 (5.1)	92 (4.5)
Anemia	111 (5.5)	79 (3.9)
ALN=alendronate; Romo=romosozumab * Source: modified from Table 12-3 and 12-4 of CSR		

The overall pattern and distribution of TEAEs does not raise any additional new safety concerns.

Based on the integrated data for TEAEs from Study 142 and Study 337, the following are considered common (subject incidence >5% in at least one study) adverse reactions to romosozumab: arthralgia, headache and muscle spasms. All of these events occurred more commonly in romosozumab-treated subjects compared to placebo-treated subjects.

Laboratory Findings

Assessment of serum chemistry and hematology laboratories was performed at baseline, Month 1, Month 3, Month 6, Month 9, Month 12, Month 18 and Month 24, and then every 6 months through the end of the study (for those subjects who participated beyond 24 months).

Evaluation of abnormal serum laboratory values was conducted using Common Terminology Criteria for Adverse Events version 3 (CTCAE v3.0) grading.

During the 12-month double-blind period, the subject incidence of laboratory test results CTCAE grade ≥ 2 was 452 (22%) subjects in the romosozumab group and 470 (23%) subjects in the alendronate group. Four subjects in the romosozumab group had CTCAE grade 4 laboratory results, including 2 subjects with below-normal sodium (<120 mmol/L); 1 subject with below-normal bicarbonate (<8 mmol/L); 2 subjects with below-normal hemoglobin (< 6.5 g/dL); and 1 subject with below-normal platelet count (< 25,000/mm^3). In the alendronate group, subjects with CTCAE grade 4 laboratory results included 1 subject with above-normal glucose (> 500 mg/dL) and 1 subject with below-normal neutrophil count (< 500/mm^3).

Over the primary analysis period, the subject incidence of laboratory test results with CTCAE grade ≥ 2 was 617 (30%) subjects in the romosozumab/alendronate group and 636 (32%) subjects in the alendronate/alendronate group. Six subjects in the romosozumab/alendronate group had CTCAE grade 4 laboratory results including 3 subjects with below-normal sodium; 1 subject with below-normal potassium (< 2.5 mmol/L); 1 subject with below-normal bicarbonate; 1 subject with above-normal glucose; 2 subjects with below-normal hemoglobin; 2

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subjects with below-normal platelet count, and 4 subjects with below-normal neutrophil count. In the alendronate/alendronate group, subjects with CTCAE grade 4 laboratory results included 2 subjects with below-normal sodium; 1 subject with above-normal glucose; 3 subjects with below-normal platelet count, and 1 subject with below-normal neutrophil count.

Serum Calcium

Changes From Baseline in Serum Calcium

Mild and transitory decreases in serum albumin-corrected calcium were observed in both the romosozumab and alendronate treatment groups. At baseline, the mean albumin-corrected serum calcium levels for the romosozumab and alendronate groups, respectively, were 9.8 mg/dL (2.44 mmol/L) and 9.8 mg/dL (2.44 mmol/L). Based on earlier studies, the nadir in serum calcium appears to occur between 2 weeks and 1 month following romosozumab injection. However, in Studies 337 and 142 serum calcium was not assessed prior to Month 1. Therefore, it is possible that the nadir may have occurred prior to Month 1. At Month 1, the median percent change from baseline was -3% for subjects who received romosozumab and -2% for subjects who received alendronate. Serum calcium levels trended towards baseline over time, such that at month 12, the median percent change from baseline was -1% in both groups and remained stable for the remainder of the primary analysis period.

Low Serum Calcium

The table below lists the CTCAE grades associated with abnormal albumin-corrected serum calcium values .

Table 35 CTCAE (Version 3) Grades and Associated Abnormal Albumin-corrected Serum Calcium Values

	Hypocalcemia	Hypercalcemia
Grade 0	Normal	Normal
Grade 1	<LLN – 8.0 mg/dL	>ULN – 11.5 mg/dL
Grade 2	7.0 mg/dL – <8.0 mg/dL	>11.5 mg/dL – 12.5 mg/dL
Grade 3	6.0 mg/dL – <7.0 mg/dL	>12.5mg/dL – 13.5 mg/dL
Grade 4	< 6.0 mg/dL	>13.5 mg/dL

* LLN = lower limit of normal; ULN = upper limit of normal

During the 12-month double-blind period, no romosozumab-treated subjects with a normal serum albumin-corrected calcium at baseline had a decrease in serum albumin corrected calcium. Among alendronate-treated subjects with a normal serum albumin-corrected calcium at baseline, 3 (0.1%) had a decrease in serum corrected calcium to grade 1 and 2 (< 0.1%) had a decrease to grade 2 during the 12-month double-blind period.

During the primary analysis period, of subjects with a normal serum albumin-corrected calcium at baseline, decreases to grade 1 were observed for 3 (0.1%) subjects in the

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romosozumab/alendronate group and 5 (0.2%) subjects in the alendronate/alendronate group, and decreases to grade 2 were observed for 1 (< 0.1%) subject in the romosozumab/alendronate group and 2 (< 0.1%) subjects in the alendronate/alendronate group. No subject had a greater than grade 2 below-normal serum corrected calcium result at any time during the study.

High Serum Calcium

During the 12-month double-blind period, no subject in either group had an above-normal corrected calcium result of CTCAE grade 4 (> 13.5 mg/dL). Two (< 0.1%) subjects in the romosozumab group and 3 (0.1%) subjects in the alendronate group had an increase in corrected serum calcium from normal at baseline to CTCAE grade 2 (> 11.5 – 12.5 mg/dL) and 1 (< 0.1%) subject in the romosozumab group had an increase in corrected serum calcium from normal at baseline to CTCAE grade 3 (> 12.5 – 13.5 mg/dL).

Over the primary analysis period, no subject in either group had an above-normal corrected calcium result of grade 4. Three (0.1%) subjects in the romosozumab/alendronate group and 4 (0.2%) subjects in the alendronate/alendronate group had an increase in corrected serum calcium from normal at baseline to grade 2 and 1 (< 0.1%) subject in the romosozumab/alendronate group had an increase from normal at baseline to grade 3.

Calcium increases are not expected given the mechanism of action of romosozumab or alendronate. The increase in calcium is likely to be due to the required calcium and vitamin D supplementation. A patient's potential underlying pathophysiology of calcium metabolism, such as hyperparathyroidism could also be unmasked due to treatment with calcium and vitamin D.

Serum Phosphorus

Changes from Baseline in Serum Phosphorus

Mild decreases in serum phosphorus in both treatment groups were also observed in both the romosozumab and alendronate treatment groups. At baseline, the mean serum phosphorus levels for the romosozumab and alendronate groups was 3.7 mg/dL. There was a decrease in serum phosphorus levels at month 1; the median percent change from baseline was -5% for subjects who received romosozumab and -5% for subjects who received alendronate. Phosphorus levels remained below baseline for the remainder of the study. At month 12, the median percent change from baseline was -5% for the romosozumab group and -5% for the alendronate group, and at month 24 was -6% for the romosozumab/alendronate group and -5% for the alendronate/alendronate group.

Low Serum Phosphorus

The following table lists the CTCAE grades associated with abnormal low phosphorus values.

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Table 36 CTCAE (Version 3) Grades for Abnormal Serum Phosphorus Values

	Hypophosphatemia
Grade 0	Normal
Grade 1	<LLN – 2.5mg/dL
Grade 2	2.0 mg/dL – < 2.5 mg/dL
Grade 3	1.0 mg/dL – < 2.0 mg/dL
Grade 4	< 1.0 mg/dL

* LLN = lower limit of normal; ULN = upper limit of normal

During the 12-month double-blind period, 5 (0.2%) subjects in the romosozumab group and 5 (0.2%) subjects in the alendronate group had a below-normal phosphorus result of CTCAE grade 3 (< 2.0 – 1.0 mg/dL); no CTCAE grade 4 (< 1.0 mg/dL) results were reported. Eighteen (0.9%) subjects in the romosozumab group and 22 (1.1%) subjects in the alendronate group had a decrease in phosphorus from normal at baseline to CTCAE grade 2 (< 2.5 – 2.0 mg/dL) and 5 (0.2%) and 4 (0.2%) subjects, respectively, had decreases to grade 3 from normal at baseline.

Over the primary analysis period, 10 (0.5%) subjects in the romosozumab/alendronate group and 7 (0.3%) subjects in the alendronate/alendronate group had a grade 3 below-normal phosphorus result; no grade 4 results were reported. Thirty (1.5%) subjects in the romosozumab/alendronate group and 29 (1.4%) subjects in the alendronate/alendronate group had a decrease from normal at baseline to grade 2 and 10 (0.5%) and 6 (0.3%) subjects, respectively, had decreases to grade 3 from normal at baseline.

Serum Alkaline Phosphatase

Changes from Baseline in Alkaline Phosphatase

At baseline, the mean ALP levels for the romosozumab and alendronate groups, respectively, were 85 U/L and 84 U/L. There was an increase in alkaline phosphatase levels at month 1 in the romosozumab group corresponding with an increase in the bone formation marker BSAP; the median percent change from baseline was 22% for subjects who received romosozumab and -3% for subjects who received alendronate. By month 12 (1 month after the last dose of romosozumab), median alkaline phosphatase levels were 7% below baseline for the romosozumab group and 22% below baseline for the alendronate group. At month 24, median percent changes from baseline were -21% in the romosozumab/alendronate group and -21% in the alendronate/alendronate group.

During the 12-month double-blind period, no subject in either treatment group had an above-normal alkaline phosphatase (ALP) result of CTCAE grade 3 (>5 – 20x ULN) or grade 4 (> 20 x ULN). Two (< 0.1%) subjects in the romosozumab group and 5 (0.2%) subjects in the alendronate group had increases in ALP from normal at baseline to CTCAE grade 2 (> 2.5 – 5 x ULN)).

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Over the primary analysis period, 1 (< 0.1%) subject in the romosozumab/alendronate group and no subjects in the alendronate/alendronate group had a grade 3 above-normal ALP result; no grade 4 results were reported. Six (0.3%) subjects in the romosozumab/alendronate group and 8 (0.4%) subjects in the alendronate/alendronate group had increases in ALP from normal at baseline to grade 2 . One subject in the romosozumab/alendronate group had an increase in ALP from normal at baseline to grade 3. In summary, the observed trends in calcium, phosphorus and alkaline phosphatase were as expected and consistent with the previously established safety profile of romosozumab (in the original BLA) and with the known safety profile of alendronate.

Potential Hy's Law Cases

Potential drug-induced liver injury was assessed by evaluating subjects' alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and ALP test results to identify cases that may have met Hy's Law laboratory criteria. No subject met the Hy's Law criterion of ALT or AST > 3 x the ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN at baseline or at any time during the primary analysis period.

Other Laboratory Parameters

No apparent trends were noted in other serum chemistry or in hematology parameters. There were no clinically meaningful changes from baseline in potassium, bicarbonate, blood urea nitrogen, creatinine, total bilirubin, albumin, total protein, red blood cell count, hemoglobin, reticulocyte count, platelet count, white blood cell count, neutrophil count, eosinophil count, basophil count, lymphocyte count, or monocyte count in either treatment group.

Laboratory data for Study 142 were consistent with the laboratory profile previously reported in the original BLA for the phase 2 and 3 romosozumab studies.

Vital Signs

No notable differences between treatment groups were observed for blood pressure, pulse, body temperature, body weight, BMI, or height.

Electrocardiograms (ECGs)

ECGs were not assessed in Study 142.

QT Interval

Since romosozumab is a monoclonal antibody and therefore a large protein product, it is unlikely to interact with cardiac cell ion channels. As described in the review of the original BLA submission, no patterns of QT abnormalities (or any other ECG abnormalities) were identified on ECGs in phase 1 and 2 romosozumab studies.

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Immunogenicity (Antiromosozumab Antibodies)

Since 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). The applicant used signal to noise values to evaluate the magnitude of the antibody response.

The antibody status through Month 18 was selected for evaluation of efficacy and safety by antibody status, as the 6-month follow-up period after completion of the 12-month romosozumab treatment phase allowed for washout of romosozumab from serum and enabled the most accurate neutralizing antibody detection. Subjects who received placebo or alendronate were not tested for antiromosozumab antibodies.

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 antiromosozumab antibodies (177 [9%] transient) and 12 (0.6%) subjects developed neutralizing antibodies.

The incidence of the development of antiromosozumab binding antibodies was similar for the primary analysis period (16% with 12% transient) when compared to the results through Month 18, as was the incidence of the development of neutralizing antibodies (0.9%).

The antiromosozumab antibodies did not affect the safety of romosozumab. The subject incidence of overall adverse events, adverse events of autoimmune disorders, adverse events potentially related to hypersensitivity and adverse events of injection site reactions during the 12-month double-blind period and overall study period was similar for subjects who had or did not have antiromosozumab antibody development through Month 18. These results for the 12-month double-blind period are summarized in the table below. Note that there are too few subjects with neutralizing antibodies to determine the impact of neutralizing antibodies on safety.

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Table 37 Subject Incidence of Treatment-emergent Injection Site Reaction, Hypersensitivity, and Autoimmune Disorders in the 12-Month Double-blind Period by Binding Anti-romosozumab Antibody Status Through Month 18 by Preferred Term (Safety Analysis Set) (20110142 Primary Analysis)

	Antiromosozumab Antibody Status through Month 18		
	Antibody Negative (N=1639) n (%)	Binding Antibody Positive (N=316) n (%)	Neutralizing Antibody Positive (N=12) n (%)
Immune-Related Treatment-Emergent Adverse Event	174 (10.6)	30 (9.5)	1 (8.3)
Autoimmune disorders	23 (1.4)	1 (0.3)	0
Hypersensitivity	104 (6.3)	17 (5.4)	0
Injection site reactions	68 (4.1)	16 (5.1)	1 (8.3)

The immunogenicity results of Study 142 are generally consistent with those of Study 337. Among subjects who received romosozumab in Study 337, 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 Study 337 (n = 3575), 634 (18%) subjects developed binding antiromosozumab antibodies and 5 (0.1%) subjects developed neutralizing antibodies.

8.2.5. Analysis of Cardiovascular Safety

This section discusses the concern regarding romosozumab's cardiovascular safety, a concern that was initially raised by the safety findings in Study 142. As mentioned in the previous section, the subject incidence rate of adjudicated positive cardiovascular serious adverse events (CV SAEs) in Study 142 was 2.5% in the romosozumab group (50 subjects) and 1.9% in the alendronate group (38 subjects) during the 12-month double-blind period of the study. This imbalance was driven by events of myocardial infarction, which occurred in 0.8% (16 subjects) in the romosozumab group and 0.2% (5 subjects) in the alendronate group, and stroke, which occurred in 0.6% (13 subjects) in the romosozumab group and 0.3% (7 subjects) in the alendronate group. An imbalance in DCRI positively-adjudicated CV SAEs was also observed in the small BMD study in men with osteoporosis (Study 174), with a higher incidence in romosozumab-treated subjects vs. placebo, with the imbalance also driven by events of myocardial infarction and stroke, although these event rates were very low limiting conclusions. An imbalance in positively-adjudicated CV SAEs was not observed between romosozumab and

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placebo in the placebo-controlled study in postmenopausal women with osteoporosis (Study 337).

Given the differences in cardiovascular safety results between the trials, it is unclear if the cardiovascular safety signal reflects a true increase in cardiovascular risk with romosozumab therapy. The three key studies were not specifically designed to assess cardiovascular safety outcomes. While there was a prespecified adjudication process for all serious cardiovascular adverse events, neither study assessed key measures associated with cardiovascular risk, such as fasting serum lipids, C-reactive protein levels and electrocardiograms. Therefore, it was not possible to assign a well-validated complete cardiovascular risk score (e.g., Framingham risk score) to study subjects, which would have enabled a more reliable characterization and interpretation of the pattern of events. Additionally, since cardiovascular events were not an expected outcome or a clear adverse event of interest, data regarding these events may not have been collected as rigorously as was necessary during the conduct of the studies to accurately capture all events. Rather, much of the analysis of cardiovascular safety data was done post-hoc after the imbalance in events in Study 142 was identified. Therefore, the reliability of the cardiovascular safety data may be limited. Another limitation of the studies is the uncertainty regarding the applicability of the cardiovascular findings to the US population and US medical practice. Since only 1.4% of the study population of Study 142 and 2.5% of the study population of Study 337 was from the US, there is concern regarding the generalizability of the cardiovascular safety findings to the US population. Another limitation in the ability to interpret the observed imbalance in myocardial infarction and stroke events and assess romosozumab's cardiovascular risk derives from the overall low number of events of myocardial infarction and stroke observed in the studies. While the pivotal fracture studies were powered to assess fracture outcomes, they were not adequately powered to assess cardiovascular outcomes. Finally, the rate of study discontinuation in Study 142 (11% in each treatment group during the 12-month double-blind period and 23% in each treatment group for the overall primary analysis period) raises additional uncertainty, as there may have been additional uncaptured cardiovascular events. Compared to Study 142, Study 337 had a similar discontinuation rate for the 12-month double-blind period (also 11% in each treatment group), and a lower rate for the overall 24-month period (16% placebo and 17% romosozumab).

To further explore the cardiovascular safety signal and the divergent results in the subject incidence of myocardial infarction and stroke in the first year among the pivotal studies, the applicant performed a comprehensive evaluation of cardiovascular safety that included a second adjudication of the adverse events reported in the pivotal phase 3 studies (337, 142 and 174). Cardiovascular adverse events were evaluated with the following 3 methods:

1. Prespecified adjudication of potential CV SAEs in Studies 337, 142, and 174 by DCRI. This adjudication was added to the study protocols before the studies were initiated. This adjudication included all deaths, serious adverse events meeting prespecified "trigger" preferred terms, and additional serious adverse events identified by DCRI during review of triggered events. Investigators also had the option to flag potential CV SAEs for

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adjudication. Serious adverse events were defined in all clinical studies based on the International Conference on Harmonisation Guideline for Good Clinical Practice (E6).

2. Posthoc review of all adverse event data (serious and nonserious) in Studies 337, 142, and 174 by the Thrombolysis in Myocardial Infarction (TIMI) Study Group to identify potential cardiovascular adverse events (full TIMI adjudication). Also performed was a readjudication by TIMI of all deaths and other serious adverse events previously adjudicated by DCRI, blinded to treatment and initial DCRI adjudication result. The triggering events and the requisite supporting documentation were the same as for the DRCI adjudication.
3. Analyses based on treatment-emergent adverse event reporting (to assure that the level of cardiovascular risk was not underestimated by the adjudication process). For adverse events reported on the eCRF that coded to standardized categories pertaining to cardiovascular and cerebrovascular events (i.e., treatment-emergent adverse event reporting), the subject incidence of adverse events was summarized using cardiovascular-related system organ class (SOC) and high level group term (HLGT) categories. As a more focused approach, narrow scope standardized MedDRA query (SMQ) and Amgen MedDRA query (AMQ) search strategies were used to summarize relevant event categories (e.g., myocardial infarction and stroke).

The applicant also performed additional nonclinical studies to evaluate biological plausibility that romosozumab might influence the rate of cardiovascular events.

The following sections provide an integrated summary of findings from the 3 pivotal studies that are relevant to the assessment of cardiovascular safety. These results are based on the final analyses of Studies 142, 337, and 174, which were the analyses presented in the Comprehensive Cardiovascular Report (CCR).

Baseline Characteristics

Although enrollment criteria allowed for populations of the same age in all 3 studies (55 to 90 years), the mean age of subjects in Study 142 was 3.5 years older than subjects in Study 337 and 2 years older than subjects in Study 174. Mean age was balanced between treatment groups within each study.

With respect to cardiovascular risk factors (e.g., diabetes, hypercholesterolemia, and hypertension), which are not necessarily indicative of a history of cardiovascular disease, the prevalences of hypercholesterolemia and diabetes were evenly distributed across studies and treatment groups. In line with the older mean age, the prevalence of hypertension was somewhat higher in 142 compared with the other 2 studies but was balanced between treatment groups. The prevalences of medical history specific to atherosclerotic cardiovascular disease (identified using MedDRA search strategies) were comparable between treatment groups in each of the pivotal phase 3 studies. In Studies 337 and 142, the use of cardiovascular-related baseline medications (i.e., started on or before study day 1 and continued during the

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study) was similar between treatment groups within each study as well as among subjects with cardiovascular-related medical history.

Cardiovascular Serious Adverse Events (Adjudication by DCRI)

CV SAEs were initially adjudicated by DCRI in Studies 337, 142, and 174. The CV SAEs were summarized according to event classifications in the DCRI charters as follows: death, cardiac ischemic events (myocardial infarction, angina requiring hospitalization, coronary revascularization), cerebrovascular events (stroke, transient ischemic attack [TIA]), noncoronary revascularization, hospitalization for heart failure, and peripheral vascular event not requiring revascularization. Positively-adjudicated cardiovascular death included cardiovascular death and death of undetermined cause. The CV SAEs were summarized for the 12-month double-blind period and the overall study period for each study. In addition, a meta-analysis of the 3 pivotal, phase 3 studies was performed.

As discussed above, in Study 142 a higher subject incidence of CV SAEs was observed in the romosozumab group compared with the alendronate group during the double-blind treatment period, specifically for events of serious myocardial infarction and stroke (Table 35). An imbalance in the subject incidence of positively adjudicated CV SAEs was also observed in Study 174 but event rates were very low, limiting conclusions. There was no imbalance observed in Study 337 during the double-blind treatment period.

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Table 38. Subject Incidence of Positively-adjudicated Cardiovascular Serious Adverse Events by Category and Study in the 12-Month Double-blind Period (Safety Analysis Set) (DCRI Adjudication of Studies 337, 142, and 174)

	Study 174		Study 337		Study 142	
Category Subcategory Subtype	Placebo (N = 81) n (%)	Romo-sozumab 210 mg QM (N = 163) n (%)	Placebo (N = 3576) n (%)	Romo-sozumab 210 mg QM (N = 3581) n (%)	Alendronate 70 mg QW (N = 2014) n (%)	Romo-sozumab 210 mg QM (N = 2040) n (%)
Number of subjects reporting adjudicated positive CV SAE	2 (2.5)	8 (4.9)	46 (1.3)	46 (1.3)	38 (1.9)	50 (2.5)
Cardiac ischemic event	**0 (0.0)**	**3 (1.8)**	**16 (0.4)**	**16 (0.4)**	**6 (0.3)**	**16 (0.8)**
Angina[a]	0 (0.0)	2 (1.2)	7 (0.2)	7 (0.2)	1 (<0.1)	0 (0.0)
Myocardial infarction[a]	0 (0.0)	1 (0.6)	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Type 1 (spontaneous)	0 (0.0)	1 (0.6)	7 (0.2)	8 (0.2)	2 (<0.1)	13 (0.6)
PCI or coronary bypass graft, without MI/angina	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular event	**1 (1.2)**	**3 (1.8)**	**11 (0.3)**	**10 (0.3)**	**7 (0.3)**	**16 (0.8)**
Stroke	1 (1.2)	3 (1.8)	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)
Hemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)	3 (0.1)
Ischemic stroke	1 (1.2)	3 (1.8)	10 (0.3)	2 (<0.1)	6 (0.3)	10 (0.5)
Undetermined stroke	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	1 (<0.1)	0 (0.0)
TIA	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)	0 (0.0)	3 (0.1)
CV Death[b]	**1 (1.2)**	**2 (1.2)**	**15 (0.4)**	**17 (0.5)**	**12 (0.6)**	**17 (0.8)**
CV-Related	0 (0.0)	1 (0.6)	9 (0.3)	6 (0.2)	5 (0.2)	10 (0.5)
Undetermined	1 (1.2)	1 (0.6)	6 (0.2)	11 (0.3)	7 (0.3)	7 (0.3)
Heart failure	**0 (0.0)**	**1 (0.6)**	**5 (0.1)**	**7 (0.2)**	**8 (0.4)**	**4 (0.2)**
Noncoronary revasc[c]	**0 (0.0)**	**0 (0.0)**	**2 (<0.1)**	**1 (<0.1)**	**5 (0.2)**	**3 (0.1)**
Peripheral vascular ischemic event not requiring revasc	**0 (0.0)**	**0 (0.0)**	**1 (<0.1)**	**4 (0.1)**	**2 (<0.1)**	**0 (0.0)**

CV = cardiovascular; DCRI = Duke Clinical Research Institute; PCI = percutaneous coronary intervention; QM = once monthly; QW = once weekly; revasc = revascularization; Romo = romosozumab; TIA = transient ischemic attack

N = Number of subjects in the safety analysis set

n = Number of subjects reporting ≥ 1 event

[a] Includes coronary revascularization procedures that may have been performed as part of adjudicated event. Other subtypes of MI (shown in the source table) included Type 2 (secondary), Type 4a (Peri-PCI), and Type 4b (Stent thrombosis).

[b] Includes fatal events adjudicated as cardiovascular-related or undetermined

[c] Non-coronary revascularization events were not adjudicated in Study 174.

*Source: Modified from Table 14-6.2.9 of CV report.

For the meta-analysis of all 3 studies, the subject incidence of positively-adjudicated CV SAEs during the 12-month double-blind treatment period was slightly higher in the romosozumab group compared to the control group (alendronate or placebo) through month 12 (104 [1.8%]

subjects and 86 [1.5%] subjects, respectively). The hazard ratio was 1.17 with a wide 95% confidence interval (0.88, 1.56), spanning 1.0.

There was no imbalance in the subject incidence of overall CV SAEs during the overall study period in Study 142 or Study 337, which includes the follow-on period after Month 12 where all subjects received alendronate (Study 142) or denosumab (Study 337) (Table 36). Of note, however, in Study 142 there was an imbalance in the subject incidence of the following two categories of CV SAEs: cardiac ischemic events (alendronate/alendronate: 1.2%; romosozumab/alendronate: 1.6%) and cerebrovascular events (alendronate/alendronate: 1.3%; romosozumab/alendronate: 2.3%). Study 174 did not have a follow-on-period; the overall study period was consistent with the 12-month double-blind period.

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Table 39. Subject Incidence of Positively-adjudicated Cardiovascular Serious Adverse Events by Study in the Overall Study Period (Safety Analysis Set) (DCRI Adjudication of Studies 337, 142, and 174)

	Study 174		Study 337		Study 142	
Category Subcategory Subtype	Placebo (N = 81) n (%)	Romosozumab 210 mg QM (N = 163) n (%)	Placebo/ Denosumab 60 mg Q6M (N = 3576) n (%)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3581) n (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2014) n (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2040) n (%)
Number of subjects reporting adjudicated positive CV SAEs	2 (2.5)	8 (4.9)	124 (3.5)	128 (3.6)	137 (6.8)	144 (7.1)
Cardiac ischemic event	**0 (0.0)**	**3 (1.8)**	**38 (1.1)**	**36 (1.0)**	**25 (1.2)**	**32 (1.6)**
Angina[a]	0 (0.0)	2 (1.2)	17 (0.5)	13 (0.4)	5 (0.2)	8 (0.4)
Myocardial infarction[a]	0 (0.0)	1 (0.6)	19 (0.5)	23 (0.6)	21 (1.0)	23 (1.1)
Type 1 (spontaneous)	0 (0.0)	1 (0.6)	17 (0.5)	20 (0.6)	14 (0.7)	17 (0.8)
PCI or coronary bypass graft, without MI or angina	0 (0.0)	0 (0.0)	3 (<0.1)	3 (<0.1)	0 (0.0)	1 (<0.1)
Cerebrovascular event	**1 (1.2)**	**3 (1.8)**	**36 (1.0)**	**43 (1.2)**	**27 (1.3)**	**47 (2.3)**
Stroke	1 (1.2)	3 (1.8)	31 (0.9)	37 (1.0)	24 (1.2)	42 (2.1)
Hemorrhagic stroke	0 (0.0)	0 (0.0)	7 (0.2)	9 (0.3)	3 (0.1)	7 (0.3)
Ischemic stroke	1 (1.2)	3 (1.8)	23 (0.6)	26 (0.7)	19 (0.9)	33 (1.6)
Undetermined stroke	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
TIA	0 (0.0)	0 (0.0)	5 (0.1)	7 (0.2)	4 (0.2)	5 (0.2)
CV Death[b]	**1 (1.2)**	**2 (1.2)**	**50 (1.4)**	**43 (1.2)**	**68 (3.4)**	**67 (3.3)**
CV-Related	0 (0.0)	1 (0.6)	29 (0.8)	20 (0.6)	27 (1.3)	36 (1.8)
Undetermined	1 (1.2)	1 (0.6)	21 (0.6)	23 (0.6)	41 (2.0)	31 (1.5)
Heart failure	**0 (0.0)**	**1 (0.6)**	**15 (0.4)**	**12 (0.3)**	**25 (1.2)**	**14 (0.7)**
Noncoronary revasc[c]	**0 (0.0)**	**0 (0.0)**	**4 (0.1)**	**2 (<0.1)**	**10 (0.5)**	**7 (0.3)**
Peripheral vascular ischemic event not requiring revasc	**0 (0.0)**	**0 (0.0)**	**3 (<0.1)**	**8 (0.2)**	**5 (0.2)**	**2 (<0.1)**

CV = cardiovascular; DCRI = Duke Clinical Research Institute; MI = myocardial infarction; PCI = percutaneous coronary intervention; QM = monthly; Q6M = every 6 months; QW = weekly; revasc revascularization; TIA = transient ischemic attack
N = Number of subjects in the safety analysis set
n = Number of subjects reporting ≥ 1 event
[a] Includes coronary revascularization procedures that may have been performed as part of adjudicated event. Other subtypes of MI (shown in the source table) included Type 2 (secondary), Type 4a (Peri-PCI), and Type 4b (Stent thrombosis).
[c] CV death events include fatal events adjudicated as cardiovascular-related or undetermined.
[d] Noncoronary revascularization events were not adjudicated in Study 174.

*Source: Modified from Table 14-6.2.11 of CV report.

For the meta-analysis of events during the overall study periods, the subject incidence of positively-adjudicated CV SAEs was balanced between the romosozumab/follow-on therapy group (i.e., romosozumab followed by denosumab [Study 337], alendronate [Study 142], or no follow-on therapy [Study 174]) and the control group (i.e., placebo/denosumab [Study 337], alendronate/alendronate [Study 142], or placebo [Study 174]) in the overall study period; hazard ratio 1.06 (95% CI 0.89, 1.25).

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MACE Composite Endpoint (Adjudication by DCRI)

Although the prespecified endpoint for the DCRI adjudication was the subject incidence of positively-adjudicated CV SAEs, it is important to understand the risk in terms of the impact on the Major Adverse Cardiac Event (MACE) composite endpoint (comprised of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), an endpoint that is commonly used to evaluate cardiovascular benefit or harm.

A post-hoc analysis of MACE was performed for the double-blind period and the overall study period for Studies 337, 142, and 174 individually. Additionally, a meta-analysis of integrated data from the 3 studies was performed for both time periods. This analysis showed an imbalance in the subject incidence of MACE in Study 142 and Study 174 during the double-blind period that was not present in Study 337.

Results for the MACE composite endpoint in the meta-analysis of the 3 studies are discussed below and listed in Table 40.

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Table 40. Summary of MACE Composite and Individual Components Through Month 12 and in the Overall Study Period (Safety Analysis Set) (DCRI Adjudication of Studies 20070337, 20110142, and 20110174)

Time Period	Through Month 12			Overall Study Period		
Endpoint Study	Placebo or Alendronate 70 mg QW (N = 5671) n/N (%)	Romosozumab 210 mg QM (N = 5784) n/N (%)	Hazard Ratio (95% CI)[a]	Control (N = 5671) n/N (%)	Treatment (N = 5784) n/N (%)	Hazard Ratio (95% CI)[a]
Composite		Figure 14-6.1.1.1			Figure 14-6.1.1.3	
20070337	29/3576 (0.8)	30/3581 (0.8)	1.03 (0.62, 1.72)	86/3576 (2.4)	95/3581 (2.7)	1.12 (0.83, 1.49)
20110142	22/2014 (1.1)	41/2040 (2.0)	1.87 (1.11, 3.14)	102/2014 (5.1)	117/2040 (5.7)	1.15 (0.88, 1.50)
20110174	2/81 (2.5)	6/163 (3.7)	1.55 (0.31, 7.69)	2/81 (2.5)	6/163 (3.7)	1.55 (0.31, 7.69)
Overall	53/5671 (0.9)	77/5784 (1.3)	1.40 (0.99, 1.99)	190/5671 (3.4)	218/5784 (3.8)	1.14 (0.94, 1.39)
CV death		Figure 14-6.1.2.1			Figure 14-6.1.2.3	
20070337	15/3576 (0.4)	17/3581 (0.5)	1.13 (0.56, 2.26)	50/3576 (1.4)	43/3581 (1.2)	0.87 (0.58, 1.31)
20110142	12/2014 (0.6)	17/2040 (0.8)	1.42 (0.68, 2.97)	68/2014 (3.4)	67/2040 (3.3)	0.98 (0.70, 1.37)
20110174	1/81 (1.2)	2/163 (1.2)	1.04 (0.09, 11.46)	1/81 (1.2)	2/163 (1.2)	1.04 (0.09, 11.46)
Overall	28/5671 (0.5)	36/5784 (0.6)	1.25 (0.76, 2.05)	119/5671 (2.1)	112/5784 (1.9)	0.94 (0.72, 1.21)
Serious myocardial infarction		Figure 14-6.1.3.1			Figure 14-6.1.3.3	
20070337	8/3576 (0.2)	9/3581 (0.3)	1.12 (0.43, 2.91)	19/3576 (0.5)	23/3581 (0.6)	1.22 (0.67, 2.24)
20110142	5/2014 (0.2)	16/2040 (0.8)	3.21 (1.18, 8.77)	21/2014 (1.0)	23/2040 (1.1)	1.10 (0.61, 1.98)
20110174	0/81 (0.0)	1/163 (0.6)	NE	0/81 (0.0)	1/163 (0.6)	NE
Overall	13/5671 (0.2)	26/5784 (0.4)	1.97 (1.01, 3.84)	40/5671 (0.7)	47/5784 (0.8)	1.17 (0.77, 1.79)
Serious stroke		Figure 14-6.1.4.1			Figure 14-6.1.4.3	
20070337	10/3576 (0.3)	8/3581 (0.2)	0.80 (0.32, 2.02)	31/3576 (0.9)	37/3581 (1.0)	1.21 (0.75, 1.94)
20110142	7/2014 (0.3)	13/2040 (0.6)	1.86 (0.74, 4.67)	24/2014 (1.2)	42/2040 (2.1)	1.75 (1.06, 2.89)
20110174	1/81 (1.2)	3/163 (1.8)	1.54 (0.16, 14.83)	1/81 (1.2)	3/163 (1.8)	1.54 (0.16, 14.83)
Overall	18/5671 (0.3)	24/5784 (0.4)	1.26 (0.68, 2.32)	56/5671 (1.0)	82/5784 (1.4)	1.45 (1.03, 2.03)

CV = cardiovascular; DCRI = Duke Clinical Research Institute; MACE = Major Adverse Cardiac Event; NE = not estimable; QM = once monthly; QW = once weekly
[a] Hazard ratio and 95% CI are based on Cox proportional hazards model; overall estimates are based on Cox proportional hazards model stratified by study comparing romosozumab versus "control" (either placebo or alendronate).
Treatment = romosozumab/denosumab, romosozumab/alendronate, or romosozumab
Control = placebo/denosumab, alendronate/alendronate, or placebo

*Source: Table 5 of Comprehensive Cardiovascular Report

12-Month Double-blind Period

In Study 142, the hazard ratio for MACE during the 12-month double-blind period was 1.87 (95% CI 1.11, 3.14) based on 41 (2.0%) subjects in the romosozumab group and 22 (1.1%) subjects in the alendronate group with MACE. Higher incidences in positively-adjudicated serious myocardial infarction (16 [0.8%] vs. 5 [0.2%] subjects) and stroke (13 [0.6%] vs. 7 [0.3%]) in the romosozumab group vs. the alendronate group contributed to the imbalance in the first year of treatment. The subject incidences of CV death were 17 (0.8%) and 12 (0.6%), respectively.

Study 337 showed no imbalance between treatment groups in the incidence of MACE during the double-blind period (0.8% for romosozumab and 0.8% for placebo; hazard ratio 1.03, 95% CI: 0.62, 1.72).

For the meta-analysis of Studies 142, 337, and 174, the incidence of MACE through Month 12 was 1.3% for romosozumab vs. 0.9% for control (placebo or alendronate); hazard ratio: 1.40 (95% CI: 0.99, 1.99).

The FDA performed an additional meta-analysis of MACE incidence through Month 12 utilizing only Study 337 and Study 142, as this analysis includes only the intended population of women with PMO. The hazard ratio was 1.38 (95% CI: 0.96, 1.99); this is essentially unchanged from that of the applicant's meta-analysis of all 3 studies (as listed above), which is not unexpected given the few MACE events in Study 174.

Additionally, given the discrepant results between Study 337 and Study 142, the FDA also investigated whether there might be a cardioprotective effect of alendronate by conducting an exploratory network meta-analysis to indirectly estimate the hazard ratio of MACE for alendronate from Study 142 vs. placebo from Study 337 during the first year of the two studies. This analysis yielded a hazard ratio of 0.55 (95% CI: 0.27-1.14) for alendronate vs. placebo. Similar results were obtained when Study 174 was also included in the meta-analysis (hazard ratio 0.57; 95% CI 0.28-1.17), suggesting a potential cardioprotective effect of alendronate. However, this exploratory network analysis cannot definitively address the cardiovascular risk of alendronate. In addition, review of the literature and placebo-controlled alendronate trials reviewed previously by FDA does not suggest a cardioprotective effect of alendronate.

Overall Study Period

Study 142 showed no imbalance between treatment groups in the incidence of MACE in the overall study period (5.7% for romosozumab/alendronate and 5.1% for alendronate/ alendronate; hazard ratio 1.15, 95% CI: 0.88, 1.50).

Study 337 showed no imbalance between treatment groups in the incidence of MACE in the overall study period (2.7% for romosozumab and 2.4% for placebo; hazard ratio 1.12, 95% CI: 0.83, 1.49).

For the meta-analysis of all 3 studies, the incidence of MACE in the overall study period was 3.8% for the romosozumab/follow-on therapy (denosumab or alendronate) group vs. 3.4% for the control (placebo or alendronate)/follow-on therapy (denosumab or alendronate) group; hazard ratio: 1.14 (95% CI: 0.94, 1.39).

Examination of the time to first MACE during the follow-on therapy period from month 12 onward in Studies 337 and 142 showed no apparent separation between treatment groups, suggesting that the imbalance in rates of cardiovascular events in Study 142 that occurred during the first 12 months of exposure was not sustained during long-term follow up after drug exposure. However, a definitive conclusion regarding persistent risk following cessation of

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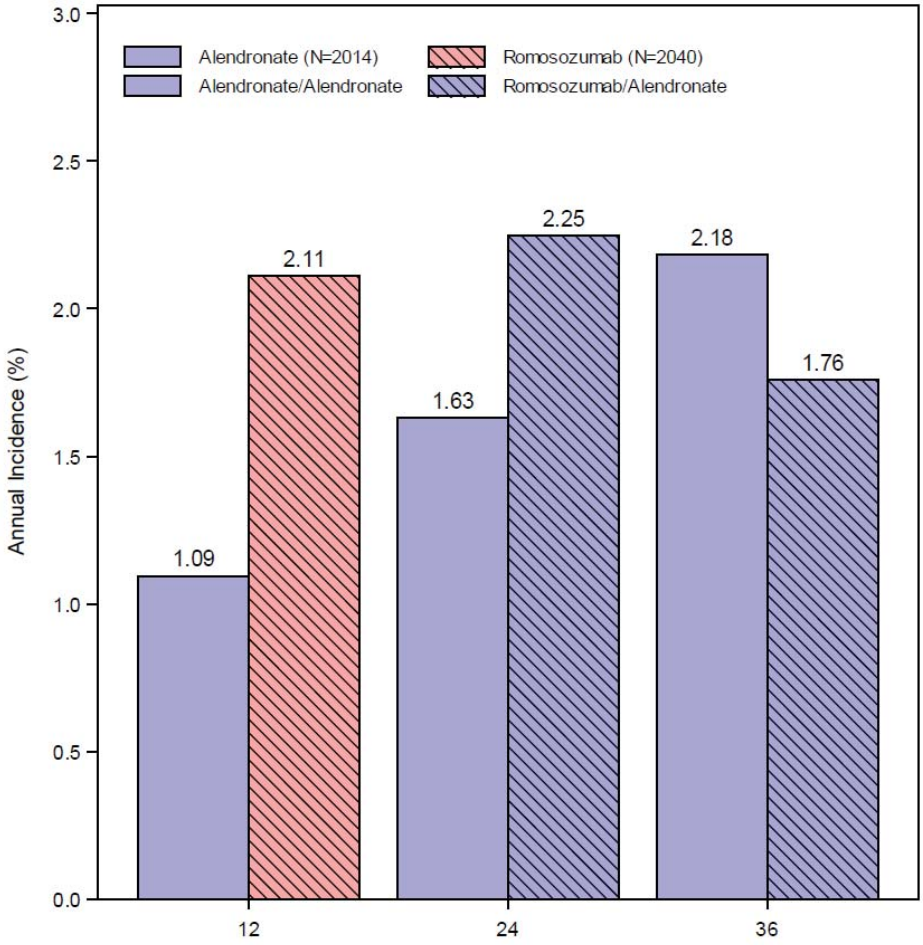
therapy cannot be made since the number of subjects at risk varied as the study progressed beyond Month 12 (due to the variability in follow-up duration for this event-driven trial).

Regarding the annual incidence rates of MACE in Study 142, the alendronate group had a low rate of cardiovascular events in the first year, with an increase in the rate of these events in subsequent years. The annual rates of events in subjects on open-label alendronate in years 2 and 3 were similar regardless of initial treatment group, and higher than what was observed in subjects on alendronate in year 1. During years 2 and 3 (i.e., during the open-label alendronate period), the annual incidences of MACE, regardless of treatment in the first year, ranged between 1.63% and 2.25%, while the incidence in the alendronate group in the first year was 1.09% (Figure 6). Of note, the annual incidence of MACE in the romosozumab group during the first year of the study (2.11%) was between the incidences observed for alendronate during years 2 and 3 in both study arms.

The reason for this pattern of MACE incidence rates by year is unclear. It may reflect chance findings, a higher risk with romosozumab or that alendronate may have had a short-term protective effect for cardiovascular outcomes. The FDA's exploratory network meta-analysis estimating the hazard ratio of alendronate vs. placebo was consistent with the possibility of the latter. The plausibility of such an effect is addressed below (under "Nonclinical and Human Genetic Data, Possible Explanations of Observed Imbalance, Epidemiology Reviews"). However, ultimately it is not possible to know the reason for these findings and we are left with the uncertainty that romosozumab may increase cardiovascular risk.

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Figure 6 Annual Incidence of MACE in Study 20110142 (DCRI Adjudication of Study 20110142)



*Source: Figure 6 of CCR

Subgroup Analyses

Subgroup analyses in the individual studies and based on a meta-analysis of all 3 studies did not identify a population at consistently increased relative risk of a MACE with administration of romosozumab, including no difference in relative risk among subjects with and without a history of prior cardiovascular disease before randomization.

Specific demographic characteristics, including age, geographic region, smoking history and history of risk factors for cardiovascular disease, such as hypercholesterolemia, hypertension, and diabetes, were evaluated to determine if one or more specific subgroups of study subjects were at increased risk for developing an on-study MACE.

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Point estimates for hazard ratios for subgroups based on geographic region were consistent with the hazard ratios of the overall population.

As expected, there was a consistently higher absolute risk of MACE for subjects with a history of cardiovascular risk factors in both Study 142 and Study 337. However, for subgroups of subjects with cardiovascular risk factors, including history of ischemic heart disease and cerebrovascular disorders as well as history of a cardiovascular or cerebrovascular event, the point estimates of the hazard ratios (romosozumab vs. alendronate) for the MACE composite endpoint through Month 12 within each of the subgroups were consistent with the hazard ratio of the overall population within each study, independent of whether the subgroup represented a higher or lower risk population.

Subgroup analysis was also performed by total cardiovascular risk score using a modified Raloxifene Use for the Heart (RUTH) criteria. Modified RUTH criteria are listed in Table 38.

Table 41 Modified-RUTH Criteria for Defining a High-risk Population for Cardiovascular Events

Baseline Cardiovascular Risk Factor	Points
Ischemic heart disease, or central nervous system haemorrhages and cerebrovascular conditions	4
Diabetes mellitus	3
Age	
≥ 70 years	2
65 to 69 years	1
Former/current smoker[a]	1
Hypertension[a]	1
High cholesterol[a]	1

[a] An extra point is added if all 3 criteria were met (ie, total of 4 points).
History of ischemic heart disease or central nervous system haemorrhages and cerebrovascular conditions is based on searching the medical history eCRF for preferred terms based on the narrow search strategy from the associated SMQ. History of diabetes and hypertension is based the hyperglycemia SMQ and hypertension SMQ, respectively. History of high cholesterol is based on the dyslipidemia SMQ excluding preferred terms associated with conditions of low cholesterol or increased HDL.

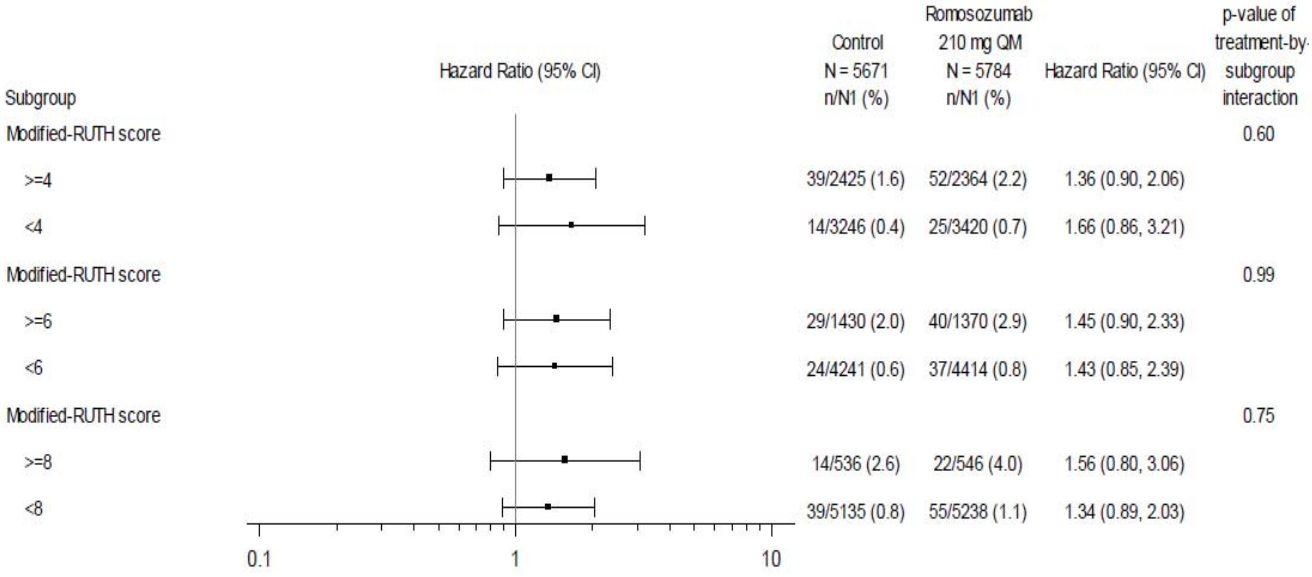
*Source: Table 1 of Supplemental Statistical Analysis Plan

Modified RUTH scores ranged from 0 (indicating no cardiovascular risk) to 13 (indicating the highest cardiovascular risk). As expected, the absolute risk of MACE increased with increasing modified RUTH score. However, hazard ratios during the double-blind treatment period indicated that the relative risk of MACE was consistent over a range of modified RUTH scores

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(Figure 7), and that there was no pattern of increasing hazard ratio with increasing modified RUTH score.

Figure 7 Subgroup Analysis by Modified RUTH Score: Subject Incidence of MACE in the Double-blind Period (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.

*Source: Figure 15 of CCR

Additionally, in response to an information request during the review cycle, the applicant performed another post-hoc evaluation of cardiovascular risk via a modified Framingham Risk Score (FRS). The FRS required modification because the age of the enrolled romosozumab pivotal study population was higher (maximum age enrolled = 90 years) than the age range in which the FRS was validated, and fasting lipid levels were not collected in the pivotal studies of romosozumab. Assumptions for total cholesterol and HDL cholesterol, and extrapolation of the score for age were based on average values for age categories in the National Health and Nutrition Examination Survey (NHANES) database for years 2007-2010. These data were supplemented with medical history and baseline medication data collected in the studies. If subjects reported events in their medical history indicative of hypercholesterolemia based on the narrow search of the hyperlipidemia SMQ or were taking a statin at baseline they were given the score for the higher category.

Analyses based on modified FRS scores were performed for the 12-month double-blind randomized romosozumab treatment period and for the overall study period in Study 337, Study 142, and Study 174. Consistent with the previous cardiovascular risk measurements, the Study 142 and Study 174 populations had higher baseline modified FRS compared with the

Study 337 population. As expected, the subject incidence of MACE was higher in patients with higher modified FRS in both treatment groups in Studies 337, 142, and 174. However, there was no consistent modified FRS subgroup that demonstrated a higher relative risk for MACE on romosozumab. As with the modified RUTH score, there was no pattern of increasing hazard ratio with increasing modified FRS. The hazard ratio was actually lower for the modified FRS subgroup with highest risk (> 20% risk) in Study 337 and 142.

The consistent hazard ratios for MACE across all geographic regions suggests that the findings are widely applicable throughout the world, and somewhat allays the concern that the cardiovascular safety findings may not be applicable to the US population (which had a very small representation in the studies as discussed previously).

Regarding the method for assigning cardiovascular risk, the applicant's use of the modified RUTH score was limited. It was not possible to estimate risk via the more widely utilized FRS, TIMI Risk Score, the Reynolds Score, or the ACC/AHA ASCVD Risk Estimator, as these require fasting lipid values, C-reactive protein (CRP) values and/or electrocardiograms, which were not performed in Studies 337 or 142. The modified RUTH score, although previously used in osteoporosis and breast cancer clinical trials to estimate cardiovascular risk, is not a widely utilized assessment of cardiovascular risk. Since the applicant imputed the hypercholesterolemia category as described above (rather than using actual measurement of serum lipid levels at baseline) to determine both the modified RUTH score and FRS scores, cardiovascular risk assessments with these scores may not be adequately predictive. However, the consistency of results for cardiovascular risk assessment and subgroup analysis using either the modified FRS or the modified RUTH score indicates that these scores likely still have some predictive value.

Sensitivity Analysis – TIMI Study Group

Results for adjudication by the TIMI Study Group were consistent with the results of the adjudication by DCRI. An increase was observed in the subcategory of positively-adjudicated TIAs (n = 11 across studies in the double-blind period for the TIMI Study Group vs. n = 6 for DCRI), but the overall number of subjects with positively-adjudicated cerebrovascular events in the first year was the same for the TIMI Study Group and DCRI (n = 48).

As listed below, from the meta-analysis of the three trials, the subject incidence of MACE and associated hazard ratios for romosozumab in the 12-month double-blind period was consistent between the modes of adjudication.

- DCRI Adjudication: Incidence 1.3% vs. 0.9%, HR 1.40 (95% CI 0.99-1.99)
- TIMI Readjudication (TIMI adjudication of events previously adjudicated by DCRI): Incidence 1.2% vs. 0.8%, HR 1.47 (95% CI 1.02-2.13)
- Full TIMI Adjudication: Incidence 1.2% vs. 0.8%, HR 1.44 (95% CI 1.00-2.08)

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The hazard ratio results for all modes of adjudication were driven by events of myocardial infarction and stroke.

Serious Adverse Events Considered Negatively Adjudicated Due to Insufficient Source Documentation

Except for cases of death, serious adverse events that lacked sufficient source documentation for definitive adjudication were considered negatively adjudicated by DCRI. At the applicant's request, DCRI retrospectively identified these events and the supporting documentation that was not available. Overall, 5.7% of adjudicated serious adverse events in Study 337, 3.9% of adjudicated serious adverse events in Study 142, and no events in Study 174 were negatively adjudicated due to insufficient documentation. A sensitivity analysis was performed in which subjects with events that were negatively adjudicated due to insufficient documentation were considered positively adjudicated in the analyses. The number of subjects with CV SAEs that were negatively-adjudicated for insufficient documentation was generally balanced between treatment groups within each study through Month 12 and the overall study period. Therefore, considering these subjects as having positively-adjudicated CV SAEs in the analysis had no overall impact on hazard ratios (Table 39).

Table 42. Subject Incidence of Positively-adjudicated Cardiovascular Serious Adverse Event or Negatively Adjudicated Due to Insufficient Documentation (Safety Analysis Set) (DCRI Adjudication of Studies 20110174, 20070337, and 20110142)

	Placebo or Alendronate 70 mg QW (N = 5671) n (%)	Romosozumab 210 mg QM (N = 5784) n (%)	Hazard Ratio[a] (95% CI)
12-Month Double-Blind Period			
DCRI pos-adj	86 (1.5)	104 (1.8)	1.17 (0.88, 1.56)
DCRI pos-adj + neg due to insufficient documentation	92 (1.6)	114 (2.0)	1.20 (0.91, 1.59)
Overall Study Period	Control	Treatment	
DCRI pos-adj	263 (4.6)	280 (4.8)	1.06 (0.89, 1.25)
DCRI pos-adj + neg due to insufficient documentation	277 (4.9)	299 (5.2)	1.07 (0.91, 1.26)

DCRI = Duke Clinical Research Institute; neg = negative; pos-adj = positively-adjudicated; QM = once monthly; QW = once weekly

[a] Hazard ratio and 95% CI are based on Cox proportional hazards mode stratified by study comparing romosozumab versus "Control" (either placebo or alendronate) in the double-blind period or comparing "Treatment" (romosozumab/denosumab, romosozumab/alendronate, or romosozumab) versus "Control" (placebo/denosumab, alendronate/alendronate, or placebo) in the overall study period.

*Source: Table 9 of CCR

Assessment of Cardiovascular Events Based on Treatment-emergent Adverse Event Reporting

Table 40 shows the outcomes of treatment-emergent adverse event reporting side-by-side with the adjudication results for DCRI and the TIMI Study Group. This comparison includes an endpoint of all-cause death because potential cardiovascular etiology could not be determined for fatal treatment-emergent adverse events without making assumptions relating to SMQs and AMQs that could bias the results. Myocardial infarction and stroke were identified by narrow search SMQ and AMQ, respectively, for treatment-emergent adverse event reporting, and by positively-adjudicated events for DCRI (based on serious adverse events) and the TIMI Study Group (based on all adverse events). The subject incidences of treatment-emergent adverse events of myocardial infarction and stroke were generally comparable to those of the adjudications. This provides assurance regarding the comprehensiveness of the adjudication process.

Table 43. Comparison of Subject Incidences of All-Cause Death, Myocardial Infarction, and Stroke Based on Treatment-emergent Adverse Event Reporting and Adjudication by DCRI and the TIMI Study Group During the 12-Month Double-blind Period (Safety Analysis Set) (Studies 20110142, 20070337, and 20110174)

	TEAE Reporting		DCRI Adjudicated		TIMI Adjudicated	
Study Adverse Event Category	Control n (%)	Romo-sozumab 210 mg QM n (%)	Control n (%)	Romo-sozumab 210 mg QM n (%)	Control n (%)	Romo-sozumab 210 mg QM n (%)
Study 20110142	(N = 2014)	(N = 2040)	(N = 2014)	(N = 2040)	(N = 2014)	(N = 2040)
Number of subjects reporting treatment-emergent events[a]	38 (1.9)	53 (2.6)	32 (1.6)	53 (2.6)	31 (1.5)	51 (2.5)
All-cause death	22 (1.1)	30 (1.5)	22 (1.1)	30 (1.5)	21 (1.0)[d]	27 (1.3)[d]
Myocardial Infarction[b]	8 (0.4)	16 (0.8)	5 (0.2)	16 (0.8)	6 (0.3)	16 (0.8)
Stroke[c]	12 (0.6)	15 (0.7)	7 (0.3)	13 (0.6)	5 (0.2)	13 (0.6)
Study 20070337	(N = 3576)	(N = 3581)	(N = 3576)	(N = 3581)	(N = 3576)	(N = 3581)
Number of subjects reporting treatment-emergent events[a]	43 (1.2)	48 (1.3)	38 (1.1)	42 (1.2)	34 (1.0)	38 (1.1)
All-cause death	24 (0.7)	29 (0.8)	24 (0.7)	29 (0.8)	20 (0.6)[d]	27 (0.8)[d]
Myocardial Infarction[b]	12 (0.3)	14 (0.4)	8 (0.2)	9 (0.3)	8 (0.2)	7 (0.2)
Stroke[c]	12 (0.3)	10 (0.3)	10 (0.3)	8 (0.2)	8 (0.2)	8 (0.2)
Study 20110174	(N = 81)	(N = 163)	(N = 81)	(N = 163)	(N = 81)	(N = 163)
Number of subjects reporting treatment-emergent events[a]	2 (2.5)	5 (3.1)	2 (2.5)	6 (3.7)	2 (2.5)	6 (3.7)
All-cause death	1 (1.2)	2 (1.2)	1 (1.2)	2 (1.2)	1 (1.2)	2 (1.2)
Stroke[c]	1 (1.2)	2 (1.2)	1 (1.2)	3 (1.8)	1 (1.2)	3 (1.8)
Myocardial Infarction[b]	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)

*Source: Table 10 of CCR

In summary, the comprehensive clinical assessment did not result in differences in the interpretation of the imbalance in cardiovascular events in Study 142 between adjudication

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committees (DCRI and TIMI). Interpretation and conclusions from Studies 337 and 174 remained unchanged following the TIMI adjudication process. In addition, incidences of CV SAEs were consistent between analyses based on treatment-emergent adverse event reporting and the adjudicated cardiovascular adverse events, providing further assurance regarding comprehensiveness and reliability of the adjudication process.

DCRP Consultation

The Division of Bone, Reproductive and Urologic Products consulted the Division of Cardiovascular and Renal Products (DCRP) to request their assistance in reviewing the cardiovascular safety signal from the meta-analysis of the 3 pivotal studies, as well the adjudication process from the DRCI and the readjudication from the TIMI group. DCRP determined that both the DRCI and TIMI adjudication processes were adequate, and the required documentation was sufficient to render an adequate adjudication. DCRP also confirmed that the DCRI and TIMI adjudications yielded similar results. DCRP concluded that the overall hazard ratio for cardiovascular events from the meta-analysis was low but with an overall marginally significant hazard ratio for romosozumab vs. comparator. Refer to their written consult for further details regarding their analysis of the applicant's comprehensive cardiovascular safety assessment.

Nonclinical and Human Genetic Data, Possible Explanations of Observed Imbalance, Epidemiology Reviews

As discussed in the nonclinical section of this memorandum, the nonclinical data suggest that there is limited biological plausibility for a causal link between sclerostin inhibition and cardiovascular risk. Sclerostin is expressed in the aorta and in vascular and valvular calcification. However, its function in these sites is not known. Expression of sclerostin in vascular smooth muscle cells in foci of vascular mineralization in animals would be unlikely to explain the early imbalance in positively-adjudicated CV SAEs observed in Study 142. The timing of the observed events, with early separation between the alendronate and romosozumab arms within the first 3 months of treatment, is not consistent with a process involving vascular calcification. In addition, sclerostin inhibition did not appear to result in the initiation of vascular calcification or exacerbation of pre-existing medial calcification associated with aging or chronic kidney disease in animals, as shown by chronic toxicology evaluation in monkeys, a species that constitutively expresses sclerostin in the aorta, and in a lifetime study in rats, a species in which sclerostin is expressed in mineralizing foci.

In response to the cardiovascular safety findings observed in Study 142, the applicant performed additional nonclinical studies to explore plausible mechanisms that could account for an increased cardiovascular risk with romosozumab, including an in vitro human platelet activation study, an in vitro vasoconstriction study, a study that assessed sclerostin expression in atherosclerotic plaques, a study in the ApoE -/- mouse model of atherogenesis and a genome

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wide association study. For further details and discussion regarding these studies, refer to Section 5 of this review.

In patients with sclerosteosis or van Buchem disease, in whom sclerostin expression is absent or reduced due to a genetic mutation, there is no evidence of early onset vascular calcification or increased cardiovascular risk in the literature or through written communications with a scientific expert on the disease (Beighton, 2011c; Beighton, 2011d). The applicant included these communications in the BLA submission. Of note, these data are limited given the rarity of the disease and would not necessarily be able to detect a modest increase in cardiovascular risk if present.

Overall, the available nonclinical data do not definitively identify a mechanism to support biological plausibility for a causal relationship of romosozumab treatment with myocardial infarction or stroke. However, the finding of an increased incidence of necrotic aortic plaques in ApoE-/- mice (in Study 124609 as described in the nonclinical section of this memorandum) may be relevant, as recently available clinical data demonstrate that necrotic coronary plaques are at high risk of rupture, potentially leading to myocardial infarction (Williams et al., 2019). Relevant nonclinical data, however, are still limited, and the role of sclerostin in the cardiovascular system is currently not well understood.

Alendronate Cardioprotection

One possible explanation for the imbalance of serious cardiovascular events in Study 142 (other than a true increased risk with romosozumab) is that alendronate may have had an early cardioprotective effect on subjects in the alendronate treatment group. The FDA's exploratory network meta-analysis indirectly estimating the hazard ratio of MACE for alendronate vs. placebo (discussed above) was consistent with this as a possibility. There is also biologic plausibility to this theory, as bisphosphonates and statins (drugs used to treat hyperlipidemia and reduce the risk of ischemic cardiovascular events) both inhibit the mevalonate pathway (however, bisphosphonates have high specificity to bone and osteoclasts). To date, studies evaluating this theory of a cardioprotective effect of alendronate (and other bisphosphonates) have yielded mixed results. The alendronate controlled clinical fracture trials did not demonstrate a cardioprotective benefit.

A recent retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority investigated the risk of cardiovascular events with and without alendronate in hip fracture patients (Sing CW et al., 2018). A total of 4594 patients treated with osteoporosis therapy were matched with 13,568 nontreated patients. Alendronate was associated with a significantly lower risk of 1-year cardiovascular mortality (hazard ratio 0.33; 95% CI, 0.17 to 0.65) and incident myocardial infarction (hazard ratio 0.55; 95% CI, 0.34 to 0.89), and a marginally significant reduction in risk of stroke at 5 years and 10 years (hazard ratio at 5 years: 0.82; 95% CI, 0.67 to 1.00; p = 0.049; hazard ratio at 10 years: 0.83; 95% CI, 0.69 to 1.01; p = 0.065). These findings were consistent in multiple sensitivity analyses.

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In contrast, a meta-analysis (Kim DH et al., 2015) that estimated the risks of cardiovascular events (including total cardiovascular events, atrial fibrillation, myocardial infarction, stroke and cardiovascular death) in 58 randomized controlled trials of bisphosphonates in adults with low bone mass found that bisphosphonates do not appear to have beneficial or harmful effects on atherosclerotic cardiovascular events. Another meta-analysis (Kranenberg G et al., 2016) reviewed 61 randomized controlled studies that reported the effects of bisphosphonates on arterial wall disease, cardiovascular events, cardiovascular mortality or all-cause mortality. There was no restriction for the type of population used in the studies. This meta-analysis found that bisphosphonates have no effect on arterial stiffness (based on 2 trials) or on cardiovascular events (based on 20 trials), but they did reduce arterial wall calcification (based on 2 trials), reduce the risk of cardiovascular mortality (based on 10 trials) and reduce all-cause mortality (based on 48 trials) in various patient groups, including osteoporosis and cancer patients.

Although a cardioprotective effect of alendronate is a possibility, we cannot assume that the observed imbalance in cardiovascular events was due to this, as such a protective effect of bisphosphonates has not been established, and the available relevant data are not conclusive.

Background Rates of Myocardial infarction and Stroke

Another possible explanation for the imbalance observed in the two treatment arms is that the rates of observed events in each treatment group of Study 142 are within the expected variation range for cardiovascular events in the study population. To explore this possibility, the applicant conducted a targeted PubMed search for background rates of serious cardiovascular outcomes reported in population-based epidemiology studies of women and men aged 55-90 years. The applicant reviewed 10 population-based epidemiology studies (5 in osteoporosis patient populations, 5 in non-osteoporosis populations). The studies identified a background incidence rate estimate for myocardial infarction as 2-10 per 1,000 person-years (PYs) in the general population and 3-13 PYs in osteoporosis population, and for stroke 1-47 and 16-38 per 1,000 PYs, respectively. For comparison, in the 3 pivotal studies, the incidence rate of positively adjudicated myocardial infarction ranged from 3 to 8 per 1,000 PYs and the incidence rate of positively-adjudicated stroke ranged from 2 to 19 per 1,000 PYs in the romosozumab arm. In the alendronate arm, the corresponding rates were 3 and 4 per 1,000 PYs, respectively. In contrast, the incidence rates in the placebo group ranged from 0-2 and 3-13 per 1,000 PYs for MI and stroke, respectively.

Based on these findings, the applicant believes that the incidence rates of positively adjudicated myocardial infarction and stroke reported among subjects in the three phase 3 studies, including subjects receiving romosozumab, are within the ranges reported in population-based studies for similarly aged cohorts of women.

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The Division of Epidemiology (DEPI) conducted an independent literature search using PubMed and EMBASE to identify population-based studies that contain information on incidence rate of MI and stroke in osteoporosis patients 50-90 years of age. After manually screening 330 titles and abstracts, DEPI identified 13 articles to be included in the qualitative synthesis, including all 5 osteoporosis studies reviewed by the applicant. The remaining 5 studies reviewed by the applicant were conducted in non-osteoporosis populations (Mozaffarian et al. 20156; Mulnier et al. 20087; Igland et al. 20148; Vangen-Lonne et al. 20159; Truelsen et al. 200610). Additionally, DEPI also identified and reviewed 8 population-based studies conducted in osteoporosis patient populations that were not included in the applicant's Comprehensive Cardiovascular Report. The 13 studies reviewed by DEPI included populations in the US, UK, Denmark, Taiwan and Hong Kong.

DEPI's literature review revealed a wider range of incidence rate estimates (for myocardial infarction: from 1.2 to 30.3 per 1,000 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).

Based on their literature review, DEPI concluded that 1) the background incidence rates of stroke and myocardial infarction vary substantially in the published literature. These substantially varied incidence rate estimates may be due to: 1) lack of validation for the case ascertainment algorithms used to identify CV SAE outcomes in administrative claims-based databases; 2) the selection of a high-risk study population (patients with a prior diagnosis of osteoporotic fracture) to derive the expected background rates; or 3) other confounding factors such as race, geographic locations, and baseline CV risk profiles which were inconsistent with the trial population. This heterogeneity may explain the wide range of the background rate estimates.

Despite the wider range of estimates derived from their literature search, DEPI, like the applicant, concluded that the incidence rates of myocardial infarction and stroke reported in the different treatment groups in Study 337 and Study 142 all fall within the expected background incidence rates in similarly aged osteoporosis populations. For full details regarding DEPI's literature search, results and analysis, refer to the consult entered in DARRTS 11-6-18.

Given that the range of incidence rates of myocardial infarction and stroke reported in the literature is very wide, it is not surprising that the rates observed in the pivotal romosozumab studies fall within this range. Therefore, although it is somewhat reassuring that the rates observed in Study 142 do fall within the reported background ranges, we cannot conclude that this explains the observed imbalance of events, as we do not have a precise, established estimate of this range.

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Summary/Assessment

Currently there is no definitive evidence to account for a mechanism by which romosozumab could lead to an increased risk of cardiac ischemic and cerebrovascular events. The only signal that may suggest potential biologic plausibility is the nonclinical finding of an increased incidence of necrotic aortic plaques in a mouse model of atherogenesis that was exposed to romosozumab (see the nonclinical section of this memorandum for details). Relevant nonclinical data, however, are still limited, and the role of sclerostin in the cardiovascular system is currently not well understood.

Although there currently is no definitive evidence to explain a mechanism by which romosozumab could increase the risk of cardiac ischemic and cerebrovascular events, there is also currently no evidence of an alternative cause or explanation for the observed imbalance in these events in Study 142. Therefore, we must consider that the imbalance in events of myocardial infarction and stroke observed in Study 142 and Study 174 may represent an increased risk of these events with romosozumab therapy and factor this potential risk into our benefit-risk assessment.

For all the reasons discussed above, it is not possible to definitively determine whether romosozumab increases cardiovascular risk, whether this is a chance finding or whether the findings reflect a cardioprotective effect of alendronate. Without definitive data resolving this uncertainty, we conclude at this time that romosozumab may increase cardiovascular risk. To ensure benefits outweigh the risks, romosozumab should be avoided in patients at high cardiovascular risk (e.g., those who have had a myocardial infarction or stroke within the preceding year).

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Adverse events were analyzed separately by age (<75 and ≥ 75). There were no notable differences in the incidence rates of adverse events between the two subgroups. Cardiovascular adverse events were analyzed by multiple different subgroups as described in Section 8.2.5.

8.2.8. Specific Safety Studies/Clinical Trials

The applicant studied patients who transitioned from bisphosphonate therapy in two studies, Study 289 and Study 223, to understand safety and efficacy parameters in this population. As

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discussed in the review of the original BLA, results from these studies do not raise any safety concerns for patients who transition to romosozumab from long-term (>3 years) bisphosphonate therapy.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Although the Wnt-beta-catenin pathway has a known role in both sclerostin signaling and some tumor suppressor signaling, there are no data to suggest a cancer risk associated with romosozumab. Nonclinical rat studies included a rat lifetime pharmacology (carcinogenicity) study at doses up to 50 mg/kg QW and results did not raise concern for carcinogenicity. In addition, the totality of the data from the romosozumab clinical program do not support a risk for cancer, although conclusions may be limited because the duration of romosozumab treatment was limited to only 1 year.

Human Reproduction and Pregnancy

No studies of romosozumab have been conducted in pregnant or breastfeeding women, and all studies have specifically excluded pregnant or breastfeeding women.

Romosozumab is not recommended for use in pregnant or premenopausal women.

No pregnancies were reported with exposure to romosozumab during any of the clinical studies of romosozumab.

Pediatrics and Assessment of Effects on Growth

Romosozumab has not been studied in children and adolescents.

This drug is indicated for postmenopausal women and is not expected to be used for a pediatric indication. A full pediatric waiver was previously obtained.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

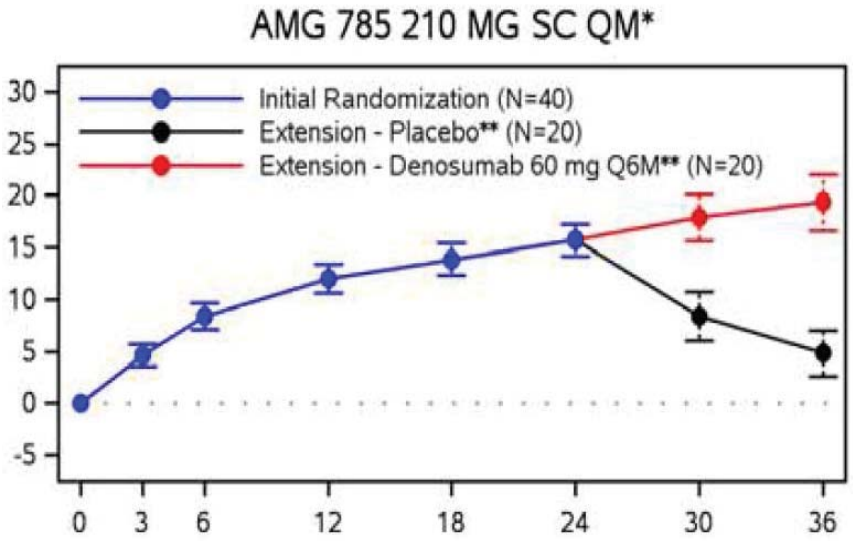
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Neither the effects of overdose of romosozumab nor an antidote to overdose are known. Data from completed phase 1 clinical studies demonstrate that romosozumab has an acceptable safety profile up to the highest dose tested (doses up to 10 mg/kg SC and 5 mg/kg IV).

There is no evidence that use of romosozumab could lead to drug abuse or dependence.

Regarding potential withdrawal or rebound, Study 326, a multi-dose study in women with low BMD that primarily evaluated the effect of different doses of romosozumab on lumbar spine BMD at Month 12, also evaluated romosozumab off-treatment effects. In this study, 5 dose levels of romosozumab were evaluated against placebo. Lumbar spine BMD at Month 12 was the primary endpoint. Subjects continued to receive romosozumab for an additional 12 months and then were randomized again within their initial treatment groups to receive placebo or denosumab for 12 months (study months 24-36). As depicted in Figure 8, for subjects who received placebo after romosozumab 210 mg monthly (n=20), mean percent change from baseline in lumbar spine BMD decreased from month 24 to 36, yet remained 5% above baseline at month 36. For subjects who received denosumab after romosozumab 210 mg monthly (n=20), lumbar spine BMD continued to increase through month 36.

Figure 8 Lumbar Spine BMD Percent Change from Baseline (Study 326 Months 0-36)



*Source: modified from Figure 10-11 of Study 326 Clinical Study Report

Study 326 also studied retreatment after subjects had been off-treatment. In this study, the retreatment phase was from months 36 to 48, during which time all participating subjects received romosozumab 210 mg QM regardless of their initial treatment. Although BMD gains and BTM levels demonstrate that retreatment with romosozumab achieve similar changes when compared to initial 12 months of romosozumab therapy, the small number of patients studied (19 subjects who received placebo from month 24-36 group and 16 subjects who received denosumab from months 24-36) limits extrapolation of results into a larger patient

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population. The safety of romosozumab in the retreatment phase (month 36 to 48) was consistent with results seen up to 24 months of romosozumab treatment and in line with expectations based on previous clinical study findings, but these findings are similarly limited by the small number of patients.

In addition, the 16 subjects in Study 326 who received active treatment for the first 48 months (romosozumab from months 0 to 24, denosumab for months 24 to 36 and romosozumab from month 36 to 48) were followed from months 48 to 72. These subjects had no indication of rebound or withdrawal effects in clinical laboratory values:

- Median percent change in albumin-corrected calcium from Month 48 to Month 72 was 0.0%
- Median iPTH level decreased through Month 60, then returned to above Month 48 level by Month 72
- Mean phosphorus level increased slightly at Month 51, then returned to approximately the Month 48 level by month 72
- Mean GFR decreased through Month 51, then increased to above Month 48 levels by Month 72.

8.2.10. Safety in the Postmarket Setting

There are little postmarketing safety data for romosozumab. Romosozumab was recently approved for use in Japan and postmarketing safety data are not available. The safety profile of romosozumab in the postmarket setting is expected to resemble the safety profile established in clinical trials. However, there is an increased concern for hypocalcemia in patients with severe renal failure who were excluded from clinical trials. These patients should be monitored for hypocalcemia during therapy. This concern will be communicated in the label.

8.2.11. Integrated Assessment of Safety

The safety profile of romosozumab in Study 142 with respect to the overall subject incidences of adverse events, serious adverse events, fatal adverse events, and adverse events leading to withdrawal of investigational product or withdrawal from the study is consistent with the adverse event profile presented in the original BLA. Results for adverse events of interest based on prespecified adverse event categories, positively adjudicated ONJ, and positively adjudicated AFF were also consistent with the data presented in the original BLA, with injection site reactions being the only adverse event of interest that was higher in romosozumab group than in the control group. The imbalance in positively adjudicated CV SAEs in Study 142 based on the prespecified DCRI adjudication (2.5% romosozumab; 1.9% for alendronate), driven by events of myocardial infarction (16 [0.8%] vs. 5 [0.2%] subjects) and stroke (13 [0.6%] vs. 7 [0.3%] subjects), is a new safety finding compared with the safety data presented in the original BLA.

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This BLA resubmission included an integrated safety analysis composed of pivotal PMO phase 3 Studies 337 and 142, as well as an integrated safety analysis from all phase 2 and 3 studies in PMO (including the supportive studies 326, 291, 156 and 289). All subjects who received romosozumab were pooled to form the total romosozumab group and all subjects who received placebo or active comparator were pooled to form the total control group. Per our request, Study 174 was excluded from all pooled safety analysis sets and only cardiovascular safety data from that study were addressed in our review of the resubmission.

New analyses integrating Study 142 into the existing populations with Study 337 and with all other phase 2 and 3 studies were provided in Module 2.7.4 of the submission. Our review of these pooled analyses did not identify any additional safety signals, other than the cardiovascular safety signal mentioned above and discussed in detail in section 8.2.5. In addition to the risk of serious cardiovascular events of myocardial infarction and stroke, the totality of the safety data demonstrates the following key risks of romosozumab that are consistent with those identified in the original BLA: hypersensitivity reactions, injection site reactions, hypocalcemia, ONJ and AFF.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

One potential statistical issue related to the co-primary endpoint of time to first clinical fractures in Study 142 was described in section 8.1.1. For time to first clinical fracture through the primary analysis period, with varied follow-up time for subjects, the pre-defined statistical analysis method was a Cox-proportional hazard model. Therefore, the Applicant's description of the clinical fracture endpoint as "subject incidence of clinical fracture through the primary analysis period", did not appear to be consistent with the analysis method. Hazard model analysis describes the relation between the fracture incidence and other potential covariates with varying follow-up time as opposed to fixed follow-up time and were appropriately labeled as risk reduction based on time to event analysis for the above endpoint. This statistical terminology issue does not impact the statistical analysis methods and results for the clinical fracture endpoint.

8.4. Conclusions and Recommendations

The safety and efficacy of romosozumab for the treatment of postmenopausal women with osteoporosis at high risk of fracture was evaluated in two large fracture efficacy trials, a placebo-controlled fracture trial 20070337 (study 337) and the active-controlled fracture trial 20110142 (study 142). These studies evaluated whether 12 months of treatment with romosozumab followed by continued therapy with an anti-resorptive agent provided fracture risk reduction in postmenopausal women.

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Study 337 (N = 7180), reviewed in the first BLA cycle, was a phase 3, randomized, double-blind, placebo-controlled, parallel-group study that assessed the efficacy and safety of romosozumab 210 mg administered subcutaneously (SC) every month (QM) for a duration of 12 months followed by denosumab 60 mg every 6 months for 12 months compared to 12 months of placebo followed by 12 months of denosumab in women with postmenopausal osteoporosis. The study demonstrated a statistically significant reduction with romosozumab compared to placebo for both co-primary endpoints, which were 1) the subject incidence of new vertebral fractures at 12 months and 2) the subject incidence of new vertebral fractures at 24 months. During the 12-month double-blind period, the subject incidence of new vertebral fracture with romosozumab was 0.5% compared to 1.8% with placebo, with a significant absolute risk reduction of 1.3% (95% confidence interval [CI]: 0.8, 1.8). and relative risk reduction of 73% (95% CI: 53, 84). At 24 months, the subject incidence of new vertebral fracture with romosozumab followed by denosumab was 0.6% compared to 2.5% with placebo followed by denosumab, with a significant absolute risk reduction of 1.9% (95% CI: 1.3, 2.5). and relative risk reduction of 75% (95% CI: 60, 84). Clinical fracture (a composite of nonvertebral and clinical vertebral fractures) and nonvertebral fracture were secondary endpoints in study 337. At 12 months, the subject incidence of clinical fracture was 2.5% in the placebo group and 1.6% in the romosozumab group with an absolute risk reduction of 1.2% (95% CI: 0.4, 1.9) and relative risk reduction of 36% (95% CI: 11, 54). However, 88% of these clinical fractures were nonvertebral fractures and the risk reduction of nonvertebral fractures when considered alone did not meet statistical significance when adjusted for multiplicity. Study 337 was not adequately designed to assess romosozumab's efficacy for reduction in hip fractures.

Romosozumab also significantly increased BMD at all sites. At month 12, compared with placebo, romosozumab increased BMD by 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 all sites at Month 24.

Study 142 (N = 4093) was a phase 3, randomized, double-blind, alendronate-controlled study that assessed the efficacy and safety of romosozumab 210 mg SC monthly for a duration of 12 months followed by alendronate 70 mg weekly compared with alendronate 70 mg weekly alone in women with postmenopausal osteoporosis with a history of fracture. Compared with Study 337, Study 142 enrolled a population at higher risk of osteoporosis-related fracture. The co-primary endpoints were 1) the subject incidence of clinical fracture (nonvertebral and clinical vertebral fracture) through the primary analysis period and 2) the subject incidence of new vertebral fracture through Month 24. The primary analysis occurred after clinical fracture events had been confirmed for at least 330 subjects and all subjects had completed the Month 24 visit. At 24 months, the subject incidence of new vertebral fracture with romosozumab followed by alendronate was 4.1% compared to 8.0% with alendronate alone, with a significant absolute risk reduction of 4.0% (95% CI: 2.5, 5.6) and relative risk reduction of 50% (95% CI: 34, 62). At the end of the primary analysis period, the subject incidence of clinical fracture with romosozumab followed by alendronate was 9.7% compared to 13.0% with alendronate alone, with a hazard ratio of 0.73 (95% CI: 0.61, 0.88), based on 464 subjects with clinical fractures with a median follow-up of 33 months. Romosozumab followed by alendronate significantly

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reduced the risk of nonvertebral fractures, a secondary endpoint, compared with alendronate alone at the primary analysis, with a hazard ratio of 0.81 (95% CI: 0.66, 0.99), based on 395 subjects with nonvertebral fractures with a median follow-up of 33 months. Study 142 was not designed adequately to assess romosozumab's efficacy for reduction in hip fractures. Regarding BMD, significantly higher increases were observed with romosozumab compared to alendronate at all sites assessed. At Month 12, treatment difference was 8.7% at the lumbar spine, 3.3% at the total hip, and 3.2% at the femoral neck. Romosozumab followed by alendronate maintained the significantly higher increases in BMD at all sites at Month 24.

The safety of romosozumab is documented with approximately 5621 subjects exposed to romosozumab for one year in the two phase 3 fracture trials. In these two trials, a total of 105 deaths occurred during the double-blind 12-month study periods. 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. 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 for fatal cardiac disorders, which occurred in 3 (0.1%) alendronate-treated subjects and 9 (0.4%) romosozumab-treated subjects. This cardiovascular safety finding along with the imbalance in adjudicated serious adverse cardiac events in study 142 is the predominant safety concern for romosozumab.

The outcomes of interest to evaluate cardiovascular risk were major adverse cardiovascular events (MACE) 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, Cardiovascular death included deaths of undetermined cause. Across the two fracture trials, 51 (0.9%) subjects in the control group and 71 (1.3%) subjects in the romosozumab group experienced a major cardiac adverse event, yielding a hazard ratio of 1.38 (95% CI: 0.96, 1.99). However, when each fracture trial is considered separately, the results diverge. In the placebo-controlled study 337, major cardiac adverse events were balanced (29 (0.8%) subjects in the control group, 30 (0.8%) subjects in the romosozumab group, hazard ratio 1.03 (95% CI: 0.62, 1.72). In the active controlled study 142 where subjects were slightly older, 22 (1.1%) subjects in the control group and 41 (2.0%) subjects in the romosozumab group experienced a major cardiac adverse event yielding a hazard ratio of 1.87 (95% CI:1.11, 3.14).

Further evaluation of potential differences between the two fracture trials did not reveal an explanation for the differences in MACE outcomes. The participants in study 142 (74 years) were slightly older than those in study 337 (71 years) with slightly higher baseline positive cardiovascular risk characteristics (79% in study 142, 75% in study 337). However, because of the small number of events in both fracture trials, subgroup analyses based on demographic characteristics and osteoporosis characteristics were not informative. Because of the early separation of events between romosozumab and alendronate groups in the Kaplan Meier

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curve, further evaluation of romosozumab's effect on platelet aggregation, vasoconstriction, and blood pressure were assessed but did not reveal concerning findings in the limited data available. It is recognized that the sclerostin gene SOST mRNA is expressed in the heart, aorta, liver, and kidney. However, nonclinical and in vitro evaluations have not provided conclusive evidence regarding an association between sclerostin inhibition and adverse cardiovascular structural or functional effects. Therefore, cardiovascular adverse events remain a potential risk with romosozumab therapy.

Other safety risks for romosozumab identified in the clinical fracture trials include the following:

Injection Site Reactions: Across both fracture trials, injection site reactions occurred in 278 (5%) women in the romosozumab group and 157 (3%) women in the control group. The most common injection site reactions were pain (94 [1.7%] women in the romosozumab group; 70 [1.3%] in the control group) and erythema (80 [1.4%] women in the romosozumab group and 14 [0.3%] women in the control group). Injection site reactions resulted in discontinuation of treatment in 7 (0.1%) romosozumab treated patients and 3 (<0.1%) patients in the control group.

In the first review cycle, injection site reactions were evaluated based on antidrug antibody status. Injection site reactions occurred in 3% of placebo treated subjects, 5% of binding antibody negative romosozumab treated subjects and 7% binding antibody positive romosozumab treated subjects. When evaluated in terms of neutralizing antibody status, injection site reactions occurred in 3% of placebo treated subjects, 7% of neutralizing antibody negative romosozumab treated subjects and 7% neutralizing antibody positive romosozumab treated subjects.

The injection site reactions reported in the fracture trials occurred using a drug product concentration of 70 mg/mL where patients required 3 injections of 1mL each to reach the 210 mg dose. The to-be- marketed formulation of romosozumab will be the 90 mg/mL concentration, where patients will need two injections of 1.17mL each. In trial 20120156 comparing the 70 mg/mL and the 90 mg/mL formulations, injection site reactions occurred in no subjects in the placebo group, 11 (9%) subjects in the 70 mg/mL romosozumab group and 13 (11%) subjects in the 90 mg/mL romosozumab group.

The potential for injection site reactions may be more pronounced with the higher concentration of romosozumab or in patients who develop binding antibodies to romosozumab.

Hypersensitivity: Like other monoclonal antibodies, romosozumab may be associated with hypersensitivity reactions. In study 337, hypersensitivity reactions were noted in 247 (7%) subjects in the placebo group and 242 (7%) subjects in the romosozumab group during the double-blind 12-month study period. In study 142, potential hypersensitivity reactions were reported for 118 (6%) subjects in the alendronate group and 122 (6%) subjects in the

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romosozumab group during the 12-month double-blind period. Clinically significant hypersensitivity reactions included angioedema, erythema multiforme, and urticaria. The potential for hypersensitivity reactions in the fracture trials are reported with use of romosozumab 70 mg/mL formulation. The to-be- marketed formulation of romosozumab will be the 90 mg/mL concentration, where patients will need two injections of 1.17mL each. Trial 20120156 was a 6-month trial that compared bone density changes of the romosozumab 70 mg/mL formulation and the romosozumab 90 mg/mL formulation. Potential hypersensitivity reactions occurred in 3 (6%) subjects in the placebo group, 3 (3%) subjects in the 70 mg/mL romosozumab group and 14 (11%) subjects in the 90 mg/mL romosozumab group.

The potential for hypersensitivity reactions may be more pronounced with the higher concentration of romosozumab.

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. One proposed mechanism for the hypocalcemia is through the rapid bone mass accrual at initiation of treatment and an increased demand for bone-mineralization substrates such as calcium. Based on earlier studies, the nadir in serum calcium appears to occur between 2 weeks and 1 month following romosozumab injection. However, in Studies 337 and 142 serum calcium was not assessed prior to Month 1. Therefore, it is possible that the nadir may have occurred prior to Month 1. In study 337, 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) was reported in a romosozumab-treated subject. In study 142, 1 (< 0.1%) adverse event of hypocalcemia was reported in each treatment group. No hypocalcemia event was reported as serious. Mild and transitory decreases in albumin-corrected calcium and a compensatory increase in iPTH were observed after initiation of romosozumab. Based on the totality of data, the risk of hypocalcemia is manageable in all romosozumab-treated patients, with an additional safeguard of monitoring serum calcium in patients with stage 5 chronic kidney disease (CKD) who are at higher risk for hypocalcemia.

Osteonecrosis of Jaw (ONJ): 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 were submitted to an independent external adjudication committee for review and adjudication. In study 337, 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 study. In study 142, 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

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predominant anabolic action of the product. The mechanism is unclear at this time and ONJ will continue to be followed closely.

Atypical Femur Fracture (AFF): 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 were submitted to an independent external adjudication committee. In study 337, no placebo subjects and one romosozumab subject had a positively adjudicated case of atypical femoral fracture. In study 142, 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.

Similar to ONJ, the occurrence of atypical femoral fracture with romosozumab therapy was not anticipated. The mechanism is unclear at this time and atypical femoral fracture will continue to be followed closely.

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone leading to an increase in fragility and fracture. The goal of osteoporosis therapy is to reduce the risk of fracture. The risk of fracture increases with age and a history of a prior osteoporosis-related fracture. In older patients, fracture, predominantly hip fracture, is associated with increased morbidity and mortality. 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 designed adequately to assess hip fracture, a positive trend in hip fracture risk reduction was seen. Similarly, 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.

When all data are considered, the benefits outweigh the risks for one year of romosozumab therapy in postmenopausal women with osteoporosis who are at high risk of fracture. Romosozumab reduces the risk of vertebral and nonvertebral fracture. Although the fracture studies were not designed adequately to assess hip fracture, the outcome with the most associated morbidity and mortality, these studies did suggest a positive trend in risk reduction for hip fractures. Because of the different cardiovascular findings in the two large trials of romosozumab, the cardiovascular risk is considered a potential risk rather than a definitive risk. Given this potential risk, and the high risk of subsequent cardiac events in the year following a myocardial infarction or stroke, patients who are candidates for romosozumab therapy who have had a myocardial infarction or stroke within the prior year should not have romosozumab initiated, as outlined in product labeling.

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The review team recommends APPROVAL for romosozumab for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. Product labeling should include a boxed warning about the cardiovascular risk including the recommendation that patients with a history of stroke or myocardial infarction within the preceding year not receive romosozumab. Additionally, the review team recommends further evaluation of the cardiovascular signal post-approval as outlined below.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was held on January 16, 2019 to discuss the cardiovascular safety findings from the romosozumab fracture trials. The committee was asked to consider if the cardiovascular safety of romosozumab was adequately characterized or if additional safety data were needed.

The questions posed to the committee with a brief overview of the committee responses are outlined below:

Discussion Question 1:
Discuss whether the cardiovascular safety of romosozumab has been 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 post-approval.

Committee Discussion: The committee members agreed that the cardiovascular safety profile of romosozumab was not adequately characterized. Committee members noted that it is unclear whether there is any increased cardiovascular risk with romosozumab, given the differences between the two trials (337 and 142). All members agreed that additional data are necessary to better characterize the potential cardiovascular risk. Most members agreed that a traditional observational study would not provide reliable data to draw conclusions regarding romosozumab's cardiovascular safety. This concern was based on the likely channeling of the use of the drug to patients with low cardiovascular risk given the Boxed Warning. Some members recommended a dedicated cardiovascular outcomes trial (CVOT) to better characterize the risk. Most members recognized that a dedicated CVOT would provide the most reliable data, although some thought it would not be feasible because it would likely require many thousands of patients and take several years to complete. Some suggested that enriching the population with patients at higher cardiovascular risk would help to overcome this limitation. Proponents of a CVOT agreed that it would need to be active-controlled rather than placebo-controlled to ensure clinical equipoise in a population at high risk of fracture. Regarding the timing of an additional study examining cardiovascular safety, all but one member agreed that the study could be conducted post-approval.

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Discussion Question 2:
Amgen is seeking an indication 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.

Discuss whether the benefit/risk profile of romosozumab could be improved by further narrowing the indicated population to patients at low cardiovascular risk, and if so, how to define the narrowed population.

Committee Discussion: The committee members agreed that romosozumab treatment provides significant benefit in preventing the morbidity and mortality associated with osteoporosis. However, because of the uncertainties surrounding the cardiovascular risk of romosozumab, some members stated that it may be challenging for physicians and patients to weigh the benefits and risks on an individual basis. Additionally, the panel members noted that withholding the drug from anyone with a single cardiovascular disease risk factor may deny them a greatly needed benefit (e.g., prevention of potential morbidity and mortality associated with severe osteoporosis). Several committee members cited data showing that the risk of MACE is highest for patients who have had a myocardial infarction or stroke within the past year. Most members agreed that the best approach would be to warn against romosozumab use in this population.

Voting Question:
Is the overall benefit/risk profile of romosozumab acceptable to support approval?

A. Yes, for Amgen's 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)
B. Yes, but for a different indication
C. No

Provide a rationale for your vote. If you voted for (b), describe the patient population in whom the benefits outweigh the risks.
Committee Vote: A: 15 B: 3 C: 1

Committee Discussion: Most committee members voted "A" in support of approval of Amgen's proposed indication for romosozumab. These panel members agreed that romosozumab is clearly effective for treating severe osteoporosis, for which therapeutic options are limited, and that these benefits outweigh the identified and potential risks. However, members recommended that an additional study be conducted post-approval to better characterize romosozumab's potential cardiovascular risk. Additionally, there was wide support among members for including a boxed warning in the label against use in patients at highest risk for MACE (at least until more is known regarding romosozumab's cardiovascular risk). One of the members who voted "B" in support of a different indication had concerns about the potential safety signal and had suggested the need for a REMS or additional pre-approval data. The other

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member who voted "B" stated that the phrase "intolerant to other available osteoporosis therapy" was too vague. The one member who voted "C" stated that there is not enough evidence to determine whether or not the benefits outweigh the risks.

10 Pediatrics

The applicant submitted an agreed initial Pediatric Study Plan iPSP on 1/12/2016 requesting a full waiver of the requirement to conduct pediatric studies, given that postmenopausal osteoporosis does not exist in the pediatric population. The iPSP was reviewed by the Pediatric Review Committee (PeRC) and PeRC concurred with the Applicant's plan for a full waiver.

During the first review cycle of this application, the applicant requested a full waiver from pediatric studies because the studies would be impossible given the lack of postmenopausal osteoporosis in the pediatric population. The request was reviewed by PeRC March 1, 2017 and PeRC agreed the request was appropriate and acceptable.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Boxed Warning	No mention of specific population for whom EVENITY should not be prescribed.	Added that EVENITY should not be prescribed for patients who have had a myocardial infarction or stroke within one year, and to consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. Added recommendation to discontinue EVENITY if myocardial infarction or stroke occurs while on therapy.
1 (Indications and Usage)	Did not discuss limitations of use.	Added language regarding one-year limitation of use.
4 (Contraindications)	Did not discuss correction of	Added language regarding

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	pre-existing hypocalcemia.	correction of hypocalcemia prior to initiation of therapy.
5 (Warnings and Precautions)	5.1 entitled (b) (4) (b) (4); no discussion of specific population for whom EVENITY should not be prescribed	5.1 retitled "Major Adverse Cardiac Events" Added that EVENITY should not be prescribed for patients who have had a myocardial infarction or stroke within one year, and to consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. Added recommendation to discontinue EVENITY if myocardial infarction or stroke occurs while on therapy.
6.1 (Adverse Reactions, Clinical Trials Experience)	Did not include major adverse cardiac event results (instead had this in Section 5).	Added results for major adverse cardiac events in Studies 337 and 142.
14 (Clinical Studies)	Results of Study 142 presented first.	Results of Study 337 presented first (the placebo-controlled study that was completed first)
	(b) (4)	
	Included results for new vertebral, nonvertebral and hip fractures at all major timepoints, regardless of statistical significance.	Removed all results that did not meet statistical significance.

12 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant did not propose a REMS for the marketing of romosozumab.

A REMS is not necessary to ensure the benefits outweigh the risks of romosozumab. Serious cardiovascular events of MI and stroke are an important potential risk; however, in the Agency's experience, REMS programs have minimal impact in mitigating the risk of MACE unless the REMS is designed specifically to limit who might receive the product. Such a REMS may not have the intended impact and is likely to require elements that would be burdensome to healthcare providers and patients. Therefore, as this product is efficacious and will be indicated for use in a higher risk population, a REMS is not necessary. Risk minimization will include communication of important risks for romosozumab through labeling including a boxed warning, limitations of use, and warning and precaution statements and a Medication Guide that alerts patients to the important risks.

13 Postmarketing Requirements and Commitment

The predominant safety concern for romosozumab is the cardiovascular safety signal seen in one of the fracture studies in postmenopausal women. The applicant proposes (b) (4)

(b) (4)

As discussed at the Advisory Committee meeting, it is unlikely that an observational study will adequately answer the question of cardiovascular safety with romosozumab use. Other options considered include either a randomized, active controlled cardiovascular outcomes study or a large simple trial where patients are randomized and with observational outcome followup. The applicant believes that neither of the randomized options are feasible because the proposed boxed warning language would limit the enrolled population to one of lower cardiovascular risk.

In conjunction with the Division of Epidemiology, we developed the following required postmarketing study:

(b) (4)



Study 2: The applicant will conduct a comparative safety study or trial
The applicant will conduct a comparative safety study or trial adequately designed and powered to rule out an unacceptable increase in risk of MI, stroke, and cardiovascular death among users of romosozumab compared to users of an appropriate comparator(s). The need, feasibility, design and milestones for this study or trial will be contingent upon the findings from study 1.

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14 Appendices

14.1. References

Ahmed LA, Center JR, Bjørnerem A, et al. Progressively increasing fracture risk with advancing age after initial incident fragility fracture: the Tromsø study. J Bone Miner Res. 2013;28(10):2214-2221.

Balasubramanian A, Zhang J, Chen L, et al. High risk of second fracture within 1, 2, 5 years after prior fracture among women 65 years or older. Abstract presented at The American Society for Bone and Mineral Research Annual Meeting; October 16–18, 2016; Atlanta, Ga. Abstract FR0233.

Bliuc D, Nguyen TV, Eisman JA, Center JR. The impact of nonhip nonvertebral fractures in elderly women and men. J Clin Endocrinol Metab. 2014;99(2):415-423.

Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA. 2009;30(5):513-521.

Brown RD, Ransom J, Hass S, et al. Use of Nursing Home After Stroke and Dependence on Stroke Severity: A Population-Based Analysis. Stroke. 1999;30:924-929.

Colón-Emeric C, Kuchibhatla M, Pieper C, et al. The contribution of hip fracture to risk of subsequent fractures: data from two longitudinal studies. Osteoporos Int. 2003;14(11):879-883.

Foulquier S, Daskalopoulos EP, Lluri G, Hermans KCM, Deb A, and Blankesteijn MW, Wnt Signaling in Cardiac and Vascular Disease. Pharmacol Rev 2018; 70:68–141.

Genant HK, Wu CY, Van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. Journal of Bone and Mineral Research. 1993;8:1137-48.

Johansson H, Siggeirsdottir K, Harvey NC, et al. Imminent risk of fracture after fracture. Osteoporos Int. 2017;28(3):775-780.

Johnell O, Kanis JA, Oden A, et al. Mortality after osteoporotic fractures. Osteoporos Int. 2004;15(1):38-42.

Johnell O et al. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporosis Int 2004; 15: 897-902.

Kado DM, Browner WS, Palermo L, et al. Vertebral fractures and mortality in older women. A prospective study. Arch Intern Med. 1999;159:1215-1220.

Kanis JA, Johnell O, Oden A, et al. Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int. 2000;11:669-674.

Khosla, S. Surrogates for fracture endpoints in clinical trials. J Bone Miner Res. 2003;18(6):1146-1149.

Kim DH, Rogers JR, Fulchino LA et al. Bisphosphonates and risk of cardiovascular events: a meta-analysis. PloS One. 2015; 10 (4).

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Kranenburg G, Bartstra JW, Weijmans M et al. Bisphosphonates for cardiovascular risk reduction: A systematic review and meta-analysis. Atherosclerosis 2016. 252: 106-115.

Krishna SM, Seto SW, Jose RJ, Jiaze Li, Morton SK, Biros E, Wang Y, Nsengiyumva V, Lindeman JHN, Loots GG, Rush CM, Craig JM, and Golledgeet J, Wnt Signaling Pathway Inhibitor Sclerostin Inhibits Angiotensin II-Induced Aortic Aneurysm and Atherosclerosis. Arterioscler Thromb Vasc Biol. 2017; 37:553-566.

Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001;285:320-323.

Morin S, Lix LM, Azimaee M, Metge C, Caetano P, Leslie WD. Mortality rates after incident non-traumatic fractures in older men and women. Osteoporosis Int. 2011;22(9):2439-2448.

National Osteoporosis Foundation (NOF). What is osteoporosis and what causes it? https://www.nof.org/patients/what-is-osteoporosis/.

Schnell S, Friedman SM, Mendelson DA, Bingham KW, Kates SL. The 1-year mortality of patients treated in a hip fracture program for elders. Geriatr Orthop Surg Rehabil. 2010;1(1):6-14.

Sing CW, Wong AY, Kiel DP, et al. Association of Alendronate and Risk of Cardiovascular Events in Patients with Hip Fracture. J Bone Miner Res. 2018; 33 (8): 1422-1434.

Tajeu GS, Delzell E, Smith W, et al. Death, debility, and destitution following hip fracture. J Gerontol A Biol Sci Med Sci. 2014;69(3):346-353.

Tran T, Bliuc D, van Geel T, et al. Population-wide impact of non-hip non-vertebral fractures on mortality. J Bone Miner Res. 2017;32(9):1802-1810.

Van Staa TP, Leufkens HGM, Cooper C. Does a fracture at one site predict later fractures at other sites: a British Cohort Study. Osteoporos Int. 2002;13:624-629.

Williams MC, Moss AJ, Dweck M et al. Coronary Artery Plaque Characteristics Associated with Adverse Outcomes in the SCOT-HEART Study. JACC. 2019; 73: 291-301.

World Health Organization. WHO Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level (Summary Meeting Report, Brussels, Belgium, 5-7 May 2004). Geneva, Switzerland: WHO Press; 2007.

World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organization. Geneva, Switzerland. 1994:1-129.

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14.2. Financial Disclosure

A Financial Disclosure form (3454) states that there was no arrangement by which compensation of the investigators or sub-investigators of the studies could be affected by the outcomes of these studies. The applicant has adequately disclosed financial interests/arrangements with clinical investigators.

A total of 10 investigators participating in Study 20110142 had disclosable financial arrangements. The sites of these investigators were in Australia, Germany, Hong Kong, and the U.S. Locations. All of these sites enrolled 3 or fewer subjects, with the exception of the one in Hong Kong, which enrolled 201 subjects.

Covered Clinical Study (Name and/or Number): 20110142

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 270		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 10		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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14.3. OCP Appendices

14.3.1. Immunogenicity

This section provides integrated immunogenicity results from all clinical studies in postmenopausal women (including newly submitted data from Study 20110142). Note that the immunogenicity results in the Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) for the original BLA submission do not include immunogenicity results from Study 20110142.

A total of 18.7% (1166 of 6244) of postmenopausal women with osteoporosis receiving romosozumab treatment in the phase 2 and phase 3 studies developed anti-drug antibodies (ADA) to romosozumab. Neutralizing antibodies (NAb) were detected in 1.0% (65/6244) of subjects. For subjects who received the recommended 210 mg romosozumab monthly dosing regimen, the ADA incidence was 18.1% (1072 of 5914). Of the subjects who developed antibodies to romosozumab, approximately 4.7% (50/1072) had antibodies that were classified as neutralizing.

The impact of immunogenicity on PK was evaluated in subjects who received romosozumab 210 mg in Studies 20060326, 20070337, 20101291, and 20110142. The presence of ADA resulted in reduced mean serum trough romosozumab concentrations by up to 22% across different time-points from Month 3 to Month 12. NAb resulted in a greater reduction in serum romosozumab concentrations based on the limited number of subjects (**Table 44**).

Table 44 Impact of Immunogenicity on Steady-State Trough Serum Romosozumab Concentrations in Pooled Studies 20060326, 20101291, 20070337, and 20110142.

	Mean±SD Serum Romosozumab Concentrations, mcg/mL (n)		
Time	**ADA Negative**	**ADA positive**	**NAb positive**
Month 3	8.65±5.83 (420)	7.03±5.17 (100)	4.76±1.86 (3)
Month 6	9.24±6.36 (462)	7.21±5.85 (112)	3.49±2.92 (7)
Month 9	10.4±6.83 (444)	8.83±7.62 (112)	3.84±4.17 (6)
Month 12	10.6±7.27 (475)	9.72±7.48 (110)	4.07±4.39 (7)

Source of data: Table 7&8, Summary of Clinical Pharmacology studies. Postmenopausal Women with Low BMD or Osteoporosis received romosozumab 210 monthly SC. ADA, anti-drug antibodies; NAb, neutralizing antibodies

Overall, there is no evidence that immunogenicity had an impact on efficacy or safety of romosozumab.

The Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) for the original BLA submission determined that there was no evidence that development of ADA had an impact on efficacy measured by bone mineral density (BMD). This finding was further supported by the results from Study 20110142 in the resubmission, in which the BMD percent change from

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baseline at the lumbar spine, total hip, and femoral neck showed comparable results between ADA negative and ADA positive subjects. Data for lumbar spine BMD are shown in Table 45.

Table 45 Effect of Immunogenicity on Lumbar Spine Bone Mineral Density Percent Change from Baseline in Study 20110142

	Lumbar Spine BMD Change% from Baseline (n)		
Time	**ADA Negative**	**ADA Positive**	**NAb Positive**
Month 12	13.7±7.2 (1421)	13.8±7.1 (283)	13.8±8.5 (11)
Month 24	15.4±8.4 (1299)	14.8±8.7 (263)	14.0±7.6 (11)
Month 36	15.1±9.3 (600)	14.4±9.5 (134)	18.1±7.1 (6)

Source of data: Table 14f-10.3.1 of the CSR 20110142

The impact of immunogenicity on fracture was assessed based on results from Studies 20070337 and 20110142. In study 20070337, 4 of 21 (19%) subjects who had a new vertebral fracture through Month 24 tested positive for ADA and none of them were positive for NAb. In Study 20110142, in subjects who had a new vertebral fracture through Month 24 (n = 75) the ADA and NAb incidences were 13.3% (10/75) and 1.33% (1/75), respectively. In general, subjects who experienced a new vertebral fracture through Month 24 had similar immunogenicity incidences for ADA and NAb compared to the overall population exposed to romosozumab.

The Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) for the original BLA submission determined that the development of anti-romosozumab binding and neutralizing antibodies did not appear to have an impact on the incidence of injection site reactions, hypersensitivity or autoimmune disorders. This finding was further supported by the results from Study 20110142 (Table 46).

Table 46 Effect of Immunogenicity on Safety by Immunogenicity Status Through Month 18 in Study 20110142

Adverse Events	**Alendronate Subjects (N = 2014)[a]**	**Romosozumab Subjects[b]**		
		ADA negative (N = 1639)	**ADA Positive (N = 316)[c]**	**NAb Positive (N=12)**
Injection site reactions, n (%)	53 (2.6%)	68 (4.1%)	16 (5.1%)	1 (8.3%)
Hypersensitivity, n (%)	118 (5.9%)	104 (6.3%)	17 (5.4%)	0
Autoimmune disorders, n (%)	35 (1.7%)	23 (1.4%)	1 (0.3%)	0

a: Subjects who received at least one dose of investigational product in the 12-month double-blind period. Immunogenicity testing was not conducted in subjects randomized to alendronate.
b: Subjects who received at least one dose of romosozumab and with at least one post-baseline anti-romosozumab antibody data through month 18
c: Sum of subjects who had pre-existing ADA (n=6) and subjects who had treatment-emergent ADA (n=310).
Source of data: Table 14-10.2.1.and 14-10.2.2 of the CSR 20110142.

14.3.2. Individual Study Summary: Study 20110142

Blood samples for measurement of serum romosozumab concentrations were collected pre-dose at baseline and at Months 1, 3, 6, 9, and 12 in a PK subgroup. The serum romosozumab concentrations are summarized in Table 477.

Table 47 Serum Romosozumab Concentrations in Study 20110142

	Trough Serum Romosozumab Concentrations (mcg/mL),					
	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12
Mean±SD (N)	0 (143)	7.7±4.5 (121)	10.2±6.5 (101)	10.7±7.1 (110)	13.2±9.5 (94)	13.4±8.9 (104)

Source of data: Table 11-3, Clinical Study Report 20110142. Subjects received SC administration of 210 romosozumab QM. Romosozumab concentrations in human serum were determined using a validated enzyme-linked immunosorbent assay (ELISA). Refer to Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) for detailed information of the assay performance and validation results.

Blood samples for immunogenicity assessment were collected at baseline, and at Months 1, 3, 6, 12, 18 and 24. Among 1955 subjects treated with romosozumab who had at least one post-baseline result through Month 18, 15.6% (310/1955) of subjects developed ADA. Among the ADA positive subjects, 3.9% (12/310) had neutralizing antibodies.

The impact of immunogenicity on PK was assessed by the subject ADA status through Month 12 (Table 488). The PK results overall showed lower mean serum romosozumab concentrations in ADA positive subjects compared to ADA negative subjects; however the difference was within 20% across all the PK time-points.

Table 48 Impact of Immunogenicity on Serum Romosozumab Concentrations in Study 20110142

Time	**Mean±SD Serum Romosozumab concentrations, mcg/mL (n)**	
	ADA Negative	**ADA Positive**
Month 1	8.0±4.4 (95)	6.9±4.7 (26)
Month 3	10.4±6.4 (81)	9.6±7.0 (20)
Month 6	11.2±7.1 (83)	9.0±6.9 (27)
Month 9	13.3±8.3 (75)	12.7±13.5 (19)
Month 12	13.5±9.0 (83)	12.5±8.8 (21)

Source of data: Table 11-4, Clinical Study Report 20110142. Subjects received SC administration of 210 romosozumab QM. Romosozumab concentrations in human serum were determined using a validated enzyme-linked immunosorbent assay (ELISA). Refer to Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) for detailed information of the assay performance and validation results.

Reference ID: 4416253

14.3.3. Population PK

The Applicant submitted two updated population PK analysis reports: Addendum 1 and Addendum 3. Compared with the original population PK report 119384A, PK results from two additional studies were included in the analysis dataset resulting in 304 additional subjects with 1257 additional serum concentrations in the latest updated population PK analysis report Addendum 3 (Table 49).

The PK parameters of the updated models (Addendum 1 and Addendum 3) are very similar to the original model. The originally identified significant covariates for clearance (body weight, eGFR, Japanese Race, and Manufacturing process) remain to be significant. Sex was additionally identified as a covariate to have significant effect on clearance and exposure. The population PK model predicted that a reference male subject has approximately 12% (95% CI: 6.0% -18.1%) higher exposure based on steady state AUC than a female subject.

No dose adjustment is necessary based on these significant covariates identified by the population PK model. Severe renal impairment and ESRD patients are predicted to have AUCss and Cmax greater than 125% of the typical reference;. Exposure-response analysis indicated that the exposure increase is not expected to have an effect on efficacy or safety, however, hypocalcemia remains a concern in ESRD patients. Other covariates are predicted to result in the change in Cmax and steady state AUC to be within 80-120% of a typical reference subject (Figure). *Refer to Office of Clinical Pharmacology Review (DARRTS Reference ID 4076576) in the original BLA submission for additional information.*

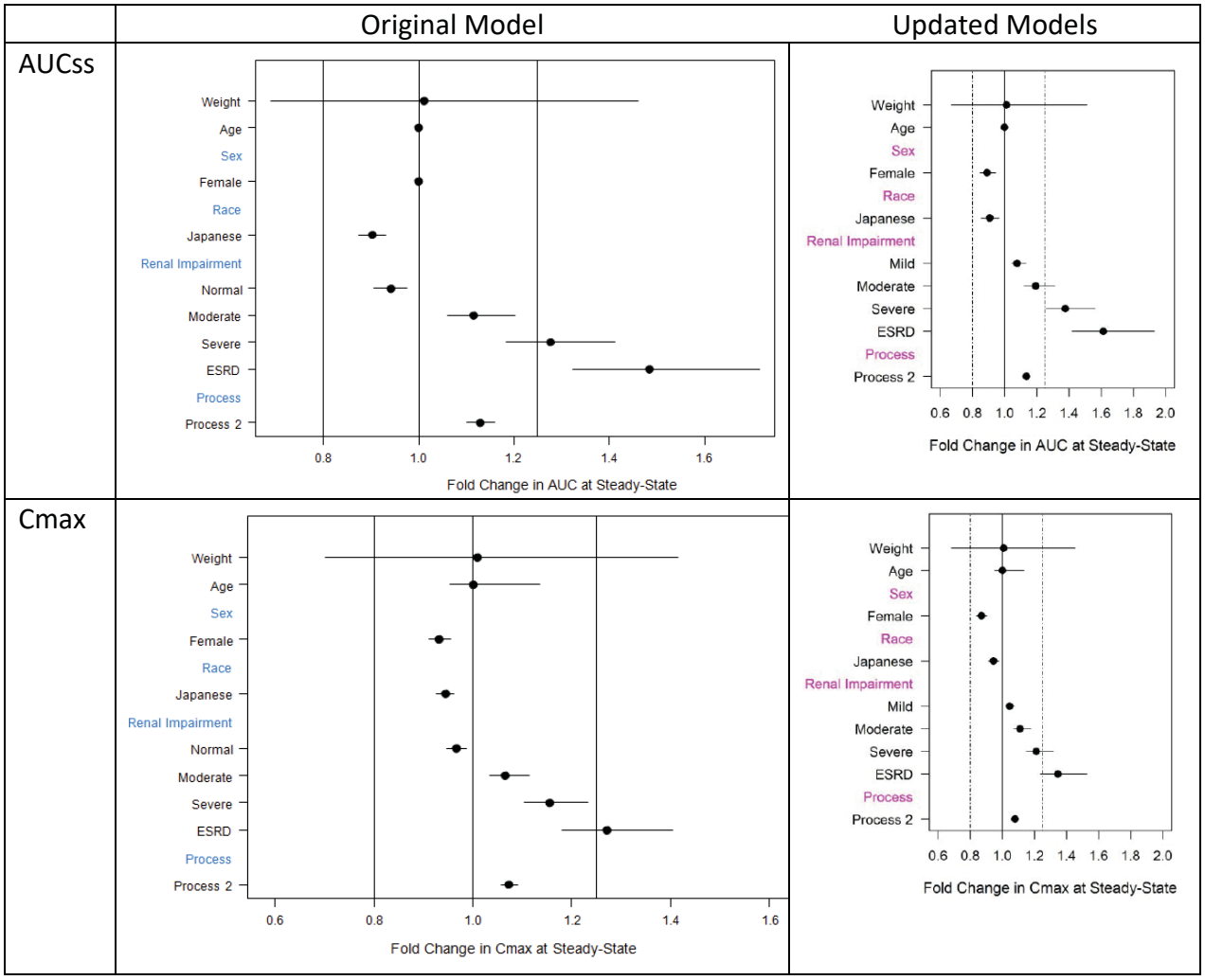
Reference ID: 4416253

Table 49: Summary of PK Dataset and Identified Significant Covariates in the Original and Updated Population PK Reports

	Report 119384A (Original)	**Addendum 1**	**Updated Model (Addendum 3)**
Study	Eight phase 1 studies: 20060220, 20060221, 20060223, 20090378, 20101180, 20120277, 20110227, and 20110253 two phase 2 studies: 20060326 and 20101291 one phase 3 study: 20070337	One additional Phase 3 study: 20110174 (in male subjects)	One additional Phase 3 Study: 20110142
Dataset	13346 concentrations from 1459 subjects	13954 concentrations from 1620 subjects with 311 males	14603 concentrations from 1763 subjects
Significant Covariates	CL (Body weight, eGFR, Japanese race, manufacturing process); V2(Body weight, age, and sex)	CL (Body weight, eGFR, Japanese race, sex, and manufacturing process); V2 (Body weight, age, and sex)	CL (Body weight, eGFR Japanese race, sex, and Manufacturing process); V2 (Body weight, age, and sex)

Reference ID: 4416253

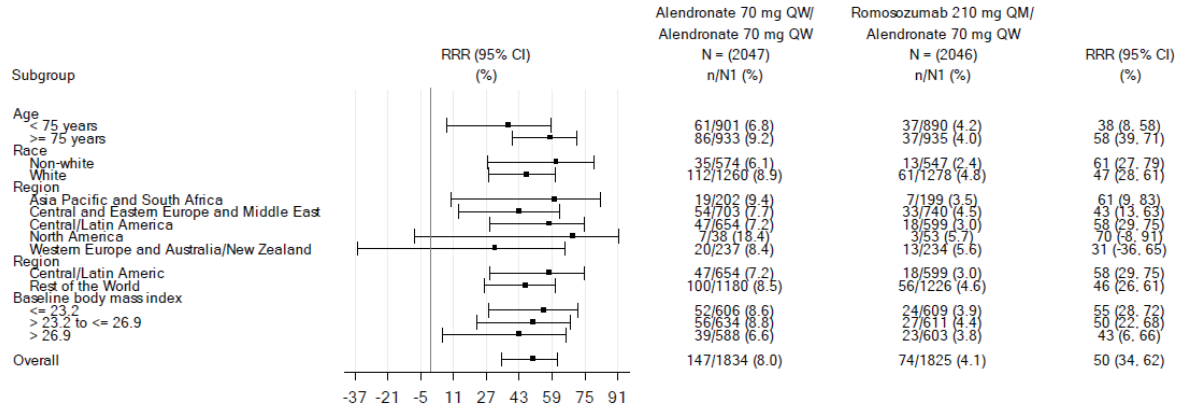
Figure 9: **Effect of Covariates on Romosozumab PK: Steady-state AUC and Cmax**



Source of data: Figure 2-1 in population PK report 119384A (left column) and Figure 16 in population PK report 119384A-Addendum 1 (right column). Note that estimates of covariates are almost identical between Addendum 1 and Addendum 3.

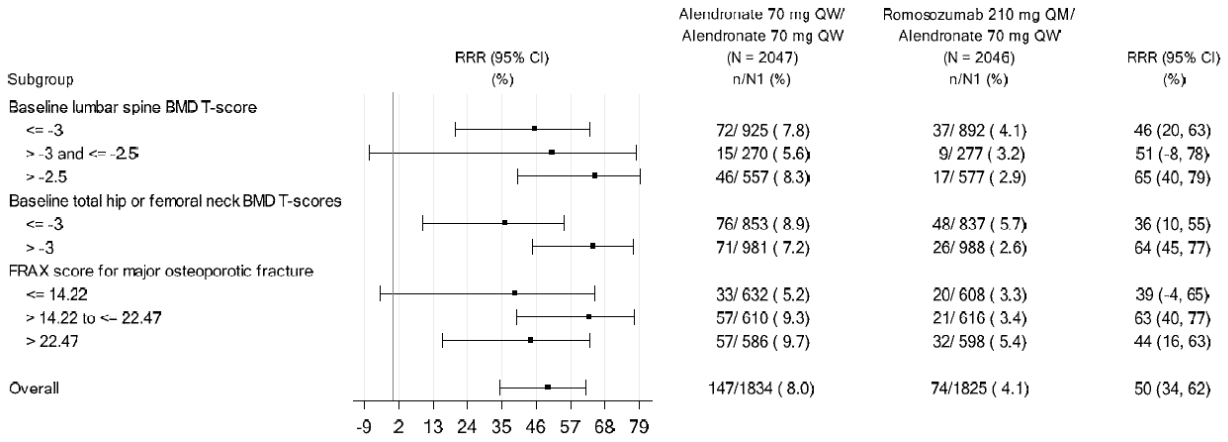
14.4. Statistical and Clinical Appendices

Figure 10. Study 20110142 Subject Incidence of New Vertebral Fracture Through Month 24 by Demographic and Physical Characteristic Subgroups (Primary Analysis Set for Vertebral Fractures, LOCF Imputation)



N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures
Relative risk reduction (RRR) and 95% CI based on the Mantel-Haenszel method adjusted for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline
Source: Figure 2 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

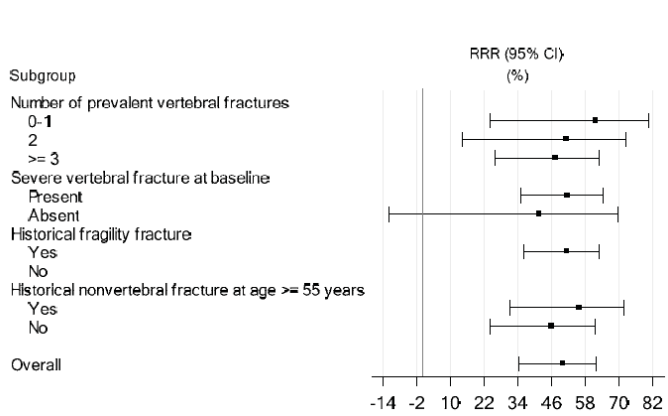
Figure 11. Study 20110142 Subject Incidence of New Vertebral Fracture Through Month 24 by Risk Factor Subgroups (Primary Analysis Set for Vertebral Fractures, LOCF Imputation)



N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures
Relative risk reduction (RRR) and 95% CI based on the Mantel-Haenszel method adjusted for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline
Source: Figure 1 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

Reference ID: 4416253

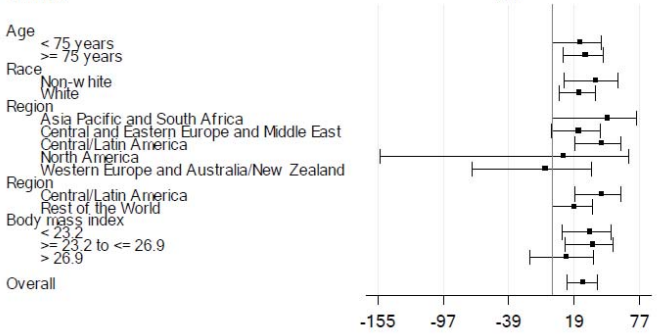
Figure 12. Study 20110142- Subject Incidence of New Vertebral Fracture Through Month 24 by Fracture History Subgroups (Primary Analysis Set for Vertebral Fractures, LOCF Imputation)



Subgroup	RRR (95% CI) (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 2047) n/N1 (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 2046) n/N1 (%)	RRR (95% CI) (%)
Number of prevalent vertebral fractures				
0-1		31/ 715 (4.3)	11/ 663 (1.7)	62 (24, 81)
2		34/ 476 (7.1)	17/ 465 (3.7)	51 (14, 72)
>= 3		82/ 640 (12.8)	46/ 689 (6.7)	47 (26, 63)
Severe vertebral fracture at baseline				
Present		121/1176 (10.3)	60/1209 (5.0)	52 (35, 64)
Absent		26/ 658 (4.0)	14/ 616 (2.3)	42 (-12, 70)
Historical fragility fracture				
Yes		147/1772 (8.3)	72/1764 (4.1)	51 (36, 63)
No		0/ 62 (0.0)	2/ 61 (3.3)	NE
Historical nonvertebral fracture at age >= 55 years				
Yes		57/ 624 (9.1)	26/ 624 (4.2)	56 (31, 72)
No		90/1210 (7.4)	48/1201 (4.0)	46 (24, 62)
Overall		147/1834 (8.0)	74/1825 (4.1)	50 (34, 62)

N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures
Relative risk reduction (RRR) and 95% CI based on the Mantel-Haenszel method adjusted for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline
Source: Figure 3 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

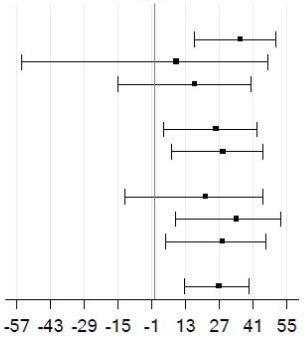
Figure 13. Study 20110142- Subject Incidence of Clinical Fracture Through Primary Analysis Period by Demographic and Physical Characteristic Subgroups (Full Analysis Set)



Subgroup	RRR (95% CI) (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW N = (2047) n/N1 (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW N = (2046) n/N1 (%)	RRR (95% CI) (%)
Age				
< 75 years		115/976 (11.8)	87/973 (8.9)	24 (0, 43)
>= 75 years		151/1071 (14.1)	111/1073 (10.3)	29 (9, 45)
Race				
Non-white		70/631 (11.1)	42/599 (7.0)	39 (10, 58)
White		196/1415 (13.9)	156/1447 (10.8)	24 (6, 38)
Region				
Asia Pacific and South Africa		24/216 (11.1)	13/213 (6.1)	49 (-1, 74)
Central and Eastern Europe and Middle East		112/798 (14.0)	93/835 (11.1)	23 (-1, 42)
Central/Latin America		90/727 (12.4)	47/674 (7.0)	44 (20, 60)
North America		7/42 (16.7)	10/55 (18.2)	10 (-153, 68)
Western Europe and Australia/New Zealand		33/264 (12.5)	35/269 (13.0)	-6 (-71, 34)
Region				
Central/Latin America		90/727 (12.4)	47/674 (7.0)	44 (20, 60)
Rest of the World		176/1320 (13.3)	151/1372 (11.0)	19 (-0, 35)
Body mass index				
< 23.2		92/683 (13.5)	62/681 (9.1)	33 (8, 52)
>= 23.2 to <= 26.9		94/709 (13.3)	62/684 (9.1)	36 (11, 53)
> 26.9		80/648 (12.3)	74/679 (10.9)	12 (-21, 36)
Overall		266/2047 (13.0)	198/2046 (9.7)	27 (12, 39)

N/N1 = Number of subjects randomized
Relative risk reduction (RRR) and 95% CI based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Figure 5 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

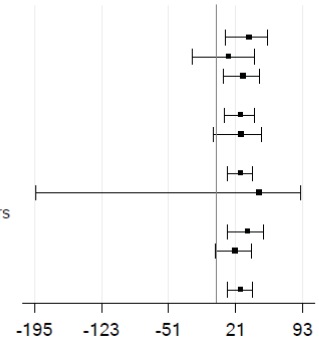
Figure 14. Study 20110142- Subject Incidence of Clinical Fracture Through Primary Analysis Period by Risk Factor Subgroups (Full Analysis Set)



Subgroup	RRR (95% CI) (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW N = (2047) n/N1 (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW N = (2046) n/N1 (%)	RRR (95% CI) (%)
Baseline lumbar spine BMD T-score				
<= -3		143/1024 (14.0)	92/997 (9.2)	36 (16, 51)
> -3 and <= -2.5		29/305 (9.5)	26/304 (8.6)	9 (-55, 47)
> -2.5		78/617 (12.6)	68/649 (10.5)	17 (-15, 40)
Baseline total hip and femoral neck BMD T-scores				
<= -3		136/961 (14.2)	101/949 (10.6)	26 (4, 43)
> -3		130/1085 (12.0)	97/1097 (8.8)	29 (7, 45)
FRAX score for major osteoporotic fracture				
<= 14.22		69/688 (10.0)	54/665 (8.1)	22 (-12, 45)
> 14.22 to <= 22.47		89/692 (12.9)	61/692 (8.8)	34 (9, 53)
> 22.47		108/660 (16.4)	82/686 (12.0)	28 (5, 46)
Overall		266/2047 (13.0)	198/2046 (9.7)	27 (12, 39)

N/N1 = Number of subjects randomized
Relative risk reduction (RRR) and 95% CI based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Figure 4 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

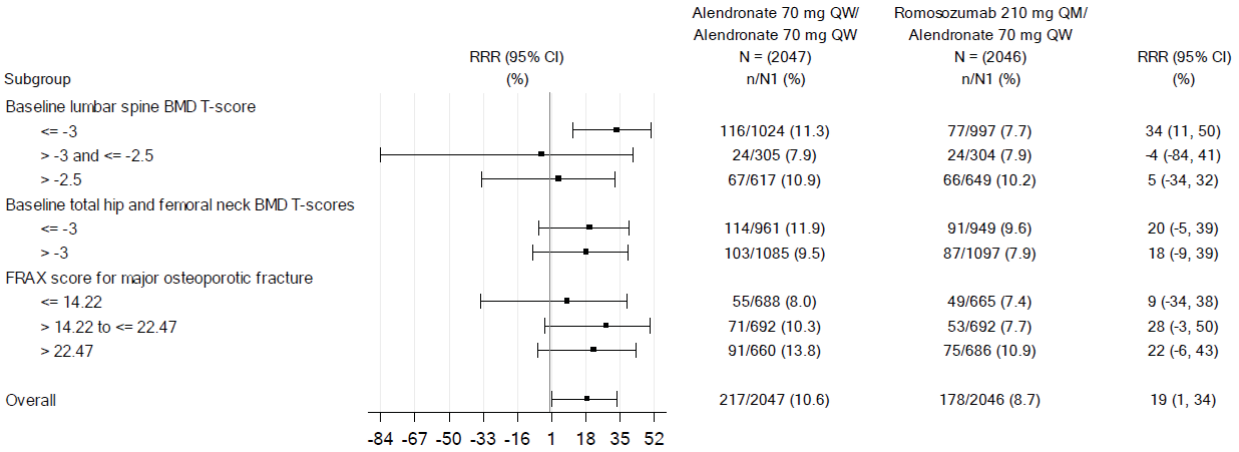
Figure 15. Study 20110142- Subject Incidence of Clinical Fracture Through Primary Analysis Period by Fracture History Subgroups (Full Analysis Set)



Subgroup	RRR (95% CI) (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW N = (2047) n/N1 (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW N = (2046) n/N1 (%)	RRR (95% CI) (%)
Number of prevalent vertebral fractures				
0-1		86/785 (11.0)	53/747 (7.1)	36 (10, 55)
2		59/533 (11.1)	50/517 (9.7)	14 (-26, 41)
>= 3		121/726 (16.7)	93/774 (12.0)	30 (8, 46)
Severe vertebral fracture at baseline				
Present		188/1321 (14.2)	145/1369 (10.6)	27 (9, 41)
Absent		78/726 (10.7)	53/677 (7.8)	27 (-3, 49)
Historical fragility fracture				
Yes		262/1982 (13.2)	196/1976 (9.9)	27 (12, 39)
No		4/65 (6.2)	2/70 (2.9)	47 (-194, 90)
Historical nonvertebral fracture at age >= 55 years				
Yes		115/692 (16.6)	79/705 (11.2)	34 (13, 51)
No		151/1355 (11.1)	119/1341 (8.9)	21 (-1, 38)
Overall		266/2047 (13.0)	198/2046 (9.7)	27 (12, 39)

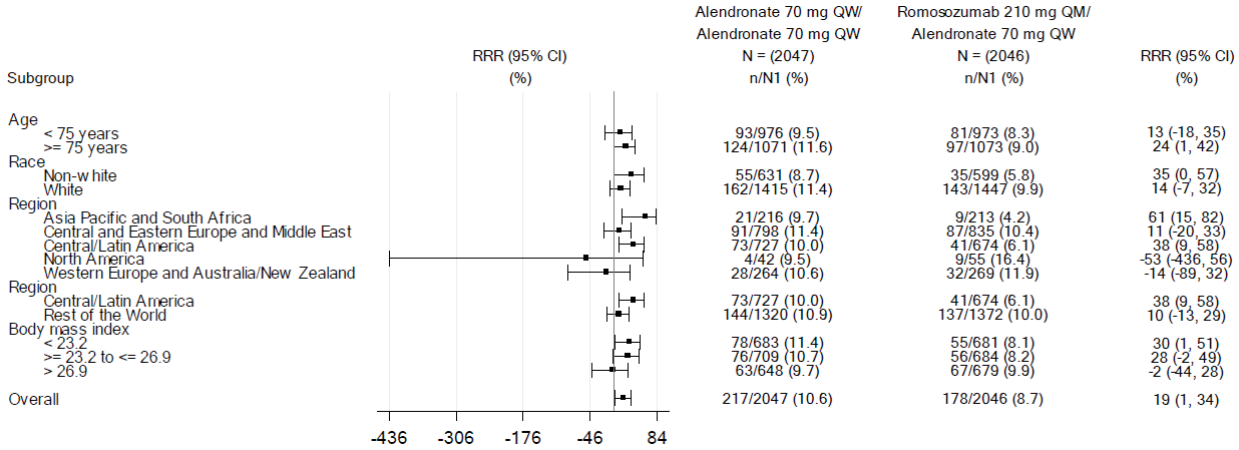
N/N1 = Number of subjects randomized
Relative risk reduction (RRR) and 95% CI based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Figure 6 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

Figure 16. Study 20110142- Subject Incidence of Nonvertebral Fracture Through Primary Analysis by Risk Factor Subgroups (Full Analysis Set)



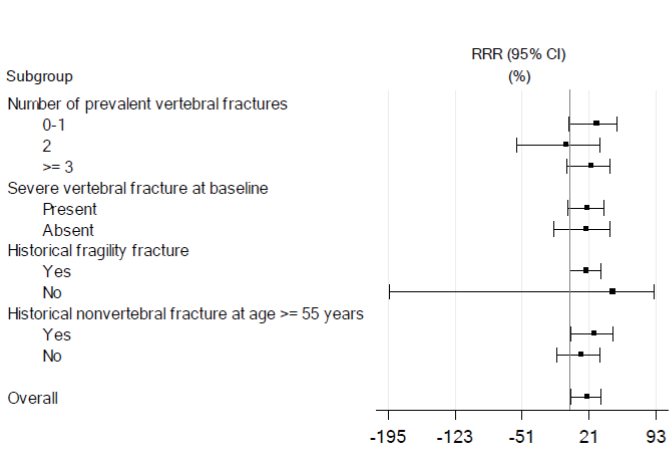
N/N1 = Number of subjects randomized
Relative risk reduction (RRR) and 95% CI based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Figure 7 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

Figure 17. Study 20110142- Subject Incidence of Nonvertebral Fracture Through Primary Analysis Period by Demographic and Physical Characteristic Subgroups (Full Analysis Set)



N/N1 = Number of subjects randomized
Relative risk reduction (RRR) and 95% CI based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Figure 8 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

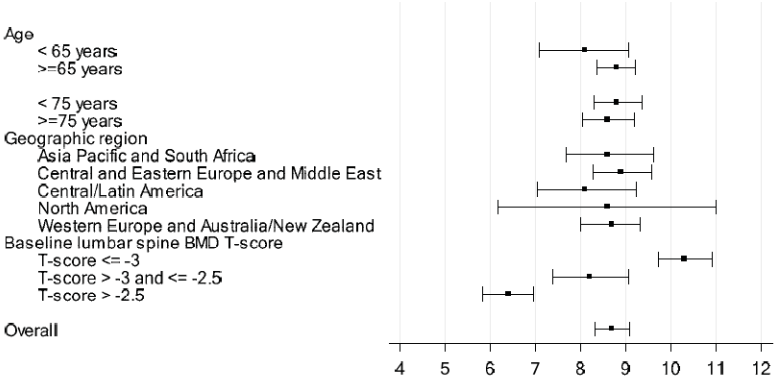
Figure 18. Study 20110142- Subject Incidence of Nonvertebral Fracture Through Primary Analysis Period by Fracture History Subgroups (Full Analysis Set)



Subgroup	RRR (95% CI) (%)	Alendronate 70 mg QW/ Alendronate 70 mg QW N = (2047) n/N1 (%)	Romosozumab 210 mg QM/ Alendronate 70 mg QW N = (2046) n/N1 (%)	RRR (95% CI) (%)
Number of prevalent vertebral fractures				
0-1		75/785 (9.6)	51/747 (6.8)	29 (-1, 50)
2		44/533 (8.3)	44/517 (8.5)	-3 (-57, 32)
>= 3		98/726 (13.5)	81/774 (10.5)	23 (-3, 43)
Severe vertebral fracture at baseline				
Present		149/1321 (11.3)	126/1369 (9.2)	20 (-2, 37)
Absent		68/726 (9.4)	52/677 (7.7)	18 (-18, 43)
Historical fragility fracture				
Yes		213/1982 (10.7)	176/1976 (8.9)	18 (0, 33)
No		4/65 (6.2)	2/70 (2.9)	47 (-194, 90)
Historical nonvertebral fracture at age >= 55 years				
Yes		96/692 (13.9)	73/705 (10.4)	27 (1, 46)
No		121/1355 (8.9)	105/1341 (7.8)	13 (-14, 33)
Overall		217/2047 (10.6)	178/2046 (8.7)	19 (1, 34)

N/N1 = Number of subjects randomized
Relative risk reduction (RRR) and 95% CI based on Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score, and presence of severe vertebral fracture at baseline.
Source: Figure 9 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

Figure 19. Study 20110142 – Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 12 by Subgroups (Primary Analysis Set for BMD)

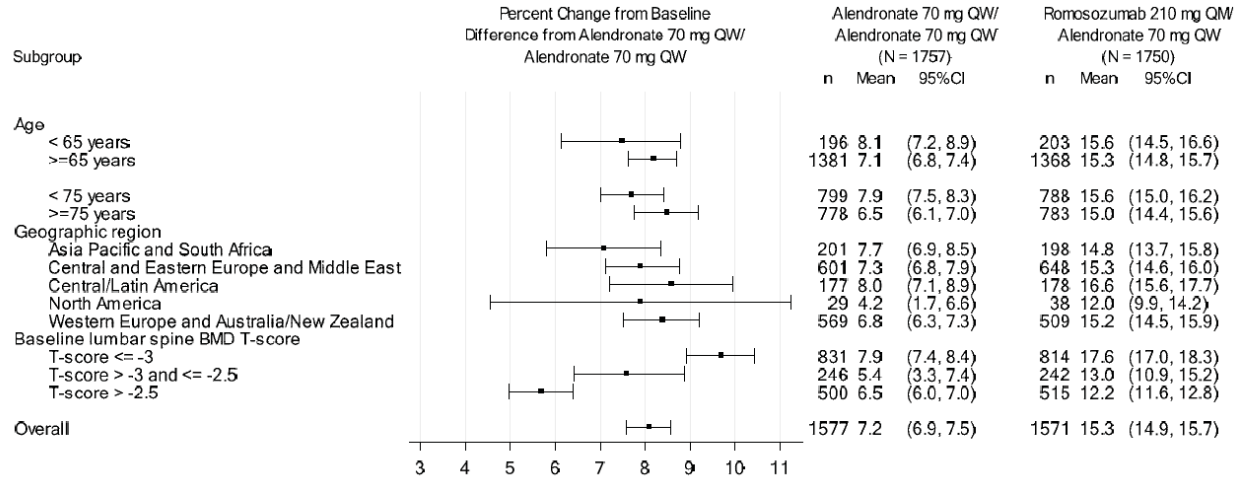


Subgroup	Percent Change from Baseline Difference from Alendronate 70 mg QW	Alendronate 70 mg QW (N = 1718) n	Mean	95%CI	Romosozumab 210 mg QM (N = 1722) n	Mean	95%CI
Age							
< 65 years		201	6.0	(5.3, 6.6)	214	14.0	(13.2, 14.8)
>=65 years		1517	4.8	(4.6, 5.1)	1508	13.6	(13.3, 14.0)
< 75 years		841	5.4	(5.0, 5.7)	848	14.2	(13.8, 14.6)
>=75 years		877	4.6	(4.2, 4.9)	874	13.2	(12.7, 13.7)
Geographic region							
Asia Pacific and South Africa		221	4.9	(4.2, 5.5)	219	13.5	(12.7, 14.3)
Central and Eastern Europe and Middle East		667	5.0	(4.6, 5.4)	702	14.0	(13.4, 14.5)
Central/Latin America		195	5.6	(4.9, 6.2)	193	13.7	(12.8, 14.6)
North America		33	2.8	(1.0, 4.5)	49	11.3	(9.6, 13.0)
Western Europe and Australia/New Zealand		602	4.9	(4.5, 5.3)	559	13.5	(13.0, 14.1)
Baseline lumbar spine BMD T-score							
T-score <= -3		906	5.6	(5.3, 6.0)	877	16.0	(15.4, 16.5)
T-score > -3 and <= -2.5		266	4.1	(2.7, 5.6)	273	12.3	(10.8, 13.9)
T-score > -2.5		546	4.2	(3.8, 4.6)	572	10.6	(10.1, 11.1)
Overall		1718	5.0	(4.7, 5.2)	1722	13.7	(13.4, 14.0)

N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 12; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by- machine type interaction; Mean= LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.
Source: Figure 10 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

Figure 20. Study 20110142 – Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 24 by Subgroups (Primary Analysis Set for BMD)

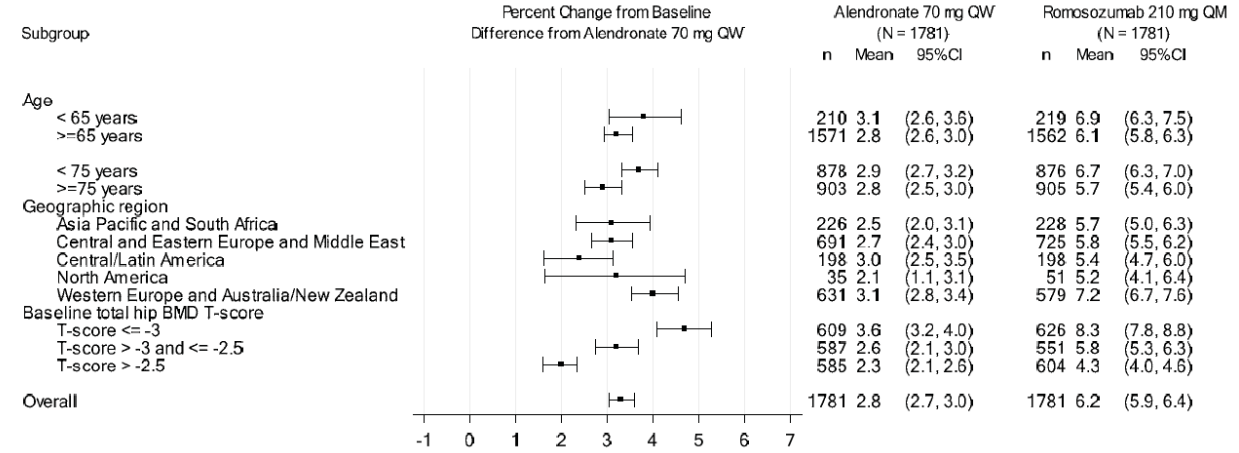


N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 24; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by- machine type interaction; Mean= LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.

Source: Figure 10 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

Figure 21. Study 20110142 - Total Hip Bone Mineral Density Percent Change From Baseline at Month 12 by Subgroups (Primary Analysis Set for BMD)

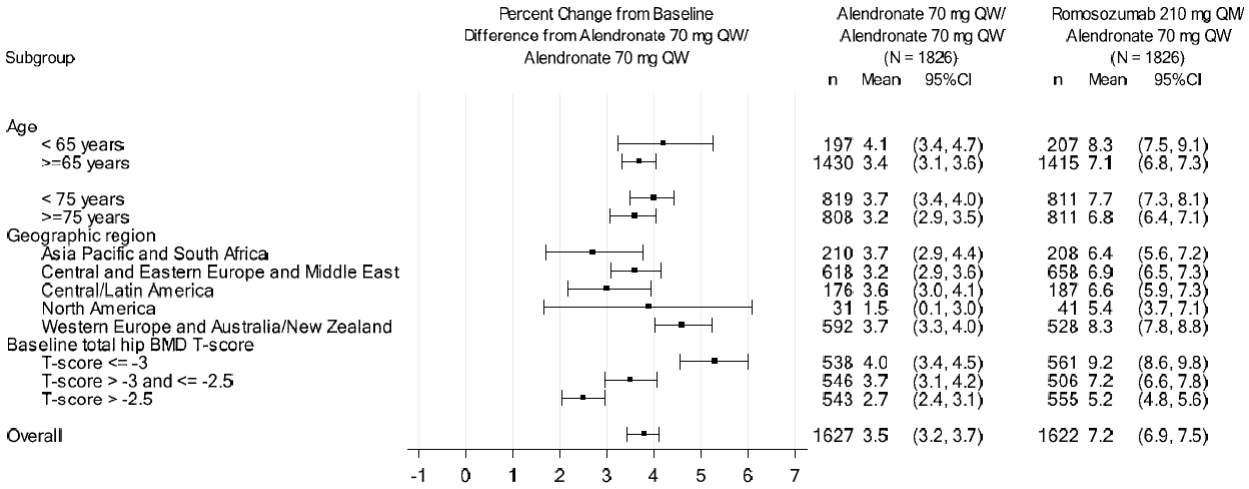


N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 12; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by- machine type interaction; Mean= LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.

Source: Figure 12 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

Figure 22. Study 20110142 - Femoral Neck Bone Mineral Density Percent Change From Baseline at Month 24 by Subgroups (Primary Analysis Set for BMD)



Subgroup	Alendronate 70 mg QW/ Alendronate 70 mg QW (N = 1826) n	Mean	95%CI	Romosozumab 210 mg QM/ Alendronate 70 mg QW (N = 1826) n	Mean	95%CI
Age						
< 65 years	197	4.1	(3.4, 4.7)	207	8.3	(7.5, 9.1)
>=65 years	1430	3.4	(3.1, 3.6)	1415	7.1	(6.8, 7.3)
< 75 years	819	3.7	(3.4, 4.0)	811	7.7	(7.3, 8.1)
>=75 years	808	3.2	(2.9, 3.5)	811	6.8	(6.4, 7.1)
Geographic region						
Asia Pacific and South Africa	210	3.7	(2.9, 4.4)	208	6.4	(5.6, 7.2)
Central and Eastern Europe and Middle East	618	3.2	(2.9, 3.6)	658	6.9	(6.5, 7.3)
Central/Latin America	176	3.6	(3.0, 4.1)	187	6.6	(5.9, 7.3)
North America	31	1.5	(0.1, 3.0)	41	5.4	(3.7, 7.1)
Western Europe and Australia/New Zealand	592	3.7	(3.3, 4.0)	528	8.3	(7.8, 8.8)
Baseline total hip BMD T-score						
T-score <= -3	538	4.0	(3.4, 4.5)	561	9.2	(8.6, 9.8)
T-score > -3 and <= -2.5	546	3.7	(3.1, 4.2)	506	7.2	(6.6, 7.8)
T-score > -2.5	543	2.7	(2.4, 3.1)	555	5.2	(4.8, 5.6)
Overall	1627	3.5	(3.2, 3.7)	1622	7.2	(6.9, 7.5)

N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 24; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline BMD value, machine type, and baseline BMD value-by- machine type interaction; Mean= LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.

Source: Figure 12 in rtq-12oct2018.pdf, submitted on 10/19/2018, eseq0061

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/s/

THERESA E KEHOE
04/08/2019 03:14:44 PM

HYLTON V JOFFE
04/09/2019 02:01:41 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: 27 September 2018

From: Fred Senatore MD, PhD, FACC

Through: Martin Rose MD, JD
Norman Stockbridge MD, PhD

To: Samantha Bell, RPM, Division of Reproductive and Urological Products

Subject: BLA 761062 (Amgen): review of the cardiovascular safety signal for romosozumab and the adjudication processes from DCRI and TIMI.

This memo responds to your consult to us requesting our assistance in reviewing the cardiovascular safety signal from a meta-analysis of three clinical trials conducted by Amgen (i.e., Applicant), as well as the adjudication process from the Duke University Clinical Research Institute (DCRI) and the re-adjudication process from the Thrombolysis in Myocardial Infarction group (TIMI) for romosozumab.

DCRP Summary and Assessment

The Applicant evaluated romosozumab for the treatment of osteoporosis in three clinical trials: 1) placebo controlled trial in osteoporotic women (study 20070337, N= 7157, 1:1 randomization); 2) alendronate-controlled trial in osteoporotic women (study 20110142, N=4054, 1:1 randomization); and 3) placebo-controlled trial in osteoporotic men (study 20110174, N= 244, 163 on romosozumab, and 81 on placebo). Each trial had a 12-month double blind period followed by an extension period. Study 20070337 had an extension of 12 additional months where subjects were treated with open label denosumab. Study 20110142 had a median extension of 24 months (median duration of study 36 months) where subjects were treated with open label alendronate until the requisite number of endpoints was achieved in this event-driven trial. Study 20110174 had an extension of an additional 3 months where the subjects were observed but not treated.

Reference ID: 4327225

The distribution of subject baseline characteristics (i.e., demographics, cardiovascular medical history, modified-RUTH cardiovascular risk score, cardiovascular medications) was similar between the romosozumab and controls arms for each study and between each study.

Cardiovascular adverse events were adjudicated by DCRI and by the TIMI group. The triggering events and the requisite supporting documentation were the same for both adjudication entities.

From a meta-analysis of the three trials, the incidence of events leading to death, myocardial infarction, or stroke in the 12-month double-blind period was low but with a marginally statistically significant hazard ratio (HR) against romosozumab that was consistent between the modes of adjudication: DCRI Adjudication: Incidence 1.3% vs 0.9%, HR 1.40 (95%CI 0.99-1.99); DCRI-matched TIMI Adjudication (*TIMI adjudication of events previously adjudicated by DCRI*): Incidence 1.2% vs 0.8%, HR 1.47 (95%CI 1.02-2.13); Full TIMI Adjudication: Incidence 1.2% vs 0.8%, HR 1.44 (95%CI 1.00-2.08). The results were driven by study 20110142. There was no imbalance in cardiovascular events in study 20070337. The HR results were driven by cardiac ischemic events (i.e., composite of myocardial infarction, angina requiring hospitalization, and coronary revascularization- either percutaneous coronary intervention or coronary artery bypass surgery), myocardial infarction, and cerebrovascular events (stroke / TIA) during the 12-month double blind study period.

There was no imbalance of events in the overall study period, most likely due to termination of romosozumab after 12 months. One exception to the results in the overall study period was a marginally statistically significant HR for stroke both by DCRI and TIMI adjudications.

The results were not impacted by baseline cardiovascular risk as measured by the modified RUTH score.

In conclusion, DCRI and TIMI adjudications yielded similar results. Meta-analysis of cardiovascular events from the three osteoporosis trials showed a low incidence but an overall marginally significant HR for romosozumab vs comparator driven by one study. Assuming a positive benefit / risk evaluation of romosozumab, the cardiovascular risk based on these low numbers of events and marginally significant HRs can be described in the label.

Background

Romosozumab (trade name Evenity) is a humanized monoclonal antibody against sclerostin and was developed for the treatment of osteoporosis in postmenopausal women. The therapeutic dosing regimen is 210 mg SC administered by a healthcare professional once each month. Sclerostin is a glycoprotein that inhibits osteoblast-mediated bone formation. By inhibiting sclerostin, romosozumab increases bone formation and decreases bone resorption.

The sclerostin gene mRNA is expressed in the heart, aorta, liver and kidney. In early development, the Applicant was concerned that inhibition of sclerostin may promote or exacerbate vascular calcification. The Applicant therefore convened an independent clinical endpoint committee (DCRI) to adjudicate reported cardiovascular serious adverse events

(SAEs) from the single pivotal trial (20070337) that supported the BLA for the treatment of postmenopausal women with osteoporosis.

Study 20070337 (FRAME) was a double-blind, placebo-controlled trial (N= 7157). Study drug (romosozumab 210 mg SC q month or placebo) was administered for 12 months followed by open-label denosumab 60 mg SC q 6 months for an additional12-month period. The co-primary efficacy endpoints were the incidence of new vertebral fracture through month 12, and through month 24. This trial met the statutory requirements for substantial evidence of effectiveness and did not show a cardiovascular safety signal. The incidence of DCRI-positively adjudicated cardiovascular SAEs was similar between the treatment groups during the 12-month and the 24-month time periods (Table 1).

Table 1: Study 20070337 DCRI-Adjudicated Positive Cardiovascular SAEs

12 Months	Placebo	Romosozumab	Odds Ratio (95% CI)
N	**3576**	**3581**	
Any Cardiovascular SAE, n (%)	**41 (1.1)**	**44 (1.2)**	**1.1 (0.7-1.7)**
Death, n (%)	**15 (0.4)**	**17 (0.5)**	**1.1 (0.6-2.3)**
Cardiac Ischemic Event, n (%)	**14 (0.4)**	**15 (0.4)**	**1.1 (0.5-2.2)**
Heart Failure, n (%)	**4 (0.1)**	**7 (0.2)**	**1.8 (0.5-6.0)**
Cerebrovascular Event, n (%)	**11 (0.3)**	**10 (0.3)**	**0.9 (0.4-2.1)**
Peripheral Vascular Event not requiring revascularization, n (%)	**1 (< 0.1)**	**3 (<0.1)**	**3.0 (0.3-28.8)**
24 Months	**Placebo**	**Romosozumab**	**Odds Ratio (95% CI)**
N	**3576**	**3581**	**1.0 (0.8-1.4)**
Any Cardiovascular SAE, n (%)	**79 (2.2)**	**82 (2.3)**	**1.1 (0.6-1.8)**
Death, n (%)	**29 (0.8)**	**31 (0.9)**	**0.7 (0.4-1.3)**
Cardiac Ischemic Event, n (%)	**26 (0.7)**	**18 (0.5)**	**0.7 (0.4-1.3)**
Heart Failure, n (%)	**9 (0.3)**	**8 (0.2)**	**0.9 (0.3-2.3)**
Cerebrovascular Event, n (%)	**24 (0.7)**	**27 (0.8)**	**1.1 (0.7-2.0)**
Peripheral Vascular Event not requiring revascularization, n (%)	**2 (<0.1)**	**7 (0.2)**	**3.5 (0.7-16.9)**

Source: CSR-20070337, Table 12-10, page 221 Note: Dmab = Denosumab

The BLA was submitted 19 July 2016 with a PDUFA goal date 19 July 2017.

During the BLA review, the Applicant completed two additional studies to support supplemental BLAs following approval of the original BLA:

1. Study 20110142 (ARCH): Phase 3 randomized, double-blind, alendronate-controlled trial in postmenopausal women with osteoporosis (N= 4054). Subjects received double-blind treatment with romosozumab 210 mg SC q month or alendronate for 12 months followed by open-label alendronate until the end of the study determined by reaching the prespecified number of primary endpoint events. The primary efficacy endpoint was the incidence of fracture (non-vertebral and vertebral) and the incidence of new vertebral fracture. Median duration of the study was 36 months. First-patient-enrolled was 04 May 2012 and last-patient dosed was 22 Feb 2106. The primary analysis top-line results were available 27 Feb 2017.

2. Study 20110174 (BRIDGE): Phase 3 randomized, double-blind, placebo-controlled trial in men with osteoporosis (N= 245). Subjects received double-blind romosozumab 210 mg SC q month (n=163) or placebo (n=81) for 12 months and were followed for an additional 3 months after completion of the double-blind period for evaluation of safety and immunogenicity. The primary efficacy endpoint was percent change from baseline in dual-energy x-ray absorptiometry (DXA) bone marrow density (BMD) at the lumbar spine at month 12. There was no follow-on therapy. First-patient-enrolled was 16 June 2014; the cut-off date was 27 January 2016. The study report was finalized on 21 July 2016.

The results of studies 20110142 and 20110174 demonstrated statistically significant effectiveness of romosozumab for each study's primary efficacy endpoint. However, there was a higher incidence of the DCRI-positively adjudicated cardiovascular SAEs during the first year in the romosozumab arm over the alendronate arm in study 20110142 and in the romosozumab arm over the placebo arm in study 20110174, although the latter study was too small to draw a credible conclusion (Table 2).

Table 2: Study 20110142 and Study 20110174 DCRI-Adjudicated cardiovascular SAEs

Study 20110142 (12 months)			
	Alendronate	Romosozumab	Odds Ratio (95% CI)
N	2014	2040	
MACE, n (%)	22 (1.1%)	41 (2.0%)	1.9 (1.1-3.1)
-Cardiovascular death	12 (0.6%)	17 (0.8%)	
-Non-fatal MI	5 (0.2%)	16 (0.8%)	
-Non-fatal stroke	7 (0.3%)	13 (0.6%)	
Study 20110174 (12 months)			
	Placebo	Romosozumab	Odds Ratio (95% CI)
N	81	163	
MACE, n (%)	2 (2.5%)	8 (4.9%)	1.6 (0.3-7.7)

MACE defined as composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

Source: Comprehensive Cardiovascular Report (executive summary page 9 and Table 7 page 51)

The Applicant met with the Division of Bone, Reproductive, and Urological Products (DBRUP) on 19 May 2017 to share these new cardiovascular findings. Consequently, a complete response (CR) was issued on 13 July 2017 requiring the Applicant to evaluate the newly emerged cardiovascular safety signal.

DBRUP consulted DCRP on 21 September 2017 to attend post-CR meetings with the Applicant pursuant to reconciliation strategies regarding the cardiovascular safety signal. The Applicant met with DBRUP and consulting staff from DCRP on 26 October 2017 to discuss plans to evaluate cardiovascular SAEs. Plans to re-engage DCRI and simultaneously hire the TIMI group were discussed as stated in the Meeting Minutes dated 22 Nov 2017. Advice from DCRP that were documented in the Minutes included: 1) submission of adjudication packages; 2) incorporation of atrial fibrillation/atrial flutter as a baseline risk factor; 3) evaluation of the percentage of events originally adjudicated as negative because of missing data; 4) itemization of cardiovascular events by individual study; 5) specification of particular documentation missing; 6) compilation of a list of cases adjudicated as negative because of missing data; 7) disclosure of adjudication decisions by each reviewer from the TIMI committee; and 8) pre-specification of the standardized MedDRA queries and trigger terms used by TIMI to identify additional events.

Based on the original DCRI adjudication process, an event in which insufficient information was provided yielded a negative adjudication (i.e., the event was not a cardiovascular SAE). The

original DCRI adjudication process also focused on SAEs. DCRI was requested to perform a retrospective re-review of all negatively adjudicated events in the three studies to determine if the original negative adjudication result was due to a site reported event with adequate source documentation not meeting the endpoint definition, or if the original negative adjudication result was due to a lack of recommended source documentation, and if so, what specific missing documentation resulted in the negative decision. Based on the DCRI adjudication charter, final adjudication decisions undergoing re-review would not be modified as there would be no changes to adjudication results. The re-review effort would be considered a source documentation adequacy review.

The TIMI study group was also requested to perform a posthoc adjudication of the cardiovascular adverse events in the three studies to assure that 1) relevant events had not been missed and that 2) the focus on SAEs in the prespecified adjudication by DCRI was not overly narrow.

Adjudication Processes

DCRI and TIMI adjudicated major adverse cardiac events (MACE) defined as cardiovascular adverse events leading to death, positively adjudicated myocardial infarction, and positively adjudicated stroke. The analysis of MACE was performed for the double-blind period and overall study period for studies 20070337 (12-month double blind, 24 months overall study period), 20110142 (12 months double blind, median 36 months overall study period), and 20110174 (12 months double blind, 15 months overall study period).

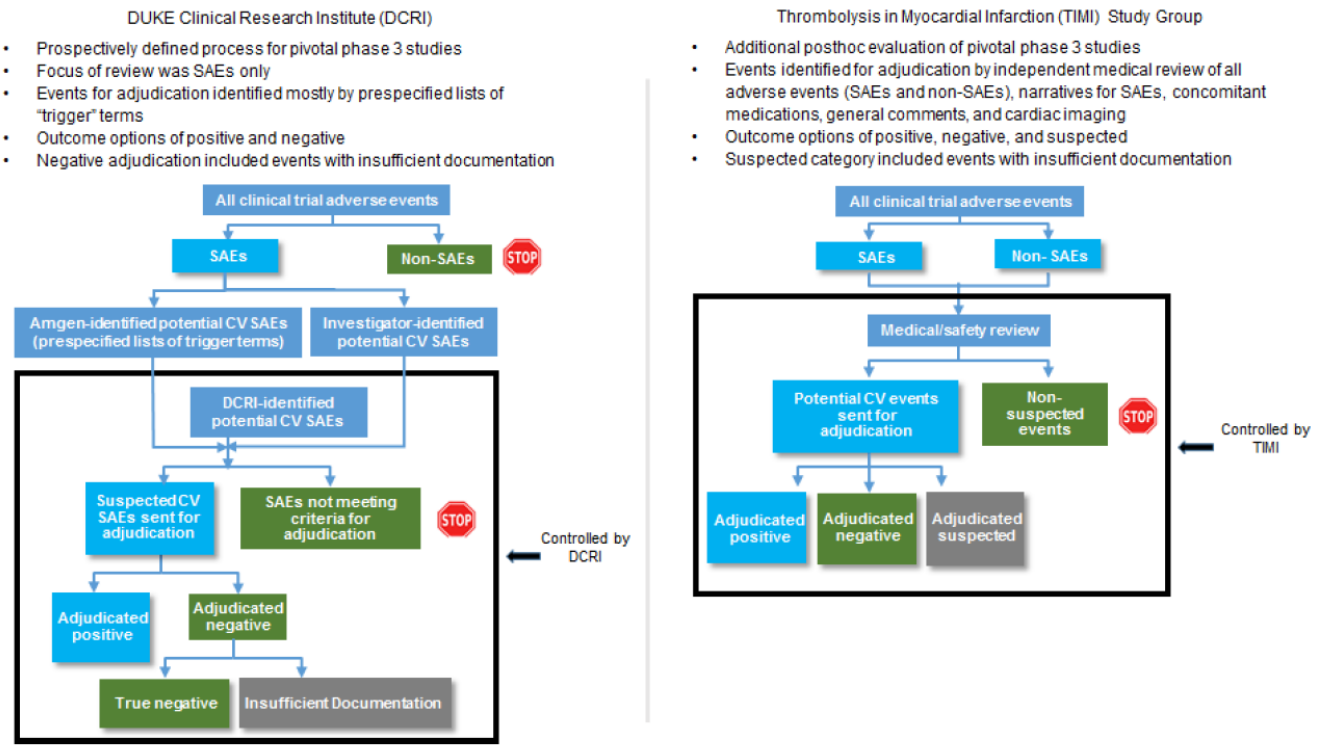
TIMI did not submit a written adjudication report because, as explained by the Applicant, TIMI's role was to confirm the DCRI adjudication results. The TIMI adjudication process and results, as well as those from DCRI, were reported by the Applicant in their Comprehensive Cardiovascular Report that included the DCRI and TIMI charters.

DCRI and TIMI independent adjudication processes are illustrated in Figure 1. The key distinctions between the adjudication processes were: 1) The TIMI group adjudicated all adverse events (serious and non-serious) meeting the triggers for adjudication; and 2) The TIMI group adjudicated an event as either positive, negative, or suspected (i.e., insufficient information was not categorically assigned a negative adjudication).

Events triggering adjudication for both the DCRI and TIMI processes are summarized in Table 3. The specific triggers included death (all events), cerebrovascular events, cardiac ischemic events, heart failure, non-coronary revascularization, and peripheral vascular events not needing revascularization. These triggers were the same for both adjudication processes. However, the DCRI trigger for heart failure required hospitalization whereas hospitalization was not explicitly stated as a requirement for heart failure adjudication in the TIMI process. The required source documentation to support the adjudications for each trigger was similar for both adjudication processes (Table 4).

Reviewer Assessment: The adjudication processes were adequate, and the required documentation was sufficient to render an adequate adjudication.

Figure 1: Overview of DCRI and TIMI Adjudication Processes of Cardiovascular Adverse Events in studies 20070337, 20110142, and 20110174



CV = cardiovascular; DCRI = Duke Clinical Research Institute; SAE = serious adverse event; TIMI = Thrombolysis in Myocardial Infarction

Source: Adjudication charters in Module 5.3.5.3

Source: Comprehensive Cardiovascular Report (figure 22)

Table 3: Events triggering Adjudication for DCRI and TIMI

DCRI	TIMI
Death-all events **-Cardiovascular (due to MI, sudden cardiac death, HF or shock, stroke, cardiovascular interventions, cardiovascular hemorrhage, other cardiovascular causes-pulmonary embolism or peripheral arterial)** **-non-Cardiovascular (cancer, lower respiratory, renal, GI, infection, accidents, non-intracranial hemorrhage, complications of elective non-Cardiovascular surgery, neurodegenerative conditions)** **-undetermined**	**Death-all events** **-Cardiovascular (due to MI, sudden cardiac death, HF or shock, stroke, cardiac procedures, cardiovascular hemorrhage, other cardiovascular causes-pulmonary embolism or peripheral arterial)** **-non-Cardiovascular (pulmonary, renal, GI, hepatobiliary, pancreatic, infection, inflammatory/autoimmune, hemorrhage, non-Cardiovascular procedure)** **-undetermined**
Cerebrovascular Event **-Stroke (Ischemic, Hemorrhagic, Uncertain)** **-TIA**	**Cerebrovascular Event** **-Stroke (Ischemic, Hemorrhagic, Uncertain)** **-TIA**
Cardiac Ischemic Event **-MI (STE, ST-dep, TWA, Path QW, biomarkers, MI Types 1-T5)** **-Angina requiring hospitalization** **-Coronary Revascularization (PCI or CABG)**	**Cardiac Ischemic Events** **-MI (STE, ST-dep, TWA, Path QW, biomarkers, MI Types T1-T5)** **-Hospitalization for Unstable Angina** **-Coronary Revascularization (PCI or CABG)**
Heart Failure Hospitalization (signs & symptoms)	**Heart Failure (signs & symptoms)** **-Heart Failure Hospitalization** **-Urgent Visit (no hospitalization)**
Non-coronary Revascularization	**Non-coronary Revascularization**
Peripheral Vascular Events not needing revasc (requires hospitalization and symptoms: dry gangrene, ulceration, severe claudication, acute kidney injury, amputation)	**Peripheral Vascular Events not needing revasc. (requires hospitalization and symptoms: dry gangrene, ulceration, severe claudication, acute kidney injury, amputation)**

Source: Clinical Events Classification Charter (DCRI: pages 1-96; TIMI: pages 96-169)

Table 4: Comparative Sample Source Documents for Adjudication: DCRI and TIMI

Event	DCRI	TIMI
Death	-Death summary -Autopsy report -Investigator Narrative	-Death Summary -Autopsy Report -Investigator Narrative (if no source documents available) -Death Certificate
Cerebrovascular Event	-Discharge Summary -Neurology Consult Notes -CT/MR report -Autopsy report -Investigator Narrative	-Discharge Summary -Neurology Consult Notes -CT/MR/Angiogram Reports -Autopsy Report - Investigator Narrative (if no source documents available) -Admission History / Physical -Progress Notes
Cardiac Ischemic Event	-Discharge Summary -Procedure Reports (PCI/CABG) -ECGs (event, pre/post event) -Cardiac Markers with ULN -Investigator Narrative	-Discharge Summary -Procedure Reports - ECGs (event, pre/post event) -Cardiac Biomarkers prior 30 days and during hospitalization -Investigator Narrative (if no source documents available) -Admission History / Physical -Coronary Revascularization Report (PCI or CABG) -Autopsy Report
Heart Failure	-Discharge Summary -Admission Hx / Physical -Medication Records -Chest X-ray Reports -BNP Results -Pulmonary Wedge Pressure -Investigator Narrative	-Discharge Summary -Admission History / Physical -Progress / Consult Notes -Chest X-ray/ Imaging Reports -BNP / NT-pro BNP Results -Right Heart Cath Results - Investigator Narrative (if no source documents available) -Cardiac Echo -Cardiac Ischemia Biomarkers
Non-coronary revascularization	- Discharge Summary -Procedure Reports -Investigator Narrative	-Discharge Summary - Admission History / Physical -Admission History / Physical -Fontaine / Rutherford Claudication scales -Imaging Reports -Ankle/Brachial Index -Percutaneous Procedure Reports -Surgical Revascularization Reports -Autopsy Report - Investigator Narrative (if no source documents available)
Peripheral vascular event not needing revasc.	-Discharge Summary -Procedure Reports	-Discharge Summary -Admission History / Physical -Fontaine / Rutherford Claudication scales -Imaging Reports -Ankle/Brachial Index -Procedures other than revasc (i.e., amputation) -Autopsy Report -Investigator Narrative (if no source documents available)

Source: Clinical Events Classification Charter (DCRI: page 32; TIMI: page 128-129)

Adjudication Results

Baseline Characteristics

The baseline characteristics were generally similar between the arms of each trial and between each trial (Table 5). The mean ages ranged from 71 to 74 years. Approximately 26%-29% of the subjects in the two large trials in osteoporotic women (20070337 and 20110142) were smokers (current or former), and 50-63% of the subjects in the small trial of osteoporotic men (20110174) were current/former smokers. Most of the subjects in all three trials had an estimated glomerular filtration Incidence between 60-90 mL/min/1.73m^2.

Approximately 75% of the subjects in the romosozumab program had a cardiovascular-related disease. The cardiovascular medical histories were generally similar between the arms of each trial and between each trial, including cardiac risk as determined by the modified RUTH score (Table 6).

The modified RUTH score was used by the Applicant in this analysis (Table 7) and was developed to assess cardiovascular risk in women enrolled in the Raloxifene Use for The Heart (RUTH) study (Mosca, 2001). Women with $\geq$ 4 risk points were at increased risk for cardiovascular events. Women with < 4 risk points were of low cardiovascular risk as assessed in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial as shown in Figure 2 (Keech, 2005). The MORE dataset (N = 5133) showed an approximate overall 2% incidence of coronary events and an approximate overall 2% incidence of cerebrovascular events in the placebo arm (n=2576); and an approximate overall 2% incidence of coronary events and approximate overall 1% incidence of cerebrovascular events in the Raloxifene arm (n=2557). Those subjects classified as low risk (n=4457, mean risk score 1.6 $\pm$ 1.0) had an approximate 1% incidence of coronary events and an approximate 1% incidence of cerebrovascular events in both the placebo arm (n=2259) and in the Raloxifene arm (n=2198), respectively. Those subjects classified as high risk (n=676, mean risk score 5.0 $\pm$ 1.7) had an approximate 7% incidence of coronary events and an approximate 6% incidence of cerebrovascular events in the placebo arm (n=317); and an approximate 5% incidence of coronary events and an approximate 3% incidence of cerebrovascular events in the Raloxifene arm (n=359).

Approximately 60% of the subjects in the intention-to-treat population of the romosozumab program were taking at least one cardiovascular-related medication (e.g., aspirin, antiplatelet, beta-blocker, anticoagulant, angiotensin-II receptor blocker, ACE-inhibitors, statins). Approximately 20-38% of the subjects were on a specific medication (Table 8). In subjects who had a cardiovascular related condition at baseline, the prevalence of baseline cardiovascular medications was higher: approximately 75% were on at least one cardiovascular medication with 22-50% taking specific medications (Table 9). The use of cardiovascular-related baseline concomitant medications was generally evenly distributed between the arms of each trial as well as between each trial.

Table 5: Baseline Demographics

	Study 20070337		Study 20110142		Study 20110174	
	Placebo N=3576 n (%)	Romosozumab N= 3581 n (%)	Alendronate N= 2014 n (%)	Romosozumab N=2040 n (%)	Placebo N=81 n (%)	Romosozumab N=163 n (%)
Age (years)						
Mean (SD)	71 (7)	71 (7)	74 (8)	74 (8)	71 (7)	72 (7)
Median	70	70	75	75	72	73
Min, Max	55, 89	55, 90	55, 90	55, 90	55, 85	56, 89
Age Group						
< 75 years	2641 (69)	2464 (69)	965 (48)	970 (48)	53 (65)	93 (57)
≥ 75 years	1115 (31)	1117 (31)	1049 (52)	1070 (53)	28 (35)	70 (43)
Smoking Hx						
Current/Former	1037 (29)	982 (27)	591 (29)	533 (26)	51 (63)	81 (50)
Never	2539 (71)	2599 (73)	1423 (71)	1506 (74)	30 (37)	82 (50)
Unknown	0	0	0	1 (<0.1%)	0	0
eGFR (mL/min/1.73m^2)						
<15	0	0	0	0	0	0
15-<30	8 (0.2)	10 (0.3)	7 (0.3)	4 (0.2)	0	0
30-<60	625 (18)	734 (21)	479 (24)	509 (25)	13 (16)	21 (13)
60-<90	2526 (71)	2406 (67)	1195 (59)	1259 (62)	55 (68)	111 (68)
>90	416 (12)	431 (12)	333 (17)	267 (13)	13 (16)	31 (19)
Missing	1 (<0.1)	0	0	1 (<0.1)	0	0

Source: Comprehensive Cardiovascular Report (section 4.1)

Table 6: Cardiovascular Related Medical History

	Study 20070337		Study 20110142		Study 20110174	
Safety Dataset	**Placebo**	**Romosozumab**	**Alendronate**	**Romosozumab**	**Placebo**	**Romosozumab**
Disease History	**N=3576**	**N= 3581**	**N= 2014**	**N=2040**	**N=81**	**N=163**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any CV related ds	**2703 (76)**	**2649 (74)**	**1603 (80)**	**1618 (79)**	**58 (72)**	**126 (77)**
Hyperlipidemia	**1408 (39)**	**1379 (39)**	**675 (34)**	**709 (35)**	**32 (40)**	**63 (39)**
Hypertension	**1919 (54)**	**1890 (53)**	**1227 (61)**	**1248 (61)**	**44 (54)**	**83 (51)**
Diabetes	**472 (13)**	**452 (13)**	**276 (14)**	**245 (12)**	**14 (17)**	**22 (14)**
Cardiovascular	**2331 (65)**	**2327 (65)**	**1456 (72)**	**1497 (73)**	**54 (67)**	**108 (66)**
-Ischemic Heart	**343 (10)**	**318 (9)**	**257 (13)**	**295 (15)**	**18 (22)**	**26 (16)**
-MI	**77 (2)**	**76 (2)**	**50 (3)**	**71 (4)**	**6 (7)**	**9 (6)**
-Revascularization	**48 (1)**	**51 (1)**	**42 (2)**	**40 (2)**	**11 (14)**	**10 (6)**
-Afib/flutter	**76 (2)**	**58 (2)**	**76 (4)**	**93 (4)**	**4 (5)**	**7 (4)**
Cerebrovascular*	**198 (6)**	**179 (5)**	**186 (9)**	**149 (7)**	**11 (14)**	**15 (9)**
-Ischemic CVA/TIA	**185 (5)**	**169 (5)**	**176 (9)**	**140 (7)**	**10 (12)**	**15 (9)**
-Stroke	**95 (3)**	**83 (2)**	**81 (4)**	**58 (3)**	**6 (7)**	**6 (4)**
RUTH Score						
Mean (SD)	**3.6 (2.5)**	**3.5 (2.5)**	**4.1 (2.5)**	**4.0 (2.6)**	**5.2 (3.1)**	**4.2 (2.7)**
Median	**3.0**	**3.0**	**3.0**	**3.0**	**5.0**	**3.0**
Min, Max	**0, 13**	**0, 13**	**0, 13**	**0, 13**	**0, 13**	**0, 13**
m-RUTH Score >8	**306 (9)**	**287 (8)**	**213 (11)**	**241 (12)**	**17 (21)**	**18 (11)**
m-RUTH Score < 8	**3270 (91)**	**3294 (92)**	**1801 (89)**	**1799 (88)**	**64 (79)**	**145 (89)**
m-RUTH Score ≥ 6	**794**	**761**	**598**	**556**	**NA**	**NA**
m-RUTH Score < 6	**2872**	**2820**	**1416**	**1484**	**NA**	**NA**
m-RUTH Score ≥ 4	**1438**	**1360**	**936**	**923**	**NA**	**NA**
m-RUTH Score < 4	**2138**	**2221**	**1078**	**1117**	**NA**	**NA**

Source: Comprehensive Cardiovascular Report (section 4.2, Table 14-6.4.1.3 for study 20110142, Table 14-6.4.1.5 for study 2007033); Note: * Cerebrovascular includes CNS hemorrhage; m-RUTH = modified RUTH = modified-Raloxifene Use for The Heart; NA = not available

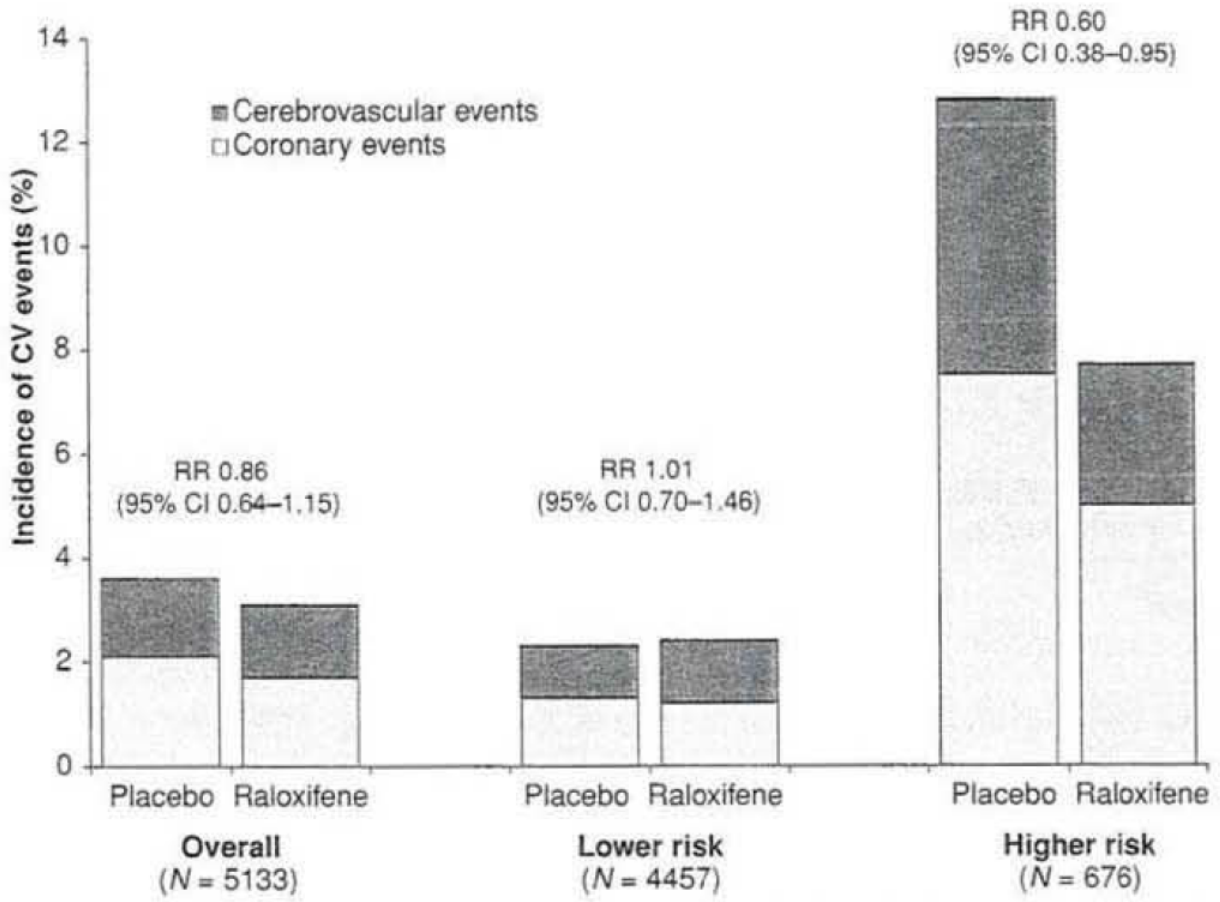
Reference ID: 4327225

Table 7: Modified RUTH Score

Baseline Cardiovascular Risk Factor: Modified Ruth Score	Points
Ischemic heart disease, CNS hemorrhage, Cerebrovascular Conditions	**4**
Diabetes Mellitus	**3**
Age	
≥ 70 years	**2**
65-69 years	**1**
Former/Current smoker[1]	**1**
Hypertension[1]	**1**
High Cholesterol[1]	**1**
1: extra point if all three are present. Score ranges from 0 (no cardiovascular risk) to 13 (highest cardiovascular risk).	

Source: Supplemental Statistical Analysis Plan-23 Apr 2018

Figure 2: Incidence of coronary and cerebrovascular events during the Multiple Outcomes of Raloxifene Evaluation (MORE) trial



Source: Keech, 2005

Table 8: Cardiovascular-related Baseline Concomitant Medications

	Study 20070337		Study 20110142		Study 20110174	
	Placebo N=3576 n (%)	Romosozumab N= 3581 n (%)	Alendronate N= 2014 n (%)	Romosozumab N=2040 n (%)	Placebo N=81 n (%)	Romosozumab N=163 n (%)
Subjects with Cardiovascular Meds	2065 (58)	2018 (56)	1238 (62)	1254 (62)	53 (65)	94 (58)
Aspirin	713 (20)	751 (21)	437 (22)	449 (22)	24 (30)	45 (28)
Antiplatelet Drugs	755 (21)	801 (22)	473 (24)	483 (24)	28 (35)	46 (28)
Beta-Blockers	729 (20)	716 (20)	478 (24)	518 (25)	21 (26)	39 (24)
Anticoagulants	815 (23)	837 (23)	559 (28)	578 (28)	31 (38)	47 (29)
A-II Receptor Antagonists	600 (17)	578 (16)	374 (19)	347 (17)	15 (19)	23 (14)
Statins	943 (26)	913 (26)	476 (24)	498 (24)	31 (38)	45 (28)
ACE Inhibitors	702 (20)	730 (20)	490 (24)	532 (26)	20 (25)	29 (18)

Source: Comprehensive Cardiovascular Report (section 4.3)

Table 9: Cardiovascular-related Baseline Concomitant Medications in Subjects with Cardiovascular-related Past Medical History

	Study 20070337		Study 20110142		Study 20110174	
	Placebo N=2703 n (%)	Romosozumab N= 2649 n (%)	Alendronate N= 1603 n (%)	Romosozumab N=1618 n (%)	Placebo N=58 n (%)	Romosozumab N=126 n (%)
Subjects with Cardiovascular Meds	2007 (74)	1965 (74)	1212 (76)	1228 (76)	50 (86)	93 (74)
Aspirin	681 (25)	717 (27)	422 (26)	437 (27)	23 (40)	45 (35)
Antiplatelet Drugs	721 (27)	764 (29)	456 (28)	471 (29)	26 (45)	46 (37)
Beta-Blockers	713 (26)	703 (27)	473 (30)	508 (31)	20 (35)	38 (30)
Anticoagulants	783 (29)	802 (30)	538 (34)	563 (35)	29 (50)	47 (37)
A-II Receptor Antagonists	599 (22)	577 (22)	374 (23)	347 (21)	15 (26)	23 (18)
Statins	941 (35)	912 (34)	475 (30)	495 (31)	31 (53)	45 (36)
ACE Inhibitors	699 (26)	730 (28)	489 (31)	529 (33)	20 (35)	29 (23)

Source: Comprehensive Cardiovascular Report (section 4.3)

Adjudicated Event Analysis

DCRI: In the overall study period for the three studies, there were 5070 reported SAEs of which 1150 were adjudicated (Figure 3). Of these, 697 were adjudicated positively (criteria for cardiovascular event satisfied) and 453 were adjudicated negatively (criteria not met). Of the negatively adjudicated events, 400 had sufficient information but did not meet the criteria for an

event, and 53 were adjudicated as negative due to insufficient information. The missing information was associated with cardiac ischemic, heart failure, peripheral vascular and cerebrovascular events and was mostly discharge summaries, medical records, hospital records, imaging, ECGs, and additional information not provided due to subject withdrawal of consent (Comprehensive Cardiovascular Report-Listing 16-2.5).

TIMI: In the overall study period for the three studies, there were 80,214 adverse events of which 1329 were adjudicated (Figure 4). Of these, 690 were adjudicated positively, 39 were adjudicated as suspected events, 23 events were assessed as duplicate, and 577 were adjudicated negatively.

A sensitivity analysis was performed by the Applicant to ascertain whether a negative adjudication by DCRI due to insufficient information impacted the overall assessment of a potential cardiovascular safety signal. The Applicant assumed that all negatively adjudicated events due to insufficient information were positive. The results for the 12-month double-blind period and the overall study period respectively showed no difference in the HR comparing romosozumab and control between DCRI-positively adjudicated events and DCRI-positively adjudicated events + negatively adjudicated events due to insufficient documentation assumed positive for the sensitivity analysis (Table 10).

A side-by-side comparison of DCRI and TIMI adjudications from reported treatment-emergent adverse events for all-cause death, myocardial infarction, and stroke for the 12-month double-blind period in each study is presented in Table 11. The incidence of positively adjudicated all-cause deaths, myocardial infarction, and stroke endpoints was low (*i.e., 1.3%-2.6% in the romosozumab arm; 1.2%-1.9% in the placebo arm*) and similar between the DCRI and TIMI adjudications for all the studies. These numbers were similar to the overall incidence of coronary events and cerebrovascular events in the MORE trial.

The incidence of positively adjudicated endpoints between the placebo and romosozumab arms in study 20070337 was virtually identical to each other.

In both the DCRI and TIMI adjudications, there was a small numerical increase in the incidence of all the endpoints in study 20110142 for the romosozumab arm vs the alendronate arm: all-cause death (DCRI: 30 {1.5%} vs 22 {1.1%}; TIMI: 27 {1.3%} vs 21 {1.0%}); myocardial infarction (DCRI: 16 {0.8%} vs 5 {0.2%}; TIMI: 16 {0.8%} vs 6 {0.3%}); and stroke (DCRI: 13 {0.6%} vs 7 {0.3%}; TIMI: 13 {0.6%} vs 5 {0.2%}).

In study 20110174, the number of positive adjudications was too small to render an inference.

Meta-analyses of adjudicated events from studies 20070337, 20110142, 20110174 displayed by Forrest Plots are found in the Appendix.

The HR for positively adjudicated events leading to death, myocardial infarction, and stroke for romosozumab vs control based on DCRI, DCRI-matched TIMI, and full TIMI adjudications through the double-blind 12-month period are shown in Figure 5 for all three studies, Figure 6 for study 20110142, and Figure 7 for study 20070337. Analogous results for the overall study

periods are respectively shown in Figure 8 for all three studies, Figure 9 for study 20110142, and Figure 10 for study 20070337. The HR comparing romosozumab to control in the double-blind 12-month period were marginally significant and consistent between the modes of adjudication: DCRI Adjudication: Incidence 1.3% vs 0.9%, HR 1.40 (95%CI 0.99-1.99); DCRI-matched TIMI Adjudication: Incidence 1.2% vs 0.8%, HR 1.47 (95%CI 1.02-2.13); Full TIMI Adjudication: Incidence 1.2% vs 0.8%, HR 1.44 (95%CI 1.00-2.08).

These results were driven only by study 20110142 (DCRI Adjudication: Incidence 2.0% vs 1.1%, HR 1.87, 95%CI 1.11-3.14; DCRI-matched TIMI Adjudication: Incidence 1.9% vs 1.0%, HR 1.96, 95%CI 1.14-3.36; and Full-TIMI Adjudication: Incidence 1.9% vs 1.0%, HR 1.96, 95%CI 1.14-3.36) during the 12-month double blind period. Despite statistical significance in this trial, the incidences were low.

Study 20070337 showed no cardiovascular safety signal with any mode of adjudication during the 12-month period.

The HR values regressed to neutrality for the overall study period by all adjudication modalities in all three studies.

A meta-analysis of the time to first occurrence of positively adjudicated cardiovascular adverse events leading to death, myocardial infarction or stroke through the double-blind 12-month period for the three trials is shown in Figure 11 for DCRI and Figure 12 for TIMI. Analogous results for the overall study periods are shown in Figure 13 for DCRI and Figure 14 for TIMI. The data showed a low incidence of events and a marginally significant HR for romosozumab vs comparator (DCRI: Incidence 1.3% vs 0.9%, HR 1.40, 95%CI 0.99-1.99; TIMI: Incidence 1.2% vs 0.8%, HR 1.44, 95%CI 1.00-2.08) for the 12-month period. This was driven by study 20110142 comparing romosozumab to alendronate showing a low rate of events but statistically significant HRs (DCRI: Incidence 2.0% vs 1.1%, HR 1.87, 95%CI 1.11-3.14; TIMI: Incidence 1.9% vs 1.0%, HR 1.96, 95%CI 1.14-3.36). The HR regressed towards neutrality when incorporating data from the overall study period.

A meta-analysis of the time to first occurrence of positively adjudicated cardiovascular adverse events leading to death, myocardial infarction, or stroke through the double-blind 12-month period stratified by modified RUTH score is shown in Figure 15 for DCRI and Figure 16 for TIMI. Analogous results for the overall study periods are shown in Figure 17 for DCRI and Figure 18 for TIMI. There was a trend towards a cardiovascular safety signal for romosozumab vs comparator for all subgroups of the modified RUTH score (i.e., < 4, ≥ 4, <6, ≥ 6, <8, ≥ 8) as adjudicated by DCRI and TIMI for the 12-month period. The trend was attenuated for all modified-RUTH subgroups in the overall study period, more pronounced in the TIMI adjudication.

A series of meta-analyses was conducted to evaluate the HR of romosozumab vs comparator for components of the composite of death, myocardial infarction, and stroke.

The time to first occurrence of positively adjudicated cardiovascular adverse events leading to death through month 12 is shown in Figure 19 for DCRI and Figure 20 for TIMI. Analogous results for the overall study period are shown in Figure 21 for DCRI and Figure 22 for TIMI. The results showed no trend towards a mortality safety signal.

A meta-analysis of the time to first occurrence of positively adjudicated cardiovascular adverse events leading to myocardial infarction through month 12 is shown in Figure 23 for DCRI and Figure 24 for TIMI. Analogous results for the overall study period are shown in Figure 25 for DCRI and Figure 26 for TIMI. The results showed a low incidence of events, a statistically significant HR for myocardial infarction by DCRI adjudication (Incidence 0.4% vs 0.2%, HR 1.97, 95%CI 1.01-3.84) and a non-statistically significant HR by TIMI adjudication (Incidence 0.4% vs 0.2%, HR 1.69, 95%CI 0.87-3.27) for the 12-month period. These results were driven by study 20110142 showing statistically significant results with both adjudication processes (DCRI: Incidence 0.8% vs 0.2%, HR 3.21, 95%CI 1.18-8.77; TIMI: Incidence 0.8% vs 0.3%, HR 2.67, 95%CI 1.05-6.83). The HR regressed to neutrality for the overall study periods.

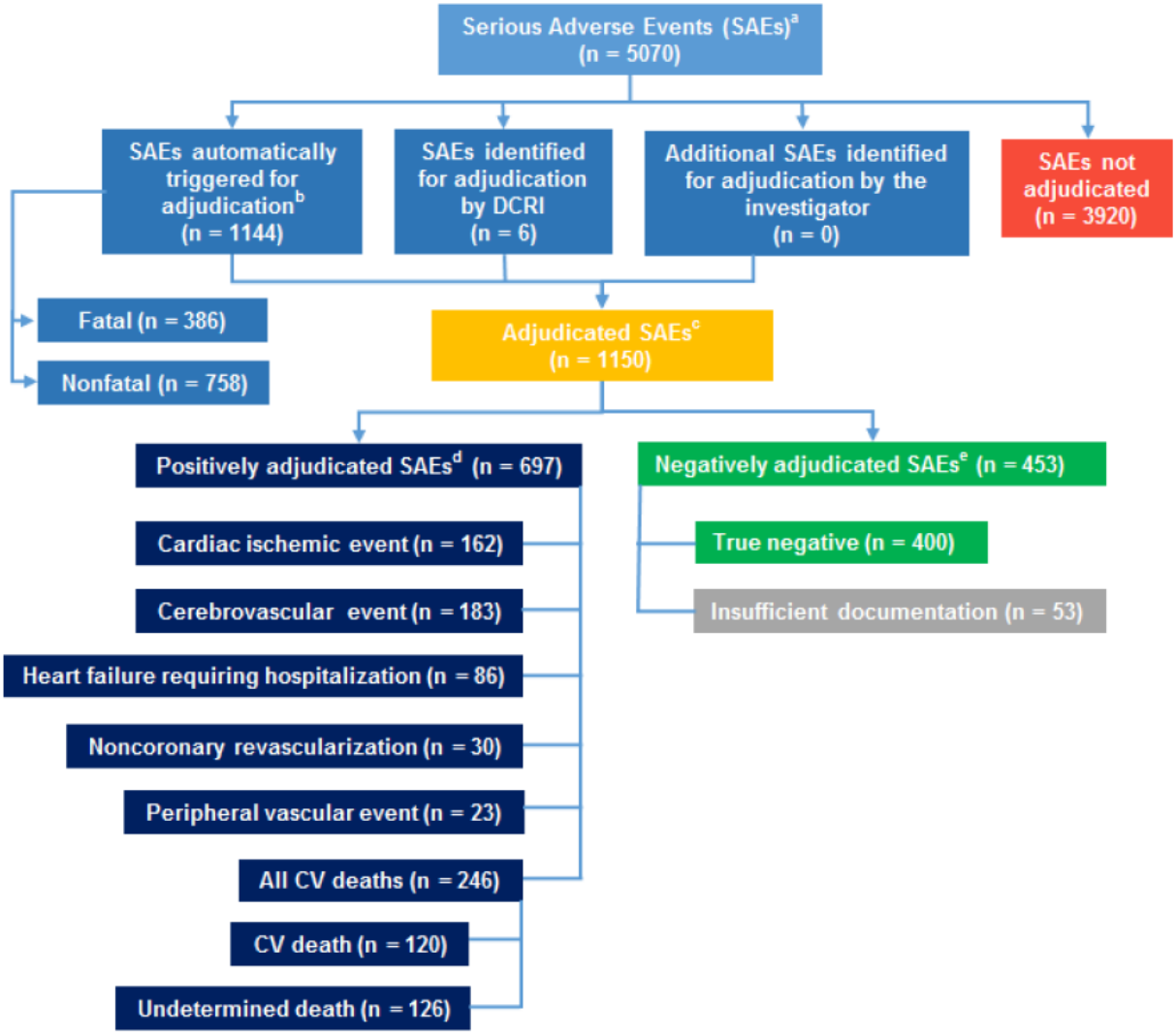
A meta-analysis of the time to first occurrence of positively adjudicated cerebrovascular adverse events (stroke + TIA) through month 12 is shown in Figure 27 for DCRI and Figure 28 for TIMI. Analogous results for the overall study period are shown in Figure 29 for DCRI and Figure 30 for TIMI. The results showed a low incidence of events. There was a non-statistically significant HR for cerebrovascular events by DCRI adjudication for the 12-month period (Incidence 0.5% vs 0.3%, HR 1.45, 95%CI 0.81-2.60) but a statistically significant HR by TIMI adjudication (Incidence 0.6% vs 0.2%, HR 2.32, 95%CI 1.24-4.33). This was driven by study 20110142 (DCRI: Incidence 0.8% vs 0.3%, HR 2.29, 95%CI 0.94-5.58; TIMI: Incidence 0.9% vs 0.2%, HR 3.61, 95%CI 1.34-9.74). The HR for cerebrovascular events was statistically significant for the overall study period by DCRI adjudication (Incidence 1.6% vs 1.1%, HR 1.44, 95%CI 1.05-1.98) and by TIMI adjudication (Incidence 1.7% vs 1.2%, HR 1.42, 95%CI 1.04-1.94). These results were also driven by study 20110142.

The incidence of positively-adjudicated stroke as a component of cerebrovascular events was low with a non-significant HR in the 12-month period by DCRI and TIMI adjudication (Figure 31, Figure 32): (DCRI: Incidence 0.4% vs 0.3%, HR 1.26, 95%CI 0.68-2.32; TIMI: Incidence 0.4% vs 0.2%, HR 1.61, 95%CI 0.83-3.12). However, the results were marginally significant for positively adjudicated stroke for the overall study period (Figure 33, Figure 34) (DCRI: Incidence 1.4% vs 1.0%, HR 1.45, 95%CI 1.03-2.03; TIMI: Incidence 1.3% vs 1.1%, HR 1.26, 95%CI 0.90-1.77). These results were driven by study 20110142 (DCRI: Incidence 2.1% vs 1.2%, HR 1.75, 95%CI 1.06-2.89; TIMI: Incidence 1.9% vs 1.2%, HR 1.58, 95%CI 0.95-2.64).

A triggering event for both DCRI and TIMI adjudication was cardiac ischemic event that consisted of myocardial infarction, angina requiring hospitalization, and coronary revascularization by either percutaneous coronary intervention or coronary artery bypass surgery. A meta-analysis of the time to first occurrence of positively adjudicated cardiac ischemic events through month 12 is shown in Figure 35 for DCRI and Figure 36 for TIMI. Analogous results for the overall study period are shown in Figure 37 for DCRI and Figure 38 for TIMI. The results showed a low incidence of events. Through the 12-month double-blind period,

the DCRI adjudication showed a non-significant HR (Incidence 0.6% vs 0.4%, HR 1.54, 95%CI 0.90-2.63) for the three studies but a statistically significant result in study 20110142 (Incidence 0.8% vs 0.3%, HR 2.68, 95%CI 1.05-6.84). TIMI adjudication showed the same results (Incidence 0.5% s 0.4%, HR 1.48, 95%CI 0.84-2.61) driven by study 20110142 (Incidence 0.8% vs 0.3%, HR 2.84, 95%CI 1.12-7.20). These signals were attenuated for the overall study periods.

Figure 3: DCRI Adjudication of SAEs in the Overall Study Period



[a] Includes serious adverse events in the overall study period for randomized subjects in Studies 20070337, 20110142, or 20110174.

[b] Events meeting a predefined preferred term trigger list and all fatal adverse events were automatically sent for cardiovascular adjudication. Adjudicated events which were based on the predefined search list may have been triggered for readjudication by DCRI to change the event classification, but these events were considered to be triggered based on the predefined search list.

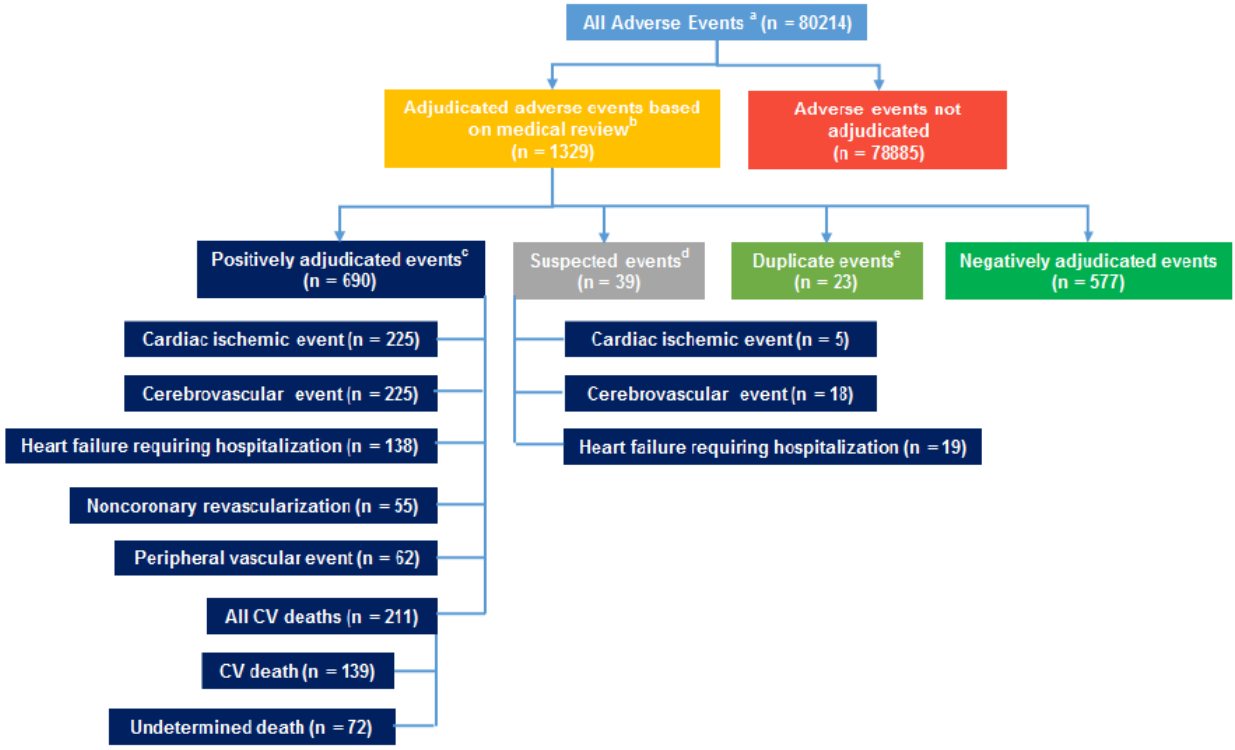
[c] Includes all serious adverse events sent to DCRI for adjudication by physicians with expertise in cardiology, osteoporosis, internal medicine, or neurology.

[d] An event was considered positively-adjudicated if the adjudication result was positive for any prespecified cardiovascular category.

[e] Negatively-adjudicated events were reviewed posthoc to identify events that were negative due to insufficient documentation and to identify the missing information that prevented definitive adjudication.

Source: Comprehensive Cardiovascular Report-Appendix 4 and Table 14-1.1

Figure 4: TIMI Adjudication of AEs in the Overall Study Period



[a] Includes adverse events in the overall study period for randomized subjects in Studies 20070337, 20110142, or 20110174.

[b] Events were identified for adjudication by medical review of all adverse events in Studies 20070337, 20110142, and 20110174.

[c] An event was considered positively-adjudicated if the adjudication result was positive for any prespecified cardiovascular category.

[d] Suspected events were those with insufficient documentation for definitive adjudication.

[e] The TIMI Study Group considered the event to be a duplicate of another event already adjudicated by DCRI.

Source: Comprehensive Cardiovascular Report-Appendix 3 and Table 14-1.2

Table 10: Sensitivity Analysis: Impact of Negative Adjudication due to Insufficient Information

	Control	Romosozumab	HR (95%CI)
	N=5671	N=5784	
	n (%)	n (%)	
12-month double-blind period			
DCRI pos-adj	86 (1.5)	104 (1.8)	1.2 (0.9-1.6)
DCRI pos-adj + neg due to insufficient documentation	92 (1.6)	114 (2.0)	1.2 (0.9-1.6)
Overall study period			
DCRI pos-adj	263 (4.6)	280 (4.8)	1.1 (0.9-1.3)
DCRI pos-adj + neg due to insufficient documentation	277 (4.9)	299 (5.2)	1.1 (0.9-1.3)

Source: Comprehensive Cardiovascular Report (Table 9)

Table 11: Comparison of Subject Incidences of All-cause death, myocardial infarction, and stroke based on treatment-emergent adverse events adjudicated by DCRI and TIMI for the 12-month Double Blind Period

	TEAE Reporting		DCRI Adjudicated		TIMI Adjudicated	
Study	Control	Romosozumab	Control	Romosozumab	Control	Romosozumab
AE Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Study 20070337	N=3576	N=3581	N=3576	N=3581	N=3576	N=3581
# Subjects with TEAEs	43 (1.2)	48 (1.3)	38 (1.1)	42 (1.2)	34 (1.0)	38 (1.1)
-All-cause deaths	24 (0.7)	29 (0.8)	24 (0.7)	29 (0.8)	20 (0.6)	27 (0.8)
-Myocardial Infarction	12 (0.3)	14 (0.4)	8 (0.2)	9 (0.3)	8 (0.2)	7 (0.2)
-Stroke	12 (0.3)	10 (0.3)	10 (0.3)	8 (0.2)	8 (0.2)	8 (0.2)
Study 20110142	N= 2014	N=2040	N= 2014	N=2040	N= 2014	N=2040
# Subjects with TEAEs	38 (1.9)	53 (2.6)	32 (1.6)	53 (2.6)	31 (1.5)	51 (2.5)
-All-cause deaths	22 (1.1)	30 (1.5)	22 (1.1)	30 (1.5)	21 (1.0)	27 (1.3)
-Myocardial Infarction	8 (0.4)	16 (0.8)	5 (0.2)	16 (0.8)	6 (0.3)	16 (0.8)
-Stroke	12 (0.6)	15 (0.7)	7 (0.3)	13 (0.6)	5 (0.2)	13 (0.6)
Study 20110174	N=81	N=163	N=81	N=163	N=81	N=163
# Subjects with TEAEs	2 (2.5)	5 (3.1)	2 (2.5)	6 (3.7)	2 (2.5)	6 (3.7)
-All-cause deaths	1 (1.2)	2 (1.2)	1 (1.2)	2 (1.2)	1 (1.2)	2 (1.2)
-Myocardial Infarction	0	1 (0.6)	0	1 (0.6)	0	1 (0.6)
-Stroke	1 (1.2)	2 (1.2)	1 (1.2)	3 (1.8)	1 (1.2)	3 (1.8)

Source: Comprehensive Cardiovascular Report (Table 10)

References

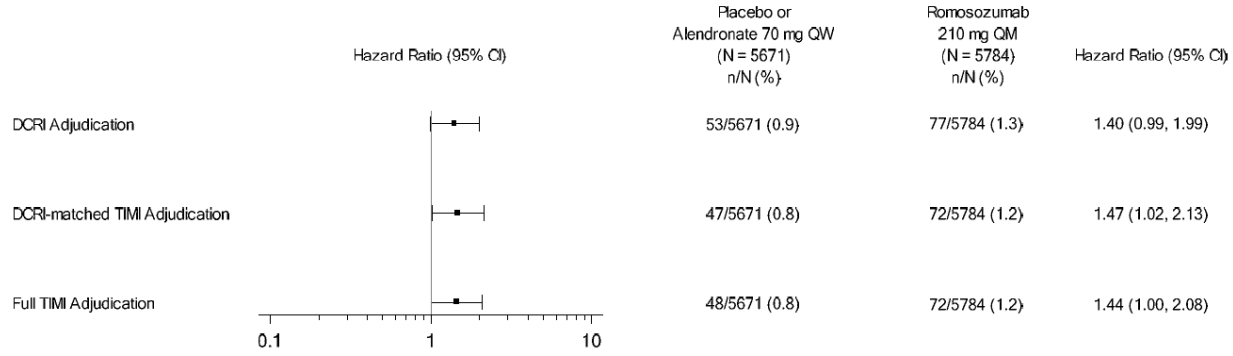
Keech, C, et al., 2005, Year-by-year analysis of cardiovascular events in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, Current Medical Research and Opinions, 21 (1): 135-140

Mosca, L, et al., 2001, Design and Methods of the Raloxifene Use for The Heart (RUTH) Study, American Journal of Cardiology, 88: 392-395

Appendix

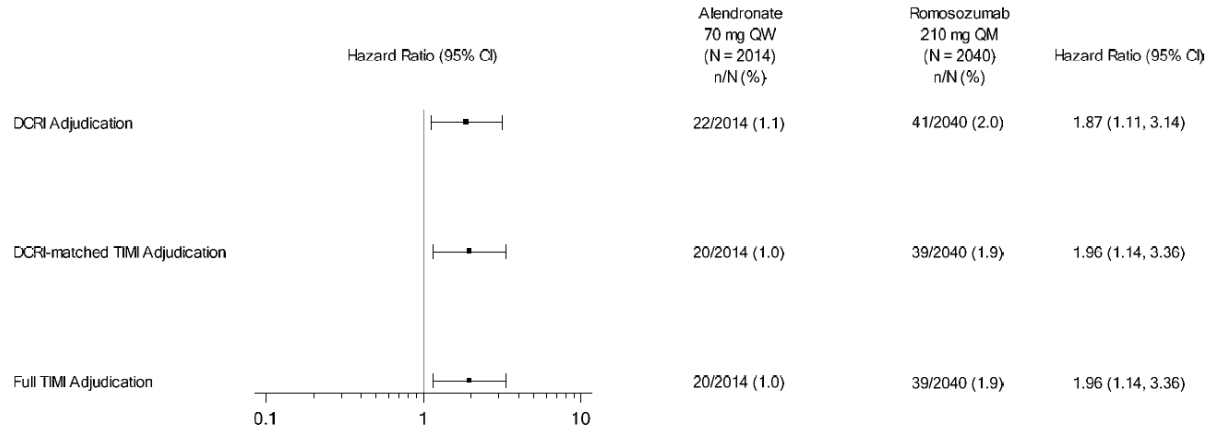
Forrest Plots (Meta-analyses of Adjudicated Events from Studies 20070337, 20110142, 20110174)

Figure 5: Hazard Ratio of Positively Adjudicated Cardiovascular Adverse Events leading to Death, Myocardial Infarction, or Stroke based on DCRI, DCRI-matched TIMI, and Full TIMI through Month 12: all 3 studies



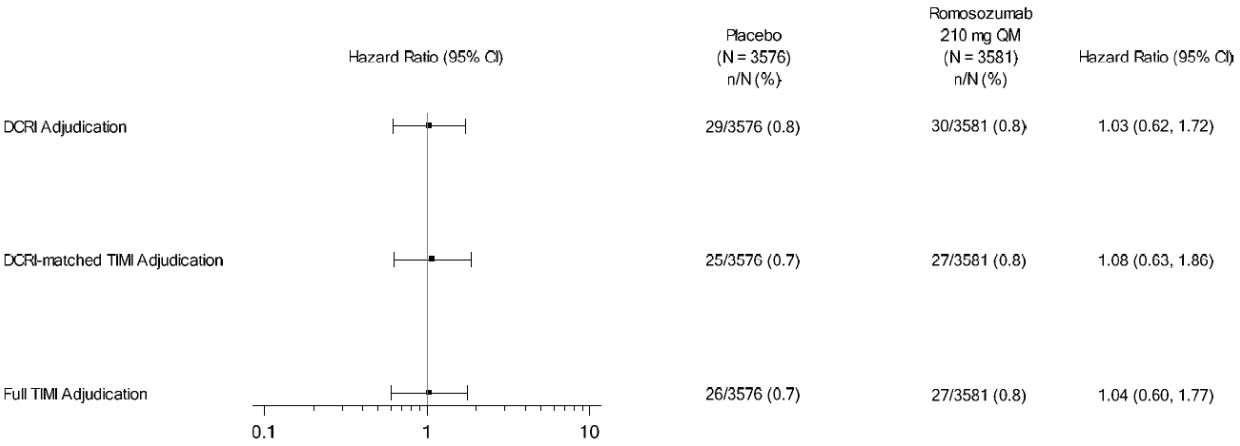
Source: Comprehensive Cardiovascular Report (Figure 14-6.16.1.1)

Figure 6: Hazard Ratio of Positively Adjudicated Cardiovascular Adverse Events leading to Death, Myocardial Infarction, or Stroke based on DCRI, DCRI-matched TIMI, and Full TIMI through Month 12: study 20110142



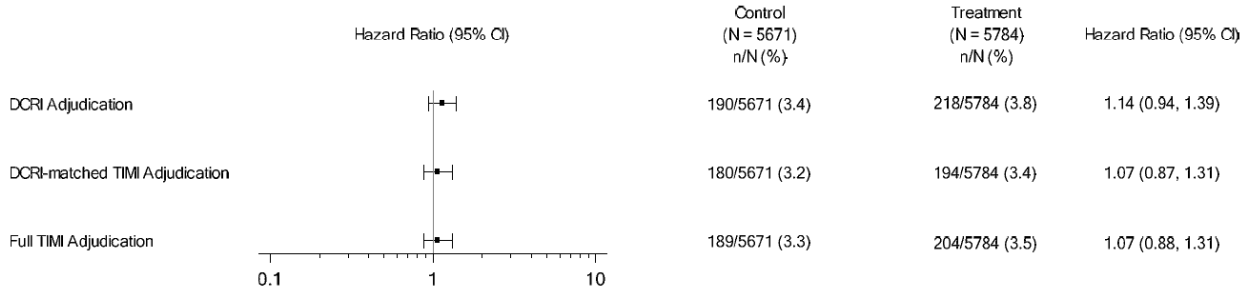
Source: Comprehensive Cardiovascular Report (Figure 14-6.16.1.2)

Figure 7: Hazard Ratio of Positively Adjudicated Cardiovascular Adverse Events leading to Death, Myocardial Infarction, or Stroke based on DCRI, DCRI-matched TIMI, and Full TIMI through Month 12: study 20070337



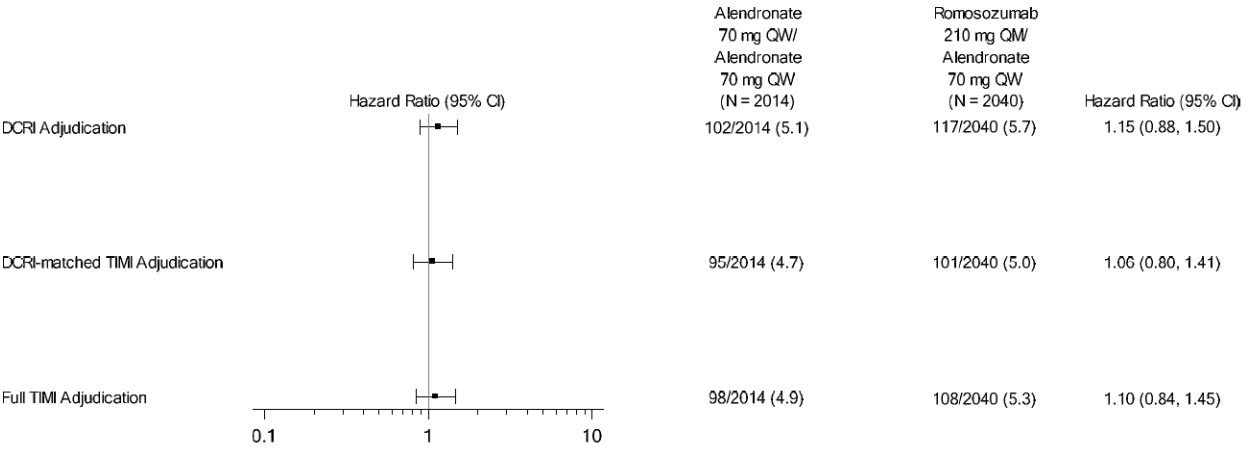
Source: Comprehensive Cardiovascular Report (Figure 14-6.16.1.3)

Figure 8: Hazard Ratio of Positively Adjudicated Cardiovascular Adverse Events leading to Death, Myocardial Infarction, or Stroke based on DCRI, DCRI-matched TIMI, and Full TIMI for Overall Study Period: all 3 studies



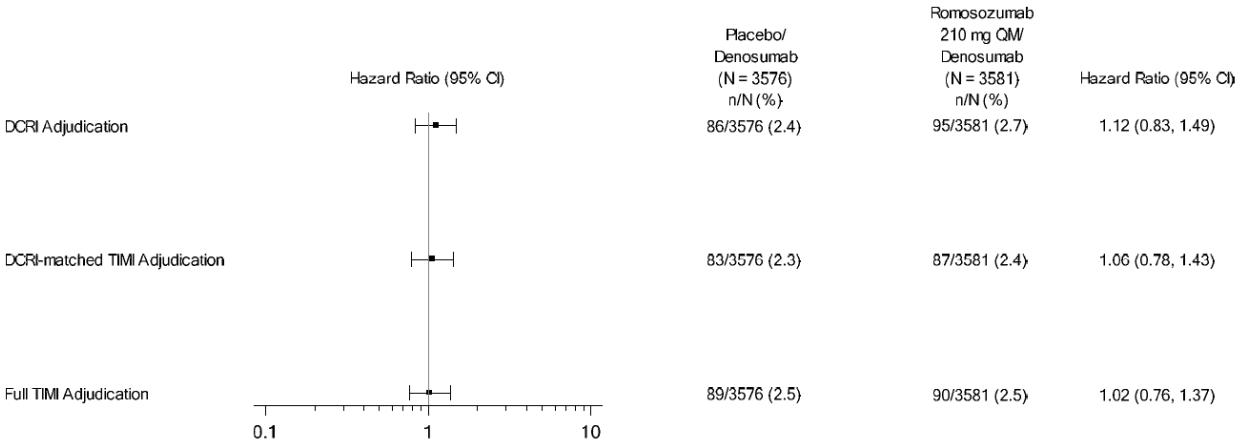
Source: Comprehensive Cardiovascular Report (14-6.16.1.4)

Figure 9: Hazard Ratio of Positively Adjudicated Cardiovascular Adverse Events leading to Death, Myocardial Infarction, or Stroke based on DCRI, DCRI-matched TIMI, and Full TIMI for Overall Study Period: study 20110142



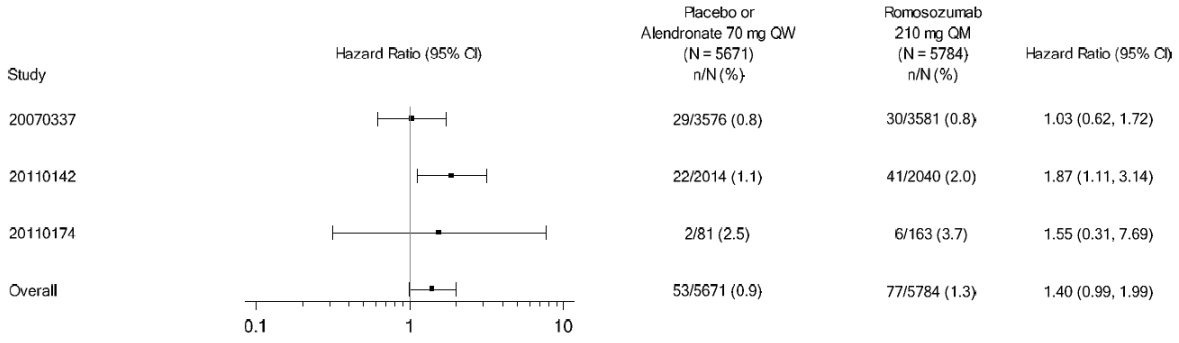
Source: Comprehensive Cardiovascular Report (14-6.16.1.5)

Figure 10: Hazard Ratio of Positively Adjudicated Cardiovascular Adverse Events leading to Death, Myocardial Infarction, or Stroke based on DCRI, DCRI-matched TIMI, and Full TIMI for Overall Study Period: study 20070337



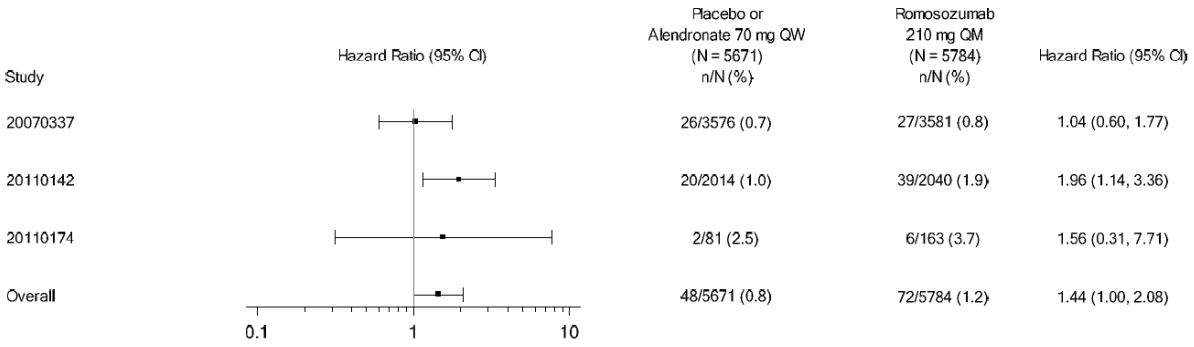
Source: Comprehensive Cardiovascular Report (14-6.16.1.6)

Figure 11: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Events Leading to Death, Myocardial Infarction, or Stroke through Month 12



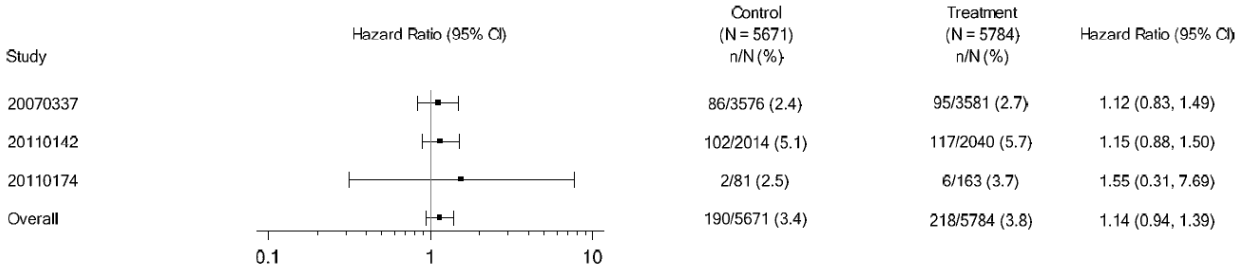
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.1.1 page 3510)

Figure 12: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Events Leading to Death, Myocardial Infarction, or Stroke through Month 12



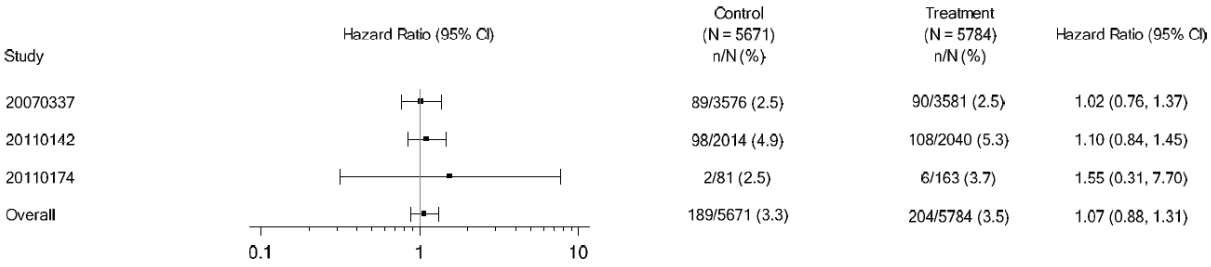
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.1.2 page 3511)

Figure 13: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Events Leading to Death, Myocardial Infarction, or Stroke for Overall Study Period



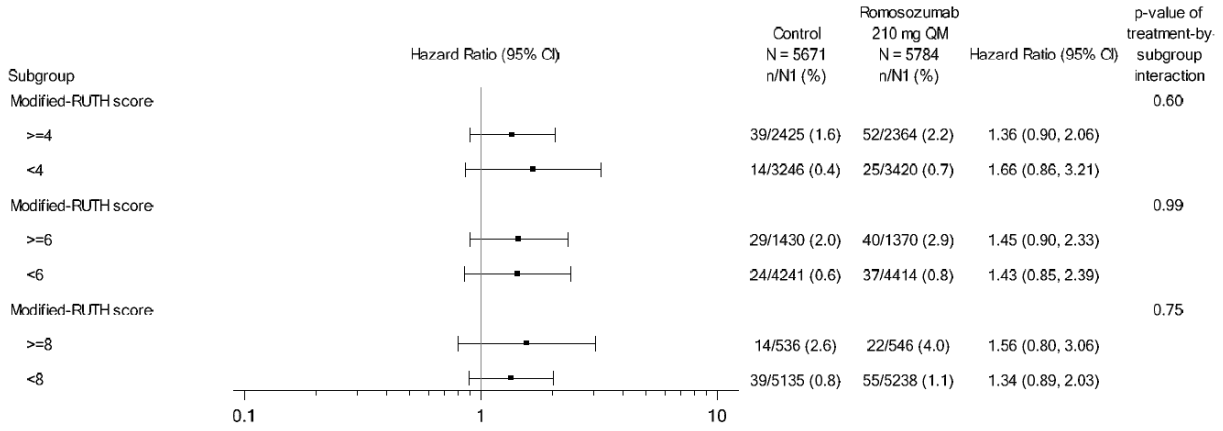
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.1.3 page 3512)

Figure 14: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Events Leading to Death, Myocardial Infarction, or Stroke for Overall Study Period



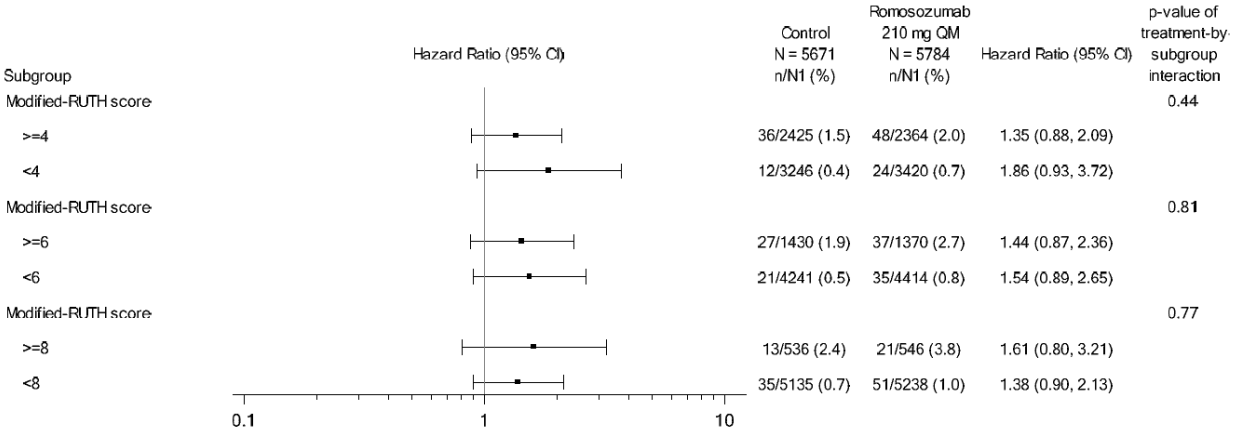
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.1.4 page 3513)

Figure 15: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Events Leading to Death, Myocardial Infarction, or Stroke through Month 12 by Modified RUTH Score Subgroup



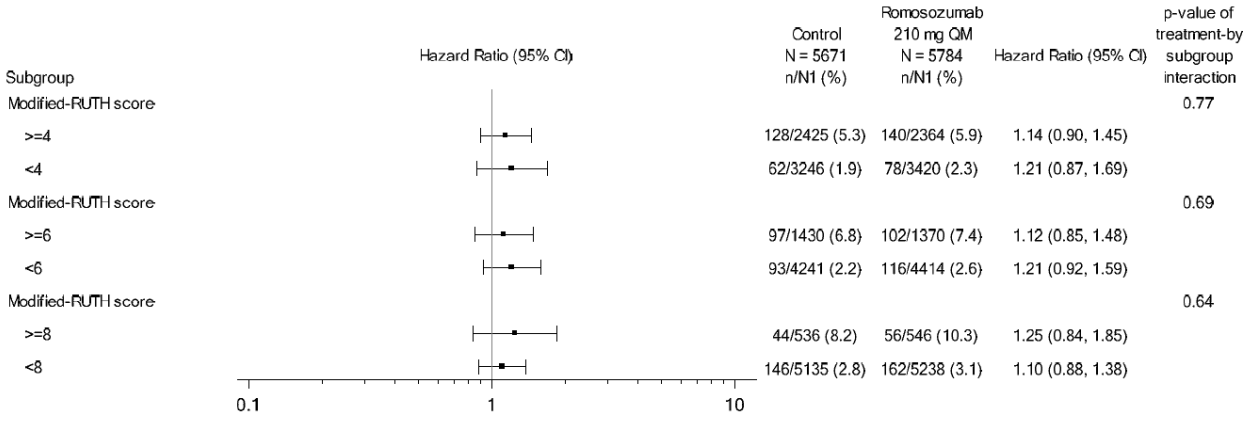
Source: Comprehensive Cardiovascular Report (Figure 14-6.4.1.1)

Figure 16: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Events Leading to Death, Myocardial Infarction, or Stroke through Month 12 by Modified RUTH Score Subgroup



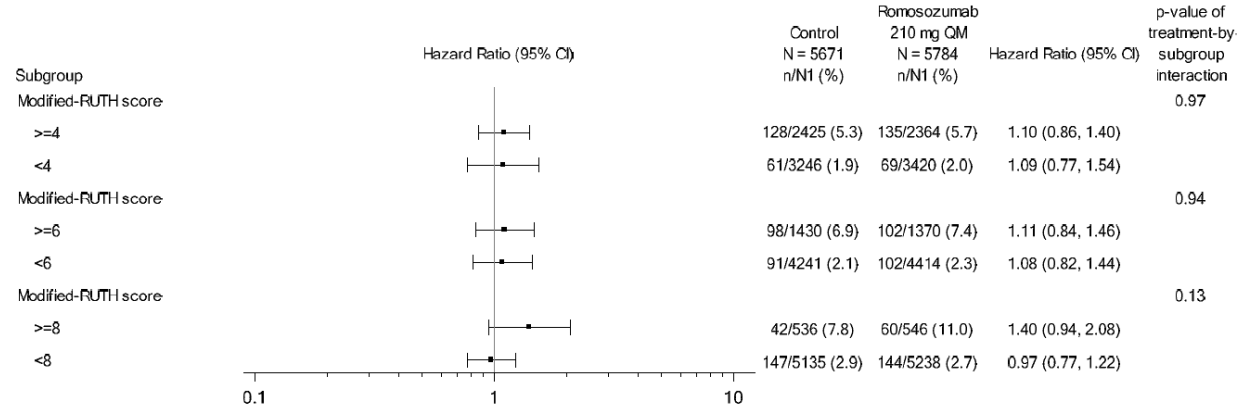
Source: Comprehensive Cardiovascular Report (Figure 14-6.4.1.2)

Figure 17: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Events Leading to Death, Myocardial Infarction, or Stroke for Overall Study Period by Modified RUTH Score Subgroup



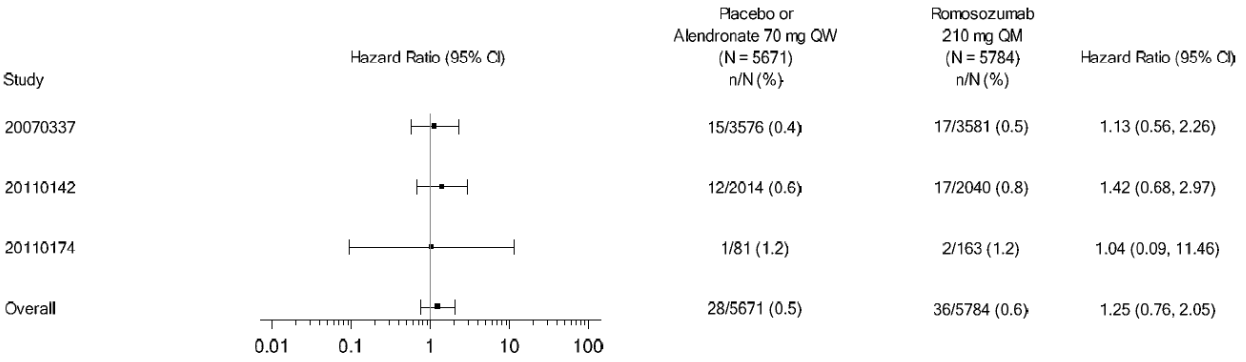
Source: Comprehensive Cardiovascular Report (Figure 14-6.4.1.7)

Figure 18: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Events Leading to Death, Myocardial Infarction, or Stroke for Overall Study Period by Modified RUTH Score Subgroup



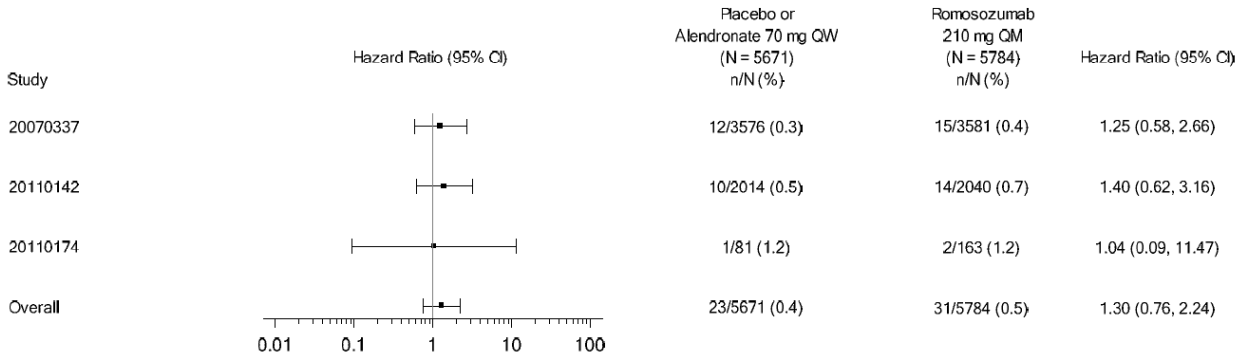
Source: Comprehensive Cardiovascular Report (Figure 14-6.4.1.8)

Figure 19: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Event leading to Death through Month 12



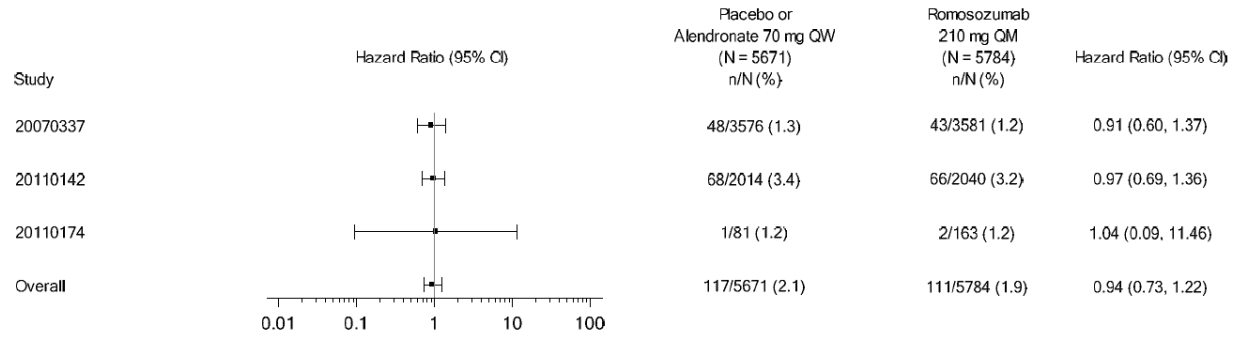
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.2.1)

Figure 20: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Event leading to Death through Month 12



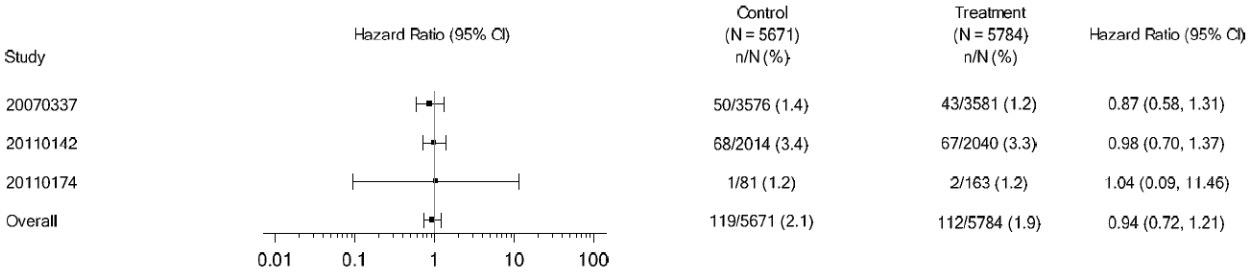
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.2.2)

Figure 21: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Event leading to Death for Overall Study Period



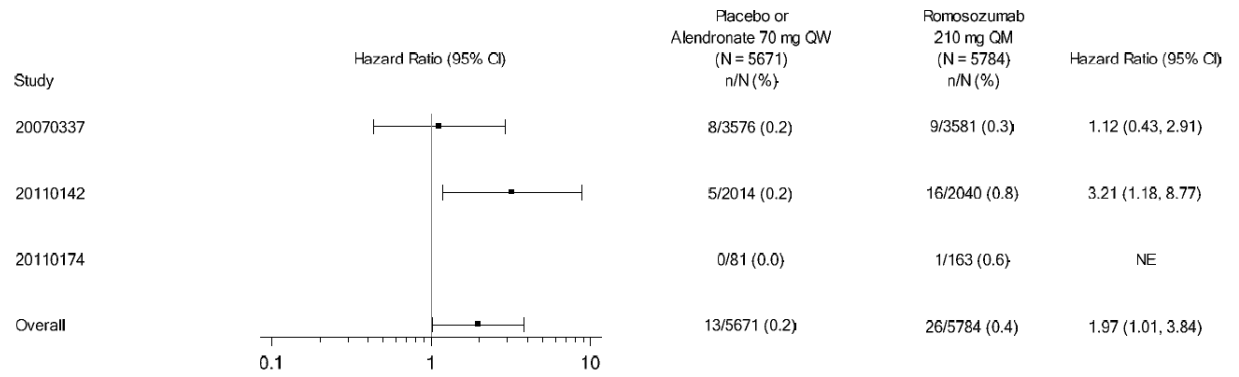
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.2.3)

Figure 22: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiovascular Adverse Event leading to Death for Overall Study Period



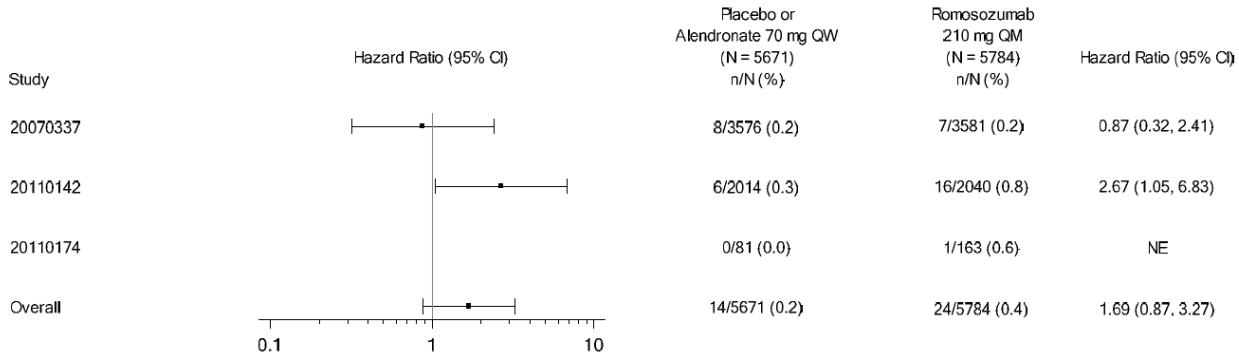
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.2.4)

Figure 23: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Myocardial Infarction through Month 12



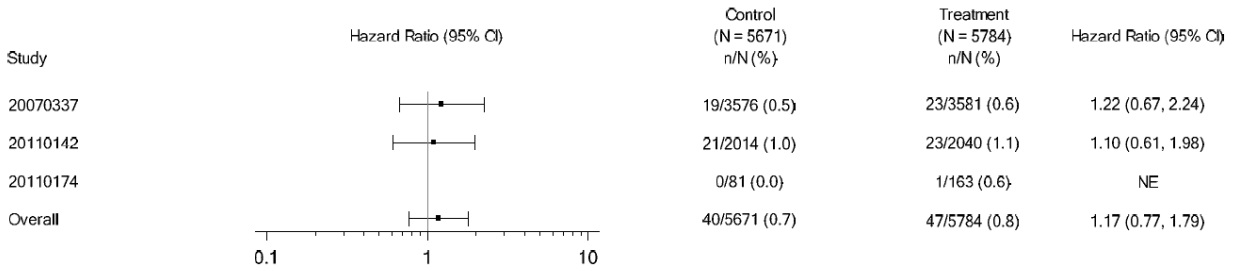
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.3.1)

Figure 24: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Myocardial Infarction through Month 12



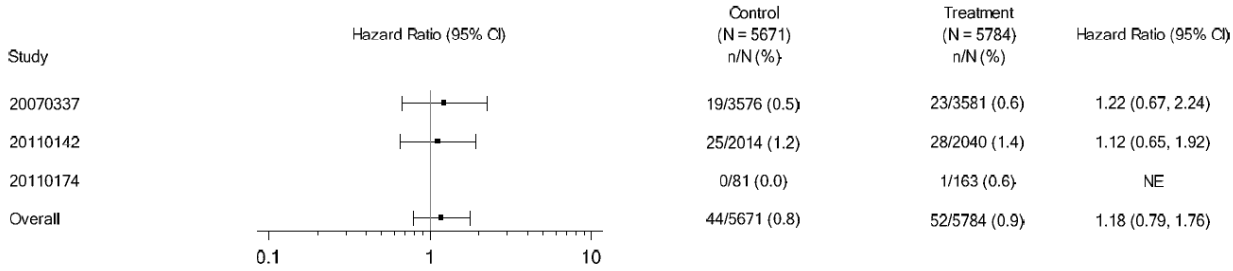
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.3.2)

Figure 25: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Myocardial Infarction for Overall Study Period



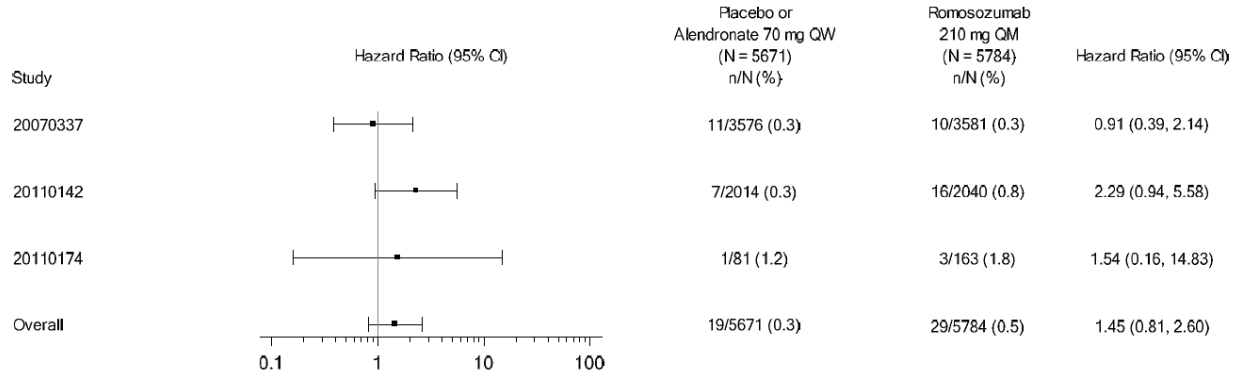
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.3.3)

Figure 26: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Myocardial Infarction for Overall Study Period



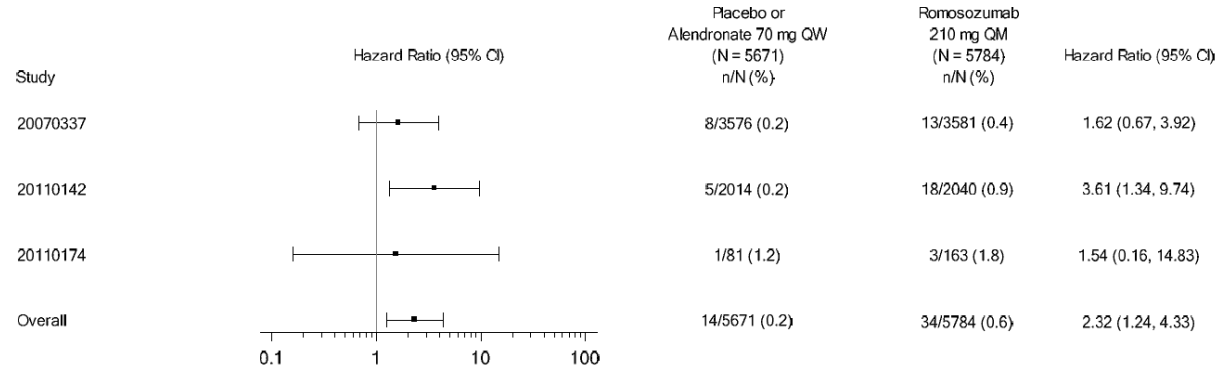
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.3.4)

Figure 27: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cerebrovascular Serious Adverse Event through Month 12



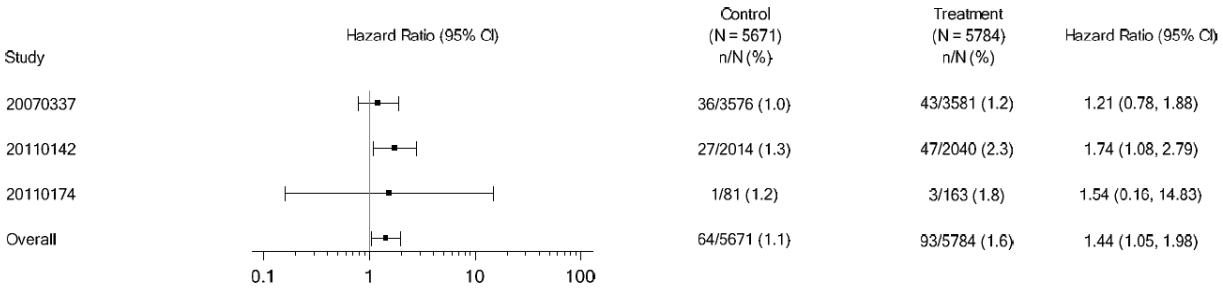
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.5.1)

Figure 28: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cerebrovascular Adverse Event through Month 12



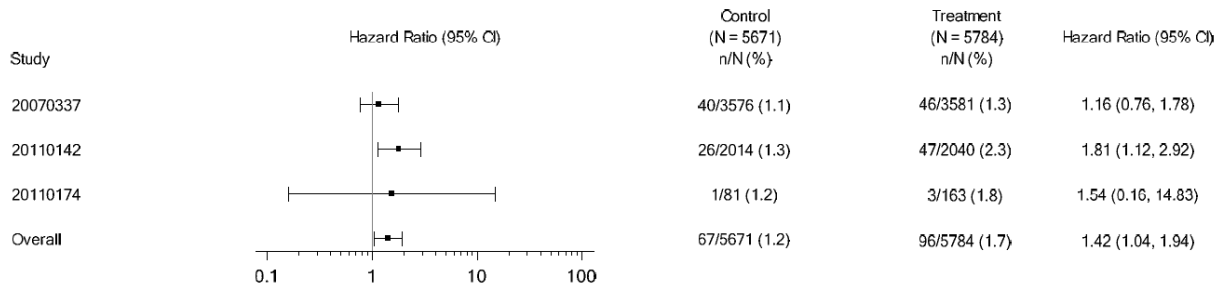
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.5.2)

Figure 29: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cerebrovascular Serious Adverse Event for Overall Study Period



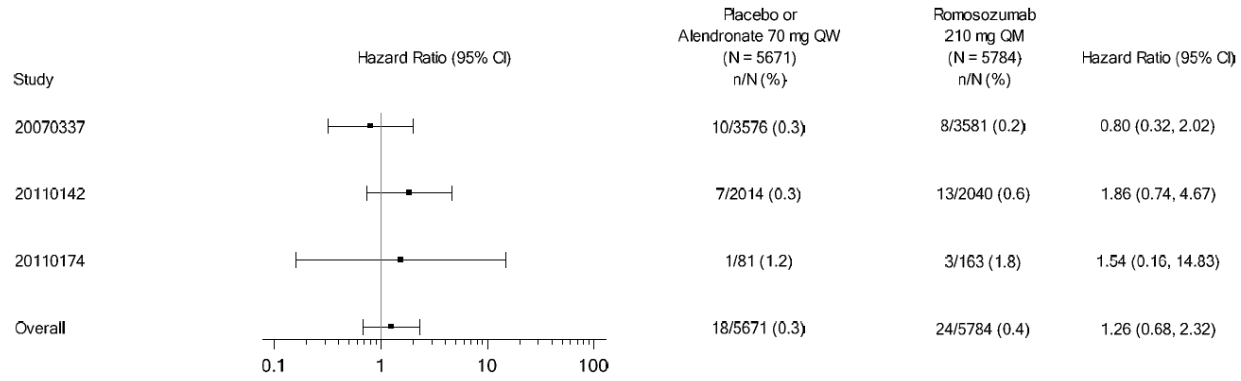
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.5.3)

Figure 30: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cerebrovascular Adverse Event for Overall Study Period



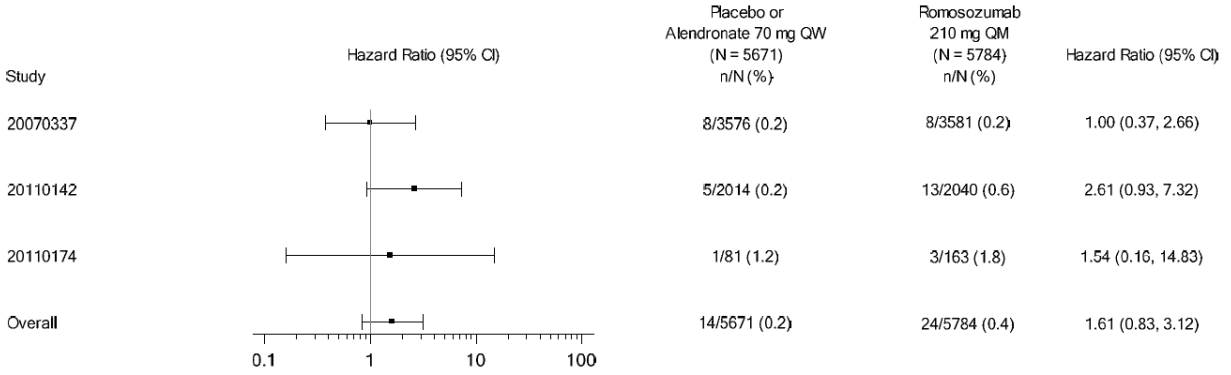
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.5.4)

Figure 31: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Serious Stroke through Month 12



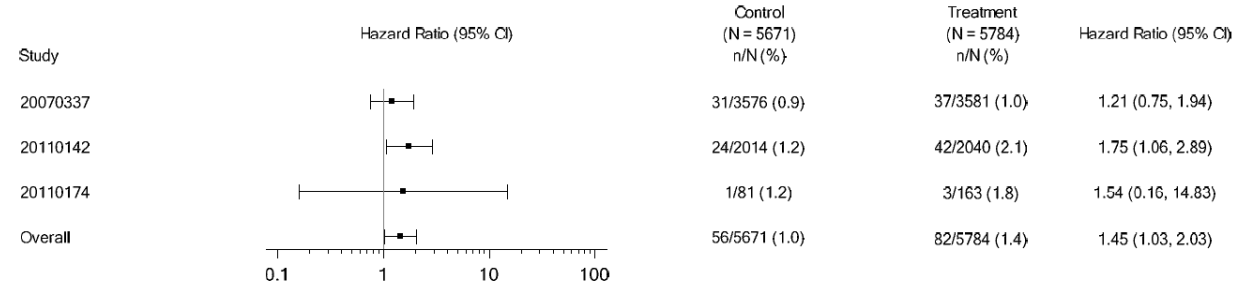
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.4.1)

Figure 32: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Stroke through Month 12



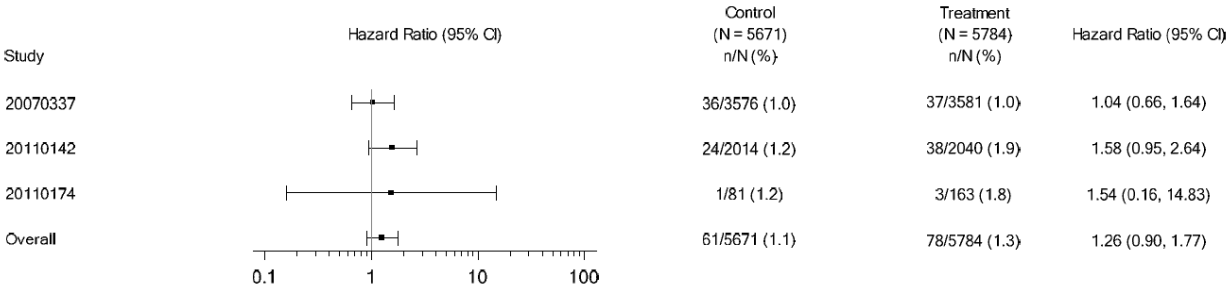
Source: Comprehensive Cardiovascular Report (Figure 14.6.1.4.2)

Figure 33: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Serious Stroke for Overall Study Period



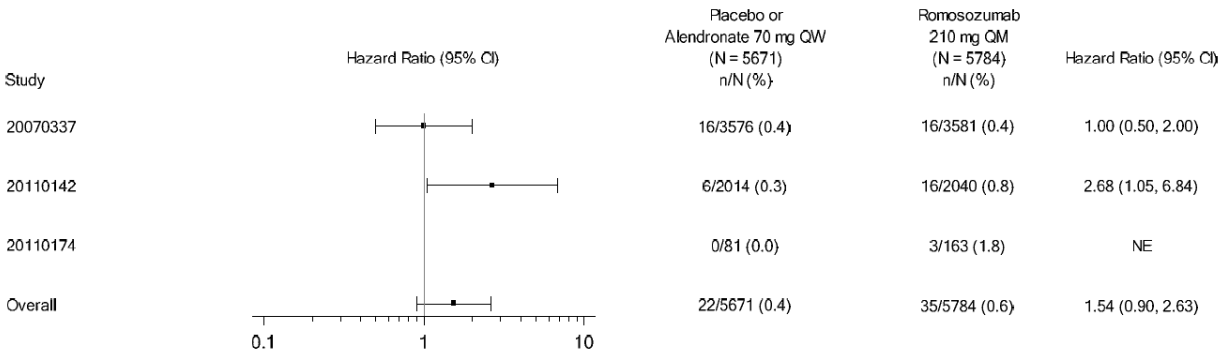
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.4.3)

Figure 34: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Stroke for Overall Study Period



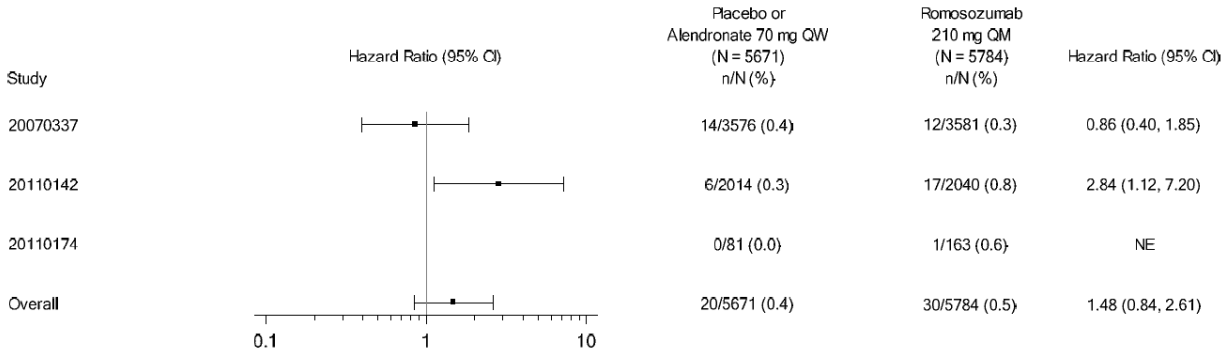
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.4.4)

Figure 35: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiac Ischemic Serious Adverse Event through Month 12



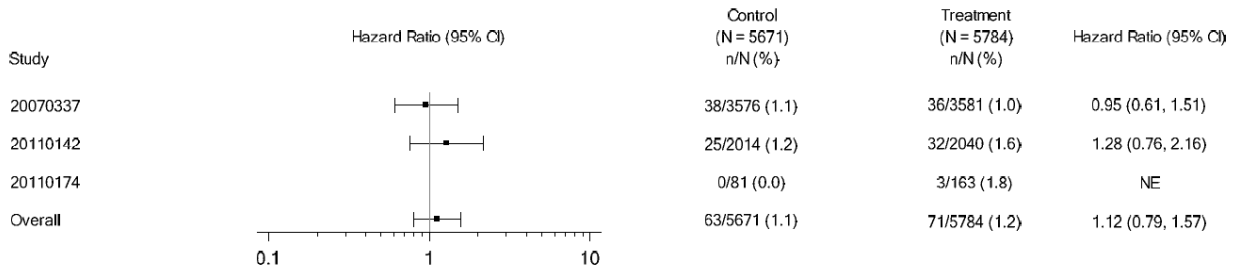
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.6.1)

Figure 36: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiac Ischemic Adverse Event through Month 12



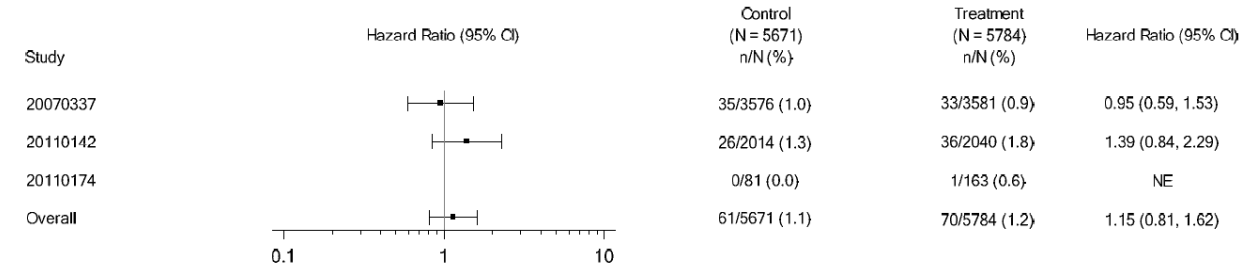
Source: Comprehensive Cardiovascular Report (Figure 14-6.1.6.2)

Figure 37: DCRI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiac Ischemic Serious Adverse Event for Overall Study Period



Source: Comprehensive Cardiovascular Report (Figure 14-6.1.6.3)

Figure 38: TIMI Adjudication: TIMI Adjudication: Time to First Occurrence of Positively Adjudicated Cardiac Ischemic Adverse Event for Overall Study Period



Source: Comprehensive Cardiovascular Report (Figure 14-6.1.6.4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FORTUNATO F SENATORE
09/27/2018

MARTIN ROSE
09/28/2018
Make sure markup does not show in final document

NORMAN L STOCKBRIDGE
09/28/2018

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	BLA 761062 000
Applicant	Amgen
Date of Submission	July 19, 2016
PDUFA Goal Date	July 19, 2017
Proprietary Name / **Non-Proprietary Name**	Evenity Romosozumab
Dosage Form(s) / Strength(s)	105 mg/1.17 mL solution in a single-use prefilled syringe for subcutaneous injection Health care providers administer two prefilled syringes for the full 210 mg romosozumab dose
Applicant Proposed Indication(s)/Population(s)	Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Action/Recommended Action for NME:	*Complete Response*
Approved/Recommended Indication/Population(s) (if applicable)	*N/A*

Material Reviewed/Consulted Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Debuene Chang
Statistical Review	Jia Guo, Mahboob Sobhan, Hepei Chen, Karl Lin, and Feng Zhou
Pharmacology Toxicology Review	Gemma Kuijpers, Andrea Benedict, Miyun Tsai-Turton, Laurie McLeod-Flynn, and Kimberly Hatfield
Office of Pharmaceutical Quality Review	Chen Sun, Juhong Liu, Joel Welch, Bo Chi, Lakshmi Narasimhan, Patricia Hughes Troost, Zhihao Qiu, Michael Shanks, and Melinda Bauerlien, David Frucht
Center for Devices and Radiological Health	Sarah Mollo and Alan Stevens
Clinical Pharmacology Review	Lin Zhou, Yow-Ming Wang, Luning Zhuang, Jeffry Florian, and Hae Young Ahn
Office of Study Integrity and Surveillance	Mohsen Rajabi Abhari, Stanley Au, Gopa Biswas, Arindam Dasgupta, Seongeun (Julia) Cho, Xingfang Li, Michael Skelly, Elise Murphy, and Sam Haidar
Office of Scientific Investigations	Bei Yu, Janice Pohlman, and Kassa Ayalew
Cross-Discipline Team Leader Review	Theresa Kehoe
Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis	Walter Fava, Lolita White, and QuynhNhu Nguyen

Reference ID: 4124009

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Romosozumab (proposed trade name Evenity) is a first-in-class sclerostin inhibitor proposed as a one-year treatment for postmenopausal osteoporosis to reduce the risk of fracture. The dosing regimen is 210 mg administered subcutaneously once monthly in the arm, abdominal wall or thigh by a health care provider. Two back-to-back injections are needed to administer the full dose.

Osteoporosis is a skeletal disorder characterized by low bone mass, compromised bone strength, and an increased risk of fracture. While osteoporosis can occur in both men and women, studies in postmenopausal women provide most of the data defining the disease and its sequelae. The goal of treatment is to reduce the risk of fracture.

The efficacy of romosozumab was evaluated in a clinical trial of postmenopausal women with osteoporosis who were receiving calcium and vitamin D supplementation. Fracture outcomes were assessed after patients received one year of treatment with romosozumab or placebo, and again after patients had subsequently received a year of treatment with denosumab.

- One year of treatment with romosozumab significantly reduced the risk of new vertebral fractures compared to placebo. The incidence of new vertebral fractures was 0.5% with romosozumab and 1.8% with placebo ($p<0.001$). The absolute risk reduction was 1.3% (95% confidence interval 0.8%-1.8%) and the relative risk reduction was 73% (95% confidence interval 53%-84%). Based on the bounds of the 95% confidence interval for the absolute risk reduction, the number needed to treat to prevent one new vertebral fracture is 56-125.

- One year of romosozumab followed by one year of denosumab significantly reduced the risk of new vertebral fractures compared to one year of placebo followed by one year of denosumab. The incidence of new vertebral fractures was 0.6% with romosozumab then denosumab and 2.5% with placebo then denosumab ($p<0.001$). The absolute risk reduction was 1.9% (95% confidence interval 1.3%-2.5%) and the relative risk reduction was 75% (95% confidence interval 60%-84%).

The robust and statistically persuasive findings ($p<0.001$) from this single fracture outcomes trial together with supportive bone mineral density data from two dose-finding trials meet the requirement for substantial evidence of effectiveness.

Romosozumab did not significantly reduce the risk of nonvertebral fractures, likely because the trial was underpowered for these events.

Based on the observation that patients previously treated with romosozumab experienced large losses of their accrued bone mineral density

after switching to placebo for one year, the beneficial effect of romosozumab on vertebral fractures is expected to wane within one year after stopping romosozumab if another osteoporosis therapy is not initiated. The application provides evidence of fracture risk reduction beyond the one year of treatment with romosozumab only for patients who subsequently received one year of treatment with denosumab.

Only 3% of the pivotal Phase 3 trial population was from North America. There were too few patients to statistically analyze fracture outcomes in this subgroup. However, the bone mineral density increases among North Americans were consistent with those for the overall trial population. These data support generalizability of the foreign data to patients in the United States.

Treatment with romosozumab for one year did not appear to have adverse cardiovascular effects compared to placebo. In contrast, topline results from an ongoing trial that became available late in the review cycle showed adverse cardiovascular effects with romosozumab compared to alendronate (an approved osteoporosis therapy). Adverse cardiovascular effects were also seen in a recently completed, small male osteoporosis trial. Reasons for the discrepant results are unclear. The hazard ratios for Major Adverse Cardiovascular Events (MACE), a composite endpoint of adjudicated serious adverse events of myocardial infarction and stroke, and cardiovascular death were:

- 1.03 (95% confidence interval 0.62, 1.72) in the pivotal Phase 3 trial included in the application
- 1.87 (95% confidence interval 1.11, 3.14) in the alendronate trial
- 1.55 (95% confidence interval 0.31, 7.69) in the male osteoporosis trial

Romosozumab's remaining safety concerns are generally infrequent and have been seen with other therapeutic biologics or with some of the other approved osteoporosis therapies. These safety concerns include:

- Hypersensitivity reactions, which were reported as serious in 0.2% of patients
- Injection site reactions (e.g., pain and erythema), which were reported in 5-10% of patients, but rarely led to treatment discontinuation
- Hypocalcemia, which was reported in less than 0.5% of patients. Those with renal impairment, particularly end-stage renal disease, appear to be particularly susceptible to hypocalcemia with romosozumab.
- Osteonecrosis of the jaw, which was reported in three patients, one currently and two previously treated with romosozumab
- Atypical femoral fracture, which was reported in two patients, one currently and one previously treated with romosozumab

About 19% of patients treated with the 210 mg romosozumab dose developed binding antibodies. About 4% of those with binding antibodies tested positive for neutralizing antibodies. The incidence of injection site reactions was slightly higher among patients with antibodies. There were no other apparent effects of antibodies on safety. Antibodies decreased romosozumab exposures by up to 25%. However, romosozumab concentrations among patients with binding antibodies were all within the range of concentrations observed in patients without binding antibodies. In general, the presence of antibodies had no apparent effect on efficacy, although it is possible that some patients may have reduced efficacy as evidenced by a romosozumab-treated patient who developed neutralizing antibodies then had persistently undetectable romosozumab

concentrations despite continued dosing.

The new data showing potential cardiovascular risk are preliminary. A full report of these data and the fracture outcomes data from the head-to-head comparison of romosozumab to alendronate are needed to determine whether there is a population for whom the benefits of romosozumab outweigh its risks, and whether risk minimization strategies beyond labeling are needed to ensure the benefits outweigh the risks. The remaining safety concerns can be adequately mitigated by labeling, including a Medication Guide.

In summary, the Division cannot determine whether the benefits of romosozumab outweigh the identified risks and uncertainties until we have completed a thorough review of the cardiovascular safety of romosozumab and its comparative efficacy from the alendronate-controlled trial. These data should be included in the resubmission.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoporosis is characterized by low bone mass and compromised bone strength. Osteoporosis increases the risk of fracture. • Osteoporosis is underdiagnosed. About 50% of postmenopausal women over 50 years of age will have an osteoporotic fracture. • Vertebral fractures are the most common site of osteoporotic fracture and can cause kyphosis, back pain, height loss, and impaired lung function. • In older patients, hip fracture is associated with loss of independence and increased mortality.	Osteoporosis increases the risk of fracture. Underdiagnosis of osteoporosis is a major public health issue. Vertebral fractures are the most common site of osteoporotic fracture. Fractures can cause morbidity. Hip fracture is associated with increased mortality in older patients.
Current Treatment Options	• The goal of treatment is to reduce the risk of fracture. Approved treatments include two drugs that stimulate bone formation (teriparatide, abaloparatide) and several drugs that inhibit bone loss (bisphosphonates, denosumab, estrogen agonists/antagonists, and calcitonin). • All approved treatments for postmenopausal osteoporosis except for calcitonin have been definitively shown to reduce the risk of fracture. • Bisphosphonates are the most widely prescribed osteoporosis medications, but use has declined because of fears related to the serious, but rare side	Multiple therapies are available for the treatment of postmenopausal osteoporosis. The goal of treatment is to reduce the risk of fracture. Many patients with osteoporosis who would benefit from therapy remain untreated. Additional therapies, such as romosozumab

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	effects of osteonecrosis of the jaw and atypical femoral fractures. • Teriparatide and abaloparatide cause osteosarcoma in rats. Because human relevance cannot be excluded, these drugs are indicated for patients at high risk of fracture and lifetime use beyond two years is not recommended.	will expand the treatment options for osteoporosis.
Benefit	• In a clinical trial of postmenopausal women with osteoporosis who were receiving calcium and vitamin D supplementation, one year of treatment with romosozumab significantly reduced the risk of new vertebral fractures compared to placebo. o The incidence of new vertebral fractures was 0.5% with romosozumab and 1.8% with placebo ($p<0.001$). The absolute risk reduction was 1.3% (95% confidence interval 0.8%-1.8%) and the relative risk reduction was 73% (95% confidence interval 53%-84%). o Based on the lower and upper bounds of the 95% confidence interval for the absolute risk reduction, the number needed to treat to prevent one new vertebral fracture is 56-125. • The statistically persuasive findings ($p<0.001$) from this single fracture outcomes trial together with the supportive bone mineral density data from two dose-finding trials provide convincing evidence of efficacy. • In the same clinical trial, one year of romosozumab followed by one year of denosumab significantly reduced the risk of new vertebral fractures compared to one year of placebo followed by one year of denosumab. o The incidence of new vertebral fractures was 0.6% with romosozumab then denosumab and 2.5% with placebo then denosumab ($p<0.001$). The absolute risk reduction was 1.9% (95% confidence interval 1.3%-2.5%) and the relative risk reduction was 75% (95% confidence interval 60%-84%).	The Applicant has provided substantial evidence of effectiveness for romosozumab when used as a one-year treatment for postmenopausal osteoporosis. Based on the bone mineral density data, the beneficial effect of romosozumab on vertebral fractures is expected to wane within one year after stopping romosozumab if another osteoporosis therapy is not initiated. Evidence of fracture risk reduction beyond the one year of treatment with romosozumab is available only for patients who subsequently received one year of treatment with denosumab. The number needed to treat to prevent one vertebral fracture after one year of treatment with romosozumab is 56-125. Romosozumab has not been shown to reduce the risk of nonvertebral fractures, likely because the trial was underpowered for this endpoint. The Phase 3 trial enrolled too few patients from the United States to statistically evaluate

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Romosozumab did not significantly reduce the risk of nonvertebral fractures, a composite of fractures from sites such as ribs, forearm, and hip. • Romosozumab's effects on bone mineral density provide strong support for initiating another osteoporosis therapy after the one-year treatment course. o After one year, the mean percent increase in bone mineral density with romosozumab compared to placebo was 12.7% (95% confidence interval 12.4%, 12.9%) at the lumbar spine, 5.8% (95% confidence interval 5.6%, 6.0%) at the total hip and 5.2% (95% confidence interval 4.9%, 5.4%) at the femoral neck. o Patients had considerable loss of these bone mineral density gains within one year of stopping romosozumab. o Patients who transitioned to one year of denosumab after completing one year of romosozumab maintained their bone mineral density gains from romosozumab after the combined two years of therapy. • Only 3% of the pivotal Phase 3 trial population was from North America. There were too few patients to statistically analyze fracture outcomes in this subgroup. However, the bone mineral density changes among North Americans were consistent with those for the overall trial population, and support generalizability of the foreign data to patients in the United States.	efficacy in this subgroup. However, based on the totality of data, it is reasonable to conclude that the foreign data are applicable to the United States population.
Risk	• Treatment with romosozumab for one year did not appear to have adverse cardiovascular effects compared to placebo. In contrast, topline results from an ongoing trial that became available late in the review cycle showed adverse cardiovascular effects with romosozumab compared to alendronate (an approved osteoporosis therapy). Adverse cardiovascular effects were also seen in a recently completed, small male osteoporosis trial. Reasons for the discrepant results are unclear. The hazard ratios for Major Adverse Cardiovascular Events (MACE), a composite endpoint of adjudicated serious adverse events of myocardial infarction and stroke, and	Romosozumab may increase the risk of major adverse cardiovascular events. There was no apparent effect when romosozumab was compared with placebo, but preliminary data from two other trials – including a large trial comparing romosozumab to alendronate – show increased risk. Reasons for the discrepant results are unclear. The other safety concerns are generally

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cardiovascular death were: o 1.03 (95% confidence interval 0.62, 1.72) in the pivotal Phase 3 trial o 1.87 (95% confidence interval 1.11, 3.14) in the alendronate trial o 1.55 (95% confidence interval 0.31, 7.69) in the male osteoporosis trial • Romosozumab's remaining safety concerns include: o Hypersensitivity reactions (reported as serious in 0.2% of patients) o Injection site reactions, such as pain and erythema (reported in 5-10% of patients, and rarely led to treatment discontinuation) o Hypocalcemia (reported in less than 0.5% of patients). Those with renal impairment, particularly end-stage renal disease, appear to be particularly susceptible to hypocalcemia with romosozumab. o Osteonecrosis of the jaw (rare – three cases in patients currently or previously treated with romosozumab) o Atypical femoral fractures (rare – two cases in patients currently or previously treated with romosozumab) • About 19% of patients treated with the 210 mg dose developed binding antibodies. About 4% of those with binding antibodies tested positive for neutralizing antibodies. The incidence of injection site reactions was slightly higher among patients with antibodies. There were no other apparent effects of antibodies on safety.	infrequent and have been seen with other therapeutic biologics or with some of the other approved osteoporosis therapies. Binding and neutralizing antibodies to romosozumab may slightly increase the risk of injection site reactions but do not appear to have other notable effects on safety.
Risk Management	• The new data showing cardiovascular risk are preliminary. A full report of these data and the fracture outcomes data from the head-to-head comparison of romosozumab to alendronate are needed to determine whether there is a population for whom the benefits of romosozumab outweigh its risks, and whether risk minimization strategies beyond labeling are needed to ensure the benefits outweigh the risks. • If romosozumab can otherwise be approved, the remaining safety concerns can be adequately mitigated by labeling, including a Medication Guide.	A full report of the cardiovascular effects and the head-to-head comparison to alendronate is needed before we can assess whether the benefits of romosozumab outweigh its risks. Labeling, including a Medication Guide for patients, will be adequate to mitigate all of the other currently identified safety concerns with romosozumab.

2. Background

Amgen submitted this Biologics License Application (BLA) for romosozumab (trade name Evenity), a first-in-class sclerostin inhibitor proposed for the treatment of postmenopausal osteoporosis. Romosozumab is not approved in any country. The proposed dosing regimen is 210 mg (given as two back-to-back injections of 105 mg) administered subcutaneously by a healthcare provider in the patient's arm, abdominal wall or thigh once monthly for 12 months.

Sclerostin, a glycoprotein produced by osteocytes, inhibits the Wingless-related integration site (Wnt) signaling pathway, leading to reduced bone formation and increased bone resorption. Patients with the rare bone disorder, sclerosteosis, have an inactivating mutation in the sclerostin gene that leads to a lack of sclerostin, and have dense bones that are resistant to fracture. Patients with Van Buchem disease lack a regulatory element of the sclerostin gene, leading to reduced sclerostin concentrations and a resistance to fractures. Based on these effects, the Applicant developed romosozumab, a humanized immunoglobulin G2 (IgG2) monoclonal antibody, that binds and inhibits sclerostin to reduce the risk of fractures in patients with osteoporosis.

This BLA was reviewed under the Prescription Drug User Fee Act (PDUFA) V "Program" because it contains a new molecular entity and was received after October 1, 2012. This document summarizes the Division's recommendations on the application.

3. Product Quality

The Office of Pharmaceutical Quality and the Center for Devices and Radiological Health recommend approval. See their reviews for details.

Evenity is a drug-device combination product containing romosozumab in a sterile, preservative-free solution within a single-use (b) (4) syringe. The syringe includes a (b) (4) (b) (4) needle. Each syringe delivers a volume of 1.17 mL containing 105 mg of romosozumab in a concentration of 90 mg/mL. Inactive ingredients include calcium, acetate, sucrose, polysorbate 20, sodium hydroxide (b) (4) and Water for Injection – none of which are novel. A syringe delivers one-half of the required dose; therefore, two back-to-back injections using two separate syringes are needed to deliver the full dose.

Romosozumab is produced from a recombinant DNA-derived Chinese Hamster Ovary (CHO) cell line using standard cell culture techniques. The Applicant provided adequate data to ensure that the product is pure and potent, and has acceptable manufacturing processes. All required pre-licensing manufacturing inspections were acceptable.

If romosozumab can be approved, the Chemistry reviewers recommend a postmarketing commitment (b) (4) (b) (4)

The Office of Pharmaceutical Quality also assessed the Applicant's assays for detecting binding and neutralizing antibodies to romosozumab. The reviewers found the assays to be adequate. Of note, the presence of romosozumab can interfere with the neutralizing assay, preventing detection of low concentrations of neutralizing antibodies. The Applicant handled this issue by including an assessment of neutralizing antibodies four months after the last dose of romosozumab in the Phase 2 and 3 trials.

The stability data support a shelf-life of 36 months for the drug product when stored at 2-8 degrees Celsius.

The Center for Devices and Radiological Health reviewed the syringe component and concluded that it is suitable for the intended use.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology reviewers recommend approval. See their review for details.

Romosozumab binds with similar affinity to human, rat and monkey sclerostin. Anti-drug antibodies developed in some rats and monkeys, lowering exposures. These animals were removed from the longer-term nonclinical studies or removed from data analyses involving pharmacokinetic evaluations. Romosozumab was highly immunogenic in rabbits so this species was not used for toxicity assessments.

The drug substance formulation used in the nonclinical studies was either identical to that used for the Phase 3 trial or adequately bridged to the Phase 3 formulation via a monkey pharmacokinetic study.

In ovariectomized rats and monkeys (animal models of postmenopausal osteoporosis), romosozumab increased bone mass and bone strength without negatively affecting bone quality.

The Applicant conducted toxicology studies up to six months duration in rats and monkeys. The reviewers attribute the main findings in these studies to the pharmacologic effect of romosozumab. For example, decreases in red blood cells, leukocytes, and platelets, and extramedullary hematopoiesis were associated with hyperostosis (excessive bone growth), and attributed to the narrowing of the hematopoietic bone marrow space. There were also decreases in serum calcium and phosphorus (attributed to use of these minerals for new bone formation). Multiples of human exposure ranged from 1 to 38-fold in rats and 1 to 93-fold in monkeys.

As discussed in the Safety Section and Benefit/Risk Assessment, the Applicant has identified a cardiovascular safety signal in an ongoing active-controlled Phase 3 trial and in a small trial in men, which was not observed in the Phase 3 trial included in the BLA. The sclerostin gene or protein is expressed in portions of the vasculature (the aorta, pulmonary artery, and calcified vascular smooth muscle cells). However, there were no adverse findings from the nonclinical program that lend support to the cardiovascular findings observed in the clinical trials. Specifically, there were no electrocardiographic effects in the one-month and six-month monkey

toxicity studies, no cardiac or vascular histopathologic findings in rats or monkeys, no radiographic evidence of vascular calcification in a 12-month monkey bone study, and no effect on the incidence of vascular calcification in a two-year rat study.

The Applicant did not assess mutagenicity because monoclonal antibodies are not expected to alter DNA or chromosomes. We recommended a rodent carcinogenicity study because of the potential for romosozumab to activate Wnt signaling, because this pathway may be involved in tumorigenesis. The 98-week carcinogenicity study in rats did not show any drug-related tumors. Two cases of osteosarcoma were seen in males in the high-dose group (19-times human exposure) that were not statistically different to control. The reviewers concluded that romosozumab is unlikely to increase the human risk of osteosarcoma.

Findings from the reproductive toxicity studies in rats included:

- No effects on fertility in rats given romosozumab at 1.5 to 56-times human exposure.
- Reduced ventral processes of the sixth cervical vertebra at 17 to 56-times human exposure. This finding represents a developmental delay but the reviewers do not consider it to be relevant because this anatomical structure is not present in humans.
- Poly- and syndactyly at 32-times human exposure. This finding is consistent with the syndactyly seen in humans who have homozygous sclerosteosis, and in mice that have a knockout of the sclerostin gene. The reviewers consider this finding to have low clinical relevance based on the exposure multiple, and timing of digit formation in the first trimester in humans when placental transfer of immunoglobulins is limited.
- Mild decreases in bone mass and size in the offspring of female rats that had been given romosozumab doses at 1.5 to 56-times human exposure.

Note that the Applicant is seeking approval in postmenopausal women, a population that is no longer of reproductive potential.

5. Clinical Pharmacology

The Clinical Pharmacology and Pharmacometrics reviewers recommend approval. See their review for details. Key findings are summarized below.

Selected pharmacokinetic parameters: Romosozumab has nonlinear pharmacokinetics, with a greater than dose-proportional increase in exposure. For example, there is a 550-fold increase in mean area under the concentration-time curve (AUC_{inf}) with a 100-fold increase in subcutaneous dosing from 0.1 mg/kg to 10 mg/kg (the proposed dose of 210 mg corresponds to 3 mg/kg for a 70 kg women).

After a single 210 mg dose to healthy subjects, the median time to maximal concentrations (Tmax) was five days (range 2-7 days) with a Cmax of 22 mcg/mL. In the pivotal Phase 3 trial,

steady state was achieved by Month 3 following once monthly dosing. At steady state, trough serum concentrations of romosozumab ranged from 8-10 mcg/mL in pre-dose samples, and the effective half-life was about 13 days.

Intrinsic and extrinsic factors: The Applicant tested a single romosozumab dose in the pivotal Phase 3 trial. The Clinical Pharmacology reviewers are not recommending dose adjustments based on intrinsic factors (e.g., age, body weight, renal impairment) or extrinsic factors (e.g., drug interactions), as summarized below.

- In a single-dose pharmacokinetic study, patients with severe renal impairment had a 29% mean increase in romosozumab Cmax and a 44% mean increase in romosozumab AUC compared to healthy subjects (smaller increases are expected in patients with mild or moderate renal impairment). These modest pharmacokinetic differences do not necessitate dosage adjustment. In contrast, mean romosozumab exposures were similar between patients with end-stage renal disease on hemodialysis and healthy subjects. The reason for the discrepancy between those with severe renal impairment and end-stage renal disease is unclear.

- Population pharmacokinetic modeling did not identify an impact of age on romosozumab exposures but noted an increase in romosozumab exposures among patients with lower body weight. Romosozumab AUC among patients in the lowest quartile of body weight was about 50% higher than in the highest quartile of body weight. These data are consistent with the bone mineral density changes seen with romosozumab in the pivotal Phase 3 trial, where percent increases at the lumbar spine were progressively smaller with increasing quartile of body weight. For example, the median increase at one year was 14.8% in the lowest quartile of body weight compared to 10.8% in the highest quartile. However, the highest quartile still had large increases in bone mineral density and had a numerically lower incidence of new vertebral fractures compared to the lowest quartile. There was also no statistical interaction between treatment and body mass index with respect to new vertebral fractures. In totality, based on these data from the pivotal Phase 3 trial, which administered the same dose to all patients regardless of body weight, there is no need for dosage adjustment based on body weight.

- The Applicant did not assess romosozumab exposures in patients with hepatic impairment, characterize the metabolic pathway of romosozumab, or conduct drug-drug interaction studies. This is reasonable because, unlike small molecule drugs which are often metabolized by hepatic enzymes, large therapeutic antibodies are typically degraded into amino acids by ubiquitous proteases.

Dose-finding: The Phase 2 dose-finding trial (20060326) in postmenopausal women with low bone mineral density included two active-comparator arms, and an extension and retreatment phase. For dose-selection for Phase 3, the Applicant focused on the initial two year treatment period and comparisons between placebo and the five tested subcutaneous romosozumab doses (70 mg monthly, 140 mg monthly, 210 mg monthly, 140 mg every three months, 210 mg every three months). There were dose-dependent increases in bone mineral density during the first year of treatment, with more gradual increases during the second year.

During the first year of treatment with romosozumab, bone turnover markers showed an increase in bone formation and a reduction in bone resorption. During the second year, the bone turnover markers showed persistent effects on bone resorption but not on bone formation.

Based on the bone mineral density data and bone turnover markers, the Applicant proposed to treat patients with romosozumab for only one year. They chose the 210 mg monthly dose for Phase 3 testing because this dose had the greatest effect on bone mineral density and bone formation markers during one year of treatment.

After the two year treatment period, patients were re-randomized to one year of denosumab or placebo. After treatment with placebo for one year, patients previously treated with romosozumab had experienced large losses of their accrued bone mineral density. These data provide an opportunity to assess what happens to bone mineral density when romosozumab is stopped without initiation of other osteoporosis therapy, and support the need for continued osteoporosis therapy after romosozumab is stopped.

Another dose-finding Phase 2 trial (20101291) was conducted in postmenopausal Japanese women with osteoporosis. This one year trial compared three romosozumab doses (70 mg, 140 mg, or 210 mg once monthly) to placebo. Findings were consistent with the other dose-finding trial, with the greatest bone mineral density gains at the lumbar spine with the 210 mg monthly dose.

Bone turnover markers: In the pivotal Phase 3 trial, the bone formation marker, type 1 N-terminal procollagen (P1NP), peaked two weeks after starting romosozumab but declined to concentrations seen with placebo at Month 9 and further declined to concentrations about 15% below placebo at Month 12. The bone resorption marker collagen type 1 C-telopeptide (CTX), nadired two weeks after starting romosozumab and remained about 25% below placebo at Month 12. These data like those from the Phase 2 dose-finding trial, support two mechanisms of action – increased bone formation (that is transient, lasting less than a year) and reduced bone resorption (that persists after one year of treatment).

Formulation changes: In the dose-finding Phase 2 trial (20060326) and the pivotal Phase 3 trial (20070337), investigators administered the 70 mg/mL formulation of romosozumab. The full 210 mg dose was given as three back-to-back 1.0 mL injections. In contrast, the to-be-marketed product uses single-use (b) (4) prefilled syringes containing 90 mg/mL of romosozumab. Health care providers will administer the 210 mg dose as two 1.17 mL injections, with each injection providing 105 mg of romosozumab. The Applicant adequately bridged the differences between the Phase 3 and to-be-marketed products with the following approach:

- A clinical pharmacology study and a separate six-month bone mineral density non-inferiority trial compared the 210 mg romosozumab dose given in the 70 mg/mL formulation to the 90 mg/mL formulation. Both formulations in these bridging trials used the Phase 3 drug substance manufacturing site. We had recommended the non-inferiority trial because formulation changes of complex protein products, such as romosozumab, could potentially

impact immunogenicity, which could in turn affect the efficacy or safety profile. This non-inferiority trial is discussed in more detail in the Efficacy and Safety sections.

- Another clinical pharmacology study compared the pharmacokinetic profile of the 210 mg romosozumab dose given in the 90 mg/mL formulation produced at the Phase 3 drug substance manufacturing site to the 90 mg/mL formulation produced at the to-be-marketed drug substance manufacturing site.

- Lastly, the Office of Pharmaceutical Quality determined that comparative analytical data, including lot release testing, additional characterization, and stability studies were sufficient to bridge the change in the commercial manufacturing site for the drug product.

Immunogenicity: One subject in the first-in-human study developed neutralizing antibodies to romosozumab following a 10 mg/kg dose. In this subject, the romosozumab concentration became undetectable on Day 7 and remained undetectable through Day 168 despite continued dosing with 1 mg/kg subcutaneously every two weeks.

About 19% of patients treated with the 210 mg dose developed binding antibodies. About 4% of those with binding antibodies tested positive for neutralizing antibodies. The 90 mg/mL formulation did not have a higher incidence of binding or neutralizing antibodies than the 70 mg/mL formulation in the head-to-head six month non-inferiority trial.

In the pivotal Phase 3 trial, romosozumab exposures were reduced by up to 25% among patients with binding antibodies compared to those who were antibody negative, with greater reductions among those with neutralizing antibodies. However, romosozumab concentrations among patients with binding antibodies were all within the range of concentrations observed in patients without binding antibodies. In addition, patients with binding antibodies had similar percent increases in bone mineral density compared to those without antibodies. Based on these data, it appears that most patients with antibodies to romosozumab should not have a reduction in efficacy, although it is possible that some patients may have reduced efficacy, as evidenced by the patient with neutralizing antibodies in the first-in-human trial who had undetectable romosozumab concentrations despite continued dosing. As discussed in the Safety section, patients with antibodies to romosozumab appear to have a slightly higher incidence of injection site reactions.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This section summarizes the design and key efficacy results for the two Phase 3 trials. See the clinical and statistical reviews and Cross-Discipline Team Leader memorandum for details.

Study 20070337: This is the multinational, randomized, double-blind, placebo-controlled, pivotal Phase 3 trial designed to establish the efficacy of romosozumab for the treatment of postmenopausal osteoporosis. Postmenopausal women 55-90 years of age at increased risk of fracture were randomized to 12 months of blinded treatment with romosozumab 210 mg given in the 70 mg/mL formulation (n=3589) or placebo (n=3591), each administered as three subcutaneous back-to-back injections once monthly in the arm, abdominal wall, or thigh. After this 12-month treatment period, all patients were switched to open-label denosumab, an antiresorptive agent, administered at the approved dose of 60 mg subcutaneously every six months for an additional 12 months. There is an ongoing open-label extension during which patients are continuing to receive denosumab for a second year – results from this extension are not included in the application. All injections were administered by study personnel. Patients also received daily calcium and vitamin D supplementation.

Post-treatment x-rays of the spine and bone mineral density assessments were performed at months 12, 24 and 36. Spine x-rays and bone mineral density images were read blindly at a central facility.

The co-primary efficacy endpoints were:

- Percentage of patients with a new morphometric (radiographically defined) vertebral fracture through Month 12
- Percentage of patients with a new morphometric vertebral fracture through Month 24

New morphometric vertebral fracture is the standard efficacy endpoint for drugs intended to treat postmenopausal osteoporosis.

The Applicant controlled type I error for the following secondary endpoints using sequential testing:

- Percentage of patients with clinical fracture (composite of nonvertebral fractures[1] and symptomatic vertebral fractures) through Month 12
- Percentage of patients with nonvertebral fracture through Months 12 and 24[2]
- Percentage of patients with clinical fracture through Month 24
- Percentage of patients with major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) through Months 12 and 24[2]
- Percentage of patients with new or worsening vertebral fracture through Months 12 and 24[2]
- Percentage of patients with hip fracture through Months 12 and 24[2]

The Applicant also included secondary endpoints for percent change from baseline to Month 12 and Month 24 in lumbar spine, total hip and femoral neck bone mineral density. These endpoints were not controlled for type 1 error.

[1] Excluded pathologic fractures and fractures of the skull, face, mandible, spine, fingers, and toes; also excluded the fractures associated with severe trauma.
[2] Alpha controlled within this step for both timepoints.

The primary analysis set for vertebral fractures and bone mineral density changes included all randomized patients who had a baseline and at least one post-baseline evaluation of the endpoint of interest at or before the time point under consideration. For bone mineral density changes, missing data were imputed using last-observation-carried-forward. All randomized patients were used for the other fracture endpoints that did not include vertebral fractures.

Results: This trial randomized 3589 patients to romosozumab and 3591 patients to placebo. About 89% of patients in both treatment groups completed the 12-month double-blind period, and about 84% of the original randomized population also completed 12 months of open-label denosumab. All patients were postmenopausal women. The age range was 55-90 years (mean 71 years), and about 31% were at least 75 years old. Approximately 57% of the patients were Caucasian and 40% were Hispanic or Latino. The mean body mass index was 24.7 kg/m^2 (range 10.0-53.8 kg/m^2). Most patients were from Central/Latin America (43%) and Central/Eastern Europe (29%). Only 3% of patients were from North America. A total of 132 patients (1.8%) were from the United States. About 18% of patients had at least one verified vertebral fracture at baseline. Baseline mean T-scores were about -2.7 at the lumbar spine (about 40% of patients had a lumbar spine T-score of ≤-3.0), -2.7 at the femoral neck, and -2.5 at the total hip.

The extent to which injections occurred at the three allowed sites (arm, abdominal wall, or thigh) is unclear. The application is receiving a Complete Response letter for unrelated reasons (see the Safety and Benefit/Risk sections) so we will ask the Applicant to include injection site data in the resubmission to ensure that all proposed injection sites were reasonably represented in the trial.

Co-primary endpoint: As shown in Table 1, the incidence of new vertebral fracture through Month 12 was significantly ($p<0.001$) lower with romosozumab compared to placebo (0.5% vs. 1.8%). Through Month 24, the incidence of new vertebral fracture was 0.6% in the romosozumab then denosumab group compared to 2.5% in the placebo then romosozumab group ($p<0.001$). The relative risk reductions were 73% (95% confidence interval 53%, 84%) through Month 12 and 75% (95% confidence interval 60%, 84%) through Month 24. Based on the upper and lower bounds of the 95% confidence interval for the absolute risk reduction, the number needed to treat to prevent one new vertebral fracture is 56-125. The statistically persuasive findings from this single fracture outcomes trial ($p<0.001$) together with the supportive bone mineral density data from the other trials provide convincing evidence of efficacy.

Table 1. Co-Primary Efficacy Endpoints: Incidence of First Vertebral Fracture (Adapted from Table 5 in the Statistical Review)

	Through Month 12		Through Month 24	
	Romosozumab N=3589	**Placebo N=3591**	**Romosozumab then Denosumab N=3589**	**Placebo then Denosumab N=3591**
n/N1 (%)	16/3321 (0.5%)[1]	59/3322 (1.8%)	21/3325 (0.6%)	84/3327 (2.5%)
p-value	<0.001		<0.001	
Absolute risk reduction[1]	1.3% (0.8%, 1.8%)		1.9% (1.3%, 2.5%)	
Relative risk reduction[1]	73% (53%, 84%)		75% (60%, 84%)	

N=number randomized; N1=number in primary analysis set for vertebral fractures
[1]95% confidence interval in parentheses

Secondary efficacy endpoints: The incidence of clinical fracture through Month 12, the first hierarchical secondary endpoint, was 1.6% with romosozumab compared to 2.5% with placebo ($p<0.01$), with a corresponding relative risk reduction of 36% (95% confidence interval 11%, 54%).

The romosozumab group had about 25% fewer nonvertebral fractures at months 12 and 24, but was not statistically superior to the placebo group at Month 12 ($p=0.10$, tested at the 0.05 alpha level) or to the placebo then denosumab group at Month 24 ($p=0.029$, tested at the 0.025 alpha level). The Applicant attributed this lack of statistical significance to reduced power. The power calculations had assumed a nonvertebral fracture incidence of 3.5% in the placebo group at 12 months and a treatment effect of at least 40%, but the observed incidence was only 2.1% and the relative risk reduction was only 25%. Because of the failed significance on nonvertebral fractures, statistical testing of the remaining hierarchical secondary endpoints should not proceed.



Bone mineral density changes: As shown in Table 2, romosozumab increased bone mineral density compared to placebo at the lumbar spine, total hip, and femoral neck at Month 12, with the largest treatment effects seen at the lumbar spine. From Month 12-24, the percent increases in bone mineral density were slightly smaller in the romosozumab then denosumab group compared to the placebo then denosumab group, which resulted in slightly smaller treatment effects at Month 24 compared to Month 12. The percent increases compared to placebo at Month 12 and Month 24 had associated p-values of less than 0.001, although these p-values are nominal because this testing was not controlled for type I error.

Subgroup analyses: As discussed in the statistical review, analyses of the co-primary efficacy endpoints were consistent across tested subgroups based on age, race (Caucasian vs. non-Caucasian) and region, with no relevant treatment-by-subgroup interactions. Through Month 24, new vertebral fracture in the North American region occurred in none of 97 patients treated with romosozumab then denosumab and five of 87 patients treated with placebo then denosumab. These are too few events to reliably assess subgroup results in this geographic region. However, mean percent changes in bone mineral density among North Americans were consistent with the

overall results at the lumbar spine, total hip, and femoral neck, supporting the applicability of the foreign data to the population in the United States.

Table 2. Bone Mineral Density Changes (Adapted from Tables 7-9 in the Statistical Review)

	Baseline	Through Month 12		Through Month 24	
		Change from Baseline (%)	LS Mean Difference from Placebo[1]	Change from Baseline (%)	LS Mean Difference from Placebo/Denosumab[1]
Lumbar Spine					
Romosozumab[2]	0.8	13.1	12.7 (12.4, 12.9) p<0.001	16.6	11.1 (10.8, 11.4) p<0.001
Placebo[3]	0.8	0.4		5.5	
Total Hip					
Romosozumab[2]	0.7	6.0	5.8 (5.6, 6.0) p<0.001	8.5	5.3 (5.1, 5.5) p<0.001
Placebo[3]	0.7	0.3		3.2	
Femoral Neck					
Romosozumab[2]	0.6	5.5	5.2 (4.9, 5.4) p<0.001	7.3	4.9 (4.7, 5.2) p<0.001
Placebo[3]	0.6	0.3		2.3	

[1]Includes 95% confidence interval in parentheses and nominal p-value for the treatment difference
[2]Romosozumab through Month 12; Romosozumab then denosumab through Month24
[3]Placebo through Month 12; Placebo then denosumab through Month 24

Study 20120156: This was a multicenter, randomized, Phase 3 trial to evaluate the non-inferiority of the to-be-marketed 90 mg/mL romosozumab concentration to the 70 mg/mL formulation used in the pivotal Phase 3 trial. There were four treatment groups randomized in a 22:5:22:5 ratio to six months of treatment with:

- Romosozumab 90 mg/mL– two back-to-back injections for a total dose of 210 mg
- Placebo 90 mg/mL – two back-to-back injections
- Romosozumab 70 mg/mL– three back-to-back injections for a total dose of 210 mg
- Placebo 70 mg/mL – three back-to-back injections

The placebo groups were included to allow for double-blinding within concentrations.

The primary efficacy endpoint was the percent change from baseline in bone mineral density at the lumbar spine. Romosozumab 90 mg/mL would be declared non-inferior to the 70 mg/mL formulation if the lower bound of the one-sided 97.5% confidence interval for the treatment difference (90 mg/mL minus 70 mg/mL) was greater than the prespecified non-inferiority margin of -2%. This margin was calculated based on the treatment effect at six months on lumbar spine bone mineral density with the 210 mg monthly dose in the dose-finding Phase 2 trial (which tested the 70 mg/mL formulation). That treatment effect was 8.0% (95% confidence interval 6.6%, 9.3%). The non-inferiority margin allows at most a 30% loss, which is our standard non-inferiority margin for bone mineral density, and is acceptable.

Results: In this trial, 118 patients were randomized to romosozumab 70 mg/mL, 123 patients were randomized to romosozumab 90 mg/mL and 53 patients were randomized to placebo. Completion rates were 89% for placebo, 93% for romosozumab 70 mg/mL, and 95% for romosozumab 90 mg/mL.

At baseline, lumbar spine bone mineral density was 0.8% across the two romosozumab arms and the placebo group. Compared to placebo, romosozumab 70 mg/mL increased lumbar spine mineral density by 8.8% and romosozumab 90 mg/mL increased lumbar spine bone mineral density by 8.4%. The LS mean treatment difference (90 mg/mL vs. 70 mg/mL formulation) was -0.4% (95% confidence interval -1.5%, 0.7%). The to-be-marketed concentration was declared non-inferior to the Phase 3 concentration because the lower bound of -1.5% is greater than the pre-specified non-inferiority margin of -2.0%. Consistent findings were seen for bone mineral density changes at the total hip and femoral neck.

8. Safety

Most of the safety data come from the pivotal Phase 3 trial, which was much larger than the other trials. The one-year placebo-controlled data from this trial were pooled with the one-year placebo-controlled data from the two dose-finding Phase 2 trials. These pooled data (hereafter referred to as the "pooled dataset") serve as the main dataset for safety analyses. Safety findings from the Phase 3 non-inferiority trial that used the to-be-marketed drug substance concentration of 90 mg/mL are of interest as well. This formulation had a similar safety profile to the 70 mg/mL formulation, except where noted below. See the Clinical review and Cross-Discipline Team Leader memorandum for a detailed discussion of safety.

Exposures: A total of 5478 patients received at least one dose of romosozumab, 3879 of whom were treated for at least one year. These exposures are adequate, and meet the International Conference on Harmonization E1A guideline recommendations for drugs that treat chronic, non-life-threatening conditions.

Deaths: In the pooled dataset, 0.8% of the romosozumab-treated patients and 0.7% of the placebo-treated patients died. There were no notable imbalances in the cause of death between treatment groups except for death due to lung cancer, which was reported in four romosozumab-treated patients and none receiving placebo. As discussed by the clinical reviewer, all four of these deaths occurred in current or former smokers, all cases of lung cancer (i.e., fatal plus non-fatal cases) were balanced between treatment groups (five cases each), and there was no overall imbalance in malignant/unspecified tumors between treatment groups (1.7% with romosozumab vs. 1.9% with placebo). These data on deaths do not raise any safety concerns.

Serious Adverse Events: In the pooled dataset, 9.5% of the romosozumab-treated patients and 8.8% of the placebo-treated patients reported at least one serious adverse event. As shown in the Clinical Review, for each of the preferred terms, there were generally very small imbalances between treatment groups (differences of less than 0.2%), sometimes favoring romosozumab and sometimes favoring placebo, none of which raise any safety concerns.

Discontinuations due to Adverse Events: In the pooled dataset, adverse events leading to discontinuation were reported in 1.2% of the romosozumab-treated patients and 1.4% of the placebo-treated patients. The only adverse events leading to discontinuation in more than one romosozumab-treated patient were arthralgia, musculoskeletal pain, and extremity pain (each

reported in three patients) and abdominal pain, back pain, and nausea (each reported in two patients). These data do not raise any safety concerns.

Common Adverse Events: In the pooled dataset, 78% of the romosozumab-treated patients and 80% of the placebo-treated patients reported at least one adverse event. The most commonly reported adverse events (with incidence above 2%) that also occurred at an incidence of at least 0.5% higher with romosozumab than placebo included nasopharyngitis (13.2% vs. 12.3%), arthralgia (12.7% vs. 11.8%), headache (6.5% vs. 5.8%), muscle spasm (4.5% vs. 3.8%), and neck pain (2.2% vs. 1.5%). These data can be labeled and do not raise major safety concerns.

Adverse Events of Interest: Adverse events of interest based on animal findings or the mechanism of action include:

Atypical Femoral Fractures and Osteonecrosis of the Jaw: Atypical femoral fractures and osteonecrosis of the jaw are associated with antiresorptive agents, and could potentially be seen with romosozumab, which has antiresorptive activity.

In the 12-month pooled dataset, there was one adjudicated case (0.03%) of atypical femoral fracture, which occurred in the pivotal Phase 3 trial in a patient treated with romosozumab for about 3.5 months, who fell from a standing height. This patient was not exposed to other products associated with atypical femoral fractures and reported prodromal pain in the affected region prior to study start. To date, four additional adjudicated cases of atypical femoral fracture have been identified in an ongoing alendronate-controlled, Phase 3 trial. One of these cases occurred in a patient who had received alendronate for 21 months after one year of romosozumab. The remaining three cases occurred in patients randomized to alendronate with treatment durations of 16, 17, and 28 months.

In the pivotal Phase 3 trial, there were two adjudicated cases of osteonecrosis of the jaw. One case occurred after nearly one year of treatment with romosozumab and the other occurred about three months after starting denosumab in a patient who was previously treated with romosozumab. In the ongoing alendronate-controlled, Phase 3 trial, there were two additional cases – one in a patient who had received alendronate for about 16 months after one year of romosozumab and one in a patient randomized to alendronate after 21 months of treatment.

The risks of atypical femoral fracture and osteonecrosis of the jaw appear rare, are well known with antiresorptive therapies, and can be handled with labeling.

Hypocalcemia: Romosozumab can cause hypocalcemia as a result of calcium influx into bone (during bone formation) and reduced calcium release from bone into the blood stream (because of decreased bone resorption). Romosozumab lowered serum calcium throughout the 12-month placebo-controlled period in the pivotal Phase 3 trial, with average reductions from baseline of about 0.1-0.2 mg/dL. There were no reported serious adverse events of hypocalcemia. To assess the extent of outliers, the Applicant reported the incidence of worst albumin-corrected serum calcium using the Common Terminology Criteria for Adverse Events version 3.0 grading system. In the pooled dataset, seven romosozumab-treated patients (0.2%) and three placebo-treated patients (<0.1%) developed grade 1 hypocalcemia (below the lower limit of normal but

no lower than 8.0 mg/dL), seven romosozumab-treated patients (0.2%) and one placebo-treated patient (<0.1%) developed grade 2 hypocalcemia (7.0-7.9 mg/dL), and no romosozumab-treated patients developed more severe hypocalcemia.

Although hypocalcemia was rare, it is important to note that the pivotal Phase 3 trial included calcium and vitamin D supplementation. In addition, patients with a screening 25-hydroxy-vitamin D concentration of 20-40 ng/mL received a loading dose of 50,000-60,000 international units of vitamin D after randomization. Those with a screening 25-hydroxy-vitamin D concentration below 20 ng/mL were excluded and those with a concentration above 40 ng/mL could still receive the vitamin D loading dose at the investigator's discretion. About three-fourths of randomized patients received the starting dose. Therefore, the risk of hypocalcemia without these interventions is unknown.

Patients with renal impairment may be at particular risk for hypocalcemia with romosozumab. In the renal impairment pharmacokinetic study, which included calcium and vitamin D supplementation, hypocalcemia was reported in none of the healthy subjects, in one of the patients with severe renal impairment, and in four of those with end-stage renal disease. This risk is not related to increased romosozumab exposures, which were comparable in those with end-stage renal disease and healthy volunteers.

The risk of hypocalcemia can be adequately managed with labeling that includes statements about the need for adequate calcium and vitamin D supplementation prior to, and during, treatment with romosozumab, as well as monitoring of serum calcium in patients at increased risk of hypocalcemia.

Hypophosphatemia: Romosozumab can cause hypophosphatemia based on the same mechanisms that can cause hypocalcemia. Sixteen romosozumab-treated patients (0.4%) and four placebo-treated patients (0.1%) developed serum phosphate in the range of 2.0-2.4 mg/dL. This risk, which appears infrequent, can be handled with labeling.

Parathyroid Hormone: The pivotal Phase 3 trial included a substudy involving 656 patients to assess the effects of romosozumab on serum parathyroid hormone. Serum parathyroid hormone increased above baseline throughout the 12-month placebo-controlled treatment period, with 38% of the romosozumab-treated patients and 15% of the placebo-treated patients having at least one parathyroid hormone measurement above the upper limit of the reference range. Most of the outliers had parathyroid hormone concentrations that were up to twice the upper limit of the reference range, although 1.7% of the romosozumab-treated patients had elevations above three times the upper limit of normal. The highest measured serum parathyroid hormone in the romosozumab-treated group was about 300 pg/mL. These findings likely reflect a compensatory increase in parathyroid hormone because of calcium sequestration in bone. In the renal impairment clinical pharmacology study, there were greater increases in serum parathyroid hormone among romosozumab-treated patients with severe renal impairment and even further increases in those with end-stage renal disease. These findings should be labeled.

Hyperostosis: Hyperostosis (excessive bone growth) with neurological consequences is seen with sclerosteosis and van Buchem disease. In the pooled dataset, the incidence of hyperostosis was

not increased with romosozumab (0.5%) compared to placebo (0.8%), nor was there an increase in adverse events related to neurological compression. A potential neurological consequence of hyperostosis is hearing loss. An audiology substudy in 498 patients did not detect a higher incidence of hearing loss with romosozumab compared to placebo.

Cardiovascular safety: The Applicant adjudicated cardiovascular events in the pivotal Phase 3 trial. During the 12-month placebo-controlled period, the romosozumab and placebo groups were balanced with regard to the incidence of adjudicated cardiovascular serious adverse events (1.3% in both arms) as well as adjudicated serious cardiac ischemic events (0.4% in both arms) and cerebrovascular events (0.3% in both arms).

However, two months prior to the action goal date, the Applicant informed us of unanticipated cardiovascular findings in an ongoing Phase 3 trial (20110142). This 4000-patient trial randomized women with postmenopausal osteoporosis to romosozumab or alendronate then had all patients take only alendronate after one year. (b) (4) (b) (4). Topline results showed a 50% mean reduction in the incidence of new vertebral fractures and a 19% mean reduction in the incidence of nonvertebral fractures with romosozumab followed by alendronate compared to alendronate alone. However, using the same adjudication process as that used in the pivotal Phase 3 trial, this trial found an imbalance during the 12-month double-blind period in adjudicated cardiovascular serious adverse events (2.5% romosozumab vs. 1.9% alendronate) as well as adjudicated serious cardiac ischemic events (0.8% romosozumab vs. 0.3% alendronate) and cerebrovascular events (0.8% romosozumab vs. 0.3% alendronate). Similar imbalances were also seen in a recently completed, small (n=244) male osteoporosis trial.

Corresponding hazard ratios through Month 12 for Major Adverse Cardiovascular Events (MACE), a composite endpoint assessing cardiovascular risk comprised of adjudicated serious adverse events of myocardial infarction and stroke as well as cardiovascular death were 1.03 (95% confidence interval 0.62, 1.72) for the pivotal Phase 3 trial, 1.87 (95% confidence interval 1.11, 3.14) for the ongoing alendronate-controlled trial, and 1.55 (95% confidence interval 0.31, 7.69) for the male osteoporosis trial.

Reasons for the discrepant trial results are unclear. We informed the Applicant that we would not be able to take a favorable action on this review cycle because we need to first conduct a thorough review of the cardiovascular issue before we can determine whether the benefits of romosozumab outweigh its risks. We stated this would not be possible in the remaining review cycle, even with a Major Amendment, because the Applicant still needs to complete their analyses of the data and put together a detailed submission of the findings. We also stated that an advisory committee meeting would likely be needed when those data are submitted.

Immunogenicity: In the pivotal Phase 3 trial, the incidence of hypersensitivity reactions, assessed using Standardized MedDRA queries, was similar among romosozumab- and placebo-treated patients, and was not increased further among those who had binding antibodies. This search strategy identified seven romosozumab-treated patients (0.2%) and no placebo-treated patients with hypersensitivity serious adverse events. Some of these cases suggest that romosozumab has the potential to cause significant hypersensitivity reactions. For example, one of the patients

developed cough, dyspnea and wheezing about 24 hours after her first romosozumab dose, followed by a rash on the back two days later. Another case involved facial edema and generalized rash about three weeks after the fifth dose, treated with a glucocorticoid and antihistamine. Another patient developed a macular truncal rash three days after the first dose and exfoliative dermatitis and angioedema on Day 28.

In the trial comparing the 90 mg/mL and 70 mg/mL formulations, there were no reports of serious adverse events of hypersensitivity, although the overall incidence of hypersensitivity reactions was numerically higher with the 90 mg/mL formulation (11.4% vs. 2.5%).

Hypersensitivity can be handled with labeling.

Injection Site Reactions: In the pivotal Phase 3 trial, injection site reactions were more common with romosozumab (5.2%) than placebo (2.9%), with a higher incidence among romosozumab-treated patients who were antibody positive (6.8%) compared to those who were antibody negative (5.0%). Similar patterns were seen according to the neutralizing antibody status but the small numbers of patients with neutralizing antibodies limit conclusions.

None of the reported injection site reactions were categorized as serious. In the pivotal Phase 3 trial, these reactions were most commonly injection site pain (1.7% with romosozumab vs. 1.3% with placebo), erythema (1.5% vs. 0.1%), and pruritis (0.7% vs. 0.2%).

In the clinical trial comparing the 90 mg/mL and 70 mg/mL formulations, the overall incidence of injection site reactions was 10.6% with the 90 mg/mL formulation and 9.2% with the 70 mg/mL formulation. The 90 mg/mL formulation had numerically higher incidences of injection site erythema (5.7% vs. 1.7% with the 70 mg/mL formulation) and injection site swelling (2.4% vs. 0% with the 70 mg/mL formulation) whereas the 70 mg/mL formulation had a numerically higher incidence of injection site pain (5.9% vs. 2.4% with the 90 mg/mL formulation).

Injection site reactions can be handled with labeling.

Bone Histomorphometry: In the pivotal Phase 3 trial, the Applicant obtained quadruple-labeled iliac bone biopsies in 34 patients at Month 2, 73 patients at Month 12, and 47 patients at Month 24. These biopsies did not identify any safety concerns.

Other Laboratory Data and Vital Signs: The clinical reviewer identified no notable effects of romosozumab on other laboratory data or on vital signs.

9. Advisory Committee Meeting

This application was not taken to advisory committee. We did not identify efficacy or safety issues requiring input from an advisory panel at the time of filing. However, the unexpected cardiovascular findings that came to light towards the end of this review cycle will likely be discussed at an advisory committee meeting during the next review cycle.

10. Pediatrics

This Application triggers the Pediatric Research Equity Act (PREA) because of the new active ingredient. The Pediatric Review Committee agreed with a full waiver. Pediatric studies would be impossible because postmenopausal osteoporosis does not occur in children.

11. Other Relevant Regulatory Issues

Trade Name / Proper Name: The Division of Medication Error Prevention and Analysis (DMEPA) has concluded that the proposed trade name "Evenity" is acceptable. However, the proper name (romosozumab), as proposed, does not include a four-digit distinguishing suffix, in accordance with the final guidance "Nonproprietary Naming of Biological Products" that issued in January 2017. DMEPA planned to address the suffix issue after approval when it appeared that the application would be approved on this review cycle. See their reviews for details. Because we are issuing a Complete Response letter, the trade name will need to be revisited during the next review cycle. We will also inform the Applicant in the Complete Response letter that we intend to assign a suffix to the proper name if/when FDA approves the application.

Financial Disclosures: Four sub-investigators from three Columbian sites that enrolled about 13% of patients in the pivotal Phase 3 trial did not return signed financial disclosures. As discussed in the clinical review, a sensitivity analysis of the co-primary efficacy endpoints excluding these four sites did not meaningfully change the results.

Inspections: The Office of Study Integrity and Surveillance (OSIS) conducted clinical and bioanalytical inspections of the key clinical pharmacology studies. The only noteworthy findings involved the bioanalytical inspection of the clinical pharmacology study used to help bridge the to-be-marketed 90 mg/mL formulation to the 70 mg/mL formulation used in the pivotal Phase 3 trial. The inspectors issued a Form 483, citing potential concerns (b) (4) (b) (4). After obtaining additional information from the Applicant, OSIS determined that the bioanalytical data from this study are acceptable. The Office of Pharmaceutical Quality reviewed the confirmatory antibody assay and found it to be adequate.

The Office of Scientific Investigations (OSI) inspected four of the 222 clinical sites involved in the conduct of the pivotal Phase 3 trial. These four sites contributed 1054 (15%) of the 7180 enrolled patients in the trial. Three of the sites were classified as NAI (no deviation from regulations). The fourth site was issued an FDA Form 483 and classified as VAI (deviations from regulations). At this site, 147 patients (44%) were randomized outside of the protocol-specified screening windows. This was attributed to delayed access to investigational product from the Applicant and backlogged randomization. There were a few other minor deviations at this site (e.g., enrollment of eight patients who should have been excluded based on their baseline serum calcium concentrations). OSI concluded that the data generated from these four sites appear acceptable to support the proposed indication but recommended that the review team further assess the delay in time to randomization.

The protocol for the pivotal Phase 3 trial specified that the screening visit can last up to 35 days and allowed for an additional 35 day rescreening window if patients needed vitamin D supplementation. After learning about the delay at the site above, we asked the Applicant to assess the extent to which such delays occurred across the pivotal Phase 3 trial. The Applicant responded that 6.7% of the randomized population had a screening duration beyond 35 days and that 1.3% had a screening duration beyond 70 days (with most of these outliers coming from two Columbian sites, one of which was inspected). The baseline spine x-rays and some of the bone mineral density images were obtained during screening. Therefore, a long delay between these baseline images and randomization could potentially allow for interval changes (e.g., new fractures) during screening that would not be captured prior to randomization. However, given that only about 1% of patients had a screening duration beyond 70 days, and that bone mineral density changes occur very slowly, it is unlikely that this delay would have meaningfully affected the overall bone mineral density results. In addition, the Applicant compared the presence or absence of fractures on screening x-rays with those seen on the first post-treatment x-ray and noted full concordance, supporting that there was no interval development of vertebral fractures between the baseline images and randomization among the patients who had a screening duration beyond 70 days.

Human Factors: The Applicant submitted Human Factors validation data from brodalumab, one of their other products to provide support that labeling will adequately communicate that two syringes are needed with romosozumab to administer one complete dose. DMEPA concluded that there were no critical differences in the use of romosozumab and brodalumab, and that the brodalumab Human Factors validation data do not show label comprehension difficulties, use task deviations, or dosing errors involving the use of two prefilled syringes to administer a complete dose. In addition, DMEPA reviewed results from the romosozumab labeling comprehension study, which evaluated the romosozumab Instructions for Use and found these results acceptable. No additional Human Factors data are needed. The Instructions for Use will be incorporated in Section 2 of the Prescribing Information if romosozumab can be approved.

12. Labeling

All labeling is deferred because the application cannot be approved on this review cycle.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None presently, but we will reassess the need for risk minimization strategies beyond labeling during the next review cycle if romosozumab can otherwise be approved.

- Other Postmarketing Requirements and Commitments

When romosozumab can be approved, the Chemistry reviewers recommend a postmarketing commitment (b) (4) (b) (4).

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/s/

HYLTON V JOFFE
07/13/2017

KENDALL A MARCUS
07/13/2017

Cross-Discipline Team Leader Review

Date	
From	Theresa Kehoe, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	BLA 761062 000
Applicant	Amgen, Inc
Date of Submission	July 19, 2016
PDUFA Goal Date	July 19, 2017
Proprietary Name / Non-Proprietary Name	Romosozumab
Dosage form(s) / Strength(s)	210 mg
Applicant Proposed Indication(s)/Population(s)	treatment of osteoporosis in postmenopausal women at increased risk of fracture
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	treatment of osteoporosis in postmenopausal women

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Reference ID: 4123729

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Romosozumab, trade name Evenity, is a sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal women. The dosing regimen is 210mg administered by a healthcare professional once monthly for one year. It is this reviewer's recommendation that romosozumab cannot be approved for this indication at this time.

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone leading to an increase in fragility and fracture. While osteoporosis can occur in both men and women, studies in postmenopausal women represent the majority of the data defining the disease and its sequelae. The risk of fracture increases with age and a history of a prior osteoporosis-related fracture. In older patients, fracture, predominantly hip fracture, is associated with increased morbidity and mortality.

The efficacy of romosozumab for the treatment of postmenopausal osteoporosis was evaluated in a 24-month, randomized, multicenter, double blind, placebo-controlled clinical trial in postmenopausal women aged 50 to 90 years (mean age of 71). Patients were randomized to receive one year of romosozumab 210mg (N = 3589) or placebo (N = 3591) once monthly by subcutaneous injection administered by a healthcare professional. During the second year of the trial, all patients received denosumab 60mg every 6 months. Patients also received daily supplemental calcium (500 to 1000 mg) and vitamin D (600 to 800 IU). 57% of patients were Caucasian, 12% were Asian, and 2% were Black; 40% were Hispanic. At baseline, the mean T-score was -2.7 at the lumbar spine and 18% of patients had at least one prevalent vertebral fracture.

The co-primary endpoints were the incidence of new vertebral fractures in patients treated with romosozumab compared to placebo at 12 months and the incidence of new vertebral fractures in patients treated with romosozumab/denosumab compared to placebo/denosumab at 24 months. Romosozumab resulted in a significant reduction in the incidence of new vertebral fractures compared to placebo at 12 months (0.5% romosozumab compared to 1.8% placebo, $p < 0.001$). The absolute risk reduction in new vertebral fracture was 1.3% at 12 months and the relative risk reduction was 73% for romosozumab compared to placebo. The incidence of new vertebral fractures at 24 months was 0.6% in patients treated with romosozumab then denosumab compared to 2.5% in patients treated with placebo then denosumab ($p < 0.001$). The relative risk reduction in new vertebral fracture at 24 months was 75% for patients treated with romosozumab/denosumab compared to patients treated with placebo/denosumab and the absolute risk reduction was 1.9%. Romosozumab significantly increased bone mineral density at all sites with a treatment difference of 13% at the lumbar spine, 6% at the total hip and 5% at the femoral neck after 12 months of therapy.

Adverse events that occurred during treatment with romosozumab, a sclerostin inhibitor, include hypocalcemia, injection site reactions, and hypersensitivity reactions. Osteonecrosis of the jaw and atypical femoral fractures also occurred.

There is a concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification. In the postmenopausal osteoporosis safety population, there was no signal suggesting concern regarding cardiovascular safety with romosozumab use. However, in newly completed trials not submitted in the application, preliminary data suggest a cardiovascular safety concern for romosozumab use in both postmenopausal women and men. These data, once available, will require in depth review prior to reaching a conclusion on cardiovascular safety with romosozumab use. Therefore, a Complete Response action is recommended for this review cycle.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoporosis is a bone disease characterized by low bone mass and deterioration of bone tissue leading to an increased risk of fracture. Osteoporosis is a silent disease until a fracture occurs • Postmenopausal women are the most common patient group to have osteoporosis. 50% of postmenopausal women over age 50 will break a bone due to osteoporosis • The risk of fracture increases with age. The risk also increases with a history of a previous osteoporosis-related fracture • In older patients, hip fracture is associated with increased loss of independence and increased mortality	Osteoporosis increases the risk of fracture in postmenopausal women. The risk of fracture increases with age and a history of a prior osteoporosis-related fracture. In older patients, fracture, predominantly hip fracture, is associated with increased morbidity and mortality
Current Treatment Options	• Current treatment options for postmenopausal osteoporosis include medications that inhibit bone loss (bisphosphonates, RANKL inhibitors, estrogen agonists/antagonists, and calcitonin) and medications that stimulate bone formation (PTH and PTHrP analogs) • Therapy can reduce the risk of vertebral fracture by up to 70% • Bisphosphonates are the most widely prescribed medications. Rare but serious side effects with bisphosphonates (osteonecrosis of the jaw and atypical femoral fractures) have influenced the use of these medications. • Densoumab also is associated with osteonecrosis of the jaw and atypical femoral fractures, which likely limits the use of the medication. • Teriparatide and abaloparatide are associated with the potential risk of osteosarcoma, which was noted in animal studies.	Multiple therapies are available for treatment of osteoporosis in postmenopausal women. Rare but serious side effects have decreased the usage of currently available therapies and many patients with osteoporosis who would benefit from therapy remain untreated. Additional therapies in a new class such as romosozumab, will expand the treatment options and potentially enhance treatment for those in need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Romosozumab was evaluated in a single 24 month randomized phase 3 trial of 7180 women with postmenopausal osteoporosis. Patients received romosozumab 210mg or matching placebo by subcutaneous injection administered by a healthcare provider once a month for 12 months. After 12 months, all patients received open-label denosumab 60mg by subcutaneous injection administered by a healthcare provider every 6 months for 2 doses. • The co-primary endpoints were incidence of morphometric (seen on xray) vertebral fracture at 12 months and 24 months. Morphometric vertebral fracture is the accepted primary endpoint for fracture trials supporting an osteoporosis indication. Secondary endpoints include incidence of clinical fracture and incidence of nonvertebral fracture and change in bone mineral density • Romosozumab reduced the risk of vertebral fractures with an absolute risk reduction of 1.3% and a relative risk reduction of 73% at month 12 and an absolute risk reduction of 1.9% and a relative risk reduction of 75% at month 24 • Romosozumab reduced the risk of clinical fractures with an absolute risk reduction of 1.2% and a relative risk reduction of 36% at month 12. However, clinical fracture is a composite endpoint of symptomatic vertebral fractures and nonvertebral fractures. In the fracture trial, 88% of clinical fractures were nonvertebral fractures. Romosozumab did not have significant reductions in nonvertebral fracture at 12 or 24 months. • Romosozumab increased bone mineral density after 12 months of therapy at the lumbar spine 13%, total hip 6% and femoral neck 5%.	Treatment with romosozumab 210mg monthly for one year significantly increases bone mineral density at the lumbar spine and hip with accompanying significant vertebral fracture risk reduction in postmenopausal women with osteoporosis Treatment with denosumab 60mg every 6 months for one year following romosozumab therapy maintained the bone mineral density increases and vertebral fracture benefit
Risk	• The safety data for romosozumab include 7384 patients, of which 3695 received romosozumab 210mg once monthly for one year. • Hypocalcemia, injection site reactions, and hypersensitivity reactions are safety concerns with romosozumab use • Osteonecrosis of the jaw and atypical femoral fractures also occurred in the romosozumab trials, usually associated with additional anti-resorptive medication use.	Romosozumab was associated with hypocalcemia, injection site reactions, and hypersensitivity reactions. Osteonecrosis of the jaw and atypical femoral fractures also occurred. Antibody formation occurs in 20% of patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Antibody formation against romosozumab occurred in 20% of patients on romosozumab, neutralizing capability occurred in 5% of patients with binding antibodies. The presence of antibodies can reduce romosozumab exposure but do not appear to affect the effectiveness of romosozumab. • There was no signal for cardiovascular safety in the safety population for this initial application. However, additional preliminary safety data from other romosozumab trials suggest a concern regarding the cardiovascular safety of romosozumab in both postmenopausal women and men	but generally does not appear to affect efficacy. There remains a concern regarding the cardiovascular safety of romosozumab. While no signal was seen in the placebo-controlled trials reviewed, new preliminary data from additional trials do show a safety signal. Therefore, these newly completed trials need to be submitted and reviewed in depth prior to reaching a conclusion on cardiovascular safety with romosozumab use.
Risk Management	• For the known risks of hypocalcemia, injection site reactions, hypersensitivity reactions, osteonecrosis of the jaw and atypical femoral fractures, prescribing information and a Medication Guide for patients are sufficient to mitigate the risk of romosozumab. • However, further analysis of the data regarding cardiovascular safety with romosozumab use is needed prior to decisions regarding romosozumab approval for treatment of osteoporosis in postmenopausal women and the need for any risk management plan.	The concerns regarding cardiovascular safety with romosozumab use must be resolved before romosozumab can be approved and a risk management plan developed, if needed. This will require in depth review of the safety signals in the full reports of the newly completed trials once they are submitted.

2. Background

The Applicant, Amgen, Inc. has submitted this Biologics License Application (BLA) under section 351 of the Public Health Services Act for romosozumab seeking an indication for the treatment of postmenopausal women with osteoporosis at increased risk of fracture. The proposed dose is 210 mg romosozumab once monthly. Romosozumab 210 mg is administered by a healthcare provider as 2 separate subcutaneous injections utilizing two single-use prefilled syringes. Romosozumab, also referred to as AMG785 in the application, is an IgG2 humanized monoclonal antibody that binds and inhibits sclerostin. The pharmacologic class proposed by the Applicant in labeling is "sclerostin inhibitor". 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), inhibiting Wnt signaling and reducing osteoblast-mediated bone formation. Inhibition of sclerostin leads to a transient stimulation of bone formation and inhibition of bone resorption. Romosozumab is first in class with sclerostin inhibitors being a new therapeutic class of osteoporosis therapies.

Osteoporosis is a systemic skeletal disease characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and increased risk of fracture. The goal of therapy is to reduce the risk of fracture. Currently, there are nine different molecular entities, many with multiple formulations and regimens, approved for the treatment of postmenopausal osteoporosis (see Table 1, page 24 of the primary clinical review).

The romosozumab IND (100391) was opened in November 2006. An End-of Phase 2 meeting was held in 2011. The Applicant proposed to conduct a 12-month placebo-controlled phase 3 fracture trial. After discussion, the Division advised that the duration of the study should be a minimum of 2 years. It was acceptable that romosozumab treatment be limited to one year. However, in that case all subjects (placebo and romosozumab treated subjects) should receive the same active control product for the second year. The endpoints could be coprimary – new vertebral fracture at 12 months and at 24 months.

3. Product Quality

The review team from the Office of Biotechnology Products recommends *approval* of Evenity (romosozumab). Romosozumab is a humanized IgG2 monoclonal antibody that binds to and inhibits sclerostin.

Drug Substance: Romosozumab is produced from a recombinant DNA-derived Chinese Hamster Ovary (CHO) cell line using standard cell culture techniques. The master cell bank (MCB) and working cell bank (WCB) have been adequately characterized and tested. The drug substance manufacturing begins with (b) (4) (b) (4) (b) (4) Tables 1 and 2, pages 7 – 19 of the Integrated Quality

Assessment outline the critical quality attributes of the romosozumab drug substance. The data provided in the BLA supports a shelf life of (b) (4) months for the romosozumab drug substance when stored at (b) (4).

Drug Product Manufacturing: Drug product manufacturing process steps (b) (4) (b) (4) (b) (4). Table 3 and 2, pages 23 – 26 of the Integrated Quality Assessment outlines the critical quality attributes of the romosozumab drug product.

Drug Product: Evenity (romosozumab) is a combination product with the drug product presented in single-use prefilled syringes with a romosozumab concentration of 90 mg/mL. Each prefilled syringe contains 105 mg romosozumab in 1.17 mL volume. Other excipients in the 1.17 mL volume include calcium (0.61 mg), acetate (3.8 (b) (4) mg), sucrose (70 mg), polysorbate 20 (0.07 mg), sodium hydroxide (b) (4) and Water for Injection. Evenity is a sterile, preservative-free, clear to opalescent, colorless to light yellow solution for subcutaneous injection. The pH of the solution is 5.2.

The container closure system consists of a 1 mL (b) (4) syringe with an (b) (4) needle covered with an (b) (4) needle shield and a (b) (4) plunger-stopper (b) (4) (b) (4).

The dose of romosozumab, 210 mg, requires injection of two prefilled syringes. Evenity is packaged as a carton containing two single use prefilled syringes. The stability data in the BLA support a shelf life of 36 months for Evenity when stored at the recommended storage condition of 2 - 8°C.

Microbiology: Both the drug substance and drug product quality microbiology parts of this BLA are recommended for *approval*. Please see Dr. Bo Chi's drug substance quality microbiology review and Dr. Lakshmi Rani Narasimhan's drug product quality microbiology review for complete details.

Facilities:
(b) (4) This site manufactures the drug substance and preforms drug product lot release and stability testing. A pre-license inspection was conducted by reviewers from OBP and DIA and covered the manufacturing operations for romosozumab DS including quality assessment procedures, manufacturing process, facilities and equipment, material management, data entry, contamination prevention, laboratory controls, and training programs. Assessment was made in accordance with ICH Q7A. A three-item 483 with respect to equipment performance qualification, laboratory record documentation, and document review, was issued. This site is recommended for approval from a facilities assessment standpoint.

(b) (4) This site is a multiproduct facility responsible for drug product manufacture, drug product in-process and lot release testing, and inspection. The most recent inspection was conducted on (b) (4) and resulted in VAI with final compliance decision of approve. CGMP coverage was provided for (b) (4) (b) (4) profiles during the inspection, and found acceptable. Based on the firm's compliance history and current acceptable GMP status, and the fact that the facility, similar processes, and most of the equipment (b) (4) proposed for romosozumab manufacture are currently approved (b) (4), the pre-license inspection of (b) (4) facility was waived for this BLA. This site is recommended for approval from a facilities assessment standpoint.

Amgen, Inc (Amgen Thousand Oaks, ATO, FEI 2026154): This site is responsible for the DS master cell bank and working cell bank storage, and working cell bank production. The most recent inspection was a limited GMP inspection conducted in (b) (4) in response to two Risk Evaluation and Mitigation Strategies. The inspection was NAI. This site is recommended for approval from a facilities assessment standpoint.

Amgen Manufacturing Limited (AML, Juncos, PR, FEI 1000110364): This site is responsible for drug substance and drug product lot release and stability testing as well as drug product packaging and labeling. The most recent inspection was (b) (4) and resulted in VAI with final compliance decision of approve. This site is recommended for approval from a facilities assessment standpoint.

(b) (4) This site is responsible for drug substance unprocessed bulk mycoplasma and adventitious viral testing; and drug product container closure integrity for stability testing. The most recent inspection was conducted on (b) (4) and resulted in NAI. This site is recommended for approval from a facilities assessment standpoint.

Amgen Technology Ireland (Amgen Dun Laoghaire, ADL, FEI 3002808497): This site is responsible for drug substance lot release and stability testing; and drug product lot release and stability testing. The most recent inspection was conducted on (b) (4) and resulted in VAI with final compliance decision of approve. This site is recommended for approval from a facilities assessment standpoint.

Environmental Assessment: A claim for a categorical exclusion is being made under 21 CFR 25.31 (c). This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance. This waiver request is acceptable.

Device considerations: A consultation for review of the device components of the romosozumab drug product was obtained from the General Hospital Devices Branch (GHDB)/ Office of Device Evaluation/Center for Devices and Radiological Health (CDRH). The recommendation is that the device constituent parts of the combination product ***can be a******pproved***. Please see the consult completed by Sarah Mollo for complete details.

Labeling: The primary and secondary container closure labeling review have been conducted and changes recommended to the Applicant. Further labeling negotiations will be deferred until the next review cycle.

Postmarketing Commitments: The OBP review team recommends the following postmarketing commitment:

(b) (4)

After further discussion regarding the updated action plan for this BLA, OBP recommends that this PMC remain under consideration for the next review cycle as the Applicant would have insufficient time to address the PMC prior to the anticipated application resubmission.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology team is recommending that this BLA ***can be approved.*** The Applicant has conducted a complete pharmacology/toxicology program, which has been reviewed by the pharmacology/toxicology team. Please see the reviews from Dr. Gemma Kuijpers, Dr. Andrea Benedict, Dr. Laurie McLeod-Flynn, and Dr. Miyun Tsai-Turton for complete details.

Romosozumab is a humanized IgG2 monoclonal antibody that binds to and inhibits sclerostin. Sclerostin has an inhibitory effect on bone formation. Sclerostin is produced by the osteocyte and can bind to low density lipoprotein receptor related protein (LRP) 4, LRP5, or LRP6 receptors. Sclerostin interaction with LRP5/6 leads to inhibition of the Wnt/beta-catenin signaling pathway and ultimately decreased bone formation and increased bone resorption. Romosozumab binds to sclerostin and inhibits the interaction of sclerostin and LRP5/6, allowing increased bone formation.

Pharmacology: The Applicant conducted in vitro and in vivo pharmacology studies with sclerostin-antibodies. In vitro studies showed high affinity binding of romosozumab to sclerostin, which led to blockade of the sclerostin-mediated inhibition of bone matrix mineralization in a mouse calvarial cell line.

Bone quality studies of up to 12 months in duration were conducted in ovariectomized rats and monkeys. The doses used were up to 19x human exposure in rats and 22x human exposure in monkeys, based on AUC. Romosozumab increased bone mass and strength of lumbar spine,

tibia, femur, and radius in a dose- and time-dependent manner. The bone changes consisted of increases in trabecular thickness in vertebrae and long bone metaphyses, as well as increases in cortical thickness in long bones. The noted effects were due to stimulation of bone formation concomitant with suppression of bone resorption mostly at trabecular and endosteal bone surfaces. In monkeys, both formation and resorption responses were transient and peaked at 10 weeks. Based on bone mass vs. strength correlations, bone quality was maintained at all evaluated sites.

Toxicology: Toxicity studies of up to 6-month duration were conducted in rats and monkeys. The main findings were related to the pharmacologic effect of romosozumab, specifically increasing bone formation and bone density with evidence of hyperostosis affecting the bone marrow. Findings included decreases in calcium and phosphorus levels and decreases in RBC, WBC and platelets with evidence of extramedullary hematopoiesis. Exposure multiples in the 6-month studies ranged from 1-38x and 1-93x human exposure, in rats and monkeys, respectively.

Because of rapidly accumulating knowledge of the role of sclerostin, LRP 5/6, and Wnt beta-catenin signaling, the Applicant included evaluation of multiple potential clinical safety concerns in the clinical trials. This approach was based on the weight of evidence from nonclinical studies, clinical studies and published literature. As outlined in Dr. Kuijper's review, there is no nonclinical evidence suggesting romosozumab would increase the risk for osteoarthritis, vascular calcification, increased longitudinal bone growth, hyperostosis, altered hematopoiesis, sarcopenia, altered glucose metabolism, or exacerbation of TNFα-mediated inflammation. Additionally, the nonclinical data do not support a concern about tumor induction or promotion due to activation of Wnt signaling.

With specific regard for vascular calcification, aged OVX monkeys treated for up to 12 months with doses equivalent to 1 and 22 times human exposure at 210 mg monthly did not result in aortic calcification.

Qualification of impurities: This drug product contains no novel excipients. Other product related impurities have been adequately qualified.

Genotoxicity: The genotoxicity potential of romosozumab was not evaluated. Romosozumab is a protein product and lacks non-protein or linkage material and therefore is unlikely to react with DNA or chromosomal material.

Carcinogenicity: Osteosarcoma has previously been observed with the bone anabolic agents. In rats treated for 2 years with parathyroid hormone (PTH) and parathyroid hormone related peptide (PTHrP) analogues, osteosarcoma and other bone tumors developed at low human exposure multiples. For romosozumab, a carcinogenicity study was conducted in Sprague Dawley rats. The rats were dosed for up to 98 weeks with 0, 3, 10, 50 mg/kg/week of romosozumab, equivalent to 1-19x human exposure. The study did not show any significant increases in tumor incidences. A low incidence of osteosarcoma (2/54) was observed in high dose males at 19x romosozumab human exposure. The large exposure multiple suggests that romosozumab is unlikely to increase the human risk of osteosarcoma.

Reproductive toxicology: Romosozumab's reproductive toxicity was evaluated in rat fertility and early embryonic development, embryofetal development and pre- and postnatal development (PPND) studies. Findings in the embryonic studies included reduced ventral processes of the 6th cervical vertebrae at doses of 100 and 300 mg/kg (17-56x human exposure). This finding is not considered clinically relevant due to lack of the anatomical structure in humans. Fetal poly- and syndactyly were observed in the embryofetal study at 32x human exposure. This finding is consistent with the syndactyly observed in sclerostosis patients and in SOST knockout mice. The finding is of low clinical relevance based on the exposure multiple, and the timing of digit formation in the first trimester in humans, when placental transfer of immunoglobulins is limited. In the PPND study, there were small decreases in bone mass and size in the F1 offspring at 1.5-56x human exposure of unclear biological significance. None of these findings are considered relevant for the postmenopausal indication.

Labeling: In the first two rounds of label negotiations, the nonclinical team made changes to the proposed product labeling including Sections 8, 12.1, 13.1, and 13.2. Further label negotiations have been deferred at this time because the application will be receiving a Complete Response letter.

5. Clinical Pharmacology

The clinical pharmacology team is recommending that this BLA ***can be approved***; please see Dr. Lin Zhou's review for complete details.

General clinical pharmacology: Romosozumab is administered as a subcutaneous injection once monthly for 12 months. The 210 mg dose requires 2 syringes of 105 mg each with injection of the second syringe occurring immediately after the first syringe. The estimated bioavailability of a romosozumab 210 mg was 81%. The median time to maximum romosozumab concentration (Tmax) was 5 days (range: 2 to 7 days) following subcutaneous administration. The mean (SD) maximum serum concentration (Cmax) was 22.2 (5.8) mcg/mL and the mean area under the concentration-time curve (AUC) was 389 (127) mcg*day/mL. Steady-state concentration was reached by month 3.

Intrinsic factors:
Renal Impairment: Mineral metabolism is impaired in patients with renal disease. A renal impairment study was conducted with romosozumab because of the potential for effects related to mineral metabolism, a pharmacodynamic effect of romosozumab. The population pharmacokinetic analysis indicated an increase in romosozumab exposure with increasing severity of renal impairment.

A clinical study of subjects with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2) or end-stage renal disease (ESRD) requiring hemodialysis was conducted with the proposed romosozumab 210 mg dose. In subjects with severe renal impairment, mean C_{max} and AUC were 29% and 44% higher compared to healthy subjects. However most subjects with severe

renal impairment had C_{max} and AUC values that overlapped with the exposure range seen in healthy subjects. In subjects with ESRD on hemodialysis, mean romosozumab exposure was similar to healthy subjects. The number of subjects with hypocalcemia was 0/8 healthy subjects, 1/8 subjects with severe renal impairment, and 4/8 in subjects with ESRD requiring hemodialysis. There was no increased exposure to romosozumab in hemodialysis subjects, so the hypocalcemia is likely due to combination of underlying alterations in mineral metabolism associated with renal disease itself and romosozumab effects.

Drug-Drug interactions: No formal drug-drug interaction studies have been performed. Romosozumab is a humanized monoclonal antibody, is not metabolized by CYP enzymes, and therefore, has a very low risk of drug-drug interactions.

Bisphosphonate: The pharmacokinetics of romosozumab was similar in patients transitioning from alendronate therapy.

Demographic interactions: Based on a population pharmacokinetic analysis, no notable difference in pharmacokinetics with age (20–89 years), gender, or race were noted.

Formulation bridging: The Phase 3 fracture trial in postmenopausal women with osteoporosis used romosozumab 70 mg/mL in a glass prefilled syringe (PFS) presentation containing drug substance and drug product manufactured at Amgen Thousand Oaks (ATO). The planned commercial drug substance process was transferred from ATO to (b) (4) (Amgen Rhode Island, [ARI]). The commercial 90 mg/mL (b) (4) PFS drug product manufacturing process was transferred from ATO to (b) (4).

The Applicant conducted a single-dose, randomized pharmacokinetic equivalence study to demonstrate the comparative bioavailability of the clinical trial 70 mg/ml formulation and the 90 mg/mL formulation (study 20120277). In addition, a clinical study was conducted comparing bone mineral density changes achieved with romosozumab 210 mg delivered as three 1.0 mL PFS injections of the 70 mg/mL concentration and romosozumab 210 mg delivered as two 1.17-mL PFS injections of the 90 mg/mL concentration (study 20120156). Both study 20120277 and 20120156 utilized drug substance and drug product manufactured at ATO. To support the new drug substance manufacturing site, the Applicant conducted a single-dose, randomized pharmacokinetic bioequivalence study to demonstrate the comparative bioavailability between the 90 mg/ml formulation manufactured at ATO and ARI. While the drug substance manufacturing sites were different, both the ATO and the ARI drug product were manufactured at ATO. To support drug product manufactured at (b) (4) the Applicant is relying upon analytic comparability.

Study 20120277 is an open label, single dose, parallel group study in healthy subjects that compared the pharmacokinetic profile of a single dose of romosozumab 210 mg delivered as three 1.0 mL PFS injections of the 70 mg/mL concentration (Process 2 at ATO) with two 1.17-mL PFS injections of the 90 mg/mL concentration (Process 2 at ATO). A total of 172 subjects were randomized (87 received the 70 mg/mL formulation, 85 received the 90 mg/mL formulation). Of the randomized subjects, the Applicant included 166 subjects in the PK analysis (82 in the 70 mg/mL group, 84 in the 90 mg/mL group). The geometric mean ratio

(90% CI) of test (90 mg/mL) to reference (70 mg/mL) for C_{max} was 0.992 (0.909 , 1.082), AUC_{last} 0.897 (0.814 , 0.989), and AUC_{inf} 0.896 (0.813 , 0.987). However, as outlined in the clinical pharmacology primary review, on FDA analysis when 2 subjects were excluded, the CI for C_{max} and AUC_{last} remained in the range demonstrating bioequivalence (0.8 – 1.25) but the lower bound of the 90% CI for AUC_{inf} fell to 0.799. The clinical pharmacology team accepts that comparability has been established because AUC_{inf} is based on extrapolated data and the extrapolation method may not be the most appropriate method due to romosozumab's drug disposition. Additionally, the small difference in AUC_{inf} would not be expected to have clinical implications. This reviewer agrees with the clinical pharmacology rationale.

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical site for study 20120277. Concerns were raised regarding drug stability during the freeze-thaw stability for method validation. These concerns were conveyed to the Applicant and the Applicant reevaluated the freeze-thaw stability and provided additional data. Upon review of the data, the data from the bioanalytical portion of study 20120277 are reliable.

Study 20120156 is a 6 month, randomized, placebo controlled study evaluating the BMD changes of romosozumab 210 mg delivered using three 1.0 mL PFS injections of the 70 mg/mL concentration and romosozumab 210 mg delivered using two 1.17-mL PFS injections of the 90 mg/mL concentration in postmenopausal women with osteoporosis. Please see the primary statistical review and the primary clinical review, pages 86-90 for complete details.

Subjects were randomized 22:5:22:5 to romosozumab 210 mg as two injections of 90 mg/mL in 1.17 mL PFS; placebo as two 1.17 mL PFS injections; romosozumab 210 mg as three injections of 70 mg/mL in 1mL PFS; placebo as three 1 mL PFS injections. Subjects also received calcium (500 – 1000mg daily) and vitamin D (600 – 800 IU daily) supplementation. The primary endpoint was change in lumbar spine BMD at month 6. The noninferiority margin was set based on data from the Phase 2 trial 20060326. In this trial, the treatment difference for romosozumab 210 mg (3 injections of 70 mg/mL) at 6 months was 8% (95% CI : 6.6 , 9.3). Therefore, 30% of the lower bound of the CI yields a NI margin of 2%.

A total of 294 subjects were enrolled into the trial (118 received 70 mg/mL, 123 received 90 mg/mL, 53 received placebo) and 273 (93%) subjects were included in the primary analysis data set (110 (93%) 70 mg/mL, 117 (95%) 90 mg/mL, 44 (83%) placebo). The change from baseline to month 6 in BMD was 9.6% for 70 mg/mL, 9.2% for 90 mg/mL, and 0.8% for placebo. The difference between the 70 mg/mL concentration and the 90 mg/mL concentration is 0.4% (95% CI: -1.5 , 0.7). Therefore, BMD increases achieved with treatment of romosozumab 210 mg delivered using the 90 mg/mL formulation are not inferior to romosozumab 210 mg delivered using the 70 mg/mL formulation at 6 months.

Study 20150197 is an open label, single dose, parallel group study in healthy subjects that compared the pharmacokinetic profile of a single dose of romosozumab 210 mg using two 1.17-mL PFS injections of the 90 mg/mL concentration using drug substance manufactured at ATO (Process 2, (b) (4) scale) versus drug substance manufactured at ARI (Process 2, (b) (4) scale). A total of 188 subjects were randomized (96 ATO, 92 ARI). Of the randomized

subjects, 186 were included in the PK analysis (96 ATO, 90 ARI). The geometric mean ratio (90% CI) of test (ARI) to reference (ATO) for C_{max} was 0.92 (0.86 , 0.98), AUC_{last} 0.91 (0.84 , 0.99), and AUC_{inf} 0.90 (0.83 , 0.98). The FDA analysis confirmed the applicant's analysis and comparability between ATO and ARI was demonstrated.

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the clinical site for study 20120197 and recommends accepting the clinical data.

Comparable bioavailability and/or clinical data are not required to support the switch in DP manufacturing from ATO to (b) (4). The Applicant adequately demonstrated that the ATO and (b) (4) drug products are analytically comparable. Because there are no significant process changes that could impact safety or potency, analytical comparability is sufficient to support the (b) (4) DP manufacturing.

TQT study: Because romosozumab is a large protein product that is unlikely to interact with cardiac cell ion channels, a thorough QT study was not required or performed.

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 is not available. The Applicant used signal to noise values to evaluate the magnitude of the antibody response.

Romosozumab's immunogenicity potential was assessed in all clinical studies of healthy volunteers and postmenopausal women. In Phase 1 studies 66/832 (8%) subjects developed binding antibodies to romosozumab after at least a single dose of drug product. Neutralizing antibodies developed in 18 subjects (27% of subjects with binding antibodies, 2% of all Phase 1 subjects).

In the Phase 2 and 3 studies, 20% of subjects developed binding antibodies and 5% with binding antibodies developed neutralizing antibodies. In some cases, the antibodies were transient and the antibody assays were negative by the last time point tested. A transient romosozumab response was seen in approximately 50% of subjects with positive binding antibodies. A transient response occurred in 24% of subjects of subjects with positive neutralizing antibodies.

The 24 month dose finding study was extended to include one year off of romosozumab followed by a one year retreatment phase. In the initial treatment period, 60/ 255 (24%) subjects exposed to romosozumab developed binding antibodies and 8 (13%) of those subjects developed neutralizing antibodies. There was not an apparent dose-related trend in antibody formation. During months 24 to 36, 45 of 179 (25%) subjects exposed to romosozumab had positive binding antibodies at month 36. Six (13%) subjects with binding antibodies were positive for neutralizing antibodies. During repeat exposure to romosozumab (month 36 to 48), 22 (16%) subjects who were antibody positive prior to retreatment were negative for

binding antibodies in the retreatment phase, 11 (8%) subjects who were positive prior to retreatment remained positive during the retreatment phase and 2 (1%) subjects developed new binding antibodies to romosozumab. No subjects developed new neutralizing antibody to romosozumab during retreatment.

Effects of anti-drug antibody development on romosozumab pharmacokinetics: The development of antibodies to romosozumab resulted in reduced serum concentrations of romosozumab. In phase 1 studies, one subject enrolled in a single dose study who developed neutralizing antibodies to romosozumab was inadvertently then enrolled in a multi-dose study. In the second study (second exposure to romosozumab), the subject received a dose of 1mg/kg of romosozumab. Romosozumab serum concentration rose to 2010 ng/ml on Day 5, dropped below the lower limit of quantification (BQL = 50 ng/mL) on Day 7 and remained BQL through the PK sampling window up to 168 days, despite continued dosing once every two weeks.

In the Phase 3 studies of 6 months duration or longer, the presence of binding antibodies appeared to decrease romosozumab exposure up to 25% at months 3, 6, and 9. 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 on romosozumab antibody on BMD. In the fracture efficacy trial 20070337, the month 15 antibody status was used for evaluation. As outlined in the table below, at months 12 and 24, subjects who developed antibodies experienced similar BMD increases to subjects without antibodies to romosozumab. Additionally, the assay S/N ratio did not appear to affect the BMD results.

Study 20070337 : Efficacy Parameters Based on Antibody Status at Month 15			
	ADA negative	ADA binding Ab positive	ADA neutralizing Ab positive
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)
Source: compiled by reviewer from immunogenicity testing summary			

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 7% of romosozumab antibody positive subjects.

Labeling: The Office of Clinical Pharmacology recommends edits to the Special Populations and Clinical Pharmacology sections of the proposed product labeling. Further labeling discussions with the Applicant are deferred at this time.

Postmarketing Studies: No postmarketing studies are recommended by the clinical pharmacology review team.

6. Clinical Microbiology

Romosozumab is not an antimicrobial agent. Clinical microbiology studies are not applicable to this BLA. The microbiology product quality of the romosozumab drug substance and combination drug/device product is discussed in Section 3 of this review.

7. Clinical/Statistical- Efficacy

The Applicant is seeking an indication for treatment of postmenopausal osteoporosis. This is the first osteoporosis indication for this product and fracture efficacy data are required to support approval. The Division has generally accepted a robust result (p value <0.01) from a single phase 3 fracture trial with supportive bone mineral density data from the dose finding study for approval of an initial osteoporosis indication. The Applicant conducted one key fracture efficacy trial (20070337) with supportive evidence from the dose-finding trial 20060326.

Because there is a large single fracture efficacy trial, an integrated summary of efficacy will not be the focus of this review. The dose-finding trial 20060326 is presented and discussed, followed by the efficacy findings of trial 20070337.

Trial 20060326: Please refer to the clinical review, pages 65 – 82 for complete details. Trial 20060326 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 SC every 6 months. The second extension (months 36 to 48) is for a retreatment phase with romosozumab. The third extension remains ongoing and includes 24 months of zoledronic acid 5 mg once yearly or no treatment. All subjects also were to take at least 1000 mg calcium and at least 800 IU Vitamin D daily. During the romosozumab retreatment phase, subjects were to receive a 50,000 IU oral vitamin D loading dose.

For the initial 24 months study, postmenopausal women with low bone mass were randomized to receive placebo or romosozumab as follows:

- romosozumab 70 mg (50 subjects) or placebo (10 subjects) SC monthly
- romosozumab 140 mg (50 subjects) or placebo (10 subjects) SC monthly
- romosozumab 210 mg (50 subjects) or placebo (10 subjects) SC monthly

- romosozumab 140 mg (50 subjects) or placebo (10 subjects) SC every 3 months
- romosozumab 210 mg (50 subjects) or placebo (10 subjects) SC every 3 months

Two additional arms were open label:

- alendronate 70 mg po weekly for the first 12 months. Subjects were then switched to romosozumab 140 mg monthly for months 12 – 24.
- teriparatide 20mcg SC daily for the first 12 months. Subjects were discontinued after 12 months.

Subjects and study personnel were blinded to treatment (romosozumab or placebo) and dose (70mg/140mg/210mg) but not to dose frequency.

For the first 24 months of the study, romosozumab was provided in single-use 5 mL vials containing approximately 1 mL of study medication (70 mg/mL romosozumab). Placebo presentation was identical. For the month 36 – 48 romosozumab retreatment phase, romosozumab was presented in a single-use 1 mL prefilled syringe containing the 70 mg/mL formulation.

The primary endpoint is change in lumbar spine BMD at month 12. Secondary endpoints included change in lumbar spine, femoral neck and total hip BMD at month 6; change in femoral neck, total hip, and distal 1/3 radius BMD at month 12; change in bone turnover markers (P1NP, CTX, OC, BSAP) at months 1, 2, 3, 6, 9, and 12. All active control analyses are exploratory. For all endpoints, the placebo group was pooled. Additionally, the study included a bone biopsy substudy, which included 32 subjects, and a quantitative CT (QCT) substudy, which enrolled 172 subjects.

Study Population: The enrolled postmenopausal population included 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. As outlined in the table below, 92% of subjects completed the initial 12 months of the study and 87% completed the study to month 24.For the open label alendronate arm, after the first year, subjects in the alendronate arm were transitioned to romosozumab 140mg monthly. Overall, 51 subjects were enrolled, 49 subjects completed the first 12 months of the study and 45 subjects completed through month 24. Subjects in the teriparatide arm only participated in the first 12 months of the study, 55 subjects were randomized and 46 subjects completed through month 12.

Trial 20060326: Study Subject Disposition to Month 24

	placebo	**romosozumab**				
		70 qM	**140 q3M**	**140 qM**	**210 q3M**	**210 qM**
Randomized	52	51	54	51	53	52
D/C prior to treatment	1 (2)	2 (4)	1 (2)	3 (6)	0	1 (2)
D/C 12 months	4 (8)	4 (8)	3 (6)	2 (4)	2 (4)	2 (4)
Completed 12 months	47 (90)	45 (88)	50 (93)	46 (90)	51 (96)	49 (94)
BMD Analysis	50 (96)	49 (96)	52 (96)	48 (94)	53 (100)	50 (96)
Safety Analysis	50 (96)	50 (98)	53 (98)	48 (94)	53 (100)	51 (98)
Completed 24 months	46 (88)	39 (76)	46 (85)	43 (84)	48 (91)	48 (92)

Source: CSR 20060326, table 14q-1.1

Reference ID: 4123729

For months 24 to 36, subjects who chose to continue in the study were re-randomized to receive placebo or denosumab 60 mg SC every 6 months. The teriparatide group was discontinued, the romosozumab groups were pooled and randomized while the placebo and alendronate/romosozumab 140mg qmonth groups were randomized separately. As outlined in the table below, 260 subjects chose to continue into the denosumab extension, with 131 receiving placebo and 129 receiving denosumab. For months 36 to 48, subjects who were initially in the alendronate arm were discontinued from the trial. All subjects from the original placebo or romosozumab arms who continued in the trial received romosozumab 210 mg monthly. Overall, 167 subjects enrolled in the romosozumab retreatment phase and 155 subjects completed 48 months.

Trial 20060326: Months 24 – 48: Study Subject Disposition						
Months 24 – 36, Denosumab Extension						
	placebo		**alendronate/ 140**		**romosozumab**	
Completed Month 24	**46**		**45**		**224**	
Enrolled in Extension	36		41		183	
	placebo	denosumab	placebo	denosumab	placebo	denosumab
randomized	18	18	20	21	93	90
Completed 36 months	17 (94)	18 (100)	18 (90)	19 (95)	88 (95)	88 (98)
Months 36 – 48, Romosozumab Retreatment						
Enrolled in Extension	12	16	XXX	XXX	72	67
Completed 48 months	12 (100)	14 (88)	XXX	XXX	65 (86)	64 (96)
Source: CSR20060326, tables 14r.-1.1.1.1, 14s-1.1.2.4						

Results:

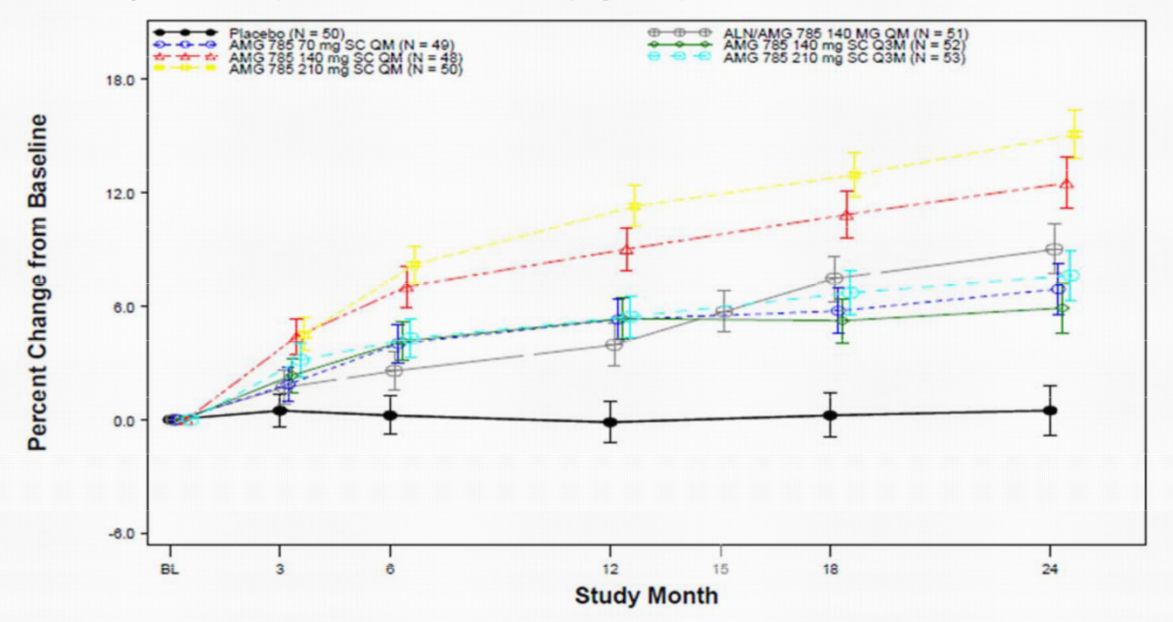
Lumbar spine BMD: In the first 24 months of the study, bone mineral density of the spine was evaluated at baseline, and months 3, 6, 12, 18, and 24.The primary endpoint is percent change in lumbar spine BMD at month 12. As outlined in the table below, treatment with all doses of romosozumab resulted in significant increases in BMD. More robust results were achieved with monthly romosozumab dosing. Treatment with alendronate 70 mg weekly resulted in a 4.1% increase in lumbar spine BMD at month 12. Treatment with daily teriparatide 20 mcg resulted in a 7.1% increase in lumbar spine BMD at month 12. Romosozumab 210 mg qmonth resulted in BMD increases that were significantly greater then both active controls ($p<0.0001$ after Hochberg adjustment).

Trial 20060326: Percent Change in Lumbar Spine BMD at Month 12, Linear Mixed Effect Model						
	placebo	**romosozumab**				
		70 qM	**140 q3M**	**140 qM**	**210 q3M**	**210 qM**
Randomized	50	49	52	48	53	50
Analysis Dataset	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
Source: Table 10.2, page 200, CSR 20060326						

Other BMD Endpoints: As outlined in the primary clinical review, romosozumab increased BMD of the hip with larger increases achieved with the monthly dosing groups. The treatment difference compared to placebo with romosozumab 210 mg monthly was 4.9% at the total hip and 4.8% 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. The treatment difference compared to placebo with romosozumab 210 mg monthly was -0.3%. The finding of no change or loss in cortical BMD of the radius is consistent with other anabolic agents.

BMD at Month 24: All subjects in the placebo and romosozumab dose groups continued on their blinded therapy for the second year of the study. Subjects in the teriparatide arm were discontinued after 12 months and subjects in the alendronate arm were transitioned to romosozumab 140 mg monthly. As shown in figure 10-8 below, BMD in the romosozumab arms did continue to increase in the second year of therapy although the increases are not as robust as those achieved in the first year of therapy.

Figure 10-8. Least Square Means (95% CI) of Percent Change From Baseline in DXA Lumbar Spine BMD (source: CSR 20060326, page 220)

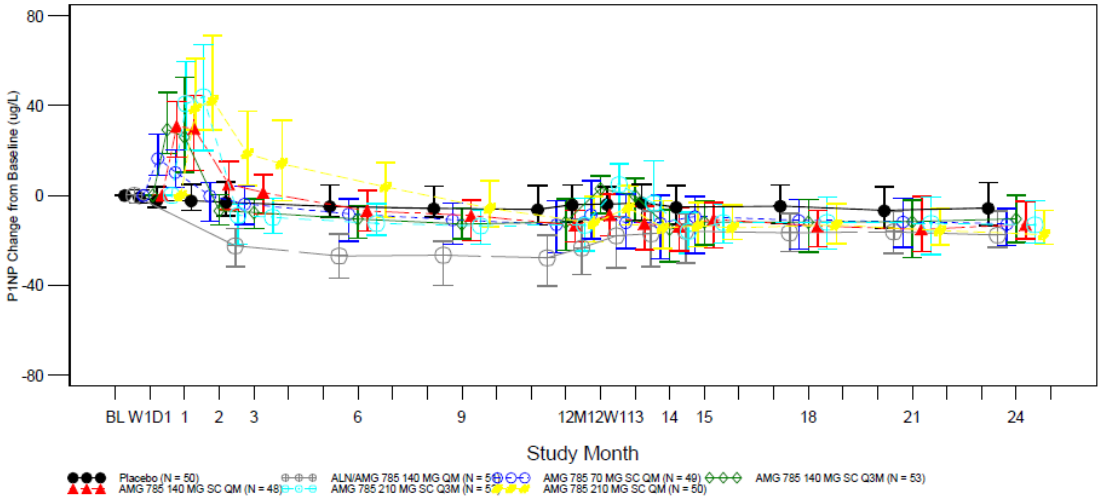


Bone Turnover Markers: Both markers of bone formation (P1NP, osteocalcin, and BSAP) and markers of bone resorption (CTX) were evaluated during the first 24 months of the study.

As shown in the figure below, P1NP, a marker of bone formation increased in all romosozumab groups and were greatest at month 1. The increases in bone formation were not maintained and levels returned to baseline by month 9. Levels remained above baseline the longest for the 210 mg monthly group (yellow). Bone formation with alendronate therapy (gray) in the first 12 months is suppressed, which is expected. In the second year, with romosozumab 140 mg monthly treatment following the alendronate therapy, bone formation does increase in a similar pattern to other romosozumab groups. The teriparatide group is not

displayed below because subjects were discontinued at 12 months. During the 12 months of teriparatide treatment, P1NP increased, reaching a plateau at month 6 and remained elevated through month 12. Therefore, stimulation of bone formation seen with romosozumab is different from the other anabolic agents available.

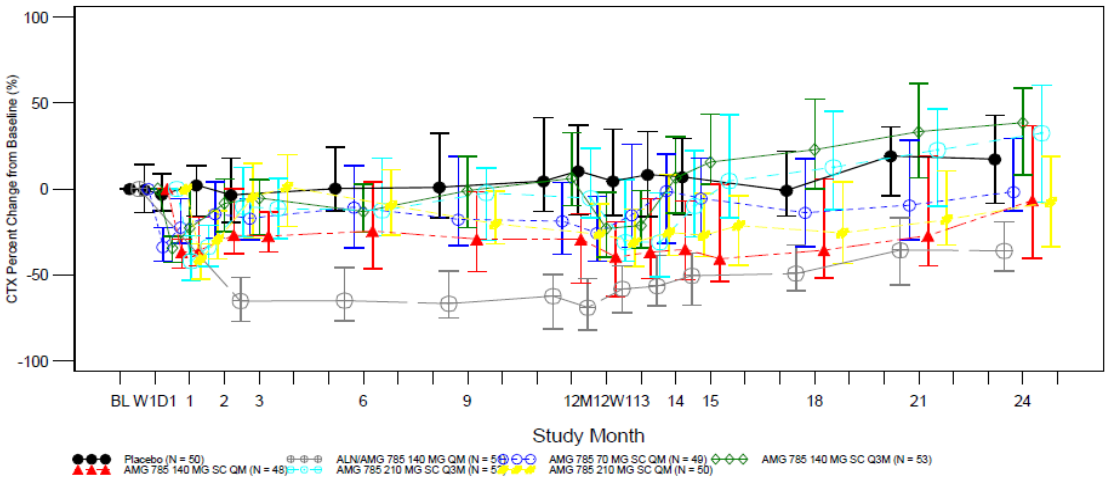
Fig 14q-4.4.3. P1NP Change From Baseline by Visit Median and Interquartiles
(Primary Efficacy Subset)
(20060326 Month 24 Interim Analysis)



Source: CSR 20060326, Figure 14q-4.4.3, page 2407

For bone resorption, serum CTX is suppressed with romosozumab therapy. As shown in the figure below, the greatest decreases are seen at month 1. Monthly dosing groups romosozumab 140 mg (red) and 210 mg (yellow) remained suppressed through month12. The largest decreases in serum CTX were seen with alendronate therapy (gray). Alendronate is an anti-resorptive agent, so the sustained decrease in CTX is expected. In the second year of the study during treatment with romosozumab 140 mg monthly, serum CTX trended up toward baseline.

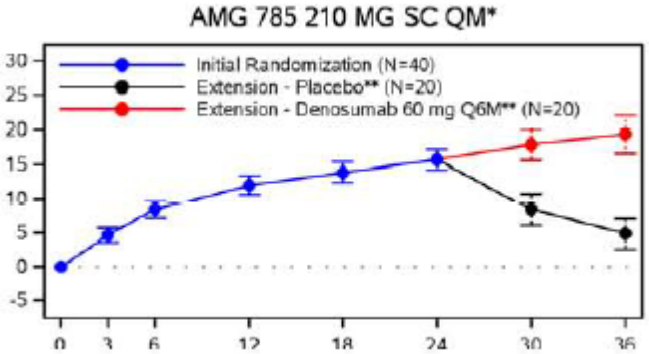
Fig 14q-4.5.1. Serum CTX Percent Change From Baseline by Visit Median and Interquartiles
(Primary Efficacy Subset)
(20060326 Month 24 Interim Analysis)



Source: CSR 20060326, Figure 14q-4.5.1, page 2409

Denosumab Extension: During months 24 to 36, subjects who chose to participate in the denosumab extension were randomized to receive either denosumab or placebo. As displayed in the figure below, treatment with denosumab resulted in increases in BMD. Cessation of osteoporosis therapy and treatment with placebo resulted in BMD returning to baseline 12 months after romosozumab is discontinued. Similar results were seen for total hip and femoral neck BMD.

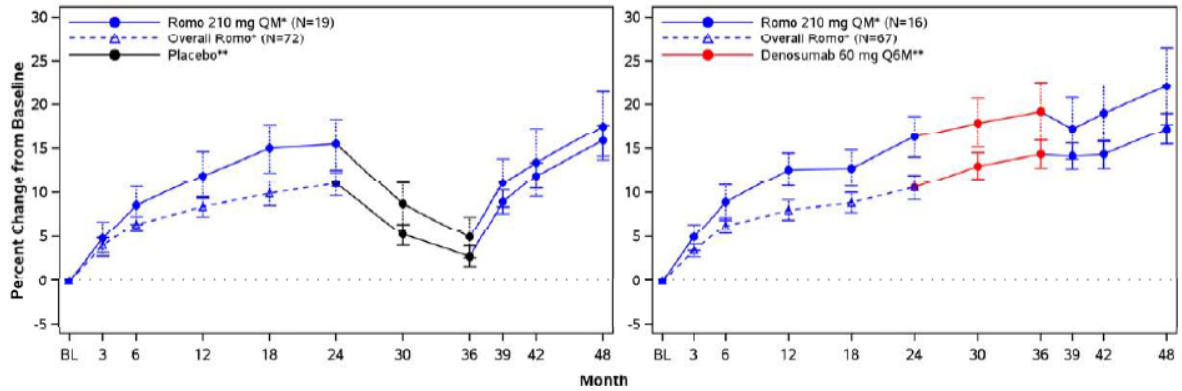
Figure 10-11. Lumbar Spine BMD Percent Change From Baseline by Visit



Source: CSR 20060326 Figure 10-11, page 225

Romosozumab Retreatment: Subjects who completed months 36 of the denosumab extension could elect to participate in the romosozumab retreatment. All subjects who participated in the month 36 to 48 extension received romosozumab 210 mg monthly. As displayed in the figure below, following placebo, retreatment with romosozumab had a similar pattern of BMD increase as was seen with initial romosozumab treatment. Following the antiresorptive medication denosumab, there appears to be a 6 month lag before BMD with romosozumab retreatment begins to increase.

Figure 10-14. DXA Lumbar Spine BMD Percent Change From Baseline by Visit



Source: CSR 20060326 Figure 10-14, page 234

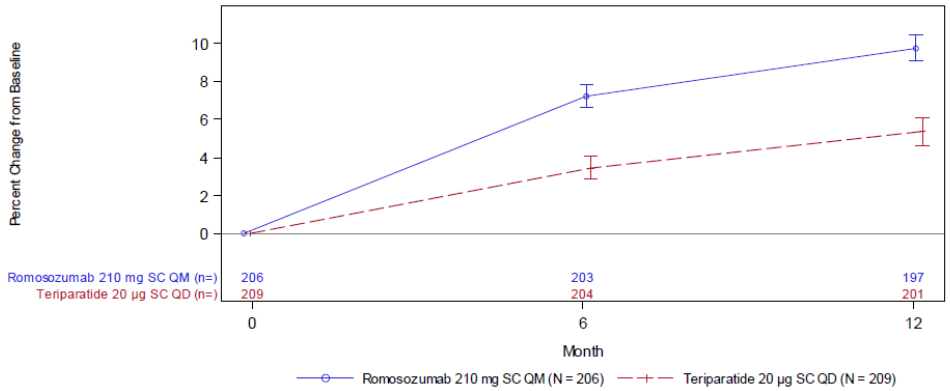
Conclusions: The data from trial 20060326 demonstrate dose-related increases in bone mineral density with romosozumab therapy. Bone mineral density increases are more robust with monthly dosing as compared to every 3 month dosing. At the End-of Phase 2 meeting, the Applicant proposed the 210 mg monthly dose for further development. This is the only dose

that was statistically better then both alendronate and teriparatide. The Division recommended that both the 140 mg monthly dose and the 210 mg monthly dose be taken into Phase 3 as the BMD responses were similar. The Applicant chose to take 210 mg monthly for evaluation in the fracture efficacy trial. Therefore, it is unknown as to whether a lesser dose of the medication would achieve fracture efficacy results. The Applicant also proposed limiting romosozumab therapy to one year of treatment. The Division agreed that the data support limiting dosing to one year of therapy.

Trial 20101291 is a randomized, placebo-controlled, dose-finding study is Japanese women with osteoporosis. Please see the primary clinical review, pages 82-86 for complete details. BMD changes with romosozumab are consistent with the findings from trial 20060326.

Trial 20080289 is a randomized, open-label study to evaluate the effect of romosozumab compared to teriparatide in patients previously treated with bisphosphonates. While this study is not sufficient to support any comparative claims, it does offer some information on BMD response to romosozumab in subjects previously treated with bisphosphonates. Enrolled subjects were required to have been taking a bisphosphonate for at least 3 years prior to screening and to have been treated in the last year and immediately prior to screening with alendronate 70mg weekly, or equivalent. As outlined in the figure below, there is no apparent lag in BMD increases achieved with romosozumab therapy in subjects previously treated with bisphosphonates.

Figure 14-4.8. Lumbar Spine Bone Mineral Density by DXA Percent Change From Baseline by Visit (Repeated Measures Model)
(Primary Efficacy Analysis Set, Observed Data)
(20080289 Month 12 Final Analysis)



Source: CSR 20080289, page 213

Trial 20070337: Trial 20070337 is a 24-month, multicenter, double-blind, randomized, placebo-controlled study evaluating healthcare provider administered monthly subcutaneous romosozumab 210 mg for the treatment of postmenopausal osteoporosis (PMO). The coprimary endpoints of the study are incidence of new morphometric (radiographic) vertebral fractures at month 12 and 24 months. 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 is designed as double blind in the first year, and then all subjects will receive healthcare provider administered open label denosumab 60 mg every 6

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

Study population: Trial 20070337 enrolled postmenopausal women with osteoporosis age 50 to 90 years. Osteoporosis was defined as a BMD T-score at the total hip or femoral neck of ≤ -2.5. Subjects with a history of hip fracture, severe vertebral fracture, or more than 2 moderate vertebral fractures were excluded from the study. Subjects with metabolic bone disease, 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 was targeting 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.

Study treatments: Subjects were randomized 1:1 to receive either romosozumab 210 mg or matching placebo by subcutaneous (SC) injection every month for the first 12 months of the trial. Injections were administered by a healthcare provider. The dose of 210 mg required three 1 mL syringes of 70 mg/mL romosozumab. 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. After the 12-month double-blind placebo-controlled treatment period, all subjects entered the 12-month open-label denosumab treatment period where they received denosumab 60 mg SC every 6 months in an open-label fashion while still remaining blinded to their initial treatment assignment (romosozumab or placebo). Denosumab injections were also administered by a healthcare provider. Subjects were to receive daily calcium (500 to 1000 mg) and vitamin D (600 to 800 IU) supplementation.

Efficacy measures: The coprimary endpoints of trial 20070337 are subject incidence of new morphometric vertebral fracture 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 by the central read facility 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.

A central radiologic facility, (b) (4) was used for fracture assessment, DXA and quantitative CT readings. The central read facility managed DXA readings and DXA quality control including cross calibration with a central phantom and longitudinal quality control conducted by the study sites and reviewed by the central facility.

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. Subject incidence of new vertebral fracture through months 12 and 24
2. Subject incidence of clinical fracture through month 12
3. Subject 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. Subject incidence of clinical fracture through month 24
5. Subject 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. Subject 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. Subject 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)

The Applicant defined several analysis dataset populations. The primary analysis population for vertebral fractures included all randomized subjects who had a baseline and at least one post-baseline evaluation for vertebral fracture at or before the specific timepoint under consideration. The full analysis population for all other fracture assessments (nonvertebral fracture, clinical fracture, major nonvertebral fracture, major osteoporotic fracture, hip fracture) included all randomized subjects. The primary efficacy analysis population for BMD and patient reported endpoints included all randomized subjects who had a baseline and at least one post baseline evaluation of the endpoint of interest at or before the specific timepoint under consideration.

Results:

Disposition: As outlined in the table below, 7180 (3589 romosozumab, 3591 placebo) subjects were randomized into the trial. As outlined in the table below, approximately 84% of subjects completed the two years of the trial. The most common reason for discontinuation was withdrawal of consent. Subjects could complete the trial after discontinuing study drug. For the 24-month study period, approximately 83% of subjects completed study drug dosing.

Trial 20070337: Subject Disposition			
	Placebo/ Denosumab	**Romosozumab/ Denosumab**	**Total**
Randomized	**3591**	**3589**	**7180**
Never received study drug	9 (0.3)	14 (0.3)	23 (0.3)
Treated	**3582**	**3575**	**7157**
Discontinued	559 (16)	595 (17)	1154 (16)
Withdrew Consent	314 (9)	346 (10)	660 (9)
Death	44 (1)	49 (1)	93 (1)
Adverse Event	53 (2)	47 (1)	100 (1)
Lost to follow-up	42 (1)	49 (1)	91 (1)
Required alternative therapy	2 (<0.1)	4 (0.1)	6 (<0.1)
Other*	104 (3)	100 (3)	204 (3)

Reference ID: 4123729

Trial 20070337: Subject Disposition			
	Placebo/ Denosumab	**Romosozumab/ Denosumab**	**Total**
Completed to month 12	**3205 (89)**	**3185 (89)**	**6390 (89)**
completed study drug to month 12	3135 (87)	3103 (86)	6238 (87)
Completed to month 24	**3032 (84)**	**2994 (83)**	**6026 (84)**
completed study drug to month 24	3001 (84)	2932 (82)	5932 (83)
*Other includes administrative decision, noncompliance, ineligibility determined, protocol deviation, and other (not defined by Applicant) Source: CSR20070327, table 14-1.1			

Demographics: The demographics of the enrolled population are well matched between the treatment groups and are outlined in the table below. The mean age of enrolled postmenopausal women is 71 years and 31% of the population was over age 75. The predominant race was white and not Hispanic or Latino ethnicity. The mean weight of the population was 58 kg with a large weight range of 22 to 133 kg. The mean lumbar spine T-score was -2.7, 18% had a vertebral fracture at baseline, and 35% had a history of any osteoporotic fracture after age 45.

Trial 20070337: Subject Demographics			
	Placebo/ Denosumab	**Romosozumab/ Denosumab**	**Total**
Randomized	**3591**	**3589**	**7180**
Age (mean (SD)	71 (6.9)	71 (7.0)	71 (7.0)
age range, years	55 - 90	55 - 90	55 - 90
≥ 65 years, n (%)	2834 (79)	2821 (79)	5655 (79)
≥ 75 years, n (%)	1121 (31)	1119 (31)	2240 (31)
Race			
White	2052 (57)	2063 (58)	4115 (57)
Asian	441 (12)	425 (12)	866 (12)
Black or African American	74 (2)	77 (2)	151 (2)
American Indian/ Alaskan Native	63 (2)	64 (2)	127 (2)
Hawaiian/Pacific Islander	1 (<0.1)	0	1 (<0.1)
Multiple	59 (2)	60 (2)	119 (2)
Other*	901 (25)	900 (25)	1801 (25)
Ethnicity			
Hispanic or Latino	1416 (39)	1427 (40)	2843 (40)
Not Hispanic or Latino	2175 (61)	2162 (60)	4337 (60)
Weight, kg (SD)	58 (11)	58 (11)	58 (11)
weight range, kg	28 - 133	22 - 127	22 - 133
Lumbar spine T-score, mean (SD)	-2.7 (1.04)	-2.7 (1.04)	-2.7 (1.04)
Prevalent vertebral fracture, n (%)			
yes	645 (18)	672 (19)	1317 (18)
no	2839 (79)	2795 (78)	5634 (78)
not readable	107 (3)	122 (3)	229 (3)
Any osteoporotic fracture, n(%)	1258 (35)	1270 (35)	2528 (35)
*Other (not defined by Applicant) Source: CSR20070327, tables 9-2, 9-3, pages 129-133			

Morphometric Vertebral Fracture: Radiographs for evaluation of new morphometric vertebral fractures were obtained at months 6, 12, and 24. The coprimary endpoint is the incidence of new morphometric vertebral fracture at month 12 and month 24. As outlined in the table below, at month 12, the incidence of new vertebral fractures is 1.8% in the placebo group and 0.5% in the romosozumab group. The absolute risk reduction is 1.3% with a relative risk reduction of 73%. At month 24, the incidence of new vertebral fractures is 2.5% in the placebo/denosumab group and 0.6% in the romosozumab/denosumab group. The absolute risk reduction is 1.9% with a relative risk reduction of 75%.

Trial 20070337: New Morphometric Vertebral Fracture		
	Placebo/ Denosumab	**Romosozumab/ Denosumab**
N	**3591**	**3589**
Month 12		
N, primary analysis population	3322	3321
Crude incidence, n (%)	59 (1.8)	16 (0.5)
Absolute Risk Reduction (95% CI)	1.3% (0.79 , 1.80)	
Relative Risk Reduction (95% CI)	73% (53 , 84)	
p-value	<0.001	
Month 24		
N, primary analysis population	3327	3325
Crude incidence, n (%)	84 (2.5)	21 (0.6)
Absolute Risk Reduction (95% CI)	1.9% (1.30 , 2.49)	
Relative Risk Reduction (95% CI)	75% (60 , 84)	
p-value	<0.001	
Source: Primary statistical review, table 5, page 11		

Reviewer comment: It is unusual to see the analysis population increase at month 24, compared to month 12. However, it is possible given the construct of the primary analysis population. If a subject had a baseline radiograph and then only had spine radiograph at month 24, they could be included in the month 24 analysis population and excluded from the month 12 population.

Subgroup analyses were conducted based on age (< 65 years, ≥ 65 years, < 75 years, ≥ 75 years), race, geographic region, prevalent vertebral fracture status, history of fragility fracture, history of nonvertebral fracture after age 55 years, baseline lumbar spine BMD T-score, baseline hip or femoral neck BMD T-score, baseline body mass index, and baseline World Health Organization Fracture Risk Assessment (FRAX) score for major osteoporotic fracture. As displayed in the primary statistical review Appendix A2, the reduction in new vertebral fracture risk showed similar trends in all subgroups evaluated.

Clinical and Nonvertebral Fracture: In the statistical hierarchy of fracture assessments, clinical fracture at month 12 is the first secondary endpoint. Nonvertebral fracture at month 12 and 24 is the next endpoint in the statistical hierarchy, followed by clinical fracture at month

24. Clinical fracture is defined as all nonvertebral fractures plus all symptomatic vertebral fractures. As noted in the table below, of the 148 clinical fractures in the first 12 months, 131 (88%) were nonvertebral fractures. In the first 12 months, treatment with romosozumab resulted in a significant 36% decrease in clinical fractures. However, the reduction in nonvertebral fractures was not significant in this time period.

Trial 20070337: Clinical and Nonvertebral Fracture		
	Placebo/ Denosumab	**Romosozumab/ Denosumab**
N	**3591**	**3589**
Clinical Fracture, Month 12		
Incidence, n (%)	90 (2.5)	58 (1.6)
Absolute Risk Reduction, % (95% CI)	1.2 (0.4 , 1.9)	
Relative Risk Reduction, % (95% CI)	36% (11 , 54)	
p-value (alpha level)	0.008 (0.05)	
Nonvertebral Fx, Month 12		
Incidence, n (%)	75 (2.1)	56 (1.6)
Absolute Risk Reduction, % (95% CI)	0.8 (0.1 , 1.4)	
Relative Risk Reduction, % (95% CI)	25 (-5 , 47)	
p-value (alpha level)	0.096 (0.05)	
Nonvertebral Fx, Month 24		
Incidence, n (%)	129 (3.6)	96 (2.7)
Absolute Risk Reduction, % (95% CI)	1.0 (0.2 , 1.9)	
Relative Risk Reduction, % (95% CI)	25% (3 , 43)	
p-value (alpha level)	0.029 (0.025)	
Clinical Fracture, Month 24		
Incidence, n (%)	147 (4.1)	99 (2.8)
Absolute Risk Reduction (95% CI)	1.4 (0.5 , 2.4)	
Relative Risk Reduction (95% CI)	33 (13 , 48)	
p-value	not tested, based on statistical plan	
Source: Primary statistical review, table 6, page 12		

The Applicant attributes the lack of significance of the nonvertebral fracture reduction to a regional subgroup interaction in Central/Latin America where a lower than expected nonvertebral fracture rate in the placebo group was observed (assumed 3.5%, observed 1.2%). The observed nonvertebral fracture rate was also lower than expected in the small enrolled population in North America (assumed 3.5%, observed 1.1%). In the original 24 month sample size calculation, the Applicant assumed a nonvertebral fracture rate of 4% during the first 12 months of the trial and with a sample size of 6000 subjects the study had a power of 93% to detect a 40% decrease in nonvertebral fractures after 12 months of romosozumab compared with placebo. During the study, the pooled nonvertebral fracture rate was monitored and the Applicant observed that the rate was lower than expected. Therefore, the sample size was increased in protocol amendment number 4 using a 3.5% nonvertebral fracture rate, increasing the sample size to 6600. The total sample size of 6600 subjects was anticipated to provide 91% power to detect a 40% decrease in the risk of nonvertebral fracture after romosozumab treatment for 12 months.

(b) (4)

Other Fracture Endpoints: Other fracture endpoints included in the hierarchal testing were subject incidence of major nonvertebral fracture through months 12 and 24; subject incidence of new or worsening vertebral fracture through months 12 and 24; and subject incidence of hip fracture through months 12 and 24. For all of these endpoints, the Applicant reports adjusted p-values but based on the statistical plan, hierarchal testing should have stopped after lack of significance of nonvertebral fractures. The Applicant also conducted analyses of numerous exploratory fracture endpoints, which (b) (4) are not discussed in this review.

Bone Mineral Density: Bone mineral density was not included in the hierarchal statistical testing. Bone mineral density of the hip and lumbar spine DXA was measured at baseline, month 12 and month 24. Analyses used an ANCOVA model adjusting for treatment, age and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction, without adjustment for multiplicity.

As outlined in the table below, treatment with romosozumab resulted in significant increases in both lumbar spine and hip bone mineral density. At month 12, the treatment difference is 12.7% at the lumbar spine, 5.8% at the total hip, and 5.2% at the femoral neck. From month 12 – 24, treatment with open-label denosumab resulted in increases in bone mineral density in all groups. Despite the increase in BMD in the placebo group, the treatment difference remained similar (11.1% at the lumbar spine, 5.3% at the total hip, and 4.9% at the femoral neck).

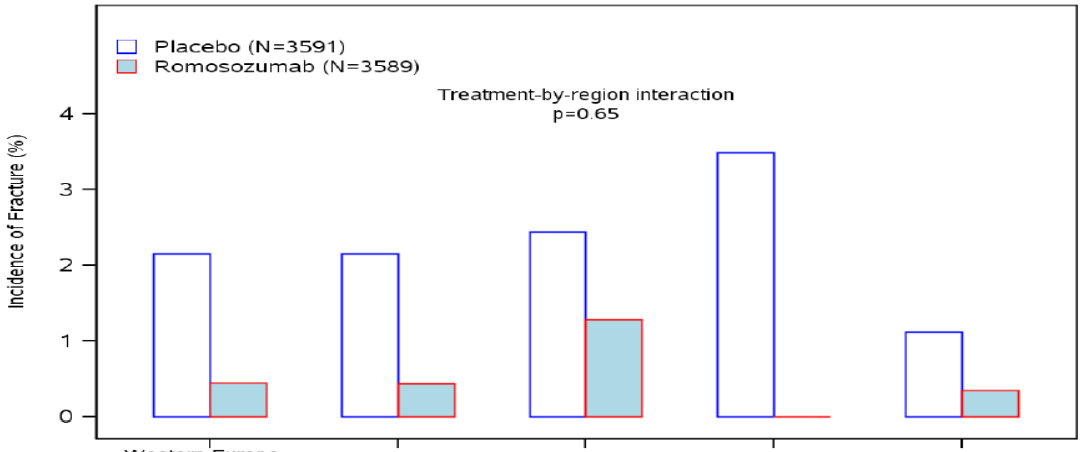
Trial 20070337: Changes in Bone Mineral Density at Month 12, LOCF		
	Placebo	**Romosozumab**
N	**3591**	**3589**
Lumbar Spine, n	3148	3151
% change from baseline, mean (SE)	0.4 (0.1)	13.1 (0.1)
Treatment Difference, LS mean (95% CI) p-value vs placebo)	12.7% (12.4 , 12.9) <0.001	
Total Hip, n	3210	3197
% change from baseline, mean (SE)	0.3 (0.1)	6.0 (0.1)
Treatment Difference, LS mean (95% CI)	5.8% (5.6 , 6.0) <0.001)	
Femoral Neck, n	3210	3197
% change from baseline, mean (SE)	0.3 (0.1)	5.5 (0.1)
Treatment Difference, LS mean (95% CI)	5.2% (4.9 , 5.4) <0.001)	
Source: adapted from primary statistical review, Tables 7-9, page 13; and from CSR 20070337 table 10-3, pages 144-145		

When subgroups including age, race, and geographic region were evaluated, changes in BMD were consistent.

Reviewer Comment: The BMD endpoints were not included in the hierarchal statistical testing. Based on this, it would be reasonable not to include the BMD findings in product labeling. However, change in BMD with therapy is an important endpoint for prescribers and given the robust findings, the statistical significance would likely remain after multiplicity adjustment. Therefore, inclusion of the BMD findings in product labeling will be considered.

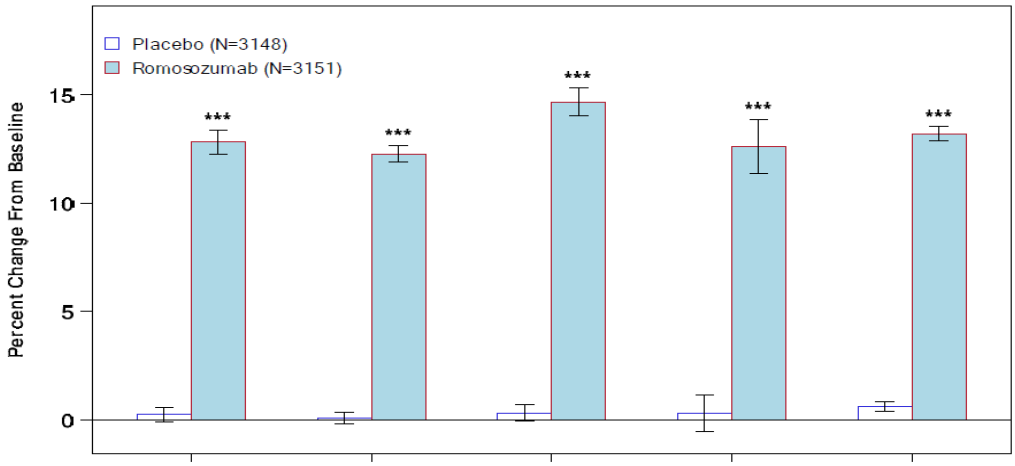
Applicability of Efficacy Findings to U.S. Patients and U.S. Medical Practice*:* Of the 7180 subjects enrolled in the fracture efficacy trial for romosozumab, 195 (2.7%) were from North America. Only a small number of fractures occurred in the North American population. Given the very small population enrolled, the Applicant was asked to justify the applicability of the study findings to the U.S. population and U.S. medical practice. As outlined in figure 18, there was no treatment by region interaction for new vertebral fractures at month 12 (source: BLA 761062, 2.7.3 Summary of Clinical Efficacy, page 126). When lumbar spine BMD was evaluated, the BMD changes were consistent across all regions (figure 19, source: BLA 761062, 2.7.3 Summary of Clinical Efficacy, page 127). Given the consistent findings across all geographic regions, the results from study 20070337 can be considered applicable to the U.S. population and U.S. medical practice.

Figure 18. Subject Incidence of New Vertebral Fracture Through Month 12 by Geographic Region (Primary Analysis Set for Vertebral Fractures) (20070337 M24 Adhoc Analysis)



	Western Europe and Australia/New Zealand	Central and Eastern Europe	Asia Pacific	North America	Central/Latin America
pbo n/N1 (%)=	10/466 (2.1%)	20/929 (2.2%)	10/411 (2.4%)	3/86 (3.5%)	16/1430 (1.1%)
romo n/N1 (%)=	2/453 (0.4%)	4/915 (0.4%)	5/392 (1.3%)	0/97 (0.0%)	5/1464 (0.3%)
RRR (95% CI)=	77% (-14%, 96%)	79% (40%, 93%)	50% (-36%, 82%)	NE	70% (17%, 89%)
p-value*=	0.041	0.001	0.19	0.054	0.014

Figure 19. Bone Mineral Density by DXA at Lumbar Spine Percent Change From Baseline at Month 12 by Geographic RegionLeast Squares Means and 95% CIs From ANCOVA Model (Primary Analysis Set for BMD, LOCF) (20070337 M24 Adhoc Analysis)



	Western Europe and Australia/New Zealand		Central and Eastern Europe		Asia Pacific		North America		Central/Latin America	
n =	445	430	865	873	391	364	79	89	1368	1395

Conclusions on the Substantial Evidence of Effectiveness: The Applicant has provided substantial evidence to support one year of romosozumab therapy for treatment of osteoporosis in postmenopausal women. Fracture risk reduction with romosozumab 210 mg SC administered by a healthcare provider once a month, is demonstrated in trial 20070337. Demonstration of fracture risk reduction is required for a treatment of osteoporosis indication. Morphometric vertebral fracture at month 12 and month 24 are the coprimary endpoints for trial 20070337. Morphometric vertebral fracture, an asymptomatic fracture diagnosed by radiograph, is an acceptable endpoint that has been used for most approved osteoporosis therapies. At 12 months, the new morphometric vertebral fracture absolute risk reduction was 1.3% and the relative risk reduction was 73% ($p<0.001$) with romosozumab compared to placebo. Romosozumab was given for one year, for the second year of the trial all subjects received denosumab. At 24 months, the new morphometric vertebral fracture absolute risk reduction was 1.9% and the relative risk reduction was 75% ($p<0.001$) with romosozumab/denosumab compared to placebo/denosumab. A significant reduction in clinical fracture was demonstrated at month 12. The clinical fracture absolute risk reduction was 1.2% and the relative risk reduction was 36% ($p=0.008$) with romosozumab compared to placebo. However, clinical fracture is a composite of nonvertebral and symptomatic vertebral fractures. Nonvertebral fractures make up 88% of the fractures in this composite endpoint and a significant reduction in nonvertebral fracture was not demonstrated with romosozumab therapy.

Supportive evidence is provided by the bone mineral density increases from trials 20070337, 20060326 and 20120156. In the clinical fracture trial 20070337, the treatment difference in lumbar spine BMD at month 12 was 12.7% with romosozumab. This is comparable to the lumbar spine BMD treatment difference of 11.5% observed in trial 20060326. Increases in hip BMD were also consistently observed with romosozumab therapy. In trial 20070337, the 12 month BMD romosozumab treatment difference compared to placebo was 5.8% at the total hip and 5.2% at the femoral neck. In trial 20060326, the treatment difference at 12 months was 4.9% at the total hip and 4.8% at the femoral neck.

Only 2.7% (195/7180 subjects) of the enrolled population for the fracture trial 20070337 was from North America. Therefore, a question of the applicability of the predominantly non-U.S. results to the U.S. population was raised. Evaluation of by-region treatment effect demonstrated no differences in the BMD response to romosozumab. Therefore, the results from trial 20070337 can be considered applicable to the U.S. population and U.S. medical practice.

8. Safety

This integrated review of safety primarily focuses on trial 20070337, the fracture efficacy trial in which 7157 subjects were enrolled and received treatment. In addition, 12 month placebo controlled safety data is available from studies 20060326 (N=419), the phase 2 dose-finding study and 20101291 (N=252), the phase 2 dose finding study in Japanese women.

Exposure: The pooled safety population is comprised of postmenopausal women with osteoporosis or low bone mass who were enrolled in placebo-controlled trials at least 12

months in duration. This includes 7384 subjects (3689 placebo, 3695 romosozumab 210mg). Of those, 7184 subjects received at least 12 months of study drug (3305 placebo, 3879 romosozumab). This safety database exceeds the population exposure recommended in the ICH E1A guideline.

Specific Safety Assessments: Special safety studies for romosozumab include assessment of immunogenicity (discussed in the clinical pharmacology/immunogenicity section of this review) 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 set up for osteonecrosis of the jaw, atypical femoral fractures, and cardiovascular events.

Safety Results:

Pooled Safety Population at 12 Months		
	Placebo	**Romosozumab 210mg**
Treated	**3689**	**3695**
Death	24 (0.7)	29 (0.8)
Serious Adverse Event	323 (9)	352 (10)
Adverse Event leading to Study Withdrawal	50 (1)	45 (1)
Adverse Event leading to Study Drug Discontinuation	96 (3)	106 (3)
Treatment Emergent Adverse Event	2938 (80)	2896 (78)
Source: ISS, table 14-6.1.1, page 59		

Deaths: A total of 53 (24 (0.7%) placebo, 29 (0.8%) romosozumab) deaths occurred in the pooled safety population. As outlined in table 28, page 110 of the primary clinical review, the most common reason stated is death not otherwise specified occurring in 5 subjects in each group. An imbalance was noted in death due to malignant lung neoplasm, which occurred in 4 subjects in the romosozumab group and no subjects in the placebo group. Dr. Chang conducted a thorough review. 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 lung neoplasm was balanced between treatment groups. I agree with Dr. Chang that the findings should be outlined in the product label.

Serious Adverse Events: In the pooled safety population, 323 (9%) subjects in the placebo group and 352 (10%) subjects in the romosozumab group experienced a serious adverse event. The most common occurrences in the romosozumab treatment group were pneumonia (10 (0.3%) placebo, 19 (0.5%) romosozumab); hypertension (5 (0.1%) placebo, 8 (0.2%) romosozumab); unstable angina (3 (<0.1%) placebo, 7 (0.2%) romosozumab); cardiac failure congestive (4 (0.1%) placebo, 7 (0.2%) romosozumab); and chronic obstructive pulmonary disease (15 (0.4%) placebo, 7 (0.2%) romosozumab).

Adverse Events leading to Study Withdrawal: In the pooled safety population, 50 (1%) subjects in the placebo group and 45 (1%) subjects in the romosozumab group discontinued from the study due to an adverse event. The most common adverse events leading to study withdrawal were arthralgia (1 placebo, 3 romosozumab); musculoskeletal pain (2 placebo, 3 romosozumab); pain in extremity (0 placebo, 3 romosozumab); abdominal pain (0 placebo, 2

romosozumab); back pain (2 placebo, 2 romosozumab); and nausea (0 placebo, 2 romosozumab).

Adverse Events leading to Study Drug Discontinuation: In the pooled safety population, 96 (3%) subjects in the placebo group and 106 (3%) subjects in the romosozumab group discontinued study drug due to an adverse event. 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).

Common Adverse Events: This discussion of common adverse events focuses on the 12 month romosozumab vs. placebo treatment period in trial 20070337, which will appear in product labeling. During trial 20070337, 2850 (80%) placebo subjects and 2806 (78%) romosozumab treated subjects experienced an adverse event/reaction. As outlined in the table below, the most common adverse events were arthralgia, nasopharyngitis, and back pain.

Trial 20070337 Common Treatment Emergent Adverse Events by PT (≥ 5% subject incidence in any treatment group)		
	Placebo	**Romosozumab**
Treated	**3576**	**3581**
At least 1 TEAE	2850 (80)	2806 (78)
Arthralgia	429 (12)	459 (13)
Nasopharyngitis	438 (12)	459 (13)
Back pain	378 (11)	375 (11)
Pain in Extremity	302 (8)	279 (8)
Fall	318 (9)	254 (7)
Headache	205 (6)	233 (7)
Hypertension	259 (7)	225 (6)
Upper respiratory tract infection, viral	227 (6)	206 (6)
Osteoarthritis	220 (6)	186 (5)
Influenza	182 (5)	169 (5)
Source: CSR20070337, table 14-6.4.1		

Adverse Events of Interest:

Hypocalcemia: Hypocalcemia has been reported with osteoporosis therapies that inhibit bone resorption. This discussion will focus on the first year of trial 20070337 when romosozumab or placebo was given. As discussed under laboratories below, 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 (corrected calcium 7.0 to 8.0 mg/dL, 1.75 to 2.0 mmol/L) was reported in a romosozumab treated subject.

Patients with renal failure have altered mineral metabolism because of the underlying renal disease and the role the kidney plays for maintaining calcium and phosphorus levels. Study

20110227 evaluated the effect of romosozumab therapy on patients with Stage 4 (eGFR 15 – 29) renal insufficiency (N=8) and subjects with end stage renal disease on hemodialysis (N=8) compared to healthy subjects (N=8). All subjects received an oral loading dose of 50,000IU vitamin D and were required to take supplemental calcium and vitamin D (amount based on the subject's baseline laboratories). No healthy subjects developed hypocalcemia. One subject in the stage 4 renal insufficiency groups developed Grade 1 hypocalcemia (corrected calcium 8.0mg/dL to LLN, or 2.0 mmol/L to LLN). Four subjects in the end stage renal disease group developed hypocalcemia, 1 subject with Grade 1 hypocalcemia, 2 subjects with Grade 2 hypocalcemia and 1 subject with Grade 3 hypocalcemia (corrected calcium 6 – 7 mg/dL; 1.5 – 1.75 mmol/L).

Reviewer Comment: I agree with Dr. Chang that the issues of hypocalcemia and the need to monitor calcium levels in renal failure patients should be described in product labeling.

Hypersensitivity: The Applicant used a narrow standardized MedDRA query (SMQ) for hypersensitivity reactions. In the pooled safety population, potential hypersensitivity reactions occurred in 253 (7%) subjects in the placebo group and 249 (7%) subjects in the romosozumab group. 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 32 (1%) placebo subjects and 48 (1%) romosozumab subjects. 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 think this event was related 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 1 (<0.1%) subjects in the placebo group and 7 (0.2) subjects in the romosozumab group. Discontinuation from the trial due to hypersensitivity reactions occurred in 2 subjects in each treatment group. Discontinuation of study drug due to potential hypersensitivity reactions occurred in 6 (0.2%) subjects in the placebo group and 11 (0.3%) in the romosozumab group.

In the pooled safety population, hypersensitivity reactions were evaluated based on antidrug antibody status. Potential hypersensitivity reactions occurred in 7% of placebo treated subjects, 7% of binding antibody negative romosozumab treated subjects and 7% binding antibody positive romosozumab treated subjects. When evaluated in term os neutralizing antibody status, potential hypersensitivity reactions occurred in 7% of placebo treated subjects, 7% of neutralizing antibody negative romosozumab treated subjects and 4% neutralizing antibody positive romosozumab treated subjects.

The potential hypersensitivity reactions reported in the pooled safety population occurred using a drug product concentration of 70 mg/mL where patients required 3 injections of 1mL each to reach the 210 mg dose. The to-be- marketed formulation of romosozumab will be the 90 mg/mL concentration, where patients will need two injections of 1.17mL each. Trial 20120156 was a 6-month trial that compared bone density changes of the romosozumab 70 mg/mL formulation and the romosozumab 90 mg/mL formulation. Potential hypersensitivity reactions occurred in 3 (6%) subjects in the placebo group, 3 (3%) subjects in the 70 mg/mL romosozumab group and 14 (11%) subjects in the 90 mg/mL romosozumab group.

Reviewer Comment: The potential for hypersensitivity reactions may be more pronounced with the higher concentration of romosozumab.

Injection Site Reactions: In the pooled safety population, injection site reactions occurred in 107 (3%) subjects in the placebo group and 192 (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%) in the romosozumab group.

In the pooled safety population, injection site reactions were evaluated based on antidrug antibody status. Injection site reactions occurred in 3% of placebo treated subjects, 5% of binding antibody negative romosozumab treated subjects and 7% binding antibody positive romosozumab treated subjects. When evaluated in terms of neutralizing antibody status, injection site reactions occurred in 3% of placebo treated subjects, 7% of neutralizing antibody negative romosozumab treated subjects and 7% neutralizing antibody positive romosozumab treated subjects.

The injection site reactions reported in the pooled safety population occurred using a drug product concentration of 70 mg/mL where patients required 3 injections of 1mL each to reach the 210 mg dose. In trial 20120156 comparing the 70 mg/mL and the 90 mg/mL formulations, injection site reactions occurred in no subjects in the placebo group, 11 (9%) subjects in the 70 mg/mL romosozumab group and 13 (11%) subjects in the 90 mg/mL romosozumab group.

Reviewer Comment: The potential for injection site reactions may be more pronounced with the higher concentration of romosozumab or in patients who develop binding antibodies to romosozumab.

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 the sclerostin inhibitor romosozumab's potential for malignant tumors. In the pooled safety population, adverse events of malignant or unspecified tumors were reported in 71 (2%) subjects in the placebo group and 61 (2%) subjects in the romosozumab group. Serious adverse events of malignant or unspecified tumors were reported in 44 (1%) subjects in the placebo group and 39 (1%) subjects in the romosozumab group.

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. In the pooled safety population, in subjects with a prior history of TNF mediated inflammatory disease, TNF mediated inflammatory adverse events occurred in 8 (13%) subjects in the placebo group and 5 (8%) subjects in the romosozumab group. In subjects without a prior history, TNF mediated inflammatory adverse events occurred in 6 (0.2%) subjects in the placebo group and 2 (<0.1%) subjects in the romosozumab group.

Osteoarthritis: Sclerostin is expressed in articular cartilage, raising concerns that sclerostin inhibition may negatively affect articular cartilage. In the pooled safety population, adverse events of osteoarthritis were reported in 320 (9%) subjects in the placebo group and 291 (8%) subjects in the romosozumab group. Serious adverse events of osteoarthritis were reported in 17 (1%) subjects in the placebo group and 7 (0.2%) 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 study, 38 subjects (25 (14%) placebo, 13 (8%) romosozumab) discontinued the study. The endpoint was change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score with ANCOVA using treatment, baseline WOMAC score, baseline BMI, and baseline age as independent variables. The baseline WOMAC total score was 36.68 in the placebo group and 39.38 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.

Hyperostosis: Hyperostosis with adverse neurologic consequences is a feature of diseases of sclerostin overexpression (sclerosteosis and van Buchem disease). The Applicant constructed a MedDRA search strategy to identify events related to hyperostosis. In the pooled safety database, adverse events of hyperostosis were reported in 29 (1%) subjects in the placebo group and 19 (1%) subjects in the romosozumab group. Most preferred terms were related to spinal stenosis. Serious adverse events of hyperostosis were reported in 5 (1%) subjects in the placebo group and 1 (<0.1%) subject 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 study, 34 subjects (18 (7%) placebo, 16 (6%) romosozumab) discontinued the study. The protocol defined hearing changes using American Speech-Language-Hearing Association (ASHA) criteria. Hearing loss is defined as increase 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 is defined as 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 is 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 anti-resorptive 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 the pooled safety population, no placebo subjects and one romosozumab subject had a positively adjudicated case of ONJ. In Trial 20070337, one additional subject who had received romosozumab had a positively adjudicated ONJ while undergoing denosumab therapy.

Additional adjudicated cases of ONJ were reported from ongoing trials, specifically Trial 20110142, a 24-month, randomized, active controlled fracture study evaluating treatment with romosozumab compared to alendronate. In the first 12 months of the study, subjects are randomized to romosozumab or alendronate. In the second year of the trial, all subjects receive alendronate. Both cases of ONJ occurred during the second year alendronate treatment period. One subject was on romosozumab then alendronate, the other subject was on alendronate then continued on alendronate.

Reviewer Comment: I agree with Dr. Chang that the product labeling should contain information about ONJ.

Atypical femoral fractures: Atypical femoral fracture is a rare adverse reaction associated with potent anti-resorptive 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 the pooled safety population, no placebo subjects and one romosozumab subject had a positively adjudicated case of atypical femoral fracture.

Additional adjudicated cases of atypical femoral fracture were reported from ongoing trials, specifically Trial 20110142. In trial 20110142, there were 5 femoral fractures sent for adjudication, four of which were positively adjudicated as atypical femoral fractures. All cases occurred in the second year alendronate treatment period. One subject was on romosozumab then alendronate; the other three subjects were on alendronate then continued on alendronate.

Reviewer Comment: I agree with Dr. Chang that the product labeling should contain information about atypical femoral fractures.

Cardiovascular Safety: 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 has identified cardiovascular adverse events as an event of interest and all deaths and potential cardiovascular-related serious adverse events from Trial 20070337 were submitted for adjudication to an external independent committee comprised of physicians with expertise in cardiology, osteoporosis, internal medicine, or neurology. Adjudicated cardiovascular events of death (including those classified as cardiovascular and those deemed of indeterminate cause and thus included among cardiovascular deaths), cardiac ischemic event, cerebrovascular event, noncoronary revascularization, heart failure, and peripheral vascular events not requiring revascularization are summarized.

As outlined in the table below, the incidence of positively adjudicated cardiovascular serious adverse events was similar between treatment groups during the first year of the trial.

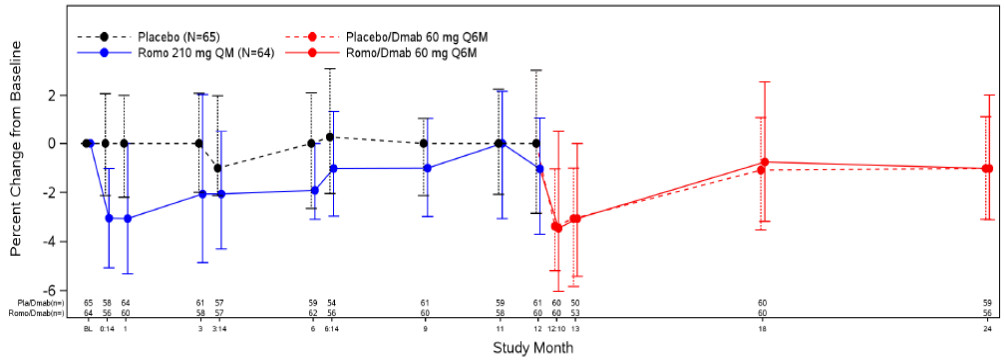
Trial 20070337 Adjudicated Positive Cardiovascular Serious Adverse Events		
	Placebo	**Romosozumab**
Treated	**3576**	**3581**
Any cardiovascular SAE, n (%)	41 (1.1)	44 (1.2)
Odds Ratio (95% CI)	1.07 (0.70 , 1.65)	
Death, n (%)	15 (0.4)	17 (0.5)
Odds Ratio (95% CI)	1.13 (0.56 , 2.27)	
Cardiac ischemic event, n (%)	14 (0.4)	15 (0.4)
Odds Ratio (95% CI)	1.07 (0.52 , 2.22)	
Heart failure, n (%)	4 (0.1)	7 (0.2)
Odds Ratio (95% CI)	1.75 (0.51 , 5.98)	
Cerebrovascular event, n (%)	11 (0.3)	10 (0.3)
Odds Ratio (95% CI)	0.91 (0.38 , 2.14)	
Peripheral vascular event not requiring revascularization, n (%)	1 (<0.1)	3 (<0.1)
Odds Ratio (95% CI)	3.00 (0.31 , 28.82)	
Source: CSR20070337, table 12-10, page 221		

Laboratories:

Calcium: Calcium levels were evaluated in the main 20070337 study as well as several substudies. The calcium substudy enrolled 1687 (854 placebo, 833 romosozumab) subjects. Approximately 9% of subjects discontinued the study. The demographic make-up of the substudy population was similar to the main study. Hypocalcemia was defined as a calcium<7.5 mg/dL. At study day 14, no subjects had a calcium less than 7.5 mg/dL.

Calcium corrected by albumin was also collected in the bone turnover marker substudy. As outlined in the figure below, the nadir in serum calcium seems to occur at day 14 through month 1. Calcium then returns toward baseline. The calcium decreases with denosumab in the second year of the trial are expected given the antiresorptive action of denosumab.

Figure 14b-7.2. Calcium Corrected by Albumin Percent Change From Baseline in Standard Unit by Visit Median and Inter-quartile Ranges (Bone Turnover Marker and Biomarker Substudy Safety Analysis Set) (20070337 M24 Analysis)



Source: CSR 20070337, page 5658

In trial 20070337, serum calcium was evaluated at baseline and months 1 , 3, 6, 9, 11, and 12 in the first year of the study. The baseline mean calcium level in both groups was 9.7 mg/dL. At month 1, the percent change was 0% in the placebo group and -2.2% in the romosozumab group.

Phosphorus: In trial 20070337, the baseline mean serum phosphorus level was 3.8 mg/dL in both treatment groups. At month 1, the percent change was 0% in the placebo group and -5.1% in the romosozumab group. Phosphorus levels remained below baseline for the remainder of romosozumab treatment, although the absolute values were in the normal range.

Parathyroid hormone: The serum iPTH and urinary calcium substudy enrolled 656 (346 placebo, 310 romosozumab) subjects. Approximately 3% of subjects discontinued the study. The demographic make-up of the substudy population was similar to the main study. The baseline median iPTH was 4.2 pmol/L in the placebo group and 4.4 pmol/L in the romosozumab group. At month 6, the median percent change in iPTH was 4% in the placebo group and 29% in the romosozumab group (nominal p-value <0.001 from Wilcoxon rank-sum test without multiplicity adjustment). This increase in iPTH was maintained with the month 12 median percent change of 8% in the placebo group and 27% in the romosozumab group (nominal p-value <0.001).

Liver Transaminases: The Applicant evaluated the pooled safety database for potential Hy's law cases, defined as ALT or AST >3x ULN, total bilirubin >2x ULN, and no other explanation for the increases. Subjects were not excluded from the studies with elevated transaminase levels. At baseline, in the pooled safety database, 6/3689 placebo subjects and 3/3695 romosozumab treated subjects had AST levels >3x ULN and 10/3689 placebo subjects and 2/3694 romosozumab treated subjects had ALT levels >3x ULN. On study, 29 /3612 placebo subjects and 9/3608 romosozumab subjects developed AST >3x ULN and 31/3613 placebo subjects and 16/3608 romosozumab treated subjects had ALT levels >3x ULN. As outlined in the clinical review pages 135 – 138, Dr. Chang has carefully reviewed the data from the most concerning potential Hy's law cases and none of the cases support a liver signal with romosozumab therapy.

Special Studies:

Bone Histomorphometry: Bone biopsies using fluorochrome labeling were obtained from 139 subjects (68 placebo/denosumab, 71 romosozumab/denosumab). A total of 154 biopsies were obtained at different timepoints during the trial. Month 2 biopsies were obtained in 34 subjects (18 placebo, 16 romosozumab); month 12 biopsies were obtained from 73 subjects (33 placebo, 40 romosozumab); and month 24 biopsies were obtained from 47 subjects (23 placebo/ denosumab, 24 romosozumab/denosumab). Some subjects had sequential biopsies – 15 subjects had biopsies at month 12 and 24 (6 placebo/denosumab, 9 romosozumab/denosumab). Qualitatively, there was no evidence or marrow fibrosis or osteomalacia. One subject who received romosozumab then denosumab had woven bone at the iliac crest. The Applicant believes this is evidence of a microcallus and a nonpathologic process.

Reference ID: 4123729

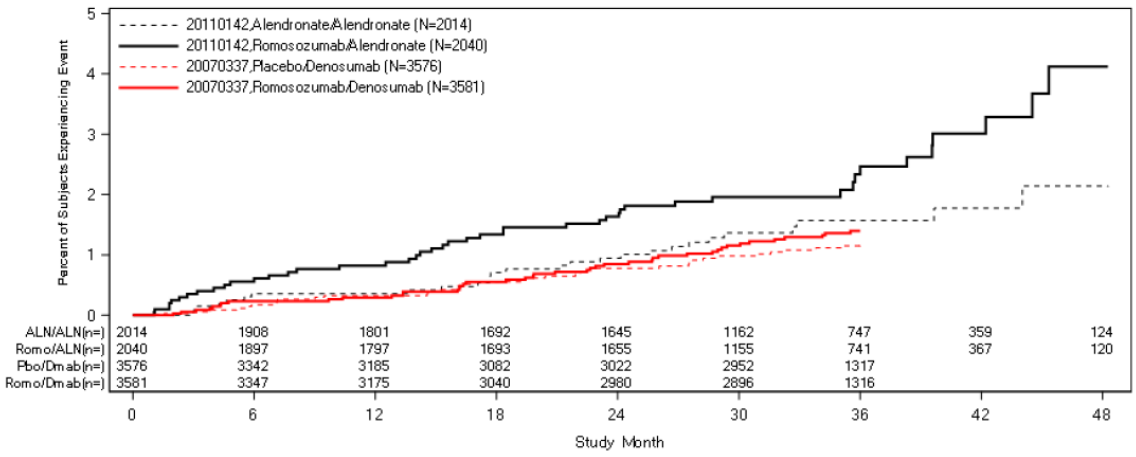
Histomorphometry: The month 2 cohort received quadruple fluorochrome labeling which is a fairly new technique. Subjects received double label at baseline, and then again at month 2. This technique is supposed to allow evaluation of baseline dynamic parameters (the first set of label) and then evaluation after 2 months of therapy (the second set of labels). Within-subject comparisons between baseline and month 2 showed evidence of osteoblast stimulation and osteoclast inhibition with increased bone formation rate and decreased eroded surface. The mineralizing capability of the bone did not appear compromised. The month 12 cohort received the standard double tetracycline labeling. Increased bone volume was observed in the romosozumab group compared to placebo but the dynamic bone formation parameters seen at month 2 had markedly decreased.

Cardiovascular safety, revisited: 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 is adjudicating all deaths and cardiovascular serious adverse events in their trials. The large phase 3 fracture trial did not show a cardiovascular safety signal. However, another large trial (20110142) that was not part of the initial marketing application was recently completed and did suggest a cardiovascular safety signal.

The Division met with the Applicant on May 19, 2017 to discuss the new safety data. Trial 20110142 is a 24 month, randomized, active control fracture study evaluating treatment with romosozumab versus alendronate. The trial enrolled 4054 postmenopausal women with osteoporosis. Preliminary analysis of safety findings revealed a clear imbalance in positively adjudicated serious cardiovascular adverse events, as displayed in the figure below (source: company presentation from May 19th).

(b) (4)

K-M Plot for Time to First Positively Adjudicated Serious Cerebrovascular Event: ARCH and FRAME (Preliminary Data)



N = Number of subjects in the safety analysis set
n = Number of subjects at risk for event at time point of interest

Reviewer Comment: The preliminary data presented at the May 19th meeting call into question the cardiovascular safety of romosozumab in the intended population. The Applicant will need to complete their review of the available data from the completed trials not submitted with this marketing application. Therefore, a Complete Response action is the only course available. After the Applicant has completed their review, the data should be submitted for review.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for romosozumab.

10. Pediatrics

The Applicant submitted an agreed initial Pediatric Study Plan iPSP on 1/12/2016 requesting a full waiver of the requirement to conduct pediatric studies, given that postmenopausal osteoporosis does not exist in the pediatric population. The iPSP was reviewed by the Pediatric Review Committee (PeRC) and PeRC concurred with the Applicant's plan for a full waiver.

In this application, the Applicant requested a full waiver from pediatric studies because the studies would be impossible given the lack of postmenopausal osteoporosis in the pediatric population. The request was reviewed by PeRC March 1, 2017 and PeRC agreed the request was appropriate and acceptable.

11. Other Relevant Regulatory Issues

Financial disclosures: The Applicant has provided financial disclosure information for studies 20060326, 20070337, 20080289, 20101291, and 20120156. Dr. Chang has reviewed the provided financial disclosure information and found that there were three sites in Columbia where four co-investigators did not submit financial disclosure information. These sites accounted for 13% of the primary analysis population for vertebral fractures. A sensitivity analysis removing these three sites was performed. As outlined in table 13, page 54 of the primary clinical review, there was no change in the new vertebral fracture coprimary endpoints.

Office of Scientific Investigations (OSI) audits: Four clinical sites participating in study 20070337 were inspected by the Office of Scientific Investigations.

Site 1-678YLY, Jose Fernando Molina Restrepo, M.D., Medellin, Columbia . This site was selected because two investigators with the same last name, in the same geographic location, and with high subject enrollment numbers (752 total between the two sites) were outliers and these clinical investigators had not been inspected previously. There were no discrepancies between source documents and FDA data listing regarding the reasons for study discontinuation for the 25 subject records inspected. A FDA Form 483, Inspectional Observations, was issued at the conclusion of the inspection for failure to conduct an

investigation in accordance with the signed statement of investigator and the investigational plan. This site was classified as VAI.

Site 1-64PLTY, Jaime Restrepo, M.D., Medellin, Columbia. This site was selected because two investigators with the same last name, in the same geographic location, and with high subject enrollment numbers (752 total between the two sites) were outliers and these clinical investigators had not been inspected previously. A total of 23 subject records were selected and reviewed for initial informed consent and data verification. Records review of the 23 subjects did not identify any subjects who did not meet the protocol inclusion/exclusion criteria. The site obtained the x-rays and DXA scans in a timely fashion. All informed consent documents reviewed were signed appropriately. No unreported adverse events were found. This site was classified as NAI.

Site 1-52SFOU, Magda Dabrowska, M.D., Poland: This site had high enrollment (264), high site efficacy effect size and no prior inspection in the past 3 years. Records of 40 out of 62 subjects who discontinued the study were reviewed, and there were no discrepancies between source documents and FDA data listings regarding the reasons for study discontinuation. This site was classified as NAI.

Site 1-3RA0SB, Chris Recknor, M.D., US: This site in the US was selected for comparison. A comprehensive case review was conducted for 19 randomized subjects. Records review included, but was not limited to, financial disclosure, training, informed consent documents, monitoring, and IRB communications, adverse events, primary efficacy, lab results, and test article control. This site was classified as NAI.

Human Factors: Romosozumab is intended to be a healthcare provider administered medication. The total dose requires two prefilled syringes, each containing 105mg romosozumab. The two PFS will be supplied in a single carton. The Applicant did not conduct a label comprehension study and instead is relying upon the human factors validation study from another product, brodalumab. The Division of Medication Error, Prevention and Analysis reviewed the materials provided (brodalumab labeling, brodalumab HF validation results) and did not identify any critical differences in the use of Evenity (romosozumab) PFS and brodalumab PFS. The human factors validation study results for brodalumab do not show label comprehension difficulties, use task deviations, or dosing errors concerning the need to use two prefilled syringes to administer a complete dose. Thus, the brodalumab PFS study results support the labeling comprehension of Evenity (romosozumab) PFS.

12. Labeling

Prescribing Information: The review team has made significant edits to the prescribing information. At this time, further work on the prescribing information has been deferred to the next review cycle.

Significant issues under discussion include whether clinical fracture data are appropriate for the clinical studies section of the product label and whether clinical fractures should be mentioned in the fracture efficacy sentence that is part of the indication.

Other Labeling: Other labeling has been deferred to the next review cycle.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS): In this review cycle, the Applicant has not proposed a REMS and the review team did not believe that one was necessary for the safe use of romosozumab. However, the new cardiovascular safety concerns will necessitate that the review team revisit the need for a REMS during the review of the new safety data if appropriate.

Postmarketing Requirements (PMRs) and Commitments (PMCs): In this review cycle, the Applicant did not propose clinical postmarketing studies and the review team did not find that a study was needed to further define the safety risks of romosozumab. However, the new cardiovascular safety concerns will necessitate that the review team revisit the need for a postmarketing safety study during the review of the new safety data if appropriate.

The OBP team is proposing a postmarketing commitment (b) (4)

(b) (4)

14. Recommended Comments to the Applicant

Deficiency:

The new safety findings from Studies 20110142 and 20110174 which identify an imbalance of incidences of cardiovascular serious adverse events with higher incidences in the romosozumab group when compared to active control alendronate or placebo raise concern regarding the cardiovascular safety of romosozumab. Although, Study 20070337 did not demonstrate a cardiovascular safety signal, these different and disparate findings between studies require detailed review once the completed final analyses of these additional studies have been submitted.

To address this deficiency:

We advise you to complete analysis of both Studies 20110142 and 20110174 and to submit these additional studies along with narratives and datasets to the Division for review.

Other Comments to the Applicant:

On January 13, 2017, FDA issued a final guidance entitled Nonproprietary Naming of Biological Products, which states that FDA intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning for certain biological products. Your 351(a) BLA is within the scope of this guidance. FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

Please note this guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA) of 1995. These provisions of the guidance describe the submission of proposed suffixes to FDA and a sponsor's related analysis of proposed suffixes, which are considered, under the PRA, as information collection. FDA is not currently implementing information collection provisions of the guidance.

However, provisions of the final guidance that do not describe the information collection provisions should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

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/s/

THERESA E KEHOE
07/12/2017

HYLTON V JOFFE
07/12/2017
I concur with Dr. Kehoe's recommendation that this application receive a Complete Response letter. See the Division Director memorandum.

BLA Clinical Review Update and Addendum

Application Type	BLA
Application Number(s)	762061
Priority or Standard	Standard
Submit Date(s)	July 19, 2016
Received Date(s)	July 19, 2016
PDUFA Goal Date	July 19, 2017
Division/Office	Division of Bone, Reproductive, and Urologic Products Office of Drug Evaluation III Center for Drug Evaluation and Research
Reviewer Name(s)	Debuene Chang MD
Review Addendum Date	June 13, 2017
Established Name	romosozumab
(Proposed) Trade Name	(Proposed) Evenity™
Applicant	Amgen
Formulation(s)	90 mg/mL solution (1.17mL) in each single-use plastic (b) (4) (b) (4) prefilled syringe (PFS); 2 injections per dose (210 mg)
Dosing Regimen	210 mg subcutaneously once a month
Applicant Proposed Indication(s)/Population(s)	Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Recommendation on Regulatory Action	Updated Recommendation: Complete Response (CR)
Recommended Indication(s)/Population	Treatment of osteoporosis in postmenopausal women.

I. Background/ Summary:

Amgen notified the Division on May 15, 2017 that it had found unanticipated results after completing preliminary high-level analysis of Study 20110142, the phase 3 randomized, double-blind, active-comparator study of romosozumab followed by alendronate compared to alendronate alone. As this phase of Study 20110142 only ended in April 2017, it had not been submitted as part of this BLA 761062 submission (b) (4). However, the study is part of IND 100391 for romosozumab for the treatment of osteoporosis.

Amgen met with the FDA on May 19, 2017 to share and discuss the unexpected results of higher incidences of cardiovascular (CV) SAEs in Study 20110142 in the romosozumab-exposed group (2.5% romosozumab versus 1.8% alendronate alone) and in a recently completed small men's study, Study 20110174 (4.9% romosozumab versus 2.5% placebo), both of which potentially impact the ongoing BLA 761062 review. The meeting minutes are available under IND 100391 Memorandum to File (FRM-ADMIN-01) from June 8, 2017.

Reference ID: 4110866

Summary/ Conclusion:

These new unexpected safety findings from Study 20110142 and Study 20110174 identify an imbalance of incidences of CV SAEs with higher incidences in the romosozumab group when compared to placebo. In contrast, the BLA Study 20070337 demonstrated balanced incidence rates of CV SAEs between study groups (1.3% romosozumab versus 1.3% placebo). Preliminary efficacy analysis of Study 20110142 continue to support efficacy for romosozumab but these different and disparate safety findings between studies will have to be reviewed in detail once the Sponsor has completed final analyses of these additional studies.

The Division advised the Sponsor at the May 19, 2017 meeting to complete analysis of both Studies 20110142 and 20110174 and to submit these additional studies along with narratives and datasets to the Division for review. The Sponsor was further advised that an Advisory Committee may be needed to review the different results of the three studies. Specifically, the Division stated the following in the meeting minutes from May 19, 2017, filed with IND 100391:

> *"With regards to the ongoing review of BLA 761062, given these findings, the FDA explained we would not be able to take a favorable action on this review cycle. Before we can consider whether the benefits of romosozumab outweigh its risks, we will need to conduct a thorough review of the cardiovascular issue, and this would not be possible in the remaining two months of the review clock… Amgen still needs to complete its analyses of the data and put together a detailed submission of the findings. The FDA also mentioned that an advisory committee meeting would likely now be needed."*

In light of this new information from Study 20110142 and 20110174 which impacts this BLA and the additional information from these studies needed to complete review of this product, I recommend that a complete response (CR) be sent to the Sponsor for this review cycle.

Reviewer Updated Recommendation: CR-Not Approvable

II. Cardiovascular (CV) SAE Findings:

A. Unexpected Results from Study 20110142:

Amgen presented the key preliminary results of Study 20110142. During the 12-month period of romosozumab vs. alendronate, adjudicated serious adverse cardiovascular events were reported in 2.5% of romosozumab-treated patients vs. 1.9% of alendronate-treated patients. This imbalance was driven by cardiac ischemic events (myocardial infarction 0.8% vs. 0.2%) and stroke (0.6% vs. 0.3%). The key cardiovascular (CV) findings for Study 20110142 are in the table below:

Reference ID: 4110866

Table 1: Positively Adjudicated CV Events in Study 20110142:

Category	12-Month Double-blind Period		Primary Analysis Period	
	Aln (N = 2014) n (%)	**Romo (N = 2040)** n (%)	**Aln/Aln (N = 2014)** n (%)	**Romo/ Aln (N = 2040)** n (%)
Number of subjects reporting treatment-emergent adjudicated positive cardiovascular serious adverse event	**38 (1.9)**	**50 (2.5)**	**122 (6.1)**	**133 (6.5)**
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular Event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart Failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death (CV related and unclassified)	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Non-coronary Revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral Vascular Ischemic Event not Requiring Revascularization	2 (<0.1)	0 (0.0)	5 (0.2)	2 (<0.1)

Aln= alendronate; Romo= romosozumab
*Death events include fatal adverse events adjudicated as cardiovascular-related or undetermined to be cardiovascular
Source: Amgen presentation May 19, 2017 meeting(slide 16)

B. CV Results in Small Men Only Study 20110174:

Amgen recently completed Study 20110174, a smaller study (N = 244 subjects) in men with osteoporosis, which was also not completed in time for submission to the BLA. In light of the recent findings for Study 20110142, Amgen analyzed Study 20110174 for CV events and found similar results with an imbalance of subjects reporting CV SAEs in the romosozumab group versus placebo (4.9% versus 2.5%).

C. CV Results in Study 20070337 (Current Submission):

There were balanced rates of CV SAEs in Study 20070337 between romosozumab and placebo patients (1.3% versus 1.3%).

III. Comparison Studies 20110142, 20070337, and 20110197:

A. Subject Incidences of Adjudicated Positive CV SAEs Between Studies:

Study 20070337, the phase 3 study for the BLA with > 7000 subjects, showed balance between the study groups for CV SAEs whereas Study 20110142, alendronate-controlled study with > 4000 subjects, showed imbalance between the two groups with higher incidences in the romosozumab group (2.5% versus 1.8%). The small men's study (N=244 subjects) Study 20110174 also showed imbalance of CV incidences with higher rates in the romosozumab group (4.9% romo versus 2.5% for placebo).
The following table 2 compares the three studies (20110174 men only study, 20070337 BLA phase 3 study, 20110142 alendronate-controlled study):

Table 2: Subject Incidence of Adjudicated Positive CV SAEs 12 Month Double-blind Period:

Category Subcategory	20110174 Placebo (N = 81) n (%)	20110174 Romosozumab 210 mg SC QM (N = 163) n (%)	20070337 Placebo (N = 3576) n (%)	20070337 Romosozumab 210 mg SC QM (N = 3581) n (%)	20110142 Alendronate 70 mg QW (N = 2014) n (%)	20110142 Romosozumab 210 mg SC QM (N = 2040) n (%)
Number of subjects reporting treatment-emergent adjudicated positive cardiovascular SAE	2 (2.5)	8 (4.9)	46 (1.3)	46 (1.3)	38 (1.9)	50 (2.5)
Cardiac ischemic event	0 (0.0)	3 (1.8)	16 (0.4)	16 (0.4)	6 (0.3)	16 (0.8)
Angina	0 (0.0)	2 (1.2)	7 (0.2)	7 (0.2)	1 (<0.1)	0 (0.0)
MI	0 (0.0)	1 (0.6)	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
No MI or angina	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular event	1 (1.2)	3 (1.8)	11 (0.3)	10 (0.3)	7 (0.3)	16 (0.8)
Stroke	1 (1.2)	3 (1.8)	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)
TIA	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)	0 (0.0)	3 (0.1)
Congestive heart failure	0 (0.0)	1 (0.6)	5 (0.1)	7 (0.2)	8 (0.4)	4 (0.2)
Death	1 (1.2)	2 (1.2)	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.8)
Cardiovascular	0 (0.0)	1 (0.6)	9 (0.3)	6 (0.2)	5 (0.2)	10 (0.5)
Undetermined	1 (1.2)	1 (0.6)	6 (0.2)	11 (0.3)	7 (0.3)	7 (0.3)
Non-coronary revascularization	0 (0.0)	0 (0.0)	2 (<0.1)	1 (<0.1)	5 (0.2)	3 (0.1)
Angioplasty	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)
Endarterectomy	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)
Stent placement	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	3 (0.1)	2 (<0.1)
Peripheral vascular event	0 (0.0)	0 (0.0)	1 (<0.1)	4 (0.1)	2 (<0.1)	0 (0.0)

Source: Amgen presentation May 19, 2017 meeting (slide17).

B. Differences Between Two Studies, 20110142 and 20070337:

1) Inclusion and Exclusion Criteria Differences:

There were differences in the criteria for inclusion/exclusion between the two patient populations which resulted in different patient populations. The following table 3 compares the differences:

Table 3: Inclusion and Exclusion Criteria for Study 20110142 (Alendronate-controlled Study-ARCH) and Study 20070337 (BLA Study-FRAME):

	Study 20110142 Alendronate-Controlled Study (ARCH)	Study 20070337 BLA Study (FRAME)
Inclusion Criteria	• Postmenopausal women age 55 to 90 years • BMD T-score ≤ -2.5 at the total hip or femoral neck **and** at least one moderate or severe vertebral fracture **or** at least 2 mild vertebral fractures or • BMD T-score ≤ -2.00 at the total hip or femoral neck **and** at least 2 moderate (SQ2) or severe (SQ3) vertebral fractures **or** a recent hip fracture (within 3 to 24 months)	• Postmenopausal women age 55 to 90 years • BMD T-score ≤ -2.5 at the total hip or femoral neck
Exclusion Criteria	• Recent osteoporosis therapy	• BMD T-score ≤ -3.5 at the total hip or femoral neck • History of hip fracture • History of any severe or more than 2 moderate vertebral fractures

Source: Amgen presentation May 19, 2017 (slide 7) with reviewer edits.

2) Baseline CV Risk Factors:

Preliminary comparisons of the three studies for baseline CV risk factors found that age was a difference between the patients in Study 20070337 and 20110142 with the subjects in 20110142 averaging 4 years older than in Study 20070337.

IV. Primary Efficacy Results from 20110142:

Primary Endpoints were consistent with 20070337 results of fracture reduction. Specifically, the preliminary results found 50% reduction in the incidence of new vertebral fracture through month 24 with romosozumab for 12 months followed by alendronate for 12 months compared to alendronate alone (relative risk = 0.50; odds ratio = 0.48; adjusted $p < 0.001$). In addition, there was a 27% reduction in the incidence of clinical fracture (clinical vertebral and nonvertebral) was demonstrated through the primary analysis with romosozumab for 12 months followed by alendronate compared to alendronate alone (adjusted $p < 0.001$, based on 464 subjects with clinical fractures.

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/s/

T D CHANG
06/13/2017

THERESA E KEHOE
06/13/2017

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	762061
Priority or Standard	Standard
Submit Date(s)	July 19, 2016
Received Date(s)	July 19, 2016
PDUFA Goal Date	July 19, 2017
Division/Office	Division of Bone, Reproductive, and Urologic Products Office of Drug Evaluation III Center for Drug Evaluation and Research
Reviewer Name(s)	Debuene Chang MD
Review Completion Date	May 3,, 2017
Established Name	romosozumab
(Proposed) Trade Name	(Proposed) Evenity™
Applicant	Amgen
Formulation(s)	90 mg/mL solution (1.17mL) in each single-use (b) (4) (b) (4) prefilled syringe (PFS); 2 injections per dose (210 mg)
Dosing Regimen	210 mg subcutaneously once a month
Applicant Proposed Indication(s)/Population(s)	Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Recommendation on Regulatory Action	Recommendation: Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of osteoporosis in postmenopausal women.

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Glossary

AC	advisory committee
ADA(s)	antidrug antibody (ies)
AE	adverse event
AFF	Atypical Femur Fracture
ALT	serum alanine aminotransferase
AMG 785	romosozumab
ANCOVA	analysis of covariance
ARI	Amgen Rhode Island
ARR	absolute risk reduction
AST	serum aspartate aminotransferase
ATO	Amgen Thousand Oaks
AUC	area under curve
BLA	biologics license application
BMD	bone mineral density
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSAP	bone-specific alkaline phosphatase
BSAP	bone specific alkaline phosphatase
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	National Cancer Institute common term criteria for AEs

Reference ID: 4093382

CYP	cytochrome P450
	(b) (4)
DBRUP	Division of Bone, Reproductive, and Urology Products
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DXA	dual-energy X-ray absorptiometry to define osteoporosis by
ECG	electrocardiogram
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EQ-5D-5L VAS	Euro QoL-5Dimensions-5levels health survey
ESRD	end stage renal disease
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FN	femoral neck
FRAX	World Health Organization Fracture Risk Assessment tool
GCP	good clinical practice
GRMP	good review management practice
HR-pQCT	high resolution peripheral quantative computed tomography (QCT)
ICH	International Conference on Harmonization
IG2	immunoglobin G2
IgG2	immunoglobulin G2
IND	Investigational New Drug
iPTH	intact parathyroid hormone
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LS	lumbar spine
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OC	osteocalcin
OCS	Office of Computational Science
ONJ	Osteonecrosis of Jaw
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
OSI	Office of Scientific Investigations
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	prefilled syringe
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMO	postmenopausal osteoporosis
PMO	post-menopausal osteoporosis
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
Q3M	every 3 months
Q4W	every 4 weeks
QM	each month
QM	each month
REMS	risk evaluation and mitigation strategy
RI	renal insufficiency
RI	renal insufficiency
RRR	relative risk reduction
SAE	serious adverse event
SAP	statistical analysis plan
sCTX	serum Type I collagen C-telopeptide
SGE	special government employee
SMQ	standardized MedDRA query
SOC	standard of care
SOST	sclerostin gene
SQ	subcutaneously
TEAE	treatment emergent adverse event
TH	total hip
TNF-α	tumor necrosis factor –α
TRAP 5b	tartrate-resistant acid phosphatase 5b
ULN	upper limits of normal
WHO	The World Health Organization
WOMAC	Western Ontario and McMaster University Arthritis Index

1 Executive Summary

1.1. Product Introduction

Romosozumab is a humanized immunoglobulin G2 (IgG2) monoclonal antibody which binds and inhibits sclerostin. This new molecular entity is a bone-forming agent with a dual effect on bone, increasing bone formatin and decreasing bone resorption. The Sponsor seeks to market romosozumab for the treatment of osteoporosis in postmenopausal women.

Postmenopausal women with osteoporosis have increase risks of bone fracture due to decreased bone mass and impaired bone structure. Sclerostin, secreted by osteocytes inhibits the canonical Wingless-related integration site (Wnt) signaling pathway in bone and decreases osteoblast-mediated bone formation as well promotes osteoclast function and bone resorption. Patients with rare disorders lacking sclerostin inform our current knowledge of sclerostin function on bone. Sclerosteosis, a rare bone disorder resulting from a mutation of the sclerostin gene (SOST) leading to a lack of sclerostin, is characterized by thick bones with normal lamellar quality but denser quality which are resistant to fracture. Patients with Van Buchem disease who lack a regulatory element of the SOST gene have reduced sclerostin and are resistant to fracture.

The proposed proprietary name, EVENITY, was submitted to IND100391 (November 25, 2015, Serial Number 0401) and the Division of Medication Error Prevention and Analysis (DMEPA) found that the name, EVENITY was conditionally acceptable (March 24, 2016, OSE review #2015-2121235). Thus, the Sponsor submitted the proposed proprietary name to this BLA on July 29, 2016 but the DMEPA review team initially denied the proposed name because it was vulnerable to confusion with a pending proposed named product, UNAMITY and not acceptable from a safety perspective. The DEMPA review team stated the following in their initial denial of the name (DMEPA review October 5, 2016):

> *"The proposed proprietary name is not acceptable from a safety perspective. The proposed name is vulnerable to name confusion with the pending proprietary name, Unamity. "*

Subsequently, the DMEPA review team reversed their decision and found the proposed name, Evenity, acceptable as UNAMITY was no longer a viable name for approval. In their review (10/17/16), the DMEPA review team stated:

> *"The proposed proprietary name is acceptable."*

Reference ID: 4093382

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Sponsor demonstrated that romosozumab was effective in the treatment of osteoporosis in postmenopausal women with a single study (2007337) which provided the primary evidence to support effectiveness.

Study 2007337 was a 24 month long, placebo-controlled, parallel-group study in 222 centers worldwide to assess efficacy and safety of 12 months of romosozumab treatment followed by 12 months of denosumab treatment, a currently approved FDA treatment (12 months romosozumab/12 months denosumab) compared to placebo followed by 12 months of denosumab (12 months placebo/12 months denosumab) in postmenopausal women with osteoporosis. The co-primary endpoints were new vertebral fractures at 12 months and 24 months.

Because the Sponsor relied on only one study, the FDA required that the Sponsor meet a persuasive efficacy level of <0.01 or less and that other non-pivotal studies support the results. The study demonstrated that 210 mg SQ QM romosozumab significantly reduced new vertebral fractures compared to placebo at 12 months and the effect persisted into month 24 when all subjects transitioned to denosumab. Specifically, romosozumab significantly reduced the risk of new vertebral fracture compared with placebo during the 12-month double-blind period (odds ratio = 0.27; $p < 0.001$), with a relative risk reduction of 73% (95% CI: 53, 84). At 24 months, the relative risk reduction persisted for subjects initially randomized to romosozumab with a relative risk reduction of 75% (95% CI: 60, 84; odds ratio = 0.24, $p < 0.001$).

Study 20070337 was the only study with fracture as a primary endpoint but three placebo-controlled studies, 20060326, 20101291, and 20120156, supported the efficacy of romosozumab with primary or secondary endpoints for bone mineral density (BMD). These studies demonstrated significant BMD percentages increased when compared to placebo at the lumbar spine, total hip and femoral neck. Bone formation markers P1NP, osteocalcin, and BSAP and bone absorption marker, sCTX, supported the romosozumab dual functions of bone formation and suppression of bone absorption.

One caveat is that in the study 20070337, patient demographics did not reflect the US population which comprised only 2.5% of the study population. Hispanic or Latino subjects encompassed 43% of the subjects in the study. But when compared by race, ethnicity, and individual geographical, each of the groups still show significant efficacy for reducing fractures and increasing BMD at the lumbar spine, hip, and femoral neck when romosozumab is compared to placebo at 12 months and 24 months.

Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Osteoporosis is characterized by bone loss, disruption of bone architecture, compromised strength and increase in fractures. About 10 million Americans have osteoporosis, and several times as many are at risk because of low bone density. Post-menopausal osteoporosis (PMO), the most common type, is driven primarily by the hormonal changes beginning at menopause. Caucasian women are at highest risk; about half will experience an osteoporotic fracture in their lifetime. PMO causes no symptoms until fractures, usually with minimal trauma, develop in the later stages. Fractures of the vertebrae, the most common type, weaken the spine and lead to additional fractures, with potential irreversible loss of height and function. Hip fractures frequently impair the ability to walk and to live independently. Both vertebral and hip fractures are associated with increased mortality. A variety of effective treatments is available, such that many fractures are now preventable. However, PMO remains seriously under-diagnosed and under-treated in the US, and additional treatment options are needed.

Romosozumab (EVENITY), a humanized immunoglobulin G2 (IgG2) monoclonal antibody that binds and inhibits sclerostin, a regulatory factor in bone metabolism and is indicated for the treatment of osteoporosis in postmenopausal women. Since sclerostin inhibits bone formation and stimulates bone resorption, romosozumab has a dual effect on bone by increasing bone formation and decreasing bone resorption. Adequate intake of calcium and vitamin D is also important for all postmenopausal women, especially those with osteoporosis

In a large phase 3 study of postmenopausal women with osteoporosis, romosozumab significantly reduced the risk of new vertebral fracture by 73% through month 12 compared with placebo with absolute risk reduction of 1.3. The risk reduction at month 12 persisted through month 24, with a 75% risk reduction after both treatment groups transitioned to antiresorptive therapy (denosumab) with absolute risk reduction of 1.9. Fewer new vertebral fractures occurred during follow-on treatment in subjects who had received romosozumab (5 fractures) compared with subjects who had received placebo (25 fractures) in the first year of study. The relative risk reductions for new vertebral fracture compare favorably with those of existing antiresorptive and bone-forming therapies. For new vertebral fracture, the treatment effects were consistent (relative risks favored romosozumab over placebo and romosozumab/denosumab over placebo/denosumab) in all subgroups of baseline characteristics examined, including age, race, geographic region, a range of baseline BMD T-scores, and subjects with a history of prior vertebral, nonvertebral, or fragility fracture. Results for bone mineral density (BMD) values were consistent across the phase 2 and phase 3 placebo-controlled studies. Romosozumab 210 mg every month (QM) demonstrated significant increases in BMD at the lumbar spine, total hip and femoral neck.

Although only 2.5% of patients were recruited in the large phase 3 study from patients in the US, the consistent results for vertebral fractures

reduction and increased BMD among all subgroups when compared to placebo support wide applicability of romosozumab effects on new vertebral fracture reduction and extrapolation of efficacy results to the US population.

The most important safety risks identified during studies include the following:

a) Atypical Femur Fracture (AFF): Since romosozumab has antiresorptive activity, as demonstrated by bone turnover markers (BTM) profiles and histomorphometry data from bone biopsies, AFF is an important potential risk for romosozumab. Atypical low-energy or low trauma fractures of the femoral shaft have been reported in patients receiving romosozumab.
b) Osteonecrosis of Jaw (ONJ): Since romosozumab has antiresorptive activity, as demonstrated by BTM profiles and histomorphometry data from bone biopsies, ONJ is an important potential risk for romosozumab. Osteonecrosis of the jaw, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving romosozumab.
c) Hypersensitivity: Like other monoclonal antibodies, romosozumab could be associated with hypersensitivity reactions. Based on medical review of the integrated safety data, hypersensitivity is considered an important identified risk with romosozumab. Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria, occurred in the romosozumab group.
d) Hypocalcemia: Inhibition of sclerostin by romosozumab leads to rapid bone mass accrual at initiation of treatment and an increased demand for bone-building substrates such as calcium. Based on the clinical trial data, hypocalcemia is considered an important identified risk. Mild and transitory decreases in albumin- corrected calcium and a compensatory increase in iPTH were observed after initiation of romosozumab Based on the totality of data, the risk of hypocalcemia is manageable with appropriate monitoring recommended for patients with stage 5 chronic kidney disease (CKD).

In clinical studies, romosozumab was well tolerated except for increased injection site reactions, hypersensitivity, and hypocalcemia seen in patients with renal disease. AFF and ONJ were rare but seen in the large clinical trial in romosozumab patients.

Romosozumab reduces the risk for vertebral fractures within one year of treatment which continues once patients transition to an antiabsorptive osteoporotic drug is both a bone forming and antiabsorptive agent increases BMD at lumbar spine, total hip, and femoral neck. The data supports effectiveness of romosozumab for both reduction of new vertebral fractures and BMD gains at the lumbar spine, total hip, and femoral neck when compared to placebo across many subgroups and will likely have wide applicability in women with PMO. From the clinical trial data, the risks for romosozumab include AFF, ONJ, hypersensitivity, and hypocalcemia. These risks were either very rare (AFF or ONJ) or were present in few patients (hypersensitivity and hypocalcemia). These risks can be managed with labeling warnings if this drug is

approved.

In summary, romosozumab is effective to reduce the risk of vertebral fractures in postmenopausal women and has qualities of bone formation and antiabsorption of bone with tolerable safety risks. The benefits to reduce new vertebral fractures in PMO outweigh the safety risks. This drug has a place in the armamentarium of treatments against osteoporosis in post-menopausal women if approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoporosis, a skeletal disorder of loss of bone mass and architecture which leads to an increased risk for fractures. • Fractures significantly impact individual quality of life, morbidity, mortality and place an economic burden on society. As an example, in hip fractures patients, only 40% of patients will regain full mobility while 40% will be transferred to nursing care and 20% of patients will die within the first year.	Osteoporosis in post-menopausal women leads to increased lifetime risk for fractures. Osteoporotic fractures cause significant morbidity and mortality.
Current Treatment Options	• Many drugs are effective: bisphosphonates, denosumab, teriparatide, raloxifene • Different formulations, dosing schedules and routes of administration: oral tablets/solution, nasal spray, injection (subcutaneous, intravenous) • Treatment can reduce nonvertebral fractures by up to about 50%; vertebral fractures by up to 70% • Minor side effects are common, and contribute to poor compliance • Fear of rare, more severe side effects is a major obstacle to treatment	Under-diagnosis and under-treatment of PMO is a critical public health issue in the US. Treatment is effective when used, but does not prevent all fractures. Availability of additional treatment options, especially those with high levels of fracture efficacy, will benefit PMO patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Even after a major fracture or with multiple risk factors, most patients do not receive appropriate treatment	
Benefit	• Romosozumab significantly reduced the risk of new vertebral fracture by 73% through month 12 compared with placebo with absolute risk reduction of 1.3. The risk reduction at month 12 persisted through month 24, with a 75% risk reduction after both treatment groups transitioned to antiresorptive therapy (denosumab) with an absolute risk reduction of 1.9. Fewer new vertebral fractures occurred during follow-on treatment in subjects who had received romosozumab (5 fractures) compared with subjects who had received placebo (25 fractures) in the first year of study.	The large clinical study demonstrated that romosozumab is effective in reducing the risk of vertebral fractures at 12 months and at 24 months (after patients transition into antiabsorptive therapy at 12 months).
	• For new vertebral fracture, the treatment effects were consistent (relative risks favored romosozumab over placebo and romosozumab/denosumab over placebo/denosumab) in all subgroups of baseline characteristics examined, including age, race, geographic region, a range of baseline BMD T-scores, and subjects with a history of prior vertebral, nonvertebral, or fragility fracture.	Because new vertebral fracture efficacy was found across all subgroups, it is likely romosozumab will have wide applicability for reducing new vertebral fractures in women with PMO.
	• Results for bone mineral density (BMD) values were consistent across the phase 2 and phase 3 placebo-controlled studies (20070337, 20101291, 20060326, and 20120156). Romosozumab 210 mg every month (QM) demonstrated significant increases in BMD at the lumbar spine, total hip and femoral neck, and the effect was seen	BMD gains at lumbar spine, total hip and femoral neck support efficacy of romosozumab across multiple studies which was maintained through transition to an antiresorptive therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	early with romosozumab treatment (as early as 3 months in Study 20060326). BMD gains were maintained or augmented further in studies that included a transition to antiresorptive therapy (denosumab) after completion of romosozumab.	
	• Romosozumab consistently increased BMD at the lumbar spine and total hip regardless of baseline BMD T-scores, age, and geographic region. When analyzed by region, the percent change in BMD at the lumbar spine and total hip was similar between North America and all other regions, and romosozumab demonstrated statistically significant increases in BMD in all regions.	Because of the consistent BMD gains found across multiple subgroups, romosozumab effects on reducing fractures will likely to have widespread applicability for women with PMO.
	• Retreatment with romosozumab after a treatment-free interval of 12 months showed comparable effects on BMD as those observed after initial exposure to romosozumab but the data is limited by small numbers of patients in each study group (i.e. N<20 in each group).	Retreatment with romosozumab appears effective on BMD gains; however, a conclusion cannot be made based on the few number of patients studied with re-treatment.
Risk	• Atypical Femur Fracture (AFF): Since romosozumab has antiresorptive activity, as demonstrated by bone turnover markers (BTM) profiles and histomorphometry data from bone biopsies, AFF is an important potential risk for romosozumab. Atypical low-energy or low trauma fractures of the femoral shaft have been reported in patients receiving romosozumab.	AFF is a risk with romosozumab as it was reported in the clinical trials but it is rare.
	• Osteonecrosis of Jaw (ONJ): Since romosozumab has antiresorptive	ONJ is a risk with romosozumab as it was reported in the clinical trials but it is rare.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	activity, as demonstrated by BTM profiles and histomorphometry data from bone biopsies, ONJ is an important potential risk for romosozumab. Osteonecrosis of the jaw, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving romosozumab.	
	• Hypersensitivity: Like other monoclonal antibodies, romosozumab could be associated with hypersensitivity reactions. Based on medical review of the integrated safety data, hypersensitivity is considered an important identified risk with romosozumab. Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria, occurred in the romosozumab group. No anaphylaxis was reported in the clinical trials.	Hypersensitivity is a risk as it was reported in the clinical trials but it was relatively rare.
	• Hypocalcemia: Inhibition of sclerostin by romosozumab leads to rapid bone mass accrual at initiation of treatment and an increased demand for bone-building substrates such as calcium. Based on the clinical trial data, hypocalcemia is considered an important identified risk. Mild and transitory decreases in albumin- corrected calcium and a compensatory increase in iPTH were observed after initiation of romosozumab. Based on the totality of data, the risk of hypocalcemia is manageable with appropriate monitoring recommended for patients with stage 5 CKD.	Hypocalcemia is a risk as it was seen in the clinical trials, mostly in renal failure patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Hyperostosis: The intended pharmacologic effect of romosozumab is an increase in BMD and bone strength; however, hyperostosis (excessive bone growth) may be a potential risk with romosozumab administration. The current data, including the audiology substudy, do not support a safety risk of hyperostosis with romosozumab use; however, given the mechanism of action for romosozumab, it is considered a potential risk. The data does not support a safety risk for hyperostosis with romosozumab.	Hyperostosis is a theoretical risk but the clinical trials did not support this risk.
Risk Management	• AFF, ONJ, hypersensitivity and hypocalcemia risks can be managed by labeling • REMS level risks were not identified during the review.	The risks for AFF and ONJ can be managed with labeling as the numbers of cases were rare and all were confounded. Hypersensitivity rates are consistent with other immunoglobulin therapies and can be managed with labeling. Hypocalcemia risks are manageable with labeling.

2 Therapeutic Context

2.1. Analysis of Condition

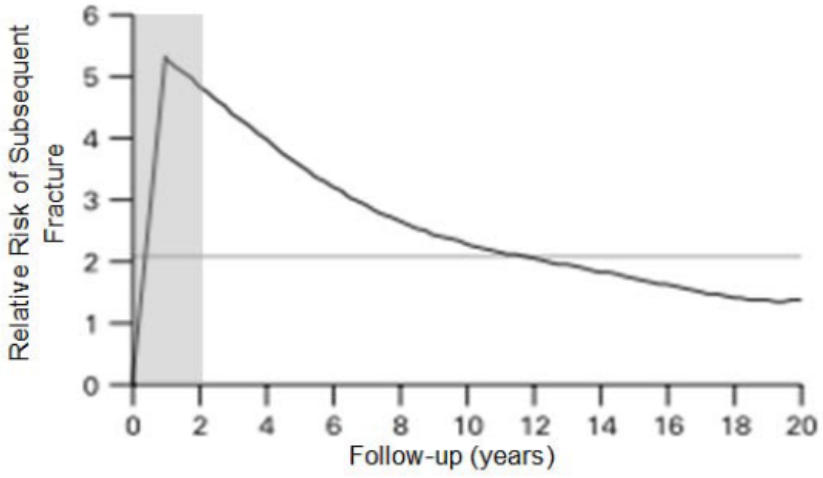
Osteoporosis is a skeletal disorder of loss of bone mass and architecture which leads to an increased risk for fractures. It currently affects 15-38% of women over 50 years of age in the US and other regions of the world. (Wade et al, 2014; Wright et al, 2014; Hernlund et al, 2013). The World Health Organization (WHO) provides criteria using dual-energy X-ray absorptiometry (DXA) to define osteoporosis by bone mineral density (BMD). A T-score is generated by measurements of the BMD at the lumbar spine, total hip, and femoral neck. Osteoporosis is defined by T-score ≤ 2.5 standard deviations from the mean BMD of a young, healthy cohort of women at the same location.

Annually, an estimated 10% (4.5 million of 44 million women) of postmenopausal osteoporosis (PMO) women across the US, Europe, Canada, Australia, and Japan will have osteoporotic fractures (Wade et al, 2014; Wright et al, 2014; Hernlund et al, 2013; Wade et al, 2012; Burge et al, 2007). These women have increased risk of multiple types of fractures such as hip, vertebral, extremity, etc. that can significantly impact individual quality of life, morbidity, mortality and place an economic burden on society (NOF, 2014; WHO, 2007; OSG, 2004). For example, in hip fractures patients, 20% of patients will die within the first year. An additional 20% of patients will be transferred to nursing care and only 40% will regain full mobility.

Osteoporotic fractures are a significant risk for subsequent fractures within a near time proximity. Vertebral fractures increase subsequent additional vertebral risk by five times as well as increase for other fractures by two to three times. Hip fractures increase subsequent risk of other fractures by 2.5 times (NOF, 2014; van Helden et al, 2006; Colón-Emeric et al, 2003). Lindsey et al, 2001 found that new vertebral fracture within one year after a previous fracture was 19%.

Van Geel et al, 2009 found that subsequent fractures occurred the most frequently within one to two years (23%) and five years (54%) after non-vertebral fractures and symptomatic fractures in PMO women, doubling the risk of an initial first fracture. The following figure 1 illustrates the risk of subsequent fractures in women after an initial nonvertebral or symptomatic fracture.

Figure 1: Relative Risk of Subsequent Fractures in Women Ages 50-80 with Clinical Fracture



Horizontal gray line = the risk of subsequent fracture at any time relative to the risk of a first fracture (ie, the risk of subsequent fracture is about double the risk of an initial fracture)

Black line = the risk of subsequent fracture relative to the risk of a first fracture by year of follow-up (ie, the risk of subsequent fracture is highest in the first 1 to 2 years after an initial fracture and remains elevated for several years after the first fracture)

Source: adapted from van Geel et al, 2009

Reviewer Comments: ***Osteoporosis, a skeletal disorder of loss of bone mass and architecture leads to an increased risk for fractures which significantly impact individual quality of life, morbidity, mortality and place an economic burden on society. As an example, in hip fractures patients, only 40% of patients will regain full mobility while 40% will be transferred to nursing care and 20% of patients will die within the first year. The risk of subsequent fractures doubles after a first fracture with second fractures most frequently within two years following the first fracture.***

2.2. Analysis of Current Treatment Options

Pharmacologic therapies for osteoporosis and the prevention of osteoporotic fractures consist of 1 class of bone-forming agents and several types of antiresorptive therapies, including bisphosphonates. Bisphosphonates are currently the standard of care in many countries; in 2011 in the US, bisphosphonates were used by 83% of women who were using any pharmacologic osteoporosis therapy (Sarpong, 2014).

Despite the availability of cost-effective and well-tolerated treatments to reduce fracture risk, postmenopausal women who have an osteoporosis-related fracture are underdiagnosed and undertreated; only about 20% receive either a BMD test or a prescription for a drug to treat

osteoporosis after a fracture (Balasubramanian et al, 2014; NOF, 2014; Diez-Perez et al, 2011; WHO, 2007; OSG, 2004).

In their respective phase 3 clinical studies, 3 antiresorptive therapies for osteoporosis (risedronate, denosumab, and zoledronic acid) demonstrated significant reductions of 60% to 65% in the risk of vertebral fractures within 1 year (see approved product labeling). For other therapies, it took between 19 months (for teriparatide) to 3 years or longer (for alendronate, ibandronate, and other therapies) to demonstrate a significant reduction in the risk of vertebral, nonvertebral, or clinical fracture.

Bone-forming therapies can provide larger improvements in bone structure and strength compared with antiresorptives; however, only 1 is available – teriparatide, a parathyroid hormone [PTH] analog. Teriparatide has some limitations, such as the need for daily injections, a relatively small BMD increase at the hip (2.6% total hip in 19 months) (Neer et al, 2001), a boxed warning of potential risk of osteosarcoma, and a treatment duration limited to a lifetime 2 year maximum. In addition, the time to onset of effect with teriparatide may leave patients relatively unprotected early in treatment. According to 1 study, about 12% of patients had a fracture in the 2 years following initiation of teriparatide use, even in persistent users, and most (64%) of those fractures occurred during the first year on therapy (Bonafede et al, 2015). Furthermore, transitioning patients from a bisphosphonate to teriparatide, which is more common than use of teriparatide as first-line treatment, can lead to reduced or delayed gains in BMD over the first year of treatment relative to treatment-naïve subjects (Miller et al, 2008; Obermayer-Pietsch et al, 2008; Ettinger et al, 2004).

In summary, by inhibiting sclerostin, romosozumab demonstrates a dual effect on bone, increasing bone formation and decreasing bone resorption, leading to rapid and substantial gains in BMD and improved bone strength. Romosozumab is administered once monthly (QM) and has a rapid onset of effect, thus offering an important additional treatment option for osteoporosis in postmenopausal women at increased risk for fracture. These patients will benefit from rapid fracture risk reduction, significant BMD gains, and improved underlying skeletal strength for ongoing fracture risk reduction with follow-on antiresorptive therapy. The following table 1 summarizes the major pharmacologic treatments for osteoporosis.

Table 1: Pharmacologic Treatments for Osteoporosis

Drug class	Product name	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues
Bisphospho - nates	Fosamax (alendronate)	1995	70 mg PO weekly (tablet or solution) 10 mg PO daily (tablet)	Osteonecrosis of the jaw (ONJ) Atypical femoral fractures (AFF) Hypocalcemia Upper GI AEs
	Fosamax Plus D (alendronate/ cholecalciferol)	2005	70 mg alendronate/2800 or 5600 IU cholecalciferol, 1 tablet weekly	

Drug class	Product name	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues
	Binosto (alendronate)	2012	70 mg PO weekly (effervescent tablet for oral solution)	
	Actonel (risedronate)	2000	Tablets: 5 mg PO daily 35 mg PO weekly 150 mg PO monthly	
	Atelvia (risedronate)	2010	35 mg PO weekly (delayed release tablet)	
	Boniva (ibandronate)	2003	150 mg PO monthly (tablet)	
	Boniva (ibandronate)	2006	3 mg IV q3 months	ONJ, AFF, hypocalcemia Renal toxicity Acute phase reactions
	Reclast (zoledronic acid)	2007	5 mg IV yearly	
Estrogen agonist/ antagonis	Evista (raloxifene)	1997	60 mg PO daily (tablet)	Venous thromboembolism Death due to stroke
PTH analog	Forteo* (teriparatide)	2002	20 mcg SC daily	Osteosarcoma (animal data) Hypercalcemia,
PTHrP analog	Tymlos (abaloparatide)	2017	80 mcg SC daily	Osteosarcoma (animal data) Hypercalcemia,
RANK ligand	Prolia* (denosumab)	2010	60 mg SC q6 months	ONJ, AFF, hypocalcemia
Calcitonin - salmon	Miacalcin**	1986	SC or IM injection, 100 IU every other day	Hypersensitivity Hypocalcemia Malignancy
	Miacalcin**	1995	Nasal spray, 200 IU daily	
	Fortical**	2005	Nasal spray, 200 IU daily	

*approved only for osteoporotic patients at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
**approved only for osteoporotic patients for whom alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies)

Excluding the calcitonin products (which were approved based on total body calcium and/or BMD data), the 7 molecular entities represented in the above table were approved for treatment of PMO based on reduction of morphometric vertebral fractures, consistent with 1994 FDA guidelines on osteoporosis drug development. Such fractures are defined solely by radiographic criteria. Although the clinical effects of such fractures vary, they are a strong predictor of subsequent fracture (vertebral and nonvertebral) and also are associated with increased mortality, therefore are considered by the Division of Bone, Reproductive, and Urology Products (DBRUP) to be a clinically relevant (rather than surrogate) endpoint.

The following table 2 lists the absolute and relative risk reductions (ARR, RRR) in new morphometric vertebral fractures (the primary endpoint) in the PMO trials of approved drugs. Risk reductions were generally apparent within 1 or 2 years and maintained through 3 years (the Forteo trial was stopped at ~19 months for safety concerns – see below). Because the trial populations differed in baseline fracture risk, ARR is highly variable between drugs/trials while RRR is more consistent. For example, the FIT-1 trial of Fosamax enrolled a high risk population (women with baseline vertebral fractures) and FIT-2 a lower risk population (no baseline fractures); fracture rates in both treatment groups were much higher in FIT-1, but relative reduction in fracture risk was nearly identical in the two studies.

Table 2: PMO fracture trials: New morphometric vertebral fractures, risk reductions by year

	12 months		**24 months**		**36 months**	
	ARR (%) (95% CI)	RRR (%) (95% CI)	ARR (%) (95% CI)	RRR (%) (95% CI)	ARR (%) (95% CI)	RRR (%) (95% CI)
Teriparatide (Forteo)			9.3* (5.5, 13.1)	65 (45, 78)		
Denosumab (Prolia)	1.4 (0.8, 1.9)	61 (42, 74)	3.5 (2.7, 4.3)	71 (61, 79)	4.8 (3.9, 5.8)	68 (59, 74)
Zoledronic acid (Reclast)	2.2 (1.4, 3.1)	60 (43, 72)	5.5 (4.4, 6.6)	71 (62, 78)	7.6 (6.3, 9.0)	70 (62, 76)
Alendronate (Fosamax-FIT 1)			7.2	62	7.0	47
Alendronate (Fosamax-FIT-2)					2.3**	48
Risedronate (Actonel-NA)	4.0	65	5.9	55	5.0	41
Risedronate (Actonel-MN)	7.7	61	13.1	59	10.9	49
Ibandronate (Boniva PO)	0.6	58	2.3	61	4.9	62
Raloxifene (Evista) ≥1 baseline fx					6.1	30 (14, 44)
Raloxifene (Evista) no baseline fx					2.4	55 (29, 71)

ARR = Absolute Risk Reduction; RRR= Relative Risk Reduction
*Forteo trial = 19 months' median exposure
**Fosamax FIT-2 trial = 48 month assessment
Sources: Prescribing information (Forteo, RIS, ZOL, DEN, RAL); Lancet 1996,348:1535 (ALN); JBMR 2004, 19:1241 (IBD)

Reviewer Comments: ***There are a number of drugs available for osteoporosis treatment. The most commonly used drugs, the bisphosphonates, have only antiabsorptive function on bone. One class of drug, teriparatide, builds bone but takes up to 19 months to reduce the risk of fractures. It carries a boxed warning on the label for the risk of osteosarcoma and has limited lifetime use of 2 years.***

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Romosozumab is a new molecular entity and currently not marketed in the US or anywhere else in the world. There are no other marketing applications or review in other divisions of the FDA but the Sponsor is developing the drug for other indications including osteoporosis in men.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following key DBRUP interactions occurred during clinical development with the Sponsor. Detail listing is in Appendix 13.5.

- DBRUP recommended that the Sponsor conduct a 2-year rodent bioassay to evaluate the carcinogenic potential of romosozumab. The Carcinogenicity Assessment Committee (CAC) returned recommendations and confirmed acceptability of the proposed Carcinogenicity Special Protocol Assessment (SPA) request for a rat lifetime pharmacology study.

DBRUP met with the Sponsor, December 12, 2012 (type C meeting), to support a new drug product concentration for romosozumab. In the clinical fracture study, a 70 mg/ mL concentration required 3 injections to reach the 210 mg dose. The Sponsor proposed to market a 90 mg/ mL concentration which would then require 2 injections to achieve the 210 mg dose. Agreement was reached regarding the analytical comparability and clinical studies need to support the new concentration.

- DBRUP gave feedback (end of phase 2 [EOP2] meeting and July 2015 Type C meeting) regarding the selection of a single dose (210 mg QM) for phase 3 study(ies), and studying effects on patients off romosozumab treatment and with retreatment.

The design of the pivotal Study 20070337 was agreed with input from DBRUP during the 2011

EOP2 meeting, and subsequent correspondences and interactions including the November 10, 2014 Type C Clinical Written Response. These agreements including the following:

- The coprimary endpoints of subject incidence of new vertebral fracture at 12 and 24 months for the pivotal, placebo-controlled study of postmenopausal women with osteoporosis are adequate to demonstrate the efficacy of romosozumab.

- DBRUP agreed that a single multi-centered pivotal study, Study 20070337, appeared adequate to support submission of an initial marketing application for this indication but the level of efficacy evidence must be more persuasive ($p < 0.01$) and supported by efficacy data from other nonpivotal studies (see DBRUP's November 10, 2014 Type C Clinical Written Response [Ref ID: 3656395]).

- Safety assessments include appropriate adjudication of cardiovascular events and inclusion of osteoarthritis, bone biopsy, calcium, and serum intact parathyroid hormone (iPTH) and urinary calcium substudies in the phase 3 study.

- DBRUP confirmed at the May 18, 2016 prefiling meeting that Study 20070337 is adequate to support Biologics Licensing Application (BLA) market application and recommended that the Sponsor provide in-depth justification around the applicability of the global study data to the intended US population and US medical practice.

3.3. Foreign Regulatory Actions and Marketing History

Romosozumab is currently not marketed in any country in the world.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was requested to audit four sites, Sites 1-52SFOU, 1-678YLY, 1-64PLTY, and 1-3RA0SB. The rationales for selection of these sites are listed below:

- Sites 1-678YLY, 1-64PLTY (Restrepo, Medellin): two investigators with same last name in same location appears unusual, high enrollment (752 total between the two sites), new investigator(s)
- Site 1-52SFOU (Dabrowska, Poland): high enrollment (264), high site efficacy effect (-2.04), relative high number of outliers, no prior inspection in the past 3 years
- Site 1-3RA0SB (Recknor, US): US site for comparison

At the time of this writing, site inspections have been completed and one site (Restrepo, Site # 1-678YLY) has been issued a preliminary voluntary action indicated (VAI) due to major issue of delayed randomization while the remaining 3 sites have been issued preliminary no action indicated (NAI). Final audit results are pending.

4.2. Product Quality

The commercial product will be presented in a single-use (b) (4) prefilled syringe (PFS) containing 1.17 mL of a 90 mg/mL solution; thus, 2 injections will be required to achieve the 210 mg dose. The drug substance for the commercial product will be manufactured at Amgen Rhode Island (ARI) using the commercial process that is referred to as Process 2 ARI.

Romosozumab drug substance was initially manufactured at Amgen Thousand Oaks (ATO) using a manufacturing process referred to as Process 1 ATO. The results of the romosozumab clinical biopharmaceutics program support the comparability of the romosozumab drug substances manufactured with Process 1 ATO, Process 2 ATO (the process used in the pivotal phase 3 Study 20070337), and Process 2 ARI (the process that will be used for commercial manufacturing).

Romosozumab drug product developed for initial clinical studies was supplied in a glass vial containing 70 mg/mL romosozumab (containing Process 1 ATO). The pivotal phase 3 clinical studies in postmenopausal osteoporosis (20070337 and 20080289) used 70 mg/mL glass PFS presentations (containing Process 2 ATO). The planned commercial product will be a (b) (4) PFS with 90 mg/mL romosozumab containing Process 2 ARI drug substance. The vial and glass PFS presentations are not currently planned for commercialization.

To confirm that changes in the manufacturing process, production site, formulation, and product presentation (vial to PFS and glass PFS to (b) (4) PFS) did not impact product quality, several comparability assessments were conducted. The results of the clinical biopharmaceutics program demonstrate that romosozumab drug substance and drug product planned for commercial use are bioequivalent to those used in the pivotal phase 3 studies.

See CMC reviews for product quality details.

4.3. Clinical Microbiology

There are no clinical microbiology issues with this product.

4.4. Nonclinical Pharmacology/Toxicology

Conclusions from the nonclinical review are outlined here. Refer to the nonclinical review by Dr. Gemma Kuijpers, DBRUP for details.

- The submitted nonclinical information is adequate and supports the safety of the proposed treatment with once-monthly subcutaneous doses of 210 mg in the intended treatment population.
- AMG785 was generally well tolerated by animals at doses equivalent to large human exposure multiples, and apart from indirect effects related to the pharmacological activity, little toxicity was observed.
- Information available from humans with sclerostin deficiency disorders or SOST knockout mice is also generally reassuring regarding bone safety, general toxicity and carcinogenicity.

embryo fetal digit anomalies observed with AMG785 treatment replicate similar observations in humans and mice with sclerostin deficiencies.

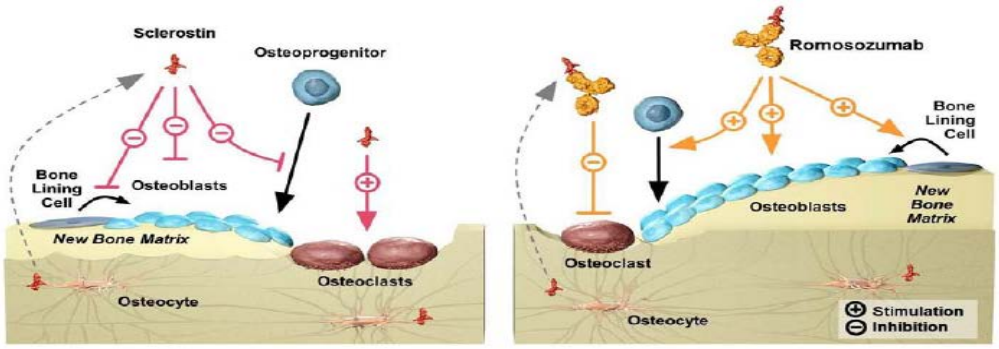
4.5. Clinical Pharmacology

Key findings from clinical pharmacology are outlined here; for details see Clinical Pharmacology review by Dr. Lin Zhou.

4.5.1. Mechanism of Action

Romosozumab (formerly known as AMG 785) is a humanized immunoglobulin G2 (IgG2) monoclonal antibody that binds and inhibits sclerostin. Romosozumab increases bone formation due to the activation of bone lining cells, increased bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells. The following figure 2 illustrates the mechanism of action for romosozumab in bone.

Figure 2: Graphic Representation of Mechanism of Action for Romosozumab



Source: Clinical Overview Figure 2 with reviewer edits.

Additionally, romosozumab results in changes to expression of osteoclast mediators, thereby decreasing bone resorption. Together, this dual-effect of increasing bone formation and decreasing bone resorption results in rapid increases in trabecular and cortical bone mass,

improvements in bone structure and strength, and fracture risk reduction.

4.5.2. Pharmacodynamics

The dose-BMD response model described the romosozumab dose-dependent BMD gains at both lumbar spine and total hip for all data including 210-mg SC QM dose of romosozumab in postmenopausal osteoporosis subjects.

The dose-BMD model demonstrated a significant relationship between romosozumab dose and frequency with BMD gains at lumbar spine and total hip. For a given dose, QM administration provided significantly greater BMD gains at lumbar spine and total hip than every 3 months (Q3M) administration, while BMD gains were similar for QM and Q3M dosing of the same cumulative dose (eg, 70 mg QM versus 210 mg Q3M). Model predicted time courses for the QM dose regimens indicated that the 210 mg dose provided the most rapid and extensive gains in BMD over the course of 12-month treatment.
The concentration-response model adequately described the relationship between romosozumab concentration, bone turnover markers (P1NP and sCTX), and BMD gains at the lumbar spine. Out of the dosing regimens studied, the highest BMD gains at 12 months were observed for 210 mg SC QM. The greatest increase in the bone formation marker P1NP, and the longest duration of P1NP increase above baseline were also obtained with the 210 mg SC QM dosing regimen.

Reviewer Comments: ***The Sponsor selected 210 mg QM, the highest dose, based on PD studies which demonstrated that romosozumab 210 mgs QM provided greater BMD gains at the lumbar spine and total hip than Q3M (i.e. 210 mg QM had greater BMD gains compared to 210 mg Q3M) and bone formation marker, P1NP, had the greatest increase and longest sustained increase above baseline at this dose.***

Immunogenicity
In the phase 2 and phase 3 clinical studies of osteoporosis in postmenopausal women, the incidence of binding and neutralizing antidrug antibodies (ADAs) was 19.9% (852 of 4289) and 1.1% (46 of 4289), respectively. The incidence of binding and neutralizing ADAs in women dosed with 210 mg QM was similar to the overall studies at 19.1% (758 of 3959) and 0.8% (31 of 3959), respectively. The presence of binding ADAs appeared to decrease romosozumab exposure up to 25% at months 3, 6, and 9. The exposures became comparable at month 12 (difference in mean values was approximately 10%) between ADA positive and ADA negative subjects. The concentration values were within the range of subjects in whom no ADAs were detected. Additionally, population PK analysis showed that the presence of ADAs did not impact on the PK of romosozumab.

For subjects who received romosozumab, the percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at month 12 and month 24 was compared among subjects who developed binding or neutralizing antiromosozumab antibodies through month 15 versus those who were negative for antiromosozumab antibodies through month 15.

At month 12, the mean percent changes in BMD at the lumbar spine were 13.1% (negative antibody status), 13.1% (positive binding antiromosozumab antibody), and 11.6% (positive neutralizing antiromosozumab antibody). Corresponding values at month 24 were 16.7%, 16.7%, and 15.1%, respectively. Percent change from baseline at the total hip and femoral neck also showed consistent results The following table 3 summarizes BMD at lumbar spine, total hip and femoral neck at month 12 and month 24 by ADA status at month 15 for patients in study 20070337.

Table 3: BMD at LS, TH, FN at Months 12 and month 24 in Study 20070337

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

Source CSR 20070337 Tables 14-10.3.1, 14-10.3.2, and 14-10.3.3 with reviewer edits.

Reviewer Comments: ***This data in totality support that a lower dose of romosozumab could have comparable efficacy than 210 mg QM when considering that BMD increased at LS, TH, and FN regardless of ADA status and that binding status decreased exposure by approximately 25%. For safety, PK values and exposure were comparable between ADA positive and negative patients by month 12. There was no increased safety AEs associated with ADA status. See section 8.3.12 Immunogenicity.***

4.5.3. Pharmacokinetics

Pharmacokinetics in Healthy Subjects

When administered to healthy subjects at single SC doses ranging from 0.1 mg/kg to 10 mg/kg, romosozumab exhibited nonlinear PK. At low doses, mean apparent clearance (CL/F) was approximately 4-fold higher at a dose of 0.1 mg/kg than at 3 mg/kg. At higher doses, between 3 mg/kg and 10 mg/kg, the PK appeared to be linear, based on relatively similar clearance and dose-normalized maximum serum concentration (Cmax) and area under the curve from time 0 to infinity (AUCinf). Generally, Cmax was observed within the first week after administration. Serum romosozumab concentrations declined with a mean half-life (t1/2) of approximately 11 to 18 days during the beta (plateau) phase and 6-7 days during the gamma (terminal) phase. The bioavailability of romosozumab was estimated to be 50% to 70% after SC administration of 1 to 5 mg/kg.

Pharmacokinetics in Patients- Post Menopausal Women

Following administration of SC doses every 4 weeks (Q4W) at 3 mg/kg for 3 months, accumulation based on mean Cmax and AUC values following 3 doses was approximately 20% to 36% more than exposure after the first dose. The mean effective t1/2 was 12.8 days after 3 doses of 3 mg/kg. Approximately linear PK was observed when comparing Cmax and AUC values following 2 mg/kg and 3 mg/kg Q4W. When multiple SC doses of romosozumab 70 mg, 140 mg, or 210 mg QM were administered to postmenopausal women with osteoporosis or low BMD, steady state was generally reached by month 3 with minimal accumulation (< 2 fold) following multiple doses and maintained at a similar level throughout the rest of the study. Ctrough was approximately dose proportional from 140 mg to 210 mg, however a more than dose-proportional increase in Ctrough was observed from 70 mg to 140 mg.

Pharmacokinetics in Patients With Renal Impairment

Because of the large molecular weight of romosozumab, renal clearance was not expected to play a role in the total clearance of romosozumab. However, chronic kidney disease (CKD) has been implicated with disturbances of the Wnt pathway with an elevated level of serum sclerostin reported in CKD subjects. A phase 1 study (Study 20110227) was conducted in healthy subjects and subjects with stage 4 renal impairment or stage 5 CKD requiring hemodialysis, to investigate the PK, PD, and safety of romosozumab in subjects with renal impairment where subjects received a single dose of 210 mg SC Results from Study 20110227 showed the exposure of romosozumab for subjects with stage 4 renal impairment was 44% higher than for subjects with normal renal function.

The population PK analysis indicated an increase in romosozumab AUC with increasing severity of renal impairment with about a 50% increase in predicted median AUC in subjects with end-stage renal disease (assuming no hemodialysis during romosozumab treatment). The predicted upper bound (95%) AUC was approximately 50% lower than the maximum exposure obtained with a 10 mg/kg single dose, which was demonstrated to be tolerated in clinical studies. The administration of romosozumab was well tolerated, with no deaths or adverse events leading to withdrawal from the study.

Reviewer Comments: ***The renal failure study 20110227 studied single dosing of 210mg in renal failure patients (stage 4 and ESRD) compared with healthy patients and found that although renal failure increase exposure of romosozumab, the increases are predicted to be less than the maximum tolerated exposure in single dosing clinical studies of up to 10 mg/ kg, a dose well tolerated by patients. Specifically, this renal failure study demonstrated there was a 50% increase in predicted median AUC, but the upper limits (95%) was still 50% below the maximum exposure found in single-dose phase 1 studies of 10 mg/kg. Patients had higher rates of elevated iPTH and hypocalcemia and AEs related to hypocalcemia when compared to the general population. See section 8.3.8 laboratories for details. The increased rates of hypocalcemia and AEs related to hypocalcemia in this renal failure patient population should be addressed in the labeling.***

Pharmacokinetics in Patients With Hepatic Impairment
Because romosozumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (eg, by cytochrome P450 [CYP] enzymes), hepatic impairment and drug interaction studies (eg, with CYP inhibitors) were not considered necessary and have therefore not been conducted.

Reviewer Comments: ***Because romosozumab, a monoclonal antibody, is not eliminated by the hepatic metabolic mechanisms, it is acceptable for the Sponsor not to conduct hepatic impairment studies.***

Population Pharmacokinetics
Population PK and PK/PD analyses in healthy subjects and postmenopausal women with low BMD or osteoporosis were performed using non-linear mixed effects modeling method and characterized absorption, distribution, and elimination of romosozumab. The key findings from the population PK analyses were the following:

- After SC administration of 210 mg romosozumab, bioavailability was high (81%) and absorption was complete in approximately 14 days. Bioavailability is nonlinear at lower doses but at higher doses such as 210 mg, it is linear. The rate of absorption was similar across the range of doses evaluated.
- Romosozumab is eliminated through a slow nonspecific elimination pathway mediated by the hepatic reticuloendothelial system (ie, linear clearance [CL]), and a rapid saturable elimination pathway (ie, target-mediated nonlinear clearance) mediated by degradation of romosozumab-sclerostin complex in the peripheral compartments, which results in a concentration dependent clearance of romosozumab.
- Sclerostin is > 95% bound for the entire dosing interval for a 210-mg SC QM regimen which suggests full target-engagement has been achieved.
- There were no differences in romosozumab PK between healthy subjects or postmenopausal women with low BMD or osteoporosis. Prior alendronate or

postmenopausal osteoporosis treatment, presence of antiromosozumab antibodies (antidrug antibodies [ADAs]), and baseline sclerostin had no impact on PK.

- Body weight, age, gender, race (Japanese versus non-Japanese), and estimated glomerular filtration rate (eGFR), were identified as having an impact on PK. The effect of body weight (on both clearance and volume) and eGFR (on clearance) had the greatest impact, with decreasing body weight or decreasing eGFR resulting in increasing romosozumab exposure. However PK/PD modeling demonstrated body weight and eGFR had minimal impact on BMD gain at 12 months, with gains in BMD over a weight range of 43 to 86 kg or across stages of renal impairment comparable (±15%) to a typical subject. Additionally, predicted exposures (95% upper bound) after 210 mg QM dosing in the lowest body weight subjects included in the analysis (< 43 kg) or subjects with end-stage renal disease (eGFR < 15 mL/min) were approximately 60% and 50% lower respectively than the exposure obtained with a 10 mg/kg dose, which was demonstrated to be tolerated in clinical studies.

Reviewer Comments: ***The Sponsor used PK/ PD modeling to determine that dose adjustment is not necessary for patient baseline characteristics which have impact on PK. Although low body weight and low eGFR had the greatest impact on increasing romosozumab exposure, PK/PD modeling demonstrated that these factors had minimal impact on BMD gain at 12 months and that the maximum exposure will still be less than the maximum tolerable dose (10 mg/ kg).***

4.6. Devices and Companion Diagnostic Issues

Drug product manufacturing processes were modified to manufacture prefilled syringes (PFS) in three presentations: 70 mg/mL and 120 mg/mL in 1 mL Long glass syringes, and 90 mg/mL in 1 mL (b) (4) syringes. Only the 90 mg/mL (b) (4) syringe presentation is intended for commercial registration and production. See section 4.2 product quality for additional information on the syringe.

Refer to the Center for Device and Radiological Health (CDRH) review for details.

4.7. Consumer Study Reviews

Not applicable as this product is for injection by health care practitioners.

5 Sources of Clinical Data and Review Strategy

5.1.Table of Clinical Studies

The following Table 4 lists the phase 3 study, 20070337, and four supportive studies (Study

20060326, 20101291, 20120156, and 20080289). Clinical efficacy and safety was based on the one trial, study 20070337 and the four supportive studies. All clinical studies including phase 1 studies completed in support of romosozumab is listed in Appendix 13.2.

Table 4: Table of Phase 2 and 3 Clinical Studies Supporting Application

Study Design Feature	Pivotal Study 20070337 (phase 3)	Placebo-controlled Supportive Studies			Active-comparator Supportive Study 20080289 (phase 3b)
		Study 20060326 (phase 2a)	Study 20101291 (phase 2b)	Study 20120156 (phase 3)	
Study design and population	Randomized, placebo-controlled in postmenopausal women with osteoporosis	Dose-ranging, randomized placebo- and active-controlled in postmenopausal women with low BMD	Dose-ranging, randomized placebo-controlled in postmenopausal Japanese women with osteoporosis	Placebo-controlled study of noninferiority of romosozumab 90 vs 70 mg/mL in postmenopausal women with osteoporosis	Open-label, randomized, teriparatide-controlled in postmenopausal women with osteoporosis transitioning from bisphosphonate therapy
Number of randomized subjects	7180 (3591 placebo; 3589 romosozumab)	419 (51 to 54 in each of 5 romosozumab groups; 52 placebo; 55 teriparatide; 51 alendronate)	252 (63 in each romosozumab group; 63 placebo)	294 (118 in 70 mg/mL, 123 in 90 mg/mL romosozumab groups; 53 placebo)	436 (218 romosozumab; 218 teriparatide)
Study duration	36 months[a]	72 months[b]	15 months	9 months[c]	12 months
Romosozumab SC doses	210 mg QM	Months 1 to 24: Romosozumab: 70 mg, 140 mg, or 210 mg SC QM or 140 mg or 210 mg SC Q3M (24 months) Control: placebo (24 months) or teriparatide 20 µg SC QD (12 months) or alendronate 70 mg PO QW (12 months) followed by romosozumab 140 mg SC QM (12 months) Months 24 to 36: placebo or denosumab 60 mg SC Q6M Months 36-48 (retreatment phase): romosozumab: 210 mg SC QM Months 48-72: zoledronic acid 5 mg IV or no intervention	70 mg, 140 mg, or 210 mg QM	210 mg QM	210 mg QM
Romosozumab treatment duration	12 months		12 months[d]	6 months	12 months[d]
Control	placebo SC		placebo SC	placebo SC	teriparatide 20 µg SC QD
History of fracture[e]	no history of hip fracture or severe vertebral or more than 2 moderate vertebral fractures	no history of vertebral fracture or fragility fracture of the wrist, humerus, hip or pelvis after age 50	no history of vertebral fracture or hip fracture	fragility fracture or ≥ 2 clinical risk factors for fracture	history of nonvertebral fracture after age 50 or vertebral fracture at any time
Concentration / Device	70 mg/mL / PFS	70 mg/mL / vial PFS for retreatment phase	70 mg/mL / PFS	70 mg/mL or 90 mg/mL / PFS	70 mg/mL / PFS
Randomization type	double-blind, stratified by age (< 75 years, ≥ 75 years) and prevalent vertebral fracture (yes, no)	double-blind (open-label alendronate or teriparatide), no stratification	double-blind, no stratification	double-blind, no stratification	open-label

Source: Clinical Overview Table 5 with reviewer edit

5.2.Review Strategy

Results of the applicant's analyses will be presented with the reviewer's commentary and edits. In certain cases of question, the statistics reviewer will be consulted to confirm or supplement the Applicants' analyses.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 20070337

6.1.1. Study Design

Overview and Objective

A Multicenter, International, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Efficacy and Safety of Romosozumab Treatment in Postmenopausal Women With Osteoporosis.

Trial Design

This was a multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study in postmenopausal women with osteoporosis, defined as low BMD at the total hip or femoral neck. Subjects were randomized 1:1 (stratified by age group [< 75 years, ≥75 years] and prevalent vertebral fracture) to receive romosozumab 210 mg subcutaneously (SC) every month (QM) or matched placebo SC QM for 12 months, after which both groups received open-label denosumab 60 mg every 6 months (Q6M) for an additional 12 months, blinded to initial treatment assignment. This 24-month primary analysis period (12 months of double-blind romosozumab or placebo followed by 12 months of open-label denosumab) was followed by a 12-month open-label extension period through month 36 (currently ongoing) in which eligible subjects continued to receive denosumab 60 mg Q6M. The current marketing application contains information for only the 24-month primary analysis period and does not contain information for the extension period through month 36.

The study included 10 substudies: Three substudies which include bone turnover markers (BTM) & biomarker substudy and two imaging substudies are discussed in section 6.1.2 efficacy results. Five substudies (calcium, serum intact PTH [iPTH] and urinary calcium, audiology and osteoarthritis) as well as bone biopsy results are discussed in the safety section 8. The remaining two substudies, pharmacokinetics or pharmacogenetic substudies, are discussed within clinical pharmacology. Each of the Study 20070337 substudies is summarized in Appendix 13.6.

Number of Subjects Planned: Approximately 6600

Diagnosis and Main Criteria for Eligibility: Subjects included postmenopausal women age 55 to 90 years with a BMD T-score at the total hip or femoral neck of ≤-2.50. Key exclusion criteria included a BMD T-score of ≤ -3.50 at the total hip or femoral neck, a hip fracture at any time, any severe or more than 2 moderate vertebral fractures, severe metabolic or bone diseases, and significant laboratory abnormalities. There were no prevalent fracture inclusion criteria and no adjustment to higher BMD inclusion criteria for prevalent fractures.

The use of agents affecting bone metabolism was also exclusionary; however, for selected therapies permissible off-treatment periods were allowed before randomization. For example, prior oral bisphosphonate therapy was allowed with the following limits:

- any dose received within 3 months prior to randomization
- more than 1 month of cumulative use between 3 and 12 months prior to randomization
- more than 3 years of cumulative use, unless last dose received ≥ 5 years prior to randomization

For IV bisphosphonates, the limits included:

- Zoledronic acid:
  - any dose received within 3 years prior to randomization
  - more than 1 dose received within 5 years prior to randomization
- IV ibandronate or IV pamidronate:
  - any dose received within 12 months prior to randomization
  - more than 3 years of cumulative use, unless last dose received ≥ 5 years prior to randomization

Investigational Products, Dose and Mode of Administration

Investigational Product: Romosozumab 210 mg SC QM or matched placebo SC QM followed by denosumab 60 mg SC Q6M.

Other Therapy: Daily calcium and vitamin D supplementation, that at a minimum was to be in the range of 500 to 1000 mg elemental calcium and 600 to 800 IU vitamin D. An initial loading dose of 50 000 to 60 000 IU vitamin D within 1 week after randomization was also administered, based on serum 25 hydroxy (OH) vitamin D concentration at screening for subjects with the following process: subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening received an initial loading dose of 50,000 to 60,000 IU vitamin D after randomization. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may also receive the vitamin D loading dose at the principal investigator's discretion. Subjects with serum 25(OH) vitamin D levels < 20 ng/ mL were excluded.

Duration of Treatment: The primary analysis period included a 24-month study period that consisted of 12 months of double-blind treatment with romosozumab or placebo, followed by 12 months of open-label treatment with denosumab. After the 24-month study period, eligible subjects who entered the extension period received an additional 12 months of open-label treatment with denosumab, for a total treatment period of 36 months. This application only contained information to the end of the 24 month study period and does not contain information for the extension from month 24 to month 36.

Fracture Analysis and Definitions:
At baseline/ screening, a single, central imaging center radiologist determined prevalent vertebral fractures on lateral-spine X-rays using the following Genant visual semiquantitative grading (SQ) scale:

- SQ grade 0 (SQ0) = no fracture
- SQ grade 1 (SQ1) = mild fracture, 20 to 25% reduction in vertebral height (anterior, middle, or posterior)
- SQ grade 2 (SQ2) = moderate fracture, 25 to 40% reduction in height
- SQ grade 3 (SQ3) = severe fracture, greater than 40% reduction in height

For incident fractures, the following listing defines each fracture type:

- New vertebral fractures occurred when there was ≥ 1 grade increase from the previous grade of 0 in any vertebra from T4 to L4 on the Genant SQ Scoring scale. All readers will be from the central imaging center. A primary reader will review radiographs as received. If a new vertebral fracture is identified, the second reader will assess the results blinded to the first reader's findings. A third reader will adjudicate if the primary and secondary readers disagree on the presence of a new vertebral fracture.
- Clinical fractures included clinical vertebral and nonvertebral fractures (excluding skull, facial, mandible, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, metacarpus, finger phalanges, and toe phalanges) that were associated with signs and/or symptoms indicative of a fracture. Clinical vertebral fractures were included regardless of trauma severity or pathologic fractures; nonvertebral fractures associated with high trauma severity or pathologic fractures were excluded. A single, central imaging center radiologist confirmed clinical fractures from either local radiology reports or from local radiographs sent to the central imaging center.
- Nonvertebral fracture was defined as a fracture present on a copy of radiographs or other diagnostic images such as computerized tomography (CT) or magnetic resonance imaging confirming the fracture within 14 days of a reported fracture, excluding skull, facial, mandible, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, metacarpus, finger phalanges, and toe phalanges. In addition,

fractures associated with high trauma severity or pathologic fractures were excluded.

- Major nonvertebral fracture was a subset of nonvertebral fractures including pelvis, distal femur (ie, femur excluding hip), proximal tibia (ie, tibia excluding ankle), ribs, proximal humerus (ie, humerus excluding elbow), forearm, and hip.
- Hip fracture was a subset of nonvertebral fractures including femur neck, femur intertrochanter, and femur subtrochanter.
- Major osteoporotic fractures included hip, forearm, or humerus fractures that were not associated with a pathologic fracture regardless of trauma severity, and clinical vertebral fractures.

Study Endpoints

- The co-primary endpoints were the subject incidence of new vertebral fracture through month 12 and through month 24.

- Secondary endpoints evaluated through month 12 and through month 24 were as follows:
  A) The subject incidence of:
     - clinical fracture (nonvertebral fracture and clinical vertebral fracture)
     - nonvertebral fracture
     - new or worsening vertebral fracture
     - major nonvertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip)
     - hip fracture
     - major osteoporotic fracture (hip, wrist, humerus, and clinical vertebral)
     - multiple new or worsening vertebral fracture
  B) Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck

- Safety endpoints through month 12 and through month 24 were:
     - subject incidence of adverse events by system organ class and preferred term
     - changes from baseline in laboratory assessments (serum chemistry and hematology)
     - and the shift between baseline and the worst value
     - changes from baseline in vital signs
     - subject incidence of antiromosozumab antibodies
     - subject incidence of antidenosumab antibodies (from month 12 to month 24)

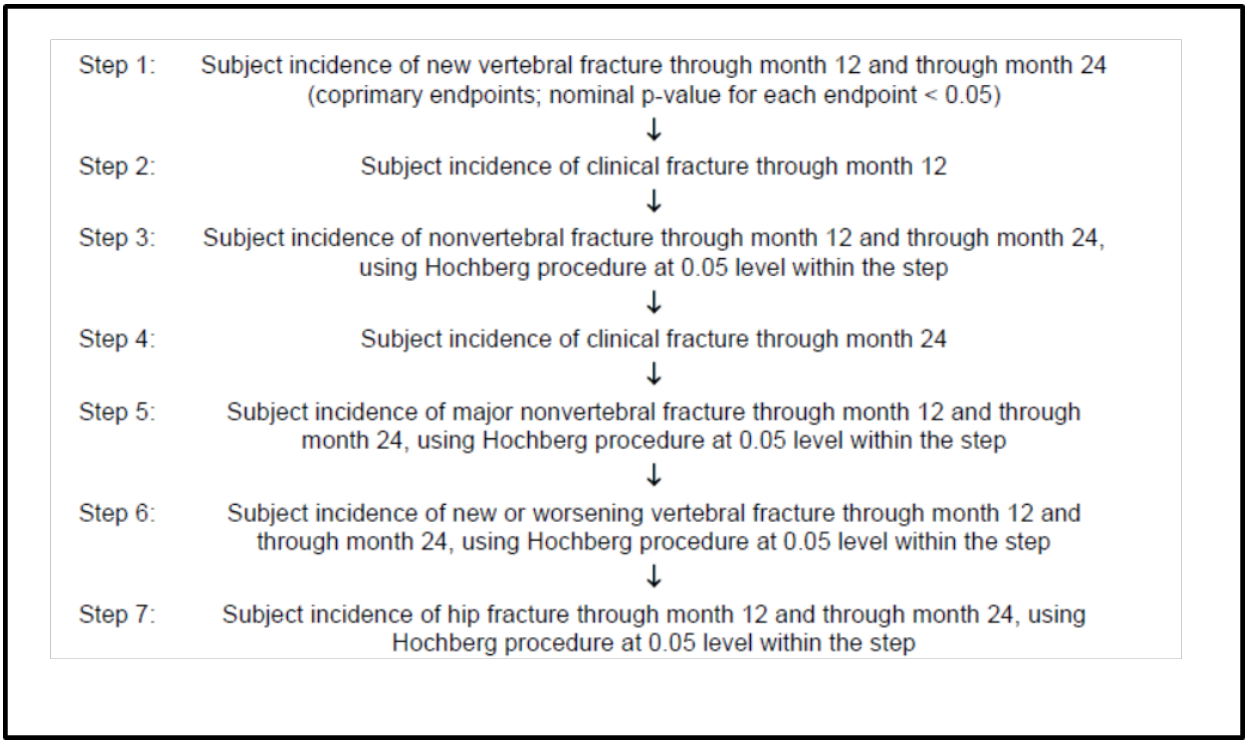
- Exploratory efficacy endpoints that describe new vertebral fractures through month 6, clinical vertebral fractures, tooth loss, health-related quality of life, pain experience and

activity restrictions during the study and after nonvertebral or clinical vertebral fractures.

Statistical Analysis Plan

A fixed-sequence testing procedure was used for multiplicity adjustment of the coprimary and a subset of secondary efficacy endpoints to maintain the overall significance level at 0.05. If the testing sequence was stopped at a particular step, the remaining endpoints in the testing sequence were not formally tested for statistical significance, and the corresponding p-values were considered descriptive. The following figure 3 graphs this pre-specified fixed-sequence testing for fracture endpoints (see definitions of fractures in the section above).

Figure 3: Pre-specified Fixed-Sequence Fracture Endpoint Testing Procedure



Source: CSR 20070337 Stat Analysis Plan with reviewer edits

The p-values for the analyses of other secondary, exploratory, and substudy endpoints were nominal without adjusting for multiplicity. All p-values were 2-sided.

Coprimary Endpoints: The primary analysis set for vertebral fractures was used for analyses of subject incidence of new vertebral fracture through month 12 and through month 24. The number and percentage of subjects with new vertebral fracture was summarized by treatment group. The significance of the treatment effect between romosozumab and placebo (month 12)

and romosozumab/denosumab and placebo/denosumab (month 24) was assessed using a logistic regression model with treatment as the main effect and age and prevalent vertebral fracture strata as covariates. The odds ratio, corresponding 95% confidence interval, and p-value of the score test were provided. Statistical significance for the coprimary endpoints was declared if the p-values for testing the treatment effects through month 12 and month 24 were both < 0.05. Point estimates of absolute risk reduction (difference in proportions, control – treatment), risk ratio (ratio of proportions, treatment over control), and the corresponding 95% confidence intervals were also calculated using the Mantel-Haenszel method adjusting for age and prevalent vertebral fracture strata.

Secondary Fracture Endpoints: Analyses of new or worsening vertebral fractures and multiple new or worsening vertebral fractures were performed on the primary analysis set using the logistic regression analysis described for the coprimary endpoints. For other fracture endpoints, a time-to-event analysis was used on the full analysis set. In this analysis, the cumulative incidence of fractures was summarized using Kaplan-Meier estimates.

The significance of the treatment effect between romosozumab and placebo (month 12) or romosozumab/denosumab and placebo/denosumab (month 24) was assessed using a stratified Cox proportional hazards model that controlled for age and prevalent vertebral fracture strata and had treatment as the independent variable. The estimated hazard ratio, corresponding 95% confidence interval, and the p-value of the score test were provided. Point estimate of the adjusted risk difference (difference in Kaplan-Meier estimates, control arm – treatment arm) and the corresponding 95% confidence interval were also provided using the inverse variance-weighted method. Adjusted p-values based on the testing sequence for secondary fracture endpoints were provided in addition to the nominal p-values from the statistical tests.

Subgroup Analyses: Subgroups analyses were performed for new vertebral fracture, clinical fracture, and nonvertebral fracture at months 12 and 24 using subgroup categories of age < 65 and ≥ 65 years, age < 75 and ≥ 75 years, prevalent vertebral fracture status (yes, no), history of fragility fracture (yes, no), history of nonvertebral fracture at age ≥ 55 years (yes, no), race (white, non-white), geographic region (Western Europe and Australia/New Zealand, Central and Eastern Europe; Asia Pacific; North America; and Central/Latin America), baseline lumbar spine BMD T-score (≤ -3, > -3 and ≤-2.5, > -2.5), baseline total hip or femoral neck BMD T-score ≤-3 vs both total hip and femoral neck BMD T-score > -3, baseline body mass index (BMI) (tertiles), and World Health Organization Fracture Risk Assessment tool (FRAX) score for major osteoporotic fracture (tertiles). The treatment-by-subgroup interaction was tested quantitatively. If the p-value for the quantitative interaction was ≤ 0.05, qualitative interaction testing was performed.

Bone Mineral Density Endpoints: The primary efficacy analysis set for BMD (month 12 and month 24) was used for analyses of percent change from baseline in BMD. The treatment

comparisons of the BMD in lumbar spine, total hip and femoral neck at months 12 and 24 were analyzed using an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) imputation as the primary analysis. The ANCOVA model included treatment, age and prevalent vertebral fracture strata, and baseline value of the endpoint. Additional covariates of machine type and machine type-by-baseline value interaction were also included. Least squares mean of the treatment difference (treatment – control), the corresponding 95% confidence interval, and p-value were used to compare treatments at each time point.

The following Table 5 summarizes statistical methods for the fracture endpoints of study 20070337:

Table 5: Summary of Analysis Methods for Fracture and BMD Endpoints Study 20070337

Endpoints	Methods
Binary endpoints Subject incidence of: • new vertebral fracture • new or worsening vertebral fracture • multiple new or worsening vertebral fracture	• Based on primary analysis set for vertebral fractures • Summarized by randomized treatment group as the number and percentage of subjects having the designated fracture type • Compared using a logistic regression model with treatment as the main effect and age and prevalent vertebral fracture strata as covariates; odds ratio, 95% CI, and p-value (score test) were provided • Also evaluated using Mantel-Haenszel method adjusting for age and prevalent vertebral fracture strata to generate point estimates of absolute risk reduction (difference in proportions, control – treatment), risk ratio (ratio of proportions, treatment over control), and 95% CIs
Time to event endpoints Subject incidence of: • nonvertebral fracture • clinical fracture • major nonvertebral fracture • major osteoporotic fracture • clinical vertebral fracture • hip fracture	• Based on full analysis set • Summarized descriptively using Kaplan-Meier estimates at time point(s) of interest (ie, month 12 and month 24) • Compared using a stratified Cox proportional hazards model controlling for age and prevalent vertebral fracture strata with treatment as the independent variable; estimated hazard ratio, 95% CI, and p-value (score test) were provided • Also evaluated using inverse variance-weighted method to produce point estimate of the adjusted risk difference (difference in Kaplan-Meier estimates at the time point of interest, control arm – treatment arm) and 95% CI • Subjects with no event of interest were censored for analysis of that event at the end of double-blind period (month 12 analysis) or at the end of the 24-month study period (month 24 analysis).
ANCOVA Model[a] Percent change from baseline in BMD by DXA for: • lumbar spine • total hip • femoral neck	• Based on primary analysis set for BMD • Compared using an ANCOVA model with treatment, age and prevalent vertebral fracture strata and baseline value of the endpoint. Additional covariates of machine type and machine type-by-baseline value interaction were included in the model for parameters derived by DXA. Least-squares mean of the treatment difference (treatment – control) and 95% CI were provided.

Source: CSR Study 20070337: Table 8-13 with reviewer edits.

Safety Endpoints: The safety analysis set was used for the safety analyses. Subject incidence of all treatment-emergent adverse events (hereafter referred to as adverse events) was tabulated by system organ class and preferred term according to the treatment actually received. Adjudicated events of osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) were

summarized by number of events and subject incidence. Adjudicated cardiovascular events were summarized as subject incidence.

Laboratory tests were also summarized over time by actual value and change from baseline for all tests, and also by percent change from baseline for select laboratory tests. Laboratory tests were summarized using Common Terminology Criteria for Adverse Events (CTCAE) shift tables of the baseline to the worst post baseline grade. The numbers and percentages of subjects exhibiting antiromosozumab antibodies (baseline and months 1, 3, 6, 12, 15, and 24) and antidenosumab antibodies (months 12 and 24) were tabulated.

Protocol Amendments

The following table 6 summarizes important changes to study design 20070337 during development.

Table 6: Summary of Important Changes in Study Design 20070337

Study Number	Protocol Amendment (Submission Date)	Description of Change
Change of primary endpoints during conduct of trial		
20070337	Protocol Amendment 1 (30 August 2012)	A coprimary objective was added to assess the effect of romosozumab treatment for 12 months followed by denosumab treatment for 12 months compared with placebo followed by denosumab treatment on the subject incidence of new vertebral fracture. This change was made following discussions with the Agency after the 19 August 2011 EOP2 Meeting (Amgen Response to Questions submitted 07 February 2012, SN 0139),
Changes in inclusion and/or exclusion criteria		
20070337	Protocol Amendment 1 (30 August 2012)	Exclusion criteria were amended with respect to prior administration of osteoporosis medications, medical history of sclerosteosis, possible diagnosis of multiple myeloma or related lymphoproliferative disorder, known to have HIV, hepatitis C virus or hepatitis-B infection or reported history or hearing loss due to excessive bone growth. Removed exclusion criteria of androgen deprivation therapy as it was not applicable to postmenopausal women.
20070337	Protocol Amendment 3 (28 May 2013)	The eligibility criteria were modified to allow participation of a wider range of patients. Specifically, the minimum age was lowered from 60 to 55 years.
Sample size modification		
20070337	Protocol Amendment 1 (30 August 2012)	The number of subjects enrolled was increased from 5,600 to 6,000 to ensure enough power to assess the effect of treatment regimens on reduction in non-vertebral fractures at the end of 24 months.

20070337	Protocol Amendment 4 (04 October 2013)	The sample size was modified based on the new assumption that the incidence rate of new vertebral and nonvertebral fracture in the placebo group was 12.5% lower than the original assumptions. Using the revised assumption of in the placebo group, the sample size for the study was increased to 6600 subjects.
Changes in study duration		
20070337	Protocol Amendment 4 (04 October 2013)	Study was extended to 36 months by including a 12 month open-label denosumab extension period, adding safety endpoints at months 30 and 36 and exploratory efficacy endpoints at month 36, while subjects remained blinded to their initial treatment assignment. These changes to Study 20070337 were made after end of phase 2 interactions with regulatory agencies.

<u>Reviewer Comments:</u> The Division informed the sponsor at the EOP2 meeting, August 19, 2011, that the 24 month fracture data would be required for an osteoporosis indication. The changes in the protocol appear to accommodate that requirement and are thus, acceptable. were made in order to accommodate that requirement.

The sample size was increased twice to insure enough patients to achieve enough power with the addition of the co-primary endpoint at 24 months and because the rate of non-vertebral fractures was 12.5% lower than the original assumptions. Age limit was lowered from age 60 to 55 in order to allow more patients into the study. Together these changes allowed the study to recruit enough subjects to complete the study.

Data Quality and Integrity: Sponsor's Assurance

Study Monitoring
The study centers were monitored by the Sponsor. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data.

Investigator Meetings and Staff Training
The sponsor organized investigator and clinical research associate meetings before study start and during the study to provide information on the investigational product, the study rationale and design, responsibilities under FDA GCP, and training on the detailed study requirements.

Standardization of Laboratory Procedures
Central laboratories and vendors were used to analyze all screening and on-study samples for serum chemistry, hematology, biomarker and BTMs (P1NP, osteocalcin [OC], bone-specific alkaline phosphatase [BSAP], serum Type I collagen C-telopeptide [sCTX], tartrate-resistant acid phosphatase 5b [TRAP 5b]), 25 (OH) vitamin D, PK, antiromosozumab antibodies, and antidenosumab antibodies, as well as X-rays, DXA data, and High Resolution peripheral QCT

(HR-pQCT) data. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors.

Lateral spine X-rays, DXA images, and HR-pQCT images were acquired according to specific instructions provided by the central imaging vendor and all images were analyzed by the central imaging center.

6.1.2. Study Results

Compliance with Good Clinical Practices

The independent ethics committee (IEC) or institutional review board (IRB) reviewed and approved the study protocol and informed consent. This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) or local regulations/guidelines.

Financial Disclosure

See Appendix 13.2 for financial disclosure. Although a number of investigators did not return their disclosure forms, 4 sub-investigators in Columbia who were involved in a significant number of subjects (955 subjects – 13% of subjects) did not return their signed financial disclosures. The following table 7 lists these sites and investigators along with reasons from the Sponsor on attempts to obtain the signed financial disclosure:

Table 7: Select List of Investigators from 3 Sites (Columbia) Participating in Study 20070337 Not Providing Financial Disclosure Information

Site No.	Physician's Name / Address	Position Held	Subjects Enrolled	Reason
(b) (6)		Sub-Investigator	419	
		Sub-Investigator	415	
		Sub-Investigator	121	Financial disclosure was never signed. PI confirmed sub-investigator had no financial interest with Amgen. Investigator no longer available.
		Sub-Investigator		Financial disclosure was never signed. PI confirmed sub-investigator had no financial interest with Amgen. Investigator no longer available.

Source: Financial Disclosure Table 8 with reviewer edits.

Reviewer Comments: ***These four sub-investigators who did not return signed financial disclosure forms are noteworthy because they were involved in a significant number of***

patients (955 patients -13% of the study). The statistics reviewer performed a sensitivity analysis on the co-primary endpoints with these sites removed and the results did not differ from the study results. See section data quality and data integrity for discussion.

Patient Disposition

The study was conducted globally at 222 centers in 25 countries: 31 centers in Central/Latin America (43% of randomized subjects), 51 centers in Central and Eastern Europe (29 % of randomized subjects), 52 centers in Western Europe and Australia/New Zealand (14 % of randomized subjects), 62 centers in Asia Pacific (12 % of randomized subjects) and 26 centers in North America (3% of randomized subjects). Countries that randomized more than 10% of subjects included Colombia (25 %), Poland (17 %), and Brazil (11 %).

A total of 16,716 subjects were screened for the study and 7180 were randomized to the romosozumab 210 mg (3589 subjects) and placebo (3591 subjects) groups. The following two tables 8 and 9 summarize subject disposition in study 20070337 for the double blind period through month 12 (table 8) and through the extension period where all patients were treated with denosumab to month 24 (table 9).

Table 8: Disposition of Subjects for the Double-Blind Period to Month 12.

	Placebo/ Denosumab 60 mg Q6M (N = 3591) n (%)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589) n (%)	All (N = 7180) n (%)
Completed double-blind period	**3205 (89)**	**3185 (90)**	**6390 (89)**
Discontinued study during double-blind period:	**386 (11)**	**404 (11)**	**790 (11)**
Consent withdrawn	253 (7)	261 (7)	514 (7)
Adverse event	39 (1)	39 (1)	78 (1)
Other	24 (0.7)	34 (0.9)	58 (0.8)
Death	20 (0.6)	27 (0.8)	47 (0.7)
Lost to follow-up	21 (0.6)	22 (0.6)	43 (0.6)
Noncompliance	16 (0.4)	9 (0.3)	25 (0.3)
Ineligibility determined	6 (0.2)	7 (0.2)	13 (0.2)
Protocol deviation	3 (<0.1)	2 (<0.1)	5 (<0.1)
Requirement for alternative therapy	2 (<0.1)	2 (<0.1)	4 (<0.1)
Administrative decision	2 (<0.1)	1 (<0.1)	3 (<0.1)

Table 9: Subject Disposition for Double-Blind Period with Extension Period to Month 24

	Placebo/ Denosumab 60 mg Q6M (N = 3591) n (%)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589) n (%)	All (N = 7180) n (%)
Completed 24-month study period	**3032 (84)**	**2994 (83)**	**6026 (84)**
Discontinued study during 24-month study Period:	**559 (16)**	**595 (17)**	**1154 (16)**
Consent withdrawn	314 (9)	346 (10)	660 (9)
Other	44 (1)	54 (2)	98 (1)
Death	44 (1)	49 (1)	93 (1)
Adverse event	53 (2)	47 (1)	100 (1)
Lost to follow-up	35 (1)	37 (1)	72 (1)
Administrative decision	15 (0.4)	20 (0.6)	35 (0.5)
Noncompliance	33 (0.9)	15 (0.4)	48 (0.7)
Ongoing	7 (0.2)	12 (0.3)	19 (0.3)
Ineligibility determined	8 (0.2)	8 (0.2)	16 (0.2)
Requirement for alternative therapy	2 (<0.1)	4 (0.1)	6 (<0.1)
Protocol deviation	4 (0.1)	3 (<0.1)	7 (<0.1)

Both Table 7 and 8 Source: CSR20070337 Table 14-1.1. with reviewer edits.

Eighty-nine percent of enrolled subjects completed the 12-month double-blind period (romosozumab, 89%; placebo, 89%) and 84 % of subjects completed the 24-month study period (romosozumab/denosumab, 83 %; placebo/denosumab, 84 %). Throughout the study, withdrawn consent was the most frequently reported reason for withdrawal from study in both treatment groups (romosozumab, 7 %; placebo, 7 % during 12-month double-blind period and romosozumab/denosumab, 10 %; placebo/denosumab, 9 % during the 24-month study period).

Protocol Violations/Deviations

A total of 254 (4 %) subjects had at least 1 important protocol deviation (including eligibility criteria deviations that were considered important) during the 24-month study period. The most frequently reported important protocol deviations pertained to subjects who missed > 3 doses of romosozumab or placebo during the double-blind period (1 % of subjects in the romosozumab group and 2 % of subjects in the placebo group). Of the 34 (0.5%) subjects who received an incorrect box for romosozumab or placebo during double-blind treatment, 14 (0.2%) received investigational product that did not match the subject's randomized treatment group. Six of these subjects were randomized to placebo and received a dose of romosozumab in error during the double-blind period. Therefore, these 6 subjects were included in the placebo group (ie, as randomized) for efficacy analyses, but in the romosozumab group (ie, as treated) for safety analyses.
During review, the Office of Scientific Investigator (OSI) noted that one of the sites, Dr. Jose FM Restrepo (Site # 1-678YLY/**68007**) in Columbia had a major issue of delayed randomization. The

Sponsor was asked to report randomization times for study 20070337. The Sponsor reported that a total of 7% (481 patients) of the subjects enrolled in Study 20070337 had a screening duration > 35 days and 1.3% (95 patients) exceeded 70 days in total screening duration. Of the subjects with a screening period longer than 70 days, the majority were between 71 and 79 days, with few subjects exceeding 90 days. The longer screening duration was predominantly observed in the Latin American region, specifically at 2 sites in Columbia.

Although required by the protocol, most subjects with a long screening period did not have repeat testing performed prior to randomization. The Sponsor examined these subjects' screening, and as applicable, baseline or on-study spinal X-rays, calcium, and vitamin D values as a surrogate for prior-to-randomization values to ensure that subjects did not have a severe fracture (or more than 2 moderate fractures), hypo- or hypercalcemia, or excessively low vitamin D levels that would have deemed them ineligible to participate. Subject listings confirm that all subjects met X-ray and vitamin D eligibility criteria and only 1 did not meet calcium eligibility criteria—with grade 1 hypercalcemia at screening and baseline.

***Reviewer Comments:* Although there was 7% screening delay > 35 days and the majority of the patients with > 70 days screening delayed were not rescreened, patient eligibility did not appear to have been affected by the delays.**

Other important protocol deviations (entered study even though entry criteria were not satisfied, missed month 12 or end of treatment lateral spine X-ray, had a calcium level below the lower limit of normal at month 11 or month 11 + 14 days and was not withdrawn, received an excluded concomitant medication) were each reported for < 1.0% of subjects in either treatment group.

***Reviewer Comments:* The low incidences and balanced protocol deviations between treatment groups do not raise concern about protocol deviations affecting interpretation of the study results.**

Table of Demographic Characteristics and Other Baseline Characteristics

Demographic characteristics were generally balanced between the 2 treatment groups. All enrolled subjects were women as required by the inclusion criteria. Overall, 57 % of randomized subjects were white and 40 % were Hispanic or Latino. The mean age of study subjects was 70.9 years (range: 55 to 90 years), and 31 % of subjects were ≥ 75 years of age at enrollment. Body composition of the study subjects included mean (SD) weight of 57.94 (10.96) kg, mean (SD) height of 153.2 (7.3) cm, and mean (SD) BMI of 24.70 (4.36) kg/m2. Table 10 summarizes the demographic characteristics in Study 20070337.

Table 10: Baseline Demographic Characteristics Study 20070337

	Placebo/ Denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589)	All (N = 7180)
Sex - n (%)			
Female	3591 (100.0)	3589 (100.0)	7180 (100.0)
Ethnicity - n (%)			
Hispanic or Latino	1416 (39.4)	1427 (39.8)	2843 (39.6)
Not Hispanic or Latino	2175 (60.6)	2162 (60.2)	4337 (60.4)
Race - n (%)			
White	2052 (57.1)	2063 (57.5)	4115 (57.3)
Asian	441 (12.3)	425 (11.8)	866 (12.1)
Black or African American	74 (2.1)	77 (2.1)	151 (2.1)
American Indian or Alaska Native	63 (1.8)	64 (1.8)	127 (1.8)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	0 (0.0)	1 (<0.1)
Multiple	59 (1.6)	60 (1.7)	119 (1.7)
Other	901 (25.1)	900 (25.1)	1801 (25.1)
Age (years)			
n	3591	3589	7180
Mean	70.8	70.9	70.9
SD	6.9	7.0	7.0
Median	70.0	70.0	70.0
Q1, Q3	65.0, 76.0	65.0, 76.0	65.0, 76.0
Min, Max	55, 90	55, 90	55, 90
Geriatric group - n (%)			
< 65 years	757 (21.1)	768 (21.4)	1525 (21.2)
≥ 65 years	2834 (78.9)	2821 (78.6)	5655 (78.8)
≥ 75 years	1121 (31.2)	1119 (31.2)	2240 (31.2)
Geographic region - n (%)			
Asia Pacific	419 (11.7)	410 (11.4)	829 (11.5)
Central and Eastern Europe	1050 (29.2)	1043 (29.1)	2093 (29.2)
Central/Latin America	1534 (42.7)	1550 (43.2)	3084 (43.0)
North America	91 (2.5)	104 (2.9)	195 (2.7)
Western Europe and Australia/New Zealand	497 (13.8)	482 (13.4)	979 (13.6)

Source: CSR 20070337: Table 14-2.1 with reviewer edits.

Baseline laboratory parameters were balanced between the 2 treatment groups including mean baseline albumin-adjusted calcium, phosphorus, and creatinine. Glomerular filtration rate was ≥ 60 mL/min/1.73 m2 for the majority of subjects (81 %). 99.7% of subjects had baseline serum concentrations of 25 (OH) vitamin D ≥ 20 ng/mL.

A minority of subjects (7 %) had used osteoporosis medications with oral bisphosphonates the most frequently reported prior osteoporosis medication (5 % of subjects). 99% of subjects reported baseline concomitant medication of calcium and vitamin D concomitant use was reported for concomitant medication. 77 % (5550 subjects) of subjects started with an initial loading dose of 50,000 to 60,000 IU vitamin D at baseline.

Reviewer Comments: Baseline demographics between the two treatment groups were similar at baseline for age, vital signs, and medical histories.

Spine radiographs showed that 18 % of subjects had at least 1 verified prevalent vertebral fracture at baseline and 22 % subjects had a history of nonvertebral fracture at or after age 45. The study had excluded patients with any prevalent severe vertebral fractures or more than 2 moderate vertebral fractures. The following table 11 summarizes prevalent fracture history of subjects.

Table 11: Prevalent Fracture History of Subjects in 20070336

	Placebo/ Denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589)	All (N = 7180)
Any historical fracture - n (%)	1469 (41)	1457 (41)	2926 (41)
Prevalent vertebral fractures - n (%)	645 (18)	672 (19)	1317 (18)
Any historical fracture on or after age 45 - n (%)			
Any	1451 (40)	1434 (40)	2885 (40)
Osteoporotic fractures	1258 (35)	1270 (35)	2528 (35)
Nonvertebral fractures	782 (22)	778 (22)	1560 (22)
Major nonvertebral fractures	597 (17)	543 (15)	1140 (15.9)

Source: CSR 20070336 Table 14-2.6. with reviewer edits.

The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were -2.72, -2.47, and -2.75, respectively. Baseline characteristics relevant to determination of the 10-year probability of a major osteoporotic fracture, according to the WHO Fracture Risk Assessment tool (FRAX), were similar between treatment groups. The mean 10-year probabilities of major osteoporotic fractures and of hip fractures calculated with femoral neck BMD were 13.4 % (range: 2.7% to 69.7%) and 5.9% (range: 0.3% to 57.9%), respectively. Baseline cardiovascular risk factors (age, smoking history, and history of hypercholesterolemia, hypertension, diabetes, or cardiovascular disease) were also similar between the 2 treatment groups.

Reviewer Comments: ***The demographics was well balanced between groups in both major characteristics and laboratory parameters which is reflective of the quality of randomization but there were demographic differences which are significant weaknesses of the trial when extrapolating the results to the US population.***

This study was conducted mostly out of the US and the race demographics differ significantly from the US population. 43% of the subjects were enrolled from Latin America and 29% were from Eastern/Central Europe while only 3 % of the subjects were enrolled from the US. There is higher enrollment of Hispanics and lower enrollment of Blacks when comparing the study demographics to the US population.

There is evidence that the predominance of South American/ Hispanic subjects enrolled in this trial affected the sample size as there were fewer new vertebral fractures found in this population than predicted. Under a protocol amendment, the sample size was increased in order to reach statistical power for the primary endpoints because this predominant population had fewer fractures than anticipated. However, the baseline prevalent vertebral fracture history is well balanced between the treatment and placebo groups (19% romosozumab versus 18% placebo patients) which support extrapolation of the study results to the US population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The investigational product (romosozumab or matched placebo PFS and denosumab PFS) was not dispensed to the subjects; all romosozumab, placebo, and denosumab injections were administered by authorized healthcare professionals at the study centers, and were documented on the eCRF.

Concomitant medications included calcium and vitamin D supplementation for all subjects.

Rescue medication – No rescue medications for osteoporosis were planned for the study.

Reviewer Comments: ***Of note, on a search of the database for concomitant medications during the double-blinded period, 15 patients on romosozumab and 12 patients in the placebo group started on a variety of osteoporotic medications, mostly bisphosphonates. 2 patients started on strontium renelate (1 in romosozumab, 1 in placebo) and 2 patients in the romosozumab group each started on a SERM or teriparatide.***

Efficacy Results – Primary Endpoint

In Study 20070337, the pivotal phase 3 study, romosozumab significantly reduced the incidence of new vertebral fractures compared with placebo through month 12 ($p < 0.001$), with a relative risk reduction of 73% (95% CI: 53%, 84%) and absolute risk reduction by % of 1.30 (95% CI: 0.79, 1.80). In addition, in subjects who received romosozumab during the first year, reduction in fracture risk persisted through the second year in subjects who transitioned from romosozumab to denosumab compared with those who transitioned from placebo to denosumab ($p < 0.001$), with a relative risk reduction of 75% (95% CI: 60%, 84%) and absolute risk reductions by % of 1.89 (95% CI: 1.30, 2.49) at month 24.

Fewer new vertebral fractures occurred during follow-on treatment in subjects who had received romosozumab compared with subjects who had received placebo in the first year of study (5 versus 25 fractures in the second year, respectively) even though both arms were receiving denosumab during the second year. The following Table 12 summarizes the co-primary endpoints with accompanying relative risk ratios and p-values, both p-values < 0.001.

Table 12: Incidence Rates of New Vertebral Fracture Through Month 12 and Through Month 24: Co-Primary Endpoints

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

N = Number of subjects randomized Note: Subjects who missed the 12 month visit are not included in the 12 month analysis but could have been included in the 24 month analysis if these subjects went on to complete the study.
N1 = Number of subjects in the primary analysis set for vertebral fractures
Positive values for absolute risk reduction and values < 1 for risk ratio and odds ratio favor romosozumab.
[a] *Based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables*
[b] *SE represents the standard error of log (risk ratio).*
[c] *Calculated from risk ratio as 100 x (1 – risk ratio)*
[d] *Based on logistic regression model adjusted for age and prevalent vertebral fracture stratification variables; p-value based on score test*
[e] *SE represents the standard error of log (odds ratio).*

Source: CSR 20070337 Table 10-1 and Table 14-4.1.1 with statistics reviewer input and reviewer edits.

Reviewer Comments: ***New vertebral fractures results through month 12 and month 24 met statistical significance (p < 0.001) for absolute risk reductions and relative risk reductions at both month 12 and month 24 which fulfilled the more persuasive requirements (p < 0.01) for a single pivotal study, a presubmission agreement.***

Subgroup analysis for co-primary endpoints:

A consistent treatment effect was found across all subgroups for the coprimary endpoints of vertebral fracture at 12 and 24 months. No significant quantitative interactions were detected through month 12 or through month 24 for any subgroup of baseline characteristics examined (age, prevalent vertebral fracture status, race, geographic region, baseline lumbar spine BMD T-score, baseline total hip/femoral neck BMD T-score, baseline BMI, FRAX score, history of nonvertebral fracture at or after age 55, and history of fragility fracture). All p-values on tests of quantitative interactions were > 0.05; therefore, no relevant treatment-by- subgroup interactions (quantitative or qualitative) were identified through month 12 or through month 24 for any subgroup.

Data Quality and Integrity – Reviewers' Assessment

Efficacy was evaluated by combining all results from all centers. No centers were removed from the analysis because of potential fraudulent data.

Three sites in Columbia where 4 co-investigators did not submit financial disclosures were analyzed to confirm that these site results did not alter the study results. This sensitivity analysis of the co-primary endpoints, removing these 3 sites (sites 68001, 68002, 68006) demonstrated that the results of the co-primary endpoints are unchanged and that both endpoints remain statistically significant. The following table 13 summarizes the co-primary endpoints, new vertebral fractures at 12 and 24 months, with these sites removed.

Table 13: Sensitivity Analysis of Co-Primary Endpoints with Sites 68001, 68002, and 68006 removed.

Statistic	Through Month 12		Through Month 24	
	Placebo (N = 3591)	Romosozumab (N = 3589)	Placebo/ Denosumab (N = 3591)	Romosozumab / Denosumab (N = 3589)
Incidence, n/N1 (%)	56/2867 (1.95)	15/2887 (0.52)	77/2872 (2.68)	19/2891 (0.66)
Risk Comparison Estimates				
Absolute risk reduction (%)* 95% CI	1.4% (0.9%, 2.0%)		2.0% (1.4%, 2.7%)	
Relative risk reduction * 95% CI	73% (53%, 85%)		75% (60%, 85%)	
p-value†	< 0.001		< 0.001	

Source: Statistics reviewer analysis with reviewer edits.

***Reviewer Comments:* As the analysis demonstrated that both the co-primary endpoints are statistically significant (p<0.001), and consistent with the findings from the pivotal study, the missing financial disclosures at these sites did not affect co-primary efficacy outcomes in the study.**

Efficacy Results – Secondary and other relevant endpoints

Analysis of results from secondary fracture endpoints followed the pre-specified fixed-sequence procedure for multiplicity adjustment of the endpoints to maintain the overall significance level at 0.05, discussed with types of fracture definitions in section 6.1.1.

- Step 1: Co-primary new vertebral fracture endpoints.

- Step 2: Clinical fractures, defined as nonvertebral fractures plus symptomatic (clinical) vertebral fractures, at 12 months was the next step in the analysis which showed that romosozumab significantly reduced the incidence of clinical fractures by 36% (95% CI:

11%, 54%) compared with placebo through month 12 (p = 0.008). The following table 14 summarizes clinical fractures results through 12 months, step 2 of the fixed-sequence procedure for multiplicity adjustment.

Table 14: Clinical Fracture Results at 12 months (Step 2 of Multiplicity Adjustment Fixed-Sequence Procedure)

Time Point Fracture Category	Proportion of Subjects with Fracture (n/N1 [%])[a] Placebo	Romosozumab	Absolute Risk Reduction (%), (95% CI)[b]	Relative Risk Reduction (%), (95% CI)[c,d]	Nominal p-value	Adjusted p-value[e]
Through Month 12						
Clinical	90/3591 (2.5)	58/3589 (1.6)	1.2 (0.4, 1.9)	36 (11, 54)	0.008	0.008

Source: CSR 20070337 Table 10.2 with reviewer edits

Reviewer Comments: Clinical fractures results through 12 months were statistically significant both nominally and when adjusted for multiplicity. Clinical fractures through 24 months were not included in this step 2 of the fixed sequence testing strategy and are located further down the sequence at step 4. Further discussion of clinical fractures results is included below under step 4 (b) (4)**.**

- Step 3: Nonvertebral fractures: The third step of the pre-specified fixed-sequence testing was to analyze nonvertebral fractures incidences at two time points, through month 12 and month 24. The relative risk reduction with romosozumab for nonvertebral fracture through month 12 (25% [95% CI: -5%, 47%]) was not statistically significant (p = 0.096). For the relative risk reduction with romosozumab for nonvertebral fracture through month 24 (25% [95% CI: 3%, 43%]), the p-value was nominally significant (p = 0.029), but did not meet statistical significance after adjusting for multiple comparisons (p = 0.057). The following table 14 summarizes nonvertebral fractures through 12 months and 24 months.

Table 15: Nonvertebral Fracture Results Through Month 12 and Month 24 (Step 3 of Multiplicity Adjustment Fixed-Sequence Procedure)

Time Point Fracture Category	Proportion of Subjects with Fracture (n/N1 [%])[a] Placebo	Romosozumab	Absolute Risk Reduction (%) (95% CI)	Relative Risk Reduction, % (95% CI)	Nominal p-value[b,c]	Adjusted p-value[d]
Through month 12						
Nonvertebral[c]	75/3591 (2.1)	56/3589 (1.6)	0.8 (0.1, 1.4)	25 (-5, 47)	0.096	0.096
Through month 24						
Nonvertebral[c]	129/3591 (3.6)	96/3589 (2.7)	1.0 (0.2, 1.9)	25 (3, 43)	0.029	0.057

Source: CSR 20070337 Table 10-2 with reviewer edits.

Reviewer Comments: ***Neither nonvertebral fracture endpoints (through 12 months or 24 months) met statistical significance when adjusted for multiplicity, both adjusted p-value > 0.05. The testing sequence ends at this step and further fracture analysis in the sequential testing strategy will result in adjusted p-values > 0.05.***

- Step 4: Clinical fractures at 24 months: The fourth step of the fixed-sequence testing was for an analysis of clinical fractures through 24 months. As the testing sequence ended at the previous step, clinical fractures through 24 months will not be statistically significant when adjusted for multiplicity. The following table 16 summarizes the clinical fractures through month 24.

Table 16: Clinical Fracture Results Through Month 24 (Step 4 of Multiplicity Adjustment Fixed-Sequence Procedure)

Time Point Fracture Category	Proportion of Subjects with Fracture (n/N1 [%])[a] Placebo	Romosozumab	Absolute Risk Reduction (%), (95% CI)[b]	Relative Risk Reduction (%), (95% CI)[c,d]	Nominal p-value	Adjusted p-value[e]
Through Month 24						
Clinical	147/3591 (4.1)	99/3589 (2.8)	1.4 (0.5, 2.4)	33 (13, 48)	0.002	0.096

Source: CSR 20070337 Table 10-2 with reviewer edits.

Reviewer Comments: ***Clinical fractures through 24 months did NOT meet clinical significance when adjusted for multiplicity as expected. The Sponsor*** (b) (4) (b) (4) ***performed subgroup analysis on clinical and nonvertebral fractures, discussed below.***

Clinical Fracture Subgroup Analysis: The subgroup analyses of clinical fracture and nonvertebral fracture through month 12 showed a significant quantitative interaction by

geographical region (p = 0.029 and p = 0.042, respectively). The nonvertebral component of clinical fractures (defined as nonvertebral fractures plus symptomatic vertebral fractures) accounted for more than 85% of clinical fractures. Nonvertebral subgroup analysis through 12 months by region showed that the Central/Latin American fracture rates were lower than expected (3.5%) with observed rates in placebo (1.2%) and no reduction in the romosozumab group (1.5%). Central/ Latin America accounted for 43% of the randomized population.

The Sponsor performed a post hoc subgroup analysis to examined Central/Latin America separately from all other regions combined (ie, rest-of-world). Through 12 months, the nonvertebral fracture rate was 2.7% in the placebo group (closer to the expected rate of 3.5%) and 1.6% in the romosozumab group (relative risk reduction 42% [95% CI: 11, 63], nominal p = 0.012 post hoc). Through month 24, the rest-of-world nonvertebral fracture rate was 4.3% in the placebo group and 2.9% in the romosozumab group (relative risk reduction 33% [95% CI: 7, 52], p = 0.016.

Baseline characteristic by region showed a lower height, lower prevalence of historical nonvertebral fractures, and lower World Health Organization Fracture Risk Assessment tool (FRAX) 10-year probabilities of major osteoporotic/ hip fractures in the Central/ Latin American population. Physical characteristics and baseline BMD T-scores at the hip and femoral neck were similar across all regions of the study.

Reviewer Comments: ***The large proportion of the study population from Central/ Latin America (43%) had regional differences with lower rates of fractures than expected when compared to the rest of the world for nonvertebral fractures. These regional differences influenced the overall fracture endpoints for nonvertebral fractures through 12 months, 24 months and clinical fractures at 24 months such that none of these fracture endpoints were statistically significant when adjusted for multiplicity. The study appears to be underpowered for these fracture endpoints since the actual fracture rate of the study subjects was less than expected.***

Reduction of clinical fractures is not an appropriate endpoint for this study for the following reasons:

1) ***The term, clinical fracture, does not have clinical meaningfulness among healthcare professionals and can be subject to different interpretation in the labeling.***
2) ***Clinical fractures at 24 months were not statistically significant when adjusted for multiplicity.***
3) ***Clinical fracture rates in this study are combined from nonvertebral fractures (85%) and clinical vertebral fractures (15%). As nonvertebral fracture endpoints were not statistically significant, the incidence rate differences for clinical fractures in the***

romosozumab group compared to placebo are from clinical vertebral fractures which were already counted in the primary endpoint.

Other Fracture Endpoints:
The relative risk reductions (95% CI) for the following fracture endpoints resulted in nominal p-values < 0.05 but adjusted multiplicity p-values were > 0.05 for major nonvertebral, new or worsening vertebral, and hip fracture categories:

- Month 12: new or worsening vertebral fracture (71% [95% CI: 51, 83]), major osteoporotic fracture (40% [95% CI: 10, 60]), multiple new or worsening vertebral fracture (89% [95% CI: 13, 99]).
- Month 24: nonvertebral fracture (25% [95% CI: 3, 43]), clinical fracture (33% [95% CI: 13, 48]), major nonvertebral fracture (33% [95% CI: 9, 51]), new or worsening vertebral fracture (74% [95% CI: 58, 84]), major osteoporotic fracture (38% [95% CI: 16, 54]), multiple new or worsening vertebral fracture (94% [95% CI: 56, 99]).

The following table 17 summarizes the other secondary fracture endpoints through month 12 and through month 24 by incidence, risk reduction, nominal p-values, and adjusted p-values.

Table 17: Summary of Other Secondary Fracture Endpoints through Month 12 and 24

Fracture Category Time Point	Incidence (n/N1 [%]) Placebo and Romosozumab[a]		Ratio[b]	Relative Risk Reduction, % (95% CI)	Nominal p-value[c,d]	Adjusted p-value[e]
Major nonvertebral[d]	Pbo	Romo				
Month 12	55/3591 (1.5)	37/3589 (1.0)	0.67	33% (-2, 56)	0.060	0.096
Month 24	101/3591 (2.8)	67/3589 (1.9)	0.67	33% (9, 51)	0.009	0.096
New or worsening vertebral[c]	Pbo	Romo				
Month 12	59/3322 (1.8)	17/3321 (0.5)	0.29	71% (51, 83)	<0.001	0.096
Month 24	84/3327 (2.5)	22/3325 (0.7)	0.26	74% (58, 84)	<0.001	0.096
Hip[d]	Pbo	Romo				
Month 12	13/3591 (0.4)	7/3589 (0.2)	0.54	46% (-35, 78)	0.18	0.18
Month 24	22/3591 (0.6)	11/3589 (0.3)	0.50	50% (-4, 76)	0.059	0.12
Major osteoporotic[d]	Pbo	Romo				
Month 12	63/3591 (1.8)	38/3589 (1.1)	0.60	40% (10, 60)	0.012	NA[f]
Month 24	110/3591 (3.1)	68/3589 (1.9)	0.62	38% (16, 54)	0.002	NA[f]
Multiple new/ worsening vertebral[c]	Pbo	Romo				
Month 12	9/3322 (0.3)	1/3321 (<0.1)	0.11	89% (13, 99)	0.011	NA[f]
Month 24	17/3327 (0.5)	1/3325 (<0.1)	0.06	94% (56, 99)	<0.001	NA[f]

Source: CSR 2070337 Table 10-2 with reviewer edits.

Reviewer Comments: ***As noted in above comments, none of the fracture endpoints after step 2 of the pre-specified fixed-sequence procedure had an adjusted p-value < 0.05. See section 6.1.1 for fracture definitions. These endpoints included major nonvertebral, new or worsening vertebral and hip fractures at both 12 and 24 months.***

Additional fracture endpoints of major osteoporotic fractures (hip, forearm, or humerus fractures not associated with a pathologic fracture regardless of trauma severity and clinical vertebral fractures) and multiple new/ worsening vertebral fractures were not in the testing sequence and each had p-values < 0.05 at both month 12 and 24 which are statistically significant. The sponsor is not seeking claims for these types of fractures in this application.

BMD endpoint:
Romosozumab significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with placebo at both month 12 and month 24.

Romosozumab had consistent effect on BMD regardless of baseline age, baseline BMD, and geographic region at the lumbar spine and total hip. The following table 18 summarizes these BMD percentile changes from baseline at both month 12 and 24 for lumbar spine, total hip and femoral neck sites where the p-value < 0.001 for all comparisons.

Table 18: Percent Change BMD at Lumbar Spine, Total Hip, and Femoral Neck at 12 and 24 Months.

	Least Squares Mean **(95% CI)** for BMD Percent Change from Baseline by DXA		
	Placebo/ denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ denosumab 60 mg Q6M (N = 3589)	Difference[a]
At month 12			
Lumbar spine	0.4 (0.2, 0.5)	13.1 (12.8, 13.3)	12.7 (12.4, 12.9)
Total hip	0.3 (0.1, 0.4)	6.0 (5.9, 6.2)	5.8 (5.6, 6.0)
Femoral neck	0.3 (0.1, 0.5)	5.5 (5.2, 5.7)	5.2 (4.9, 5.4)
At month 24			
Lumbar spine	5.5 (5.3, 5.7)	16.6 (16.3, 16.8)	11.1 (10.8, 11.4)
Total hip	3.2 (3.1, 3.3)	8.5 (8.3, 8.7)	5.3 (5.1, 5.5)
Femoral neck	2.3 (2.1, 2.6)	7.3 (7.0, 7.5)	4.9 (4.7, 5.2)

Source: CSR 20070337 Table 10-3 with statistic reviewer confirmation and reviewer edits.

Reviewer Comments: ***Romosozumab effects were statistically significant at LS, total hip, and femoral neck and its effects were consistent regardless of age groups, baseline BMD values, and regions differences. Although the Sponsor did not control BMD parameters for type 1***

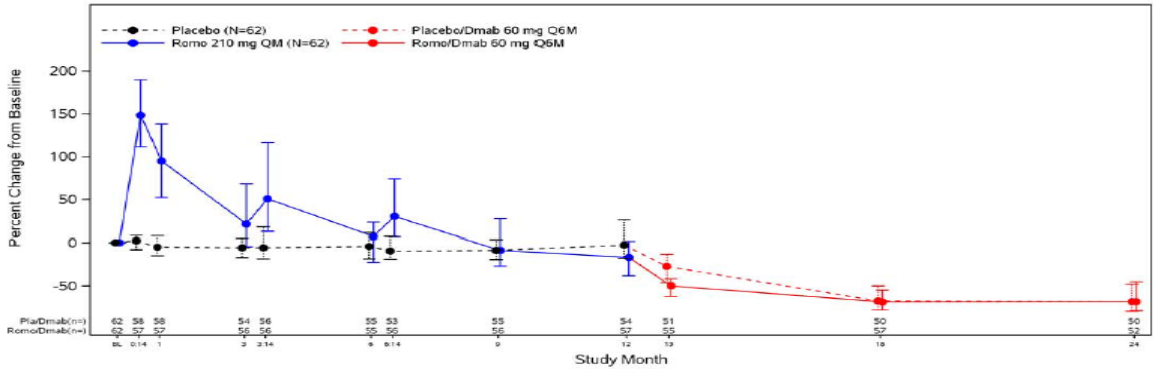
error, these findings support the primary endpoint for fracture reduction at both 12 months and 24 months in this patient population and should be included in the labeling.

Exploratory Endpoints:
New vertebra fractures at Month 6:
Through month 6, 14 (0.4%) subjects in the romosozumab group and 26 (0.8%) subjects in the placebo group had a new vertebral fracture; the relative risk reduction for romosozumab compared with placebo was 46% (95% CI: -3, 72; odds ratio = 0.54; nominal p = 0.056)

<u>Reviewer Comments:</u> Exploratory endpoint of new vertebral fractures at 6 months had a p-value = 0.056, was not statistically significant.

Substudy Results:
<u>Bone Turnover Marker and Biomarker Substudy</u>
During the first 12 months of study 20070337, in subjects randomized to romosozumab, procollagen Type 1 N-telopeptide (P1NP) showed a rapid increase that peaked at day 14 and returned to baseline by month 9. Similar to P1NP, serum concentrations of bone specific alkaline phosphatase (BSAP) and osteocalcin peaked at day 14 and declined thereafter, returning to baseline by month 12. Changes in P1NP were assessed through month 24 after the end of double-blind treatment. In both treatment groups, denosumab caused similar reductions in P1NP from months 12 to 24, although the median percent change from baseline in P1NP was significantly lower in the romosozumab/denosumab group than in the placebo/denosumab group at month 13. A rapid initial decrease in serum type 1 collagen C-telopeptide (sCTX) and TRAP5b was observed in subjects randomized to romosozumab (sCTX nadir at day 14, TRAP 5b nadir at 1 month) and levels of both bone resorption markers remained below baseline through month 12. After transition to denosumab, both arms of the study showed the expected decrease in bone resorption markers. The following figures 4 graphs P1NP percent changes from baseline by visit and study group.

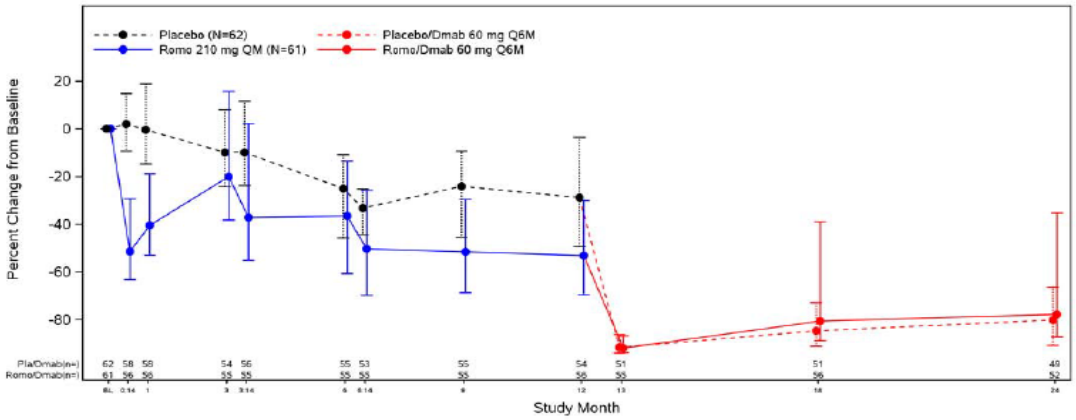
Figure 4: P1NP Percent Changes from Baseline by Study Visit



Source: CSR 20070337 figure 10-3 with reviewer edits

The following figure 5 graphs sCTX percent changes from baseline by study visit.

Figure 5: sCTX Percent Changes from Baseline by Study Visit.



Source: CSR 20070337 Figure 10-4 with reviewer edits.

Reviewer Comments: ***Bone turnover markers (BTM) are consistent with dual actions of romosozumab with bone formation and anti-absorption. Action appears to be rapid in onset within the first two weeks of initial drug application, reaching maximal effects by 2 weeks and then tapering off. In both P1NP and sCTX, there is a dose response just after each dose which tapers off by month 9. The BTM patterns support limiting use of romosozumab to one year as BTM levels demonstrate reduced response to romosozumab over time.***

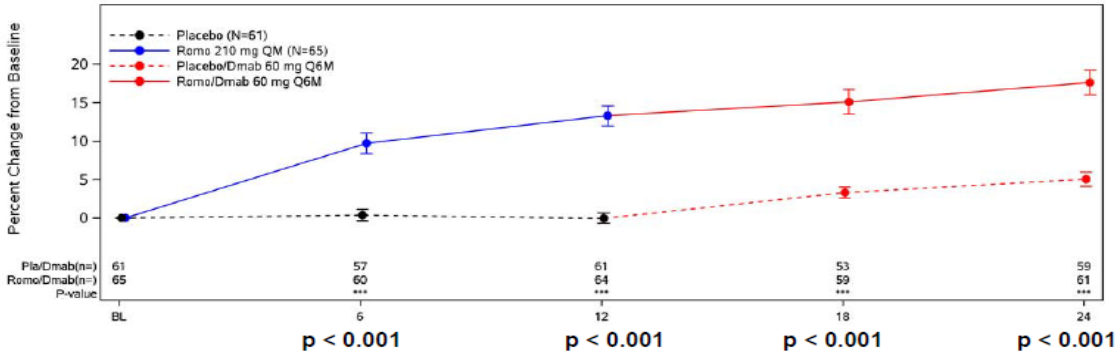
Imaging Substudies

In the overall study, romosozumab significantly increased DXA BMD at the lumbar spine, total hip, and femoral neck compared with placebo at month 12. When subjects were transitioned to denosumab, BMD continued to increase. Subjects in the Lumbar Spine and Proximal Femur DXA substudy underwent DXA assessments every six months. In these subjects, romosozumab resulted in progressive increases from baseline in BMD at these 3 sites compared with placebo beginning at month 6 ($p < 0.001$ at each site).

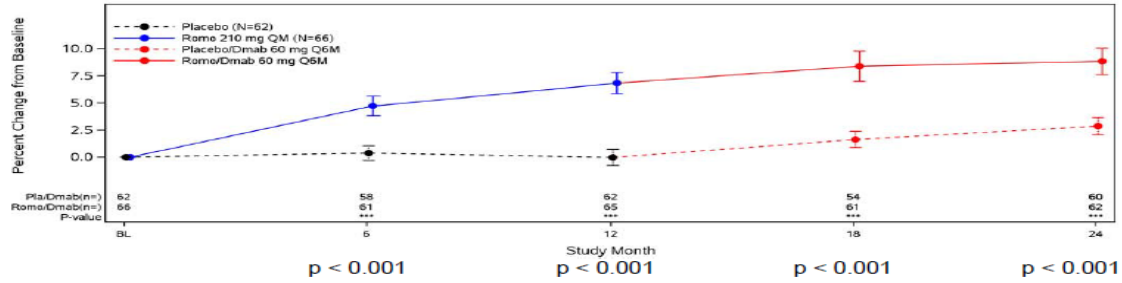
The following figure 6 demonstrates BMD percent change from baseline by visit with 95% CIs from analysis of covariance model (ANCOVA) Model for lumbar spine, total hip, and femoral neck in the imaging substudies.

Figure 6: BMD Percent Change from Baseline by Visit for Lumbar Spine, Total Hip, and Femoral Neck.

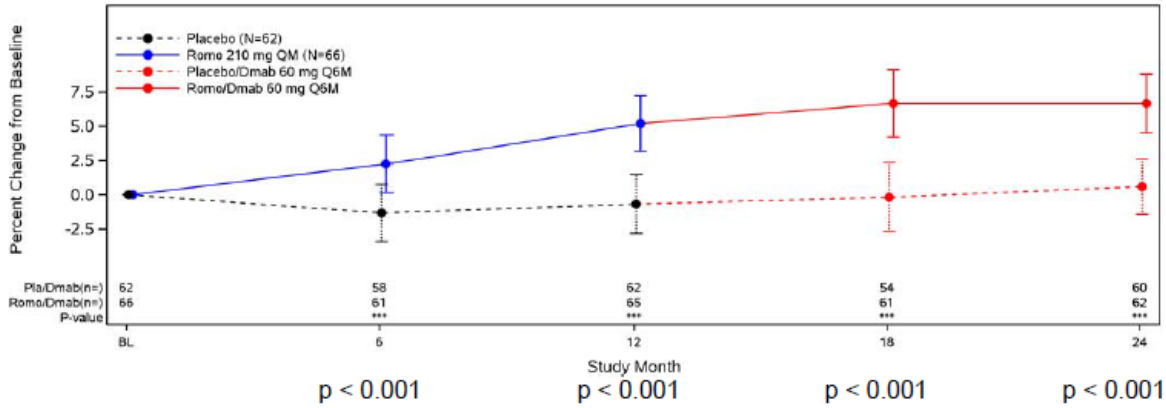
Lumbar Spine:



Total Hip:



Femoral Neck:



Source: CSR 20070337 Figure 10-2 with reviewer edits.

<u>Reviewer Comments:</u> Imaging substudies support romosozumab's effects by increasing BMD at LS, TH, and FN which is sustained after all patients are transitioned into denosumab at 12

months. Measurements were made every 6 months and are statistically significant at each timepoint.

Bone Biopsy Substudy

Changes in bone architecture, resorption, and formation were evaluated by bone histology, quantitative histomorphometry and micro-CT in the Bone Biopsy substudy (139 subjects who provided 154 biopsies). Bone quality is discussed in section 8.3.6 and bone biopsy and labeling procedures is in section 13.6.4.

Histology:

A total of 34 subjects were evaluated at month 2, 73 at month 12, and 47 at month 24 (15 of whom underwent sequential biopsy evaluation at months 12 and 24). Quadruple-labeled iliac crest bone biopsies labeled at baseline and after 2 months of treatment, (with 100% labeling compliance) covered a period of potential robust bone formation. These, as well as bone biopsies obtained at month 12, compared the effect of romosozumab with placebo. Biopsies obtained at month 24 provided a cross-sectional comparison of romosozumab for 12 months followed by denosumab for 12 months with placebo followed by denosumab. All but one subject complied with the tetracycline labeling procedure at months 12 and 24. All biopsies evaluable for histology at months 2, 12 and 24 showed normal lamellar bone, normal mineralization, and osteoid. There was no evidence of osteomalacia, marrow fibrosis, or clinically significant marrow abnormality.

The month 24 bone biopsy for one subject who received romosozumab followed by denosumab showed woven bone at the top of the iliac crest suggesting microcallus formation, consistent with a nonpathologic process. No other biopsies showed woven bone.

Histomorphometry:

Month 2: Twenty-nine subjects (15 romosozumab, 14 placebo) with quadruple fluorochrome labeling (double fluorochrome labeling at baseline and before month 2) were evaluated for histomorphometry at month 2. Within-subject comparisons between baseline and month 2 showed significant increases in single-label, double-label, and mineralizing surfaces and surface-based bone formation rates (BFR/BS) in the romosozumab group but not in the placebo group which suggests stimulation of bone formation indices in the cancellous, endocortical and intracortical compartments. Mineral apposition rate did not change significantly in the romosozumab group during that time period and no significant changes in histomorphometry parameters were noted in either romosozumab or placebo group (or between groups) in the periosteal compartment at month 2.

Median cancellous mineralizing surface percentages were similar at baseline but at month 2 the median percent change in mineralizing surface was 325% in the romosozumab group and 67% in the placebo groups. Similarly, median percent change in BFR/BS at month 2 was approximately 328% in the romosozumab group versus 80% in the placebo group.

Consistent with increased osteoblastic activity, increased tetracycline labeling at trabecular, periosteal, and endocortical sites, as well as increased osteoid thickness and volume, and bone formation rates were seen only in subjects in the romosozumab group at month 2. Evidence of decreased osteoclast activity in the romosozumab group was also seen, including lower eroded surface in the cancellous and endocortical compartments and a significantly lower median osteoclast surface in the cancellous compartment. There were no significant differences between treatment groups in cortical thickness or porosity.

Month 12: Histomorphometry evaluations were performed using bone biopsies from 73 subjects (40 romosozumab, 33 placebo) at month 12. In contrast to the increase in bone formation parameters observed at month 2, dynamic and static formation parameters at month 12 demonstrated a decrease in bone formation. Similar to month 2, eroded surface and osteoclast surface were significantly lower in the romosozumab group than in the placebo group, indicating sustained inhibition of bone resorption.

Month 24: Histomorphometry evaluations were performed using bone biopsies 47 subjects (24 romosozumab/denosumab, 23 placebo/denosumab) at month 24. After both groups had received 12 months of denosumab, evaluation of histomorphometry parameters did not reveal any significant differences between the romosozumab/denosumab and placebo/denosumab groups.

MicroCT analyses

Month 12: MicroCT analysis was performed using bone biopsies from 73 subjects (40 romosozumab, 33 placebo) at month 12. Although there were no significant differences between treatment groups for cortical parameters, significant increases in trabecular BMD and trabecular bone volume, primarily due to increased trabecular thickness were seen at month 12 in the romosozumab compared with placebo group. The thicker trabeculae in the romosozumab group were associated with a significantly lower trabecular bone pattern factor and trabecular bone surface to bone volume compared with the placebo group at month 12.

Reviewer Comments: ***Taken together, there is evidence that romosozumab supports increased trabecular bone formation but may have less or no effect on cortical bone. The histologic and histomorphometric results support significant increased bone formation indices, cancellous bone mineralization, and active osteoblastic activity with decreased osteoclastic activity at month 2 but cortical thickness or porosity did not change by morphometric measurements. The bone is normal by histology. By month 12, the data supports decreased bone formation by histomorphologic parameters and significant increased trabecular bone thickness and volume but no change in cortical parameters by micro CT analysis.***

By month 24 after both groups transition to 12 months of denosumab treatment, there is no difference in histomorphometric parameters. It is unclear if the woven bone found in the one patient treated with romosozumab/ denosumab at month 24 is related to romosozumab exposure as woven bone has not been found with other treatments for osteoporosis.

Dose/Dose Response

To be discussed in section 7.1.4

Durability of Response

Romosozumab reduced vertebral fracture risk at 12 months and the risk was sustained into month 24 when all patients transitioned to denosumab in this study. BMD increased at the lumbar spine, total hip, and femoral neck compared with placebo beginning at month 6, with progressive gains through month 12. These gains were sustained into month 24 after all patients transitioned to denosumab at month 12. Bone formation markers increased and bone resorption markers decreased during the romosozumab treatment period, reflecting the dual effect of the drug with maximal changes during the initial weeks of treatment.

Persistence of Effect

To be discussed in section 7.1.5

6.2. Supportive Placebo-Controlled Studies (20060326, 20101291, and 20120156) and Active-Comparator Controlled Study (20080289)

This section summarize each of the four supportive studies: three placebo-controlled studies: Study 20060326, 20101291, and 20120156 and one supportive active-comparator (teriparatide) controlled study 20080289. Together these studies support efficacy and safety of the single pivotal study 20070337 (in section 6.1) for BMD, BTM, dosing, drug concentration, and retreatment but only the pivotal study examined fracture endpoints. Each supportive study synopsis and study schedule is in Appendix 13.4. Section 7 will integrate the pivotal and supportive clinical studies.

6.2.1. Study 20060326

Title: A Randomized, Placebo-controlled, Multi-dose Phase 2 Study to Determine the Efficacy, Safety and Tolerability of romosozumab (AMG 785) in the Treatment of Postmenopausal Women With Low Bone Mineral Density
Indication: Postmenopausal women with low bone mineral density
Primary Objective:
For the 24-month AMG 785 treatment phase (study day 1 to month 24)

To determine the effect of treatment with AMG 785 versus placebo at month 12 on the percent change from baseline in bone mineral density (BMD) at the lumbar spine in postmenopausal women with low bone density.

Secondary Objectives:

For the 24-month AMG 785 treatment phase (study day 1 to month 24)

To study the effects of up to 12 months of treatment with AMG 785 versus placebo on the percent change from baseline

- in BMD at lumbar spine (at month 6), total hip and femoral neck (at months 6 and 12), and distal radius (at month 12), and
- in bone turnover markers (BTMs)

Exploratory Objectives:

For the 24-month AMG 785 treatment phase (study day 1 to month 24)

• To describe the effect of up to 12 months of treatment with AMG 785 versus alendronate (ALN) or teriparatide (TPTD) on the percent change from baseline in BMD (at the lumbar spine, total hip, femoral neck, and distal radius) and BTMs

• To investigate the effect of up to 24 months of treatment with AMG 785 versus placebo on the percent change from baseline in BMD (at the lumbar spine, total hip, femoral neck, and distal radius) and BTMs

• To investigate the effect of transitioning from 12 months of treatment with ALN to 12 months of treatment with AMG 785 on the percent change from month 12 in BMD (at the lumbar spine, total hip, femoral neck, and distal radius) and BTMs

• To describe the effect of 12 months of treatment with AMG 785 versus placebo or teriparatide on the percent change from baseline in quantitative computed tomography (QCT) BMD at the lumbar spine and proximal femur

***Reviewer Comments:* Although unusual for a 24 month study to have few 24 month endpoints, there is one 24-month AMG 785 (romosozumab) exploratory study endpoint comparing BMD at the lumbar spine, total hip, femoral neck, and distal radius) as well as BTMs.**

For the 12-month denosumab extension phase (month 24 to month 36)

• To describe the effect of transitioning from up to 24 months of treatment with AMG 785 to 12 months of treatment with denosumab on the percent change from month 24 in BMD (at the lumbar spine, total hip, femoral neck, and distal radius) and BTMs

• To describe the effect of transitioning from up to 24 months of treatment with AMG 785 to 12 months of placebo on the percent change from month 24 in BMD (at the lumbar spine, total hip, femoral neck, and distal radius) and BTMs

For the 12-month AMG 785 retreatment phase (month 36 to month 48)

• To describe the effect of transitioning from 24 months of treatment with AMG 785 followed by 12 months of treatment with denosumab to 12 months of treatment with AMG 785 on the percent change from month 36 in BMD (at the lumbar spine, total hip, femoral neck, and distal radius) and BTMs
• To describe the effect of transitioning from 24 months of treatment with AMG 785 followed by 12 months of placebo to 12 months of treatment with AMG 785 on the percent change from month 36 in BMD (at the lumbar spine, total hip, femoral neck, and distal radius) and BTMs

For the 24-month follow-on phase (month 48 to month 72)
• To describe the effect of transitioning from 48 months of treatment with active investigational product (IP) to 24 months without IP treatment on the percent change from month 48 in BMD (at the lumbar spine, total hip and femoral neck) and BTMs

Note: 48 months of treatment with active IP is defined as assignment to the AMG 785 → denosumab → AMG 785 treatment arms during the initial 48 months of the study.
• To describe the effect of transitioning from 12, 24, or 36 months of treatment with active IP to 24 months of treatment with zoledronic acid (ZOL) on the percent change from month 48 in BMD (at the lumbar spine, total hip and femoral neck) and BTMs

Note: 12, 24, or 36 months of treatment with active IP is defined as assignment to one of the following treatment arms during the initial 48 months of the study:
i. placebo → placebo →AMG 785
ii. placebo → denosumab →AMG 785
iii. AMG 785 →placebo →AMG 785

For the overall 72-month study phase (study day 1 to month 72)
• To investigate the utility of novel circulating biomarkers in the postmenopausal osteoporosis setting

Safety Objectives:
For the 24-month AMG 785 treatment phase (study day 1 to month 24)
• To characterize the safety and tolerability of AMG 785 vs. placebo as determined by a review of reported adverse events, vital signs, bone histology and histomorphometry, laboratory data, ECG parameters, and formation of anti-AMG 785 antibodies

For the 12-month denosumab extension phase (month 24 to month 36)
• To characterize the safety and tolerability of transitioning from up to 24 months of treatment with AMG 785 or placebo to 12 months of treatment with denosumab or placebo as determined by a review of reported adverse events, laboratory data, and formation of anti-denosumab antibodies

For the 12-month AMG 785 retreatment phase (month 36 to month 48)
• To characterize the safety and tolerability of transitioning from 24 months of treatment with AMG 785 or placebo followed by 12 months of treatment with denosumab or placebo to 12 months of treatment with AMG 785 as determined by a review of reported adverse events, laboratory data, and formation of anti-AMG 785 antibodies

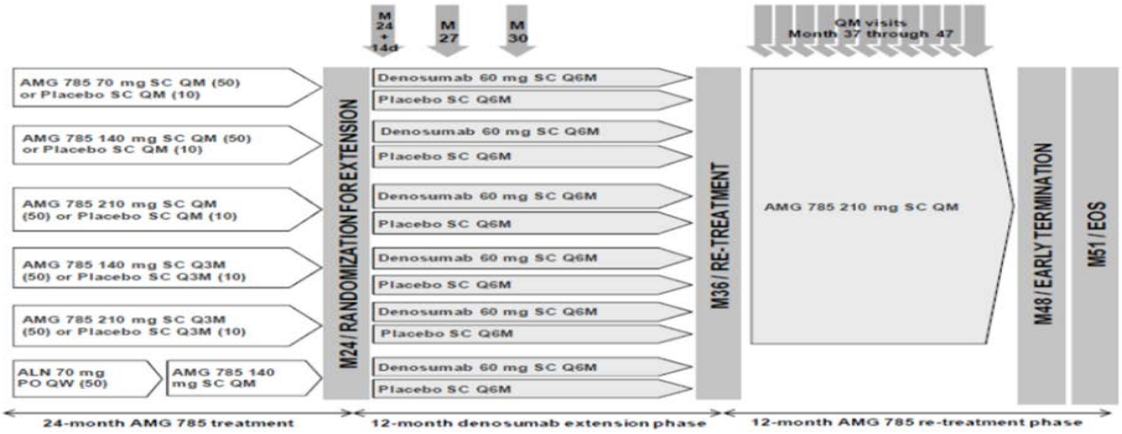
For the 24-month follow-on phase (month 48 to month 72)
• To characterize the safety and tolerability of transitioning from 12 months of retreatment with AMG 785 to 24 months of treatment with ZOL as determined by a review of reported adverse events and laboratory data
• To characterize the safety and tolerability of transitioning from 12 months of retreatment with AMG 785 to 24 months without IP treatment as determined by a review of reported adverse events and laboratory data events and laboratory data

Pharmacokinetics Objectives:
For the 24-month AMG 785 treatment phase (study day 1 to month 24)
• To characterize the serum concentration of AMG 785 in subjects randomized to an AMG 785 treatment regimen
• To characterize the serum concentration of AMG 785 in subjects that transition from ALN to AMG 785

For the 12-month AMG 785 retreatment phase (month 36 to month 48)
• To characterize the serum concentration of AMG 785 in subjects being retreated with AMG 785 following 12 months of treatment with denosumab or placebo

Study Design: Study 20060326 was a randomized, placebo-controlled, parallel-group study in postmenopausal women with low BMD at the lumbar spine, total hip or femoral neck. The study was conducted at 29 centers in Europe, North America, and Argentina. This study included a 24-month treatment phase, during which subjects received 1 of 5 doses of romosozumab, placebo, or active control (alendronate or teriparatide). This was followed by 1:1 randomization within their original treatment group to receive either denosumab or placebo in a 12-month extension phase, followed by a 12-month retreatment phase with romosozumab, followed by a 24-month follow-on phase with a single dose of zoledronic acid or no intervention. The following figure 8 is a schematic of the study design which includes randomization during the first 24 months with 12 months of denosumab/ placebo randomization phase and 12 months retreatment phase.

Figure 7 Study 20070326 Study Design Schematic of the Study



Source: From CSR20060326 Figure 10-2 with reviewer edits.

At the beginning of the study, subjects will be randomized (1:1:1:1:1:1:1:1:1) to one of five dosing regimens of AMG 785, placebo, open label ALN or open label TPTD for the first 12 months of the study. The placebo group will be further randomized and evenly distributed across the five dosing regimens defined for the AMG 785 groups. Subjects, sites and study personnel will be blinded to treatment (AMG 785/ placebo) and dose (70 mg/140 mg/210 mg AMG 785), but not to dosing frequency. Upon completion of the first 12 months of the study, subjects in the AMG 785 and placebo groups will continue their assigned treatment for an additional 12 months; subjects in the TPTD group will end study participation, and subjects in the ALN group will be transitioned to receive AMG 785 140 mg SC every month (QM) for an additional 12 months.

At the end of the 24-month AMG 785 treatment phase, eligible subjects will enter a 12-month denosumab extension phase. Subjects will be randomized 1:1 within their original treatment group to receive either 60 mg denosumab or placebo every 6 months (Q6M). Subjects not participating in the 12-month denosumab extension phase will be followed for an additional three months to month 27.

At the end of the 12-month denosumab extension phase, eligible subjects will enter a 12-month AMG 785 retreatment phase. All subjects participating in the 12-month AMG 785 retreatment phase will receive 210 mg of AMG 785 QM for 12 months. Subjects not participating in the 12-month AMG 785 retreatment phase will complete the study at month 36.

At the end of the 12-month AMG 785 retreatment phase, subjects will enter a 24-month follow-on phase. Based on the outcome of the eligibility assessment, subjects will either receive one dose of 5 mg ZOL intravenously or no intervention. Subjects not participating in the 24-month

follow-on phase will be followed for an additional 3-month observational period to month 51. The primary analysis will be performed at month 12, and exploratory analyses will be performed at month 15, month 18, month 24, month 30, month 36, month 42, month 48, month 60, and month 72.

Primary Endpoint:
For the 24-month AMG 785 treatment phase (study day 1 to month 24)
The primary endpoint is the percent change from baseline at month 12 in BMD at the lumbar spine for the individual AMG 785 groups and pooled placebo arms.

Secondary Endpoints:
For the 24-month AMG 785 treatment phase (study day 1 to month 24)
The secondary endpoints to be evaluated for the individual AMG 785 groups and pooled placebo arms are:
• Percent change from baseline at month 6 in BMD at the lumbar spine, total hip and femoral neck
• Percent change from baseline at month 12 in BMD at the total hip, femoral neck, and distal radius
• Percent change from baseline at months 1, 3, 6, 9 and 12 in BTMs (procollagen type 1 N-telopeptide [P1NP], type I collagen C-telopeptide [CTX], osteocalcin [OC], bone specific alkaline phosphatase [BSAP])

Exploratory Endpoints:
For the 24-month AMG 785 treatment phase (study day 1 to month 24)
The following exploratory endpoints are to be evaluated for AMG 785 and the ALN and TPTD groups during the first year of the study:
• Percent change from baseline at month 6 in BMD at the lumbar spine, total hip and femoral neck
• Percent change from baseline at month 12 in BMD at the lumbar spine, total hip, femoral neck, and distal radius
• Percent change from baseline at months 1, 3, 6, 9, and 12 in BTMs
(P1NP, CTX, OC, BSAP)

The following exploratory endpoints are to be evaluated for the individual AMG 785 groups and pooled placebo arms during the second year of the study:
• Percent change from baseline at month 18 in BMD at the lumbar spine, total hip and femoral neck
• Percent change from baseline at month 24 in BMD at the lumbar spine, total hip, femoral neck, and distal radius
• Percent change from baseline at months 15, 18, 21, and 24 in BTMs
(P1NP, CTX, OC, BSAP)

The following exploratory endpoints are to be evaluated for AMG 785 treated subjects following the transition from ALN during the second year of the study:
• Percent change from month 12 at month 18 in BMD at the lumbar spine, total hip and femoral neck
• Percent change from month 12 at month 24 in BMD at the lumbar spine, total hip, femoral neck, and distal radius
• Percent change from month 12 at months 13, 15, 18, 21, and 24 in BTMs (P1NP, CTX, OC, and BSAP)

The following exploratory endpoints are to be evaluated for AMG 785 versus placebo or teriparatide during the first year of the study (for a subset of subjects only):
• Percent change from baseline at month 12 in QCT BMD at the lumbar spine and proximal femur
• Percent change from baseline at month 12 in QCT variables including trabecular volumetric density at the lumbar spine
• Percent change from baseline at month 12 in QCT variables including total, cortical, and trabecular volumetric density and cortical thickness at the proximal femur

For the 12-month denosumab extension phase (month 24 to month 36)
The following exploratory endpoints are to be evaluated following the transition to denosumab or to placebo during the 12-month denosumab extension phase of the study (month 24 to month 36):
• Percent change from month 24 to month 30 in BMD at the lumbar spine, total hip and femoral neck
• Percent change from month 24 to month 36 in BMD at the lumbar spine, total hip, femoral neck, and distal radius
• Percent change from month 24 to months 27, 30, and 36 in BTMs (P1NP, CTX, OC, and BSAP)
• Percent change from baseline to month 30 in BMD at the lumbar spine, total hip and femoral neck
• Percent change from baseline to month 36 in BMD at the lumbar spine, total hip, femoral neck, and distal radius
• Percent change from baseline to months 27, 30, and 36 in BTMs (P1NP, CTX, OC, and BSAP)

For the 12-month AMG 785 retreatment phase (month 36 to month 48)
The following exploratory endpoints are to be evaluated following the transition to AMG 785 during the 12-month AMG 785 retreatment phase of the study (month 36 to month 48):
• Percent change from month 36 to months 39, 42, and 48 in BMD at the lumbar spine, total hip, and femoral neck
• Percent change from month 36 to month 48 in BMD at the distal radius
• Percent change from month 36 to months 37, 39, 42, 45, and 48 in BTMs (P1NP, CTX, OC, BSAP)

• Percent change from baseline to months 39, 42, and 48 in BMD at the lumbar spine, total hip, and femoral neck
• Percent change from baseline to month 48 in BMD at the distal radius
• Percent change from baseline to months 37, 39, 42, 45, and 48 in BTMs
(P1NP, CTX, OC, BSAP)

For the 24-month follow-on phase (month 48 to month 72)
The following exploratory endpoints are to be evaluated following the transition to ZOL or no intervention during the follow-on phase of the study (month 48 to month 72):
• Percent change from month 48 to months 54, 60, 66, and 72 in BMD at the lumbar spine, total hip, and femoral neck
• Percent change from month 48 to months 51, 54, 60, 66, and 72 in BTMs
(P1NP, CTX, OC, BSAP)
• Percent change from baseline to months 54, 60, 66, and 72 in BMD at the lumbar spine, total hip, and femoral neck
• Percent change from baseline to months 54, 60, 66, and 72 in BTMs
(P1NP, CTX, OC, BSAP)

For the overall 72-month study phase (study day 1 to month 72)
Correlation between novel biomarkers and changes in BMD and/or BTMs as well as treatment group will be summarized.

Safety Endpoints:
The following safety endpoints are to be evaluated during the 24-month AMG 785 treatment phase of the study:
Nature, frequency, and severity of adverse events and their relationship to treatment; Changes from baseline in vital signs, laboratory assessments and ECG parameters; Bone histologic and histomorphometric parameters; Subject incidence of the formation of anti-AMG 785 antibodies.

The following safety endpoints are to be evaluated during the 12-month denosumab extension phase of the study:
Nature, frequency, and severity of adverse events and their relationship to treatment; Laboratory assessments; Subject incidence of the formation of anti-denosumab antibodies.

The following safety endpoints are to be evaluated during the 12-month AMG 785 retreatment phase of the study:
Nature, frequency, and severity of adverse events and their relationship to treatment; Laboratory assessments; Subject incidence of the formation of anti-AMG 785 antibodies.

The following safety endpoints are to be evaluated during the 24-month follow-on phase of the study:
Nature, frequency, and severity of adverse events; Laboratory assessments. Pharmacokinetic Endpoints: AMG 785 serum concentrations by visit

Sample Size: Approximately 400 subjects

Summary of Subject Eligibility Criteria:
Key Inclusion Criteria for the 24-month AMG 785 treatment phase (study day 1 to month 24):
• Ambulatory, postmenopausal women, aged ≥ 55 to ≤ 85
• Low BMD measured by Dual energy X-ray Absorptiometry (DXA) and assessed by the central imaging vendor (see eligible BMD values below).

Eligible BMD values:
Lunar (g/cm2) or Hologic (g/cm2)

Lumbar Spine[a]	≤ 0.940 and ≥ 0.760	≤ 0.827 and ≥ 0.662
Total Hip[b]	≤ 0.756 and ≥ 0.567	≤ 0.698 and ≥ 0.515
Femoral Neck[b]	≤ 0.760 and ≥ 0.551	≤ 0.618 and ≥ 0.438

[a] Values correspond to T-scores between -2.0 and -3.5 as determined by the manufacturer
[b] Values correspond to T-scores between -2.0 and -3.5 Based on data for Caucasian women from the National Health and Nutritional Examination (NHANES) 1998

For assignment to the no intervention group:
• Incidence of a clinical vertebral fracture or fragility fracture of the wrist, humerus, hip, or pelvis between the month 24 and the month 48 visit
• BMD T-score of ≤ -2.5 at the lumbar spine, total hip or femoral neck, based on local read of the DXA scans at month 48

Investigational Product Dosage and Administration:
During the 24-month AMG 785 treatment phase, there will be the following five AMG 785 treatment groups:
• 70 mg subcutaneous (SC) administration every month (QM)
• 140 mg SC administration QM
• 210 mg SC administration QM
• 140 mg SC administration every 3 months (Q3M)
• 210 mg SC administration Q3M

During the 12-month denosumab extension phase (month 24 to month 36), there will be the following treatment group:
• Denosumab 60 mg SC administration every 6 months (Q6M)

During the 12-month AMG 785 retreatment phase (month 36 to month 48), there will be the following treatment group:

- AMG 785 210 mg SC administration QM

During the 24-month follow-on phase (month 48 to month 72), there will be the following treatment group:

- ZOL 5 mg intravenous administration at the 'month 48 plus 14 days' visit

Control Group:
During the 24-month AMG 785 treatment phase, there will be five placebo groups, which will be dosed at the corresponding schedules for AMG 785. In addition, there will be two active comparators groups of open label TPTD [20 µg SC every day (QD)] and ALN [70 mg by mouth (PO) every week (QW)].
During the 12-month denosumab extension phase (month 24 to month 36), there will be a placebo group which will be dosed Q6M, corresponding to the dosing schedule for denosumab.
During the 12-month AMG 785 retreatment phase (month 36 to month 48) there will not be a control group.
During the 24-month follow-on phase (month 48 to month 72) there will be a no intervention group.
Additionally, all subjects will be required to take at least 1000 mg of elemental calcium and 800 IU of vitamin D daily from screening through the end of study.

Procedures: Study Schedule Procedures in Appendix 13.4

Statistical Considerations:
The sample size is based on the comparison of AMG 785 to the pooled placebo and ALN groups, on the percent change from baseline in BMD at the lumbar spine and hip at month 12. The mean percent change in lumbar spine BMD and standard deviation are assumed to be 0 (3.6) and 5 (3.6) for the placebo and AMG 785 groups respectively. The mean percent change in hip BMD and standard deviation are assumed to be 0 (2.6) and 2 (2.6) for the placebo and AMG 785 groups respectively. Allowing for 15% drop out in the first 12 months, two-sided type I error of groups respectively. Allowing for 15% drop out in the first 12 months, two-sided type I error of 5%, a sample size of 50 per group yields over 90% power on the lumbar spine and hip BMD endpoints using the two sample t-test. The total sample size is 400 subjects. If one of the AMG 785 groups is superior to the other 4 AMG 785 groups by 1 (or 0.5) point on mean percent change in lumbar spine BMD, the probability that the superior group will be numerically largest on mean percent change in lumbar spine is 74% (or 46%).
The primary analysis of percent change in lumbar spine BMD will use a linear mixed effects model with 4 contrasts estimating the 4 pairwise differences between the 2 AMG 785 dose

schedules (QM, Q3M) and the pooled placebo group and the 2 AMG 785 dose levels (140 mg, 210 mg) and the pooled placebo group, at month 12. The Hochberg procedure will be used to control for multiple comparisons.

Subject Demographics and Disposition

Up to month 24

In total, 419 subjects were enrolled and randomized: 261 received romosozumab (51 to 54 subjects per dose group), 52 received placebo, 51 received alendronate, and 55 received teriparatide. A total of 383 subjects (91%) completed 12 months of study and 315 subjects (87%) completed the first 24 months.

Subjects randomized to the teriparatide arm ended the study at month 12 (55 randomized, 46 completed). Subjects randomized to the alendronate arm were transitioned to romosozumab 140 mg QM treatment at month 12. The baseline demographic and key characteristics were comparable across the 8 arms: all subjects were women, mean age was 66.8 years, 86.4% of subjects were white, and the mean baseline lumbar spine and total hip BMD T-scores were -2.29 and -1.53, respectively.

Months 24 to 36

A total of 260 subjects were then randomized in the denosumab extension phase of the study, 129 received denosumab 60 mg Q6M group and 131 received placebo. A total of 248 subjects (95%) completed the extension phase.

Subject demographics and baseline characteristics were recorded on entering the study and were summarized to assess potential for bias within the subset of subjects rerandomized in the denosumab extension phase. Characteristics were generally well balanced between the denosumab and placebo groups.

Months 36 to 48

A total of 167 subjects were enrolled in the romosozumab retreatment phase of the study; of these, 155 subjects (93%) completed this phase.
Demographic and baseline characteristics were generally comparable between the total group of 167 subjects in the retreatment phase and the total group of 419 subjects in the 12-month primary analysis.

Months 48-72

A total of 141 subjects continued into the follow-on phase at month 48, including 51 who were assigned to the no-intervention group and 90 subjects assigned to receive zoledronic acid. Subjects who had previously received the treatment sequence romosozumab/ denosumab/ romosozumab were assigned to receive no intervention and subjects who had previously received any other sequences were assigned to the zoledronic acid group, although 8 subjects

who received romosozumab/denosumab/ romosozumab subsequently received zoledronic acid. A total of 50 (98.0%) subjects assigned to no intervention and 88 (97.8%) who received zoledronic acid completed the follow-on phase; 1 (2.0%) subject in the no intervention group and 2 (3.4%) subjects in the zoledronic acid group discontinued the study. Demographic and baseline characteristics were generally comparable between groups, although subjects assigned to no intervention were slightly older (mean age 67.2 years versus 65.8 years for the zoledronic acid group), with a slightly higher percentage of white subjects (84.3% versus 77.8%), and higher mean time since menopause (19.6 years versus 18.1 years). Differences were noted between treatment groups in percentage of subjects in each age group category; however, overall there were similar percentages < 75 years of age in each group (no intervention: 90.2%; zoledronic acid: 92.2%).

Efficacy Results

Primary endpoint

At month 12, the mean percent change in lumbar spine BMD in the romosozumab groups ranged from 5.4% for 70 mg QM to 11.3% for 210 mg QM, compared with-0.1% in the placebo group. Increases for each of the romosozumab groups were significantly greater ($p < 0.0001$) than for the placebo group after adjusting for multiplicity. In addition, all 4 comparisons included in the confirmatory testing (QM, Q3M, 140 mg, and 210 mg) significantly favored romosozumab over placebo. The following table 19 summarizes the lumbar spine DXA BMD percent changes from baseline at 12 months in the different groups of the study.

Table 19: DXA Lumbar Spine BMD Percent Change From Baseline to Month 12 -Linear Mixed Effects Model Showing Each of Romosozumab Groups

	Placebo	ALN PO	TPTD SC	Romosozumab SC				
	Total (N = 50)	70 mg QW (N = 51)	20 µg QD (N = 49)	70 mg QM (N = 49)	140 mg Q3M (N = 52)	140 mg QM (N = 48)	210 mg Q3M (N = 53)	210 mg QM (N = 50)
Month 12								
n	47	47	46	44	49	46	51	49
LS Mean	-0.1	4.1	7.1	5.4	5.4	9.1	5.5	11.3
95% CI	(-1.2, 0.9)	(3.0, 5.1)	(6.1, 8.2)	(4.3, 6.4)	(4.4, 6.5)	(8.0, 10.2)	(4.4, 6.6)	(10.3, 12.4)
Difference from placebo[a]								
LS Mean				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, 7.1)	(10.0, 12.9)
p-value				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Difference from ALN[b]								
LS Mean				1.3	1.4	5.0	1.5	7.3
95% CI				(-0.2, 2.8)	(-0.1, 2.8)	(3.6, 6.5)	(0.0, 2.9)	(5.8, 8.7)
p-value				0.0853	0.0853	<0.0001	0.0853	<0.0001
Difference from TPTD[c]								
LS Mean				-1.8	-1.7	2.0	-1.6	4.2
95% CI				(-3.3, -0.3)	(-3.2, -0.2)	(0.5, 3.4)	(-3.1, -0.2)	(2.7, 5.6)
p-value				0.0276	0.0276	0.0276	0.0276	<0.0001

Source: CSR20060326 Table 10-2 with reviewer edits.

Secondary Endpoints
Increases in BMD from baseline were seen at the lumbar spine at month 3 and month 6, with the greatest increases occurring in the 140 mg QM and 210 mg QM groups. All increases compared with placebo were statistically significant ($p < 0.0001$).

Increases from baseline in BMD at the total hip and femoral neck were seen in some romosozumab dose groups compared with placebo at month 3, and all romosozumab dose groups at months 6 and 12, with the greatest increases occurring in the 140 mg QM and 210 mg QM groups ($p < 0.0001$). The following table 20 summarizes BMD percent changes from baseline at the total hip and femoral neck at 12 months.

Table 20: DXA Percent Change From Baseline of the Total Hip and Femoral Neck at Months 12

	Placebo	ALN PO	TPTD SC	Romosozumab				
	(N = 50)	70 mg QW (N = 51)	20 µg QD (N = 49)	70 mg QM (N = 49)	140 mg Q3M (N = 52)	140 mg QM (N = 48)	210 mg Q3M (N = 53)	210 mg QM (N = 50)
Month 12								
Total hip, n	47	47	46	44	49	46	50	49
LS Mean	-0.7	1.9	1.3	1.3	1.3	3.4	1.9	4.1
95% CI	(-1.4, -0.1)	(1.3, 2.6)	(0.7, 2.0)	(0.6, 2.0)	(0.7, 2.0)	(2.7, 4.1)	(1.3, 2.6)	(3.5, 4.8)
Difference from placebo: p-value				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Difference from ALN: p-value				0.1570	0.1899	0.0017	0.9743	<0.0001
Difference from TPTD: p-value				0.9143	0.9745	<0.0001	0.1927	<0.0001
Femoral neck, n	47	47	46	44	49	46	50	49
LS Mean	-1.1	1.2	1.1	0.6	1.8	4.2	1.4	3.7
95% CI	(-2.0, -0.2)	(0.3, 2.1)	(0.2, 2.0)	(-0.3, 1.6)	(0.9, 2.7)	(3.3, 5.1)	(0.5, 2.3)	(2.8, 4.6)
Difference from placebo: p-value				0.0044	<0.0001	<0.0001	<0.0001	<0.0001
Difference from ALN: p-value				0.3580	0.3410	<0.0001	0.7132	<0.0001
Difference from TPTD: p-value				0.4196	0.2931	<0.0001	0.6372	<0.0001

Source: CSR20060326 Table 10-4 with reviewer edits.

Compared with placebo, there was no statistically significant change in the distal 1/3 radius BMD at month 12. The following table 21 summarizes the lack of change at the distal 1/3 radius by BMD at month 12.

Table 21: DXA BMD Percent Change From Baseline at Distal 1/3 Radius

	Placebo	ALN PO	TPTD SC	Romosozumab				
	Total (N = 48)	70 mg QW (N = 46)	20 µg QD (N = 42)	70 mg QM (N = 44)	140 mg Q3M (N = 48)	140 mg QM (N = 46)	210 mg Q3M (N = 49)	210 mg QM (N = 46)
Month 12								
n	48	46	42	44	48	46	49	46
LS Mean	-0.9	-0.3	-1.7	-1.8	-1.1	-1.0	-0.4	-1.2
95% CI	(-1.8, 0.1)	(-1.2, 0.7)	(-2.7, -0.7)	(-2.8, -0.8)	(-2.1, -0.2)	(-2.0, -0.0)	(-1.3, 0.5)	(-2.1, -0.2)
Difference from Placebo								
P-value				0.1642	0.6897	0.8621	0.4565	0.6732
Difference from ALN								
P-value				0.0245	0.1949	0.2865	0.8612	0.1890
Difference from TPTD								
P-value				0.8557	0.4261	0.3155	0.0568	0.4430

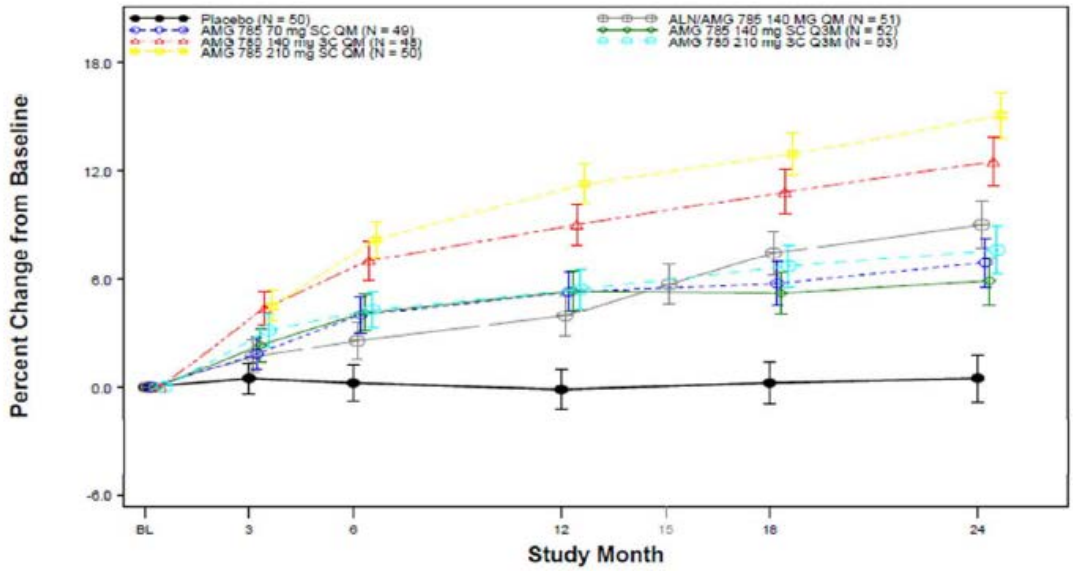
Source: CSR20060326 Table 10-5 with reviewer edits.

The bone formation markers P1NP, osteocalcin, and BSAP showed dose-related increases with a peak at month 1 in the romosozumab groups versus no increases in the placebo group. The marker levels decreased thereafter with pre-dose levels near baseline levels by 9 months and remaining there with continued dosing. For sCTX, following an initial decrease from baseline (largest at month 1), levels remained below baseline at month 12 in groups that received QM doses of romosozumab (70 mg QM, 140 mg QM, and 210 mg QM).

Exploratory Endpoints
At months 6 and 12, statistically significant increases in BMD at the total hip and femoral neck were observed in the romosozumab 140 mg QM and 210 mg QM groups versus alendronate and teriparatide. At month 12, subjects in the romosozumab 210 mg QM group demonstrated statistically significant increases in the ultradistal radius BMD compared with subjects who received placebo or teriparatide, although the difference from alendronate was not statistically significant.

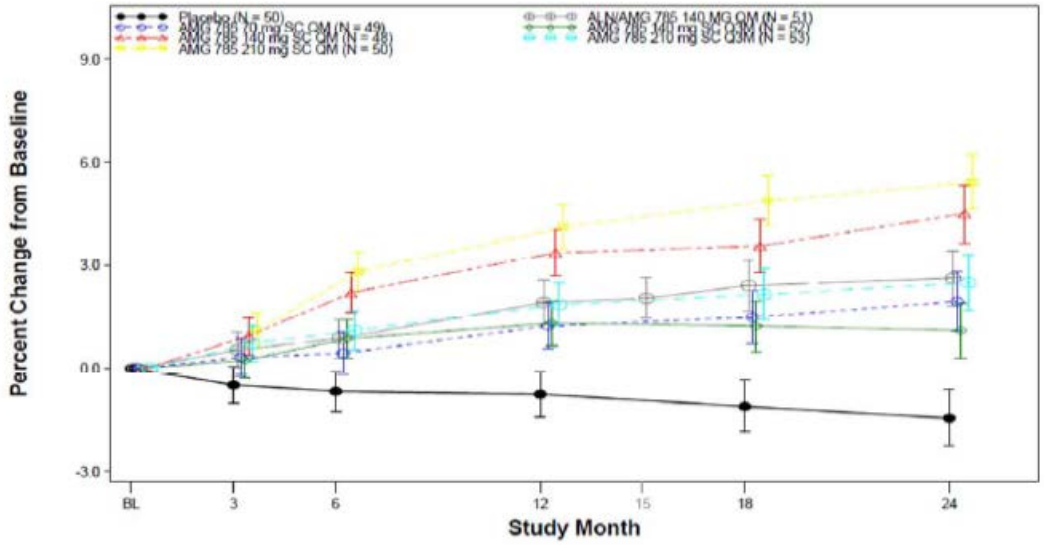
From months 12 to 24, all QM romosozumab dose regimens continued to show increases in BMD at the lumbar spine, total hip, and femoral neck; however, increases in BMD occurred more quickly during the first 12 months of treatment. During months 12 to 24, bone formation markers remained at or below baseline. For the romosozumab QM dose regimens, sCTX remained near or below baseline. The following three figures (figure 8, 9, 10) graph BMD changes for the different study groups up to month 24 for the lumbar spine, total hip and femoral neck respectively by DXA scans.

Figure 8: Lumbar Spine Percent Change from Baseline (95% CI) by DEXA scan up to Month 24



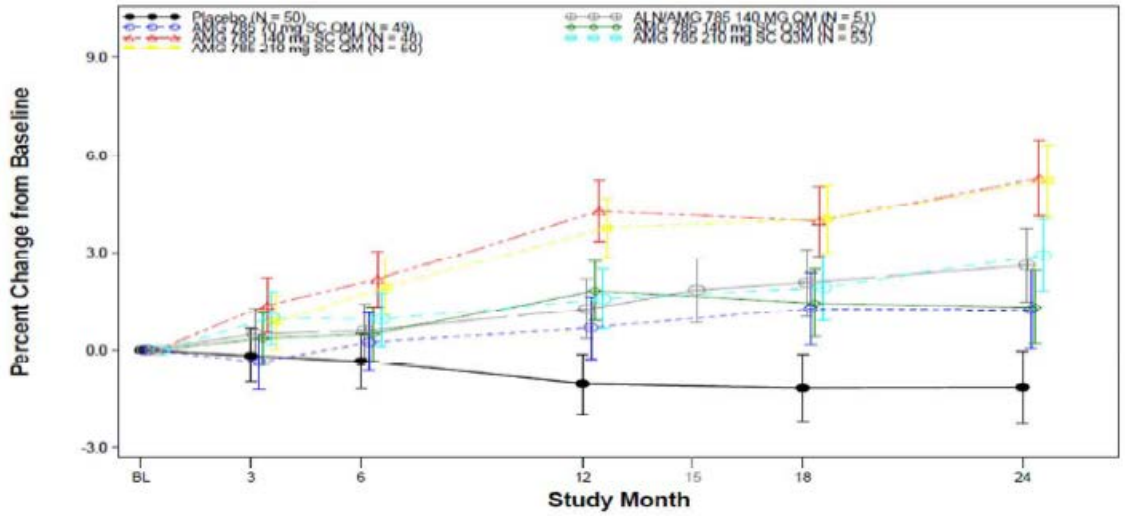
ALN = alendronate; AMG 785 = romosozumab; BL = baseline;
Source: CSR20060326 Figure 10-8 with reviewer edits.

Figure 9: Total Hip Spine Percent Change from Baseline (95% CI) by DEXA scan up to Month 24



ALN = alendronate; AMG 785 = romosozumab; BL = baseline;
Source: CSR20060326 Figure 10-9 with reviewer edits.

Figure 10: Femoral Neck Percent Change from Baseline (95% CI) by DEXA scan up to Month 24



ALN = alendronate; AMG 785 = romosozumab; BL = baseline;
Source: CSR20060326 Figure 10-10 with reviewer edits.

Reviewer Comments: ***The data supports limiting romosozumab use to 12 months as it demonstrates a tapering of BMD increases after month 12 through to month 24 at LS, TH, and FN which is consistent with decreased efficacy.***
Retreatment with romosozumab during months 36 to 48 following placebo from months 24 to 36 resulted in BMD increases at the spine and hip comparable to those seen in the group that received initial treatment with romosozumab 210 mg QM during the first 12 months.

Retreatment with romosozumab in those transitioning from denosumab yielded a more modest increase in BMD at the spine and femoral neck and maintenance of BMD at the total hip and an expectedly different shift in BTMs.

From months 48 to 72, subjects who had received continuous active treatment through month 48, and then transitioned to no intervention demonstrated a decrease in BMD at the lumbar spine, total hip and femoral neck. However, when evaluated from baseline, mean percent change in BMD remained positive at the lumbar spine at month 72. In subjects who transitioned to the zoledronic acid group at month 48, the BMD gains achieved by month 48 were overall maintained by at month 72, (-0.8% change from month 48 BMD). Overall, the mean percent change in BMD at the lumbar spine remained positive from baseline at month 72 (+12.8% for subjects of treatment sequences combined), regardless of initial romosozumab dose received.

For subjects who transitioned from active treatment to either no intervention or zoledronic acid at month 48, the levels of the bone formation marker P1NP decreased through month 72.

Levels of the bone formation markers osteocalcin and BSAP followed similar trends as P1NP. For subjects who had received romo (any dose)/dmab/rom and transitioned to no intervention at month 48, the levels of the bone resorption marker CTX were near baseline at month 48, increased at month 51, then decreased at month 72. For subjects transitioning to zoledronic acid at month 48, CTX declined to below baseline values, reached a nadir at month 51, then increased toward baseline.

***Reviewer Comments:* Further discussion of retreatment and durability will be in section 7.1.5. Onset, Duration, and Durability of Efficacy Effects.**

BMD by QCT substudy results:
Assessment of BMD by QCT was an exploratory endpoint in a QCT substudy which demonstrated that the romosozumab 210 mg QM was associated with statistically significant increases from baseline at month 12 for lumbar spine and proximal femur in BMD, BMC, and trabecular BMD compared with placebo. Romosozumab was associated with a statistically significant increase in lumbar spine cortical BMD, cortical BMC and cortical thickness compared with placebo The following table 22 summarizes QCT percent changes from baseline at the lumbar spine for BMD, BMC, and cortical thickness at month 12 in the different groups.

Table 22: QCT Changes from Baseline for BMD, BMC, and Cortical Thickness at the Lumbar Spine at Month 12 for the Treatment Groups.

Region	Placebo (N = 27)	Teriparatide 20 µg QD SC N = 30	Romo 70 mg QM (N = 20)	Romo 140 mg Q3M (N = 29)	Romo 140 mg QM (N = 18)	Romo 210 mg Q3M (N = 24)	Romo 210 mg QM N = 24	Romo 210 mg QM p-value v. Placebo	Romo 210 mg QM p-value v. TPTD
Bone mineral density	-0.8 (-2.9, 1.3)	12.9 (10.9, 14.9)	8.9 (6.4, 11.3)	8.0 (6.0, 10.1)	14.2 (11.6, 16.7)	10.7 (8.4, 12.9)	17.7 (15.5, 19.9)	< 0.0001	0.0018
Bone mineral content	-1.0 (-3.2, 1.3)	12.8 (10.7, 14.9)	8.9 (6.3, 11.5)	7.8 (5.6, 9.9)	13.9 (11.2, 16.7)	10.1 (7.7, 12.4)	17.7 (15.4, 20.1)	< 0.0001	0.0025
Peeled trabecular BMD	-2.0 (-5.5, 1.5)	20.1 (16.9, 23.4)	10.6 (6.6, 14.6)	8.8 (5.4, 12.1)	14.0 (9.8, 18.2)	10.9 (7.3, 14.6)	18.3 (14.6, 22.0)	< 0.0001	0.4625
Cortical BMD	0.4 (-1.2, 2.1)	5.7 (4.1, 7.3)	6.0 (4.1, 8.0)	6.3 (4.7, 7.9)	11.1 (9.1, 13.2)	8.5 (6.7, 10.2)	13.7 (11.9, 15.5)	< 0.0001	< 0.0001
Cortical BMC	0.7 (-2.7, 4.0)	10.9 (7.7, 14.1)	10.4 (6.5, 14.2)	9.8 (6.6, 13.1)	19.8 (15.7, 23.9)	14.9 (11.3, 18.4)	23.3 (19.7, 26.8)	< 0.0001	< 0.0001
Cortical thickness	-4.1 (-12.9, 4.6)	12.3 (4.1, 20.4)	6.8 (-3.1, 16.8)	10.1 (1.7, 18.5)	14.6 (4.0, 25.2)	15.8 (6.6, 24.9)	22.7 (13.5, 31.9)	< 0.0001	0.0958

Source: CSR 20060326 Table 10-7 with reviewer edits.

For the cortical parameters at the total femur, only cortical BMC was significantly greater in the 24 subjects in this substudy who had received romosozumab 210 mg QM in Study 20060326.

Reviewer Comments: ***QCT substudy results showed that only the 210 mg dose of romosozumab significantly increased cortical BMD and BMC when compared to placebo and teriparatide treated patients which gives supporting evidence for bone quality at this dose.***

6.2.2. Study 20101291

Title: A Randomized, Double-blind, Placebo-controlled, Multi-dose Phase 2 Study to Evaluate the Efficacy, Safety and Tolerability of Romosozumab in the Treatment of Japanese Women with Postmenopausal Osteoporosis
Indication: Postmenopausal osteoporosis (PMO)

Primary Objective:
To assess the effect of romosozumab treatment for 12 months compared with placebo on the percent change from baseline at Month 12 in bone mineral density (BMD) at the lumbar spine in Japanese women with PMO

Secondary Objectives:
To assess the effects of romosozumab treatment for up to 12 months compared with placebo on:

- The percent change from baseline at Month 6 in BMD at the lumbar spine
- The percent change from baseline at Month 6 and Month 12 in BMD at the total hip and femoral neck
- The percent change from baseline at Day 1 plus 1 week, Month 1, Month 2, Month 3, Month 6, Month 9, and Month 12 in bone turnover markers (BTMs)
- Area under the curve (AUC) through Month 12 for P1NP

Exploratory Objective:
To characterize the pharmacokinetics of romosozumab in subjects randomized to a romosozumab treatment regimen

Safety Objectives:
To characterize the safety and tolerability of romosozumab compared with placebo as determined by a review of reported adverse events, laboratory data, vital signs, and formation of anti-romosozumab antibodies.

Primary Endpoint:
The primary endpoint is the percent change from baseline in BMD at the lumbar spine at Month 12.

Secondary Endpoint(s):

- Percent change from baseline in BMD at the lumbar spine at Month 6

- Percent change from baseline in BMD at the total hip and femoral neck at Month 6 and Month 12
- Percent change from baseline in BTMs (P1NP, sCTX, OC, and BSAP) at Day 1 plus 1 week, Month 1, Month 2, Month 3, Month 6, Month 9, and Month 12
- AUC for P1NP through Month 12

Exploratory Endpoint(s):

- Romosozumab serum concentrations at Day 1, Day 1 plus 1 week, Month 1, Month 2, Month 3, Month 6, Month 9, and Month 12

Safety Endpoint(s):

The following safety endpoints are to be evaluated for the Day 1 to Month 12 period (treatment period):

- Subject incidence of adverse events
- Changes from baseline in laboratory assessments
- Changes from baseline in vital signs
- Subject incidence of the formation of anti-romosozumab antibodies

The following safety endpoints are to be evaluated for the Month 12 to Month 15 period (antibody follow-up study period):

- Subject incidence of adverse events
- Subject incidence of the formation of anti-romosozumab antibodies

Study Design:

This is a multi-center, randomized; double-blind, placebo-controlled, parallel-group study in Japanese women with PMO defined as low BMD at the lumbar spine, total hip or femoral neck. The study is designed to evaluate if romosozumab treatment for 12 months, compared with placebo, is effective in increasing the BMD at the lumbar spine, total hip and femoral neck. Approximately 220 subjects will be randomized 1:1:1:1 to receive either 70 mg, 140 mg or 210 mg romosozumab subcutaneous (SC) every month (QM) or matched placebo SC QM in a double-blind fashion for the duration of the 12-month treatment study period. Upon completion of the 12-month treatment study period, subjects will be followed for another 3 months for assessment of anti-romosozumab antibody formation.

From screening to end of study, subjects will receive daily supplementation with calcium and vitamin D. The minimum doses should be 500 mg elemental calcium and 600 IU vitamin D. The primary analysis will be performed after all subjects have had the opportunity to complete the Month 12 study visit. The final analysis will be performed after all subjects have had the opportunity to complete the Month 15 end of study visit.

Sample Size: Approximately 220 subjects

Summary of Subject Eligibility Criteria:
Subjects must be postmenopausal women age 55 to 85 years with a BMD T-score at the lumbar spine, total hip or femoral neck of less than or equal to -2.50. Subjects with a BMD T-score of less than or equal to -4.00 at the lumbar spine or with a BMD T-score of less than or equal to -3.50 at the total hip or femoral neck are not eligible to participate. Also excluded are subjects with a history of a vertebral fracture or hip fracture. Subjects with metabolic or bone diseases (other than osteoporosis) or significant lab abnormalities are not eligible for participation. The use of agents affecting bone metabolism is also exclusionary, however, for selected therapies permissible off-treatment periods prior to randomization are acceptable.

Product Dosage and Administration:
Three romosozumab treatment groups**:**

- 70 mg SC QM
- 140 mg SC QM
- 210 mg SC QM

Concomitant Medications:
From screening to end of study, all subjects will be required to take daily calcium (minimal dose 500 mg) and vitamin D (minimal dose 600 IU).
Control Group:
The control group will receive matched placebo SC QM in a blinded fashion.

Procedures: Study Schedule Procedures in Appendix 13.4

Statistical Considerations:
For the primary efficacy endpoint, comparisons of the romosozumab dose groups versus the placebo group and a test for a monotonic increasing trend in the romosozumab dose groups will be performed. These assessments will be adjusted for multiplicity using a combination of a sequential test procedure and Hochberg's method to control Type 1 error for the primary endpoint. Additionally, all pairwise comparisons of the romosozumab dose groups will be presented without correction for multiplicity. An evaluation of the dose-response relationship will also be evaluated by considering several candidate non-linear dose-response profiles from both Emax and logistic models. All pairwise comparisons will be presented for other BMD endpoints and BTM endpoints.

Subject Demographics and Disposition
A total of 252 subjects were randomized equally to the 4 different treatment groups. All randomized subjects received at least 1 dose of assigned investigational product. A total of 234 (92.9%) subjects completed 12 months of treatment. Of the 18 (7.1%) subjects who

discontinued investigational product, there was no dose-related trend. All subjects were Japanese women and the mean (SD) age was 67.7 (6.4) years.

Efficacy Results

Primary Endpoint

After 12 months of treatment, romosozumab administration resulted in a dose-dependent increase in lumbar spine BMD compared with placebo, with the largest increase in the romosozumab 210 mg group. The mean differences between each of the romosozumab groups versus placebo and within the romosozumab groups were also statistically significant ($p < 0.0001$) The following table 23 summarizes the primary endpoint of BMD percent changes from baseline at month 12 at the lumbar spine.

Table 23: Lumbar Spine BMD Percent Change From Baseline at Month 12

		Romosozumab		
	Placebo (N = 59)	70 mg SC (N = 55)	140 mg SC (N = 62)	210 mg SC (N = 59)
LS Mean	0.9	8.4	13.3	16.9
95% CI	(0.1, 1.8)	(7.6, 9.3)	(12.1, 14.5)	(15.5, 18.4)
Treatment difference from placebo				
Estimate		7.5	12.4	16.0
95% CI		(6.5, -)	(11.1, -)	(14.6, -)
p-value[a]		< 0.0001	< 0.0001	< 0.0001
Treatment difference from romosozumab 70 mg				
Estimate			4.9	8.5
95% CI			(3.6, -)	(7.1, -)
p-value[b]			< 0.0001	< 0.0001
Treatment difference from romosozumab 140 mg				
Estimate				3.6
95% CI				(2.0, -)
p-value[b]				0.0001

Source: CSR20101291 Table 10-1 with reviewer edits.

Secondary Endpoints

At month 6, statistically significant differences were observed between the percent change in lumbar spine BMD between the placebo and the romosozumab dose groups, and within the romosozumab dose groups ($p < 0.001$).

Romosozumab administration resulted in a dose-dependent increase in total hip and femoral neck BMD compared with placebo, with all dosing groups showing an increase compared with placebo at month 12. The largest increase was observed in the romosozumab 210 mg group. The 1-sided p-values for BMD changes versus placebo at months 6 and 12 were < 0.001 for the 2 highest doses.

Bone formation markers (P1NP, osteocalcin, and BSAP) in the romosozumab groups showed a rapid, transient, dose-dependent increase that peaked by month 1 compared with placebo. The values subsequently returned towards baseline, with levels in the romosozumab groups at

or below placebo at month 12. The values of sCTX in the romosozumab groups decreased compared with placebo early in treatment (maximum at day 1 plus 1 week) and were still lower than placebo at month 12.

Reviewer Comments: ***This study supports romosozumab dose-dependent efficacy on increases of BMD at the lumbar spine, total hip and femoral neck for each of the 3 romosozumab dosing groups with the largest gains in the 210 mg dose group. Bone formation markers were dose-dependent and peaked by 1 month also supports romosozumab effects on BMD. AE rates were comparable among dosing groups without dose-related trends. See section 7.1 for integrated efficacy results.***

6.2.3. Study 2012156

Title of Study: A Multicenter, Randomized, Multiple-dose Phase 3 Study to Evaluate the Noninferiority of Romosozumab at a 90 mg/mL Concentration Compared With a 70 mg/mL Concentration in Postmenopausal Women With Osteoporosis

Investigators and Study Centers: This study was conducted at 11 centers: 7 in Poland, 2 in the Czech Republic, and 2 in the United States.

Objectives: Primary
To evaluate the noninferiority of a 6-month treatment with romosozumab 210 mg administered every month (QM) using a 90 mg/mL concentration compared with romosozumab 210 mg QM using a 70 mg/mL concentration on percent changes in bone mineral density (BMD) at the lumbar spine as assessed by dual-energy X-ray absorptiometry (DXA) in postmenopausal women with osteoporosis

Secondary
To evaluate the effect of 6-month treatment with romosozumab 210 mg QM using romosozumab 90 mg/mL and 70 mg/mL on

- percent changes in DXA BMD at the total hip and femoral neck
- percent changes in bone turnover markers (BTM): bone formation marker procollagen type 1-N-telopeptide (P1NP) and bone resorption marker serum type 1 collagen C-telopeptide (CTX)

Exploratory
To characterize subjects taking placebo with regard to

- percent changes in DXA BMD at the lumbar spine, total hip, and femoral neck
- percent changes in BTMs P1NP and CTX

Safety

To evaluate the safety and tolerability of 6-month treatment with romosozumab 210 mg QM using romosozumab 90 mg/mL or 70 mg/mL and compare with the respective placebo by assessing reported adverse events, laboratory data, vital signs, and the formation of antiromosozumab antibodies over the 6-month treatment and the 3-month follow-up study periods.

Study Design
Study 20120156 was a phase 3 randomized, multiple-dose noninferiority study of romosozumab in postmenopausal women with osteoporosis designed to evaluate the noninferiority of a romosozumab 210 mg QM using a 90 mg/mL concentration (2 x 1.17mL SC) compared with romosozumab 210 mg QM using a 70 mg/mL concentration (3 x 1mL SC) over a 6 month treatment period. Subjects then entered a 3-month follow-up period with end of study at month 9.

After confirmation of eligibility, subjects were randomized in a 22:5:22:5 ratio to the following treatment groups: romosozumab 90 mg/mL, placebo 90 mg/mL, romosozumab 70 mg/mL, or placebo 70 mg/mL. Randomization was double blinded within the concentrations

From screening to EOS, subjects received daily calcium supplementation (500 to 1000 mg elemental calcium) and vitamin D supplementation (600 to 800 international units).

Number of Subjects Planned: 272

Diagnosis and Main Criteria for Eligibility: Subjects were ambulatory postmenopausal women ≥ 55 to ≤ 90 years of age at high risk for fracture. Subjects had a DXA BMD T-score of ≤ -2.50 at the lumbar spine, total hip or femoral neck. Subjects had a history of fragility fracture or met at least 2 clinical risk factors for fracture.

Investigational Products, Dose and Mode of Administration, Manufacturing Batch Number:

- Romosozumab 210 mg QM (90 mg/mL concentration) or matched placebo administered as 2 SC injections in a 1.17 mL [redacted] (b) (4) PFS.
- Romosozumab 210 mg QM (70 mg/mL concentration) or matched placebo administered as 3 SC injections in a 1.0 mL glass PFS.

Duration of Treatment: Six months of treatment followed by 3-month follow-up period

Study Endpoints:
Primary

- percent change from baseline in DXA BMD at the lumbar spine (noninferiority)

Secondary

- percent change from baseline in DXA BMD at the total hip
- percent change from baseline in DXA BMD at the femoral neck
- percent change from baseline in BTMs P1NP and CTX

Safety

For the 6-month treatment period of the study:

- subject incidence of adverse events
- change from baseline in vital signs
- change from baseline in laboratory assessments
- subject incidence of the formation of antiromosozumab antibodies

For the 3-month follow-up period of the study:

- subject incidence of adverse events
- subject incidence of the formation of antiromosozumab antibodies

For the overall study period (6-month treatment period followed by the 3-month follow-up period):

- subject incidence of adverse events
- subject incidence of the formation of antiromosozumab antibodies

Statistical Methods:

The primary analysis to assess the treatment difference for romosozumab treatment groups (romosozumab 90 mg/mL – romosozumab 70 mg/mL) in the percent change from baseline in lumbar spine BMD at month 6 employed an analysis of covariance model. The model had main effects for randomized treatment and baseline lumbar spine BMD T-score. The lower bound of the 1-sided 97.5% confidence interval (CI) of the between-treatment group difference was compared with the noninferiority margin of -2.0% for assessing noninferiority. The primary analysis included all randomized subjects who had a baseline and at least 1 post baseline BMD measurement. Subjects were analyzed according to their randomized treatment assignment, regardless of treatment received. To assess the robustness of the primary analysis for the primary endpoint, a sensitivity analysis was performed using the per-protocol analysis subset. Except for the primary noninferiority hypothesis, all inferential statistics were considered exploratory in nature. Continuous variables were summarized descriptively using mean, median, standard deviation (SD), minimum, maximum, and the number of non-missing observations. Frequencies and percentages were presented for nominal categorical variables.

The subject incidence of treatment-emergent adverse events and laboratory values over time were summarized by actual treatment received. Laboratory shift tables were provided and compared baseline laboratory values with most extreme post baseline values. Subject incidence of antiromosozumab antibodies formation was tabulated. These safety summaries used the safety analysis subset, which included all randomized subjects who received at least 1 dose of

investigational product.

Subject Demographics and Disposition

A total of 294 subjects were randomized to 3 treatment groups: 53 subjects to the placebo group, 118 subjects to the romosozumab 70 mg/mL group, and 123 subjects to the romosozumab 90 mg/mL group. All randomized subjects received at least 1 dose of either romosozumab or placebo. Twenty-three (7.8%) subjects discontinued the investigational product during the 6-month treatment period: 6 (11.3%) subjects in the placebo group, 9 (7.6%) subjects in the romosozumab 70 mg/mL group, and 8 (6.5%) subjects in the romosozumab 90 mg/mL group. All subjects were female, 99% were white, and the mean age was 67.7 years.

Efficacy Results

Primary Endpoint

After 6 months of treatment, mean (95% CI) lumbar spine BMD increased 0.8% (-0.4%, 2.1%) in the placebo group, 9.6% (8.8%, 10.4%) in the romosozumab 70 mg/mL group, and 9.2% (8.4%, 10.0%) in the romosozumab 90 mg/mL group. The mean difference between the two romosozumab groups was -1.5% which was within than the prespecified limit of -2.0. The following table 24 summarizes the two dose concentrations, 70mg/mL and 90 mg/mL by BMD on the lumbar spine at 6 months with ANCOVA model.

Table 24: BMD at Lumbar Spine at 6 months comparing dose concentrations 70 mg/ mL and 90 mg/ mL.

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

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

Source CSR20120156 Table 10-1 with reviewer edits.

Reviewer Comments: ***The two romosozumab concentrations (70 and 90 mg/ mL) both significantly increase BMD (p< 0.0001) at the LS at 6 months compared to placebo and meet noninferiority criteria with mean difference of 1.5% ((117-110)/46 = 1.5%) which is more than the prespecified limit of -2%.***

Secondary Endpoints
Statistically significant differences between both romosozumab groups and the placebo group were seen in percent change from baseline in BMD at the total hip and femoral neck (1-sided p-values for BMD changes from placebo at month 6 were < 0.0001).

The maximum P1NP increase from baseline was observed at the month 1 time point in both the romosozumab groups, and sCTX decreases were observed at months 1 and 6. Safety results are discussed under section 8 with the integrated safety review.

Reviewer Comments: ***This study bridged two different concentration levels for romosozumab by demonstrating that 210 mg SC QM for 6 months administered in the 90 mg/ mL concentration was noninferior to the 70 mg/ mL concentration. Additionally, SAEs were comparable between the placebo and romosozumab groups and AEs were as expected for the population. AE potentially related to hypersensitivity were found more in the romosozumab group but overall AE and SAE rates were balanced between placebo and romosozumab groups.***

6.2.4. Study 20080289 Active-Comparator Controlled-Teriparatide

Title of Study: An Open-label, Randomized, Teriparatide-controlled Study to Evaluate the Effect of Treatment With Romosozumab in Postmenopausal Women With Osteoporosis Previously Treated With Bisphosphonate Therapy

Reviewer Comments: ***Study 20080289 was a 12 month study comparing 12 months of treatment with romosozumab to 12 months treatment with teriparatide in PMO patients, previously treated with bisphosphonates. The primary endpoint, total hip BMD, was not sufficient for direct (head-to-head) efficacy comparisons as fracture data is required. Although the BMD data for romosozumab were comparable to studies previously reviewed, this study will not be reviewed in depth because of the insufficient endpoints for comparison.***

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Fracture was assessed as an endpoint in the pivotal Study 20070337. No other supportive studies assessed fractures as endpoints. The coprimary efficacy endpoints were subject incidence of new vertebral fracture through month 12 and month 24. Romosozumab significantly reduced the risk of new vertebral fractures compared with placebo through month 12 (odds ratio = 0.27, $p < 0.001$), with a relative risk reduction of 73% ([95% CI: 0.16, 0.47]). Vertebral fracture risk reduction persisted over the 24-month study period for subjects initially randomized to romosozumab, as romosozumab for 12 months followed by denosumab for 12 months significantly reduced the risk of new vertebral fractures compared with placebo for 12 months followed by denosumab for 12 months (odds ratio = 0.24, $p < 0.001$), with a relative risk reduction of 75% (risk ratio = 0.25 [95% CI: 0.16, 0.40]).

Sensitivity analyses demonstrated consistent and robust results for the coprimary endpoints. Similar estimates of treatment effect were obtained in sensitivity analyses based on verified stratification variables, the full analysis set, and per protocol analysis set. After controlling for baseline covariates individually and simultaneously in the primary analysis model, romosozumab (month 12) and romosozumab/denosumab (month 24) continued to demonstrate a treatment effect compared with placebo (month 12) and placebo/denosumab (month 24) for the coprimary endpoint at month 12 and month 24.

Reviewer Comments: ***New vertebral fracture results were statistically significant and robust at both the 12 month and 24 month endpoints. Fracture endpoints are important as one of the primary clinical benefit of any osteoporotic drug is to reduce morbidity of fractures in this patient population and romosozumab demonstrates efficacy which is sustained once all patients transition to denosumab.***

7.1.2. Secondary and Other Endpoints

Secondary Fracture Endpoint:
Clinical Vertebral Fractures
Clinical fractures was only studied in the pivotal study 20070337 and discussed in Section 6.1. Through month 12, 3 (< 0.1%) subjects in the romosozumab group and 17 (0.5%) subjects in the placebo group had a clinical vertebral fracture. The total number of subjects with a clinical vertebral fracture during the 24-month study period was 4 (0.1%) in the romosozumab/ denosumab group and 24 (0.7%) in the placebo/denosumab group. Romosozumab (month 12) and romosozumab/denosumab (month 24) demonstrated a relative risk reduction in clinical vertebral fractures of 83% (95% CI: 42, 95) compared with placebo through month 12 and of 83% (95% CI: 51, 94) compared with placebo/denosumab through month 24. The nominal p-values for the treatment comparisons through month 12 and month 24 were 0.001 and < 0.001, respectively but when adjusted for multiplicity, the p-values were 0.008 and 0.096.

Reviewer Comments: ***As discussed in section 7.1, clinical fractures does not have clinical***

meaningfulness as it is not a standard clinical term as defined in this study, clinical fractures at 24 months did not reach statistical significance when adjusted for multiplicity, and a primary component of clinical fractures, clinical vertebral fractures, is already accounted for in the co- primary efficacy endpoints. (b) (4)

(b) (4)

BMD Endpoints

Percent change from baseline in BMD by DXA at the lumbar spine, total hip, and femoral neck were secondary and substudy endpoints in Study 20070337 and primary and secondary endpoints in supportive studies. Assessments of BMD by QCT were secondary or substudy endpoints in Studies 20070337, 20060326 and 20080289. Across the clinical program, the data demonstrate that romosozumab treatment leads to an increase in both trabecular and cortical BMD.

The percent change from baseline in DXA BMD at month 6 and month 18 were evaluated as part of a pre-defined substudy dedicated to evaluating the time course of BMD changes (Lumbar Spine and Proximal Femur DXA Substudy [Imaging substudy II] n = 128; 66 romosozumab and 62 placebo). The data showed that romosozumab resulted in significant and progressive increases from baseline in BMD compared with placebo beginning at month 6 ($p < 0.001$ at spine, total hip and femoral neck. These BMD data allow comparisons between Study 20070337 and the supportive placebo-controlled studies. The significant increases in BMD at the lumbar spine as well as at the proximal femur imply an impact of romosozumab on bone that is predominantly trabecular, as well as bone that is mixed trabecular and cortical (corroborated by the histology substudy in Study 20070337 and QCT data from Study 20060326 and 20080289.) The following table 25 summarizes the BMD percent changes from baseline at the lumbar spine by visit across the placebo-controlled studies.

Table 25: Lumbar Spine BMD Percent Change from Baseline in Placebo-controlled Efficacy Studies.

	20060326		20101291		20120156		Total	
	Placebo (N=50)	Romosozumab 210 mg QM (N=50)	Placebo (N=61)	Romosozumab 210 mg QM (N=63)	Placebo (N=46)	Romosozumab 210 mg QM (N=227)	Placebo (N=157)	Romosozumab 210 mg QM (N=340)
DXA BMD Lumbar Spine (%)								
Month 6								
n	49	50	61	63	46	227	156	340
Mean (SD)	0.37 (3.75)	8.37 (3.91)	1.13 (2.63)	12.88 (5.44)	0.67 (3.12)	9.46 (4.61)	0.76 (3.16)	9.93 (4.89)
Treatment difference vs placebo[a]								
LS means (SE)		8.0 (0.8)		11.7 (0.8)		8.6 (0.7)		9.4 (0.4)
(95% CI)		(6.5, 9.5)		(10.2, 13.2)		(7.2, 9.9)		(8.6, 10.3)
p-value		<0.001		<0.001		<0.001		<0.001
Month 12								
n	47	47	59	59			106	106
Mean (SD)	-0.26 (2.87)	11.34 (5.00)	0.98 (3.31)	16.94 (5.63)			0.43 (3.17)	14.46 (6.01)
Treatment difference vs placebo[a]								
LS means (SE)		11.6 (0.8)		15.8 (0.8)				13.4 (0.5)
(95% CI)		(9.9, 13.2)		(14.1, 17.5)				(12.4, 14.5)
p-value		<0.001		<0.001				<0.001

Source: ISE Table 14-4.1.1 with reviewer edits.

Reviewers Comments: ***Integrated BMD from the pivotal studies and supportive placebo controlled studies demonstrate robust effects of romosozumab on BMD at the LS, total hip, and femoral neck at 12 months which carried forward into 24 months. Each measurement was made every 6 months and were statistically significant for BMD gains at the LS, total hip, and femoral neck with p < 0.001 at each timepoint.***

Bone Turnover Markers:
Bone turnover markers were discussed in section 6.2 for study 20070337. The BTM data from samples collected prior to a QM dose were similar across the placebo-controlled supportive studies showing a rapid and acute increase in P1NP (median P1NP returning to baseline levels at approximately 9 months) and a rapid decrease in sCTX that remained reduced over the romosozumab dosing period. Across the studies, the maximum P1NP increase was observed at the month 1 time point in all romosozumab groups. The maximum decrease in sCTX occurred at month 1 and sCTX levels remained below placebo at month 12. These results are similar to the pivotal study.

In all studies among bisphosphonate-naïve and bisphosphonate pretreated subjects, BTM levels during romosozumab treatment showed a generally similar pattern, reflecting the dual effect of romosozumab, with an increase in bone formation and a decrease in bone resorption. Across the studies, bone formation markers peaked and returned to baseline by approximately month 6 to 9 while bone resorption markers decreased within a month after the first dose and generally remained below placebo at month 12. Despite a general trend toward baseline, transient responses in markers of bone turnover still occurred 14 days post romosozumab dose at months 3 and 6 in Study 20070337. This same pattern was observed at the same time points in Study 20080289 and 1 week post the 12 month dose in Study 20060326. Thus across the 3 studies, BTMs responded to each romosozumab administration with transient increases over the 12 month treatment period.

Reviewer Comments: ***BTM demonstrated consistent patterns across all the studies with rapid increase in P1NP and concurrent rapid decrease of sCTX which remained reduced over the romosozumab dosing period, consistent with romosozumab's dual functions of bone formation and anti-absorption which tapers over 12 months. Although the BTM responses are reduced over subsequent doses, there remains a smaller response after each dose and is reflective of continued smaller effects of romosozumab after each dose.***

7.1.3. Subpopulations

Key Fracture Subgroup Analyses
Sensitivity subgroup analyses of key fracture endpoints including vertebral fractures, clinical fractures and nonvertebral fractures are reviewed in section 6.2 for the pivotal study 20070337 as that was the only study with fracture endpoints.

BMD Subgroup Analyses
In subgroup analyses of percent change from baseline in BMD at the lumbar spine and total hip, romosozumab through month 12 and romosozumab/denosumab through month 24 increased BMD at the lumbar spine and total hip over a range of baseline BMD T-scores. This included subjects with baseline lumbar spine or total hip BMD T-scores ≤ -3 where the LS mean treatment differences were 14.6% and 12.6% through months 12 and 24, respectively, for the lumbar spine and 6.8% and 6.4% through months 12 and 24, respectively, for the total hip. In the analyses through month 12, treatment differences across demographic subgroups (ie, age and geographic region) ranged from 12.0% to 14.4% for the lumbar spine and from 4.7% to 6.6% for the total hip and were consistent with the treatment differences observed for the overall population (12.7% for lumbar spine and 5.8% for total hip at month 12. The BMD response among those who received 50,000 IU 25, OH vitamin D during the first week of the study as compared to those who did not was not statistically different.

Reviewer Comments: ***Subgroup analyses for BMD percent change from baseline showed consistent BMD increases at LS and TH among groups when analyzed for age, geographic regions, baseline BMD T-scores including subjects with low BMD (BMD ≤ -3.0). BMD response were not statistically different between subjects who had vitamin D bolus supplementation and who did not have supplementation.***

Analysis of Study 20070337 Population and Efficacy by Region Baseline Disease by Region
Overall the baseline characteristics of the patients across the regions were similar. Although only 2.7% of the Study 20070337 population was enrolled from North America, age, and baseline BMD T-scores at the hip and femoral neck were similar between North America and other regions in the study, as were most physical characteristics. The BMI was somewhat lower in Asia Pacific, and a lower height, prevalence of historical nonvertebral fracture and FRAX 10-year probability of major osteoporotic and hip fracture was observed for subjects in the Central/Latin America region relative to most other regions.

Reviewer Comments: ***Only 2.7% of the subjects in the pivotal study were from North America. As discussed in section 6.2, regional differences in Central/ Latin America affected the fracture outcome where these patients had fewer fractures than expected.***

Selected Efficacy Endpoints by Region
New vertebral fracture risk reduction and BMD changes at the spine and the hip were consistent between North America and all other regions evaluated. For fracture endpoints, the small sample number of patients recruited in North America affected the interpretation of the primary endpoint data of the North American population was affected but the overall number of new vertebral fractures was very low, 5 vertebral fractures, (3.5%) in the placebo arm and no vertebral fractures (0.0%) in the romosozumab arm at month 12.

The data for BMD percent change from baseline consistently showed statistically significant increases in BMD at the hip and lumbar spine at month 12 compared to placebo, ranging from 12.2 to 14.4 in the lumbar spine, and 4.7 to 6.6 in the total hip. Romosozumab exposure (as assessed by Cmax and Ctrough) was comparable across subjects enrolled in North America and other regions.

Reviewer Comments: ***Although North American recruitment was minor, the new vertebral fracture results (0 romosozumab, 5 placebo) support romosozumab effects on vertebral fracture reduction, similar to the rest of the regions. BMD results were robust and consistently increased compared to placebo across all regions of the world such that there does not appear to be any regional differences. Romosozumab exposure was comparable and supports no regional differences to exposure.***

Summary of Subpopulation Analyses
Subgroup analyses of the co-primary endpoints indicated that the efficacy of romosozumab was consistent regardless of baseline characteristics examined. Likewise, subgroup analyses of percent change in BMD at the lumbar spine and total hip showed romosozumab increased BMD over a range of baseline BMD T-scores and other baseline characteristics. The effects of romosozumab across these subgroups indicate that it can be effective in increasing BMD and preventing vertebral fracture across a broad population of postmenopausal women with osteoporosis. When analyzed by region, the percent change in BMD at the lumbar spine and total hip was similar between North America and all other regions, and romosozumab demonstrated statistically significant increases in BMD in all regions.

Reviewer Comments: ***Subgroup analyses showed romosozumab had consistent vertebral fracture reduction and statistically increased BMD across regions and there were no differences by baseline characteristics for these results. However, regional differences in Latin/South America affected other fracture endpoints of nonvertebral and clinical fractures as discussed in section 6.2.***

7.1.4. Dose and Dose-Response

Romosozumab 210 mg QM for 12 months (the chosen dose, frequency and duration of treatment) was shown to be efficacious both in subjects who are treatment-naïve and in those who have previously received alendronate, and was not associated with increased adverse events compared with other dosing regimens.

The proposed dosing recommendation for submission, 210 mg SC QM, is supported by the efficacy and safety data from two supportive studies, Studies 20060326 and 20101291 in combination with PK/PD-based exposure-response analyses. The supportive studies evaluated a range of doses (Study 20060326 and Study 20101291), durations, and intervals (Study

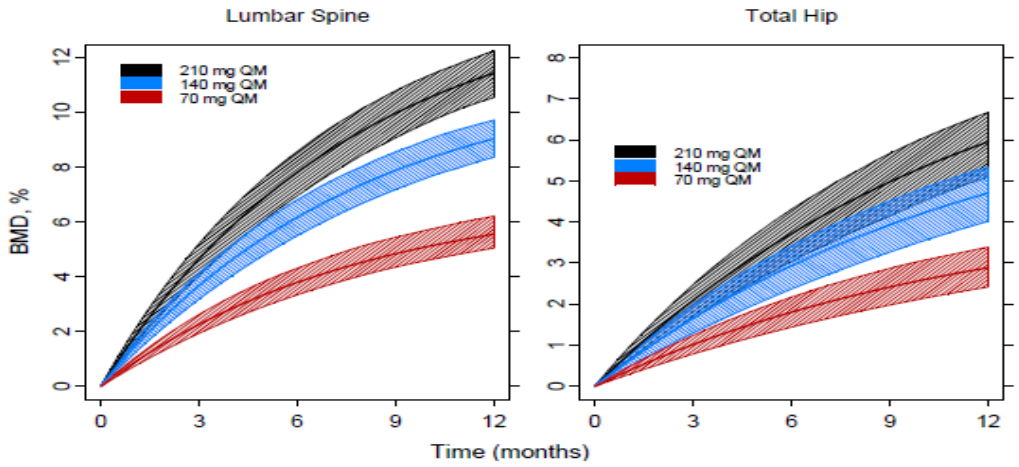
20060326) to allow identification of the most efficacious dosing regimen (dose, interval, and duration) without incurring additional adverse events. These results demonstrate that romosozumab exhibits robust dose-exposure-response relationships and support the 210 mg QM dose regimen tested in the pivotal study.

Integrated analyses of BMD data for the QM dose groups in Studies 20060326 and 20101291 demonstrated that the 210-mg QM dosing regimen resulted in the greatest increase in BMD (month 12) at the lumbar spine, total hip, and femoral neck compared with the other romosozumab dosing regimens tested (70 and 140 mg QM). Furthermore, 210 mg QM and 140 mg QM consistently increased BMD at the lumbar spine, total hip, and femoral neck at months 6 and 12 ($p < 0.001$); whereas, results for the romosozumab 70 mg QM group were less robust, in particular early in treatment when the percent change from baseline in BMD was similar to placebo at month 6 for the total hip and femoral neck. The 210 mg QM dose was also associated with greater increases in BMD at the lumbar spine and total hip than the 2 active controls, alendronate (Study 20060326) and teriparatide (Study 20060326 and Study 20080289). The 210 mg SC QM dosing regimen produced the largest and most prolonged increase in markers of bone formation, with median P1NP, BSAP and osteocalcin levels remaining above baseline for 6 to 12 months compared to 3 to 6 months for 140 mg SC QM). In contrast to the bone formation markers which exhibit increases in a dose dependent manner, the reduction in markers of bone resorption appeared to be less dose-dependent. This suggests that compared with 140 mg QM, the 210 mg QM dose of romosozumab has a greater impact on promoting bone formation without a corresponding further reduction of bone resorption.

Efficacy, as measured by BMD and BTM, was significantly lower when romosozumab was given in 3-month intervals for both of the Q3M doses tested. For example, at month 12, the 210 mg Q3M BMD efficacy was closer to the BMD efficacy achieved with 70 mg QM dosing in Study 20060326. A dose-ranging study in subjects previously treated with bisphosphonates has not been conducted, however BMD gains at the lumbar spine, total hip, and femoral neck appeared to be greater for bisphosphonate-treated subjects who transitioned to romosozumab 210 mg QM in Study 20080289 than for subjects in Study 20060326 who transitioned from alendronate to romosozumab 140 mg QM. Also, the romosozumab 210 mg QM dose does not appear to have a different safety or immunogenicity profile compared with the other regimens tested in the dose-ranging studies.

The Sponsor's PK/PD modeling and simulations support the choice of the 210-mg QM dosing which demonstrated that a romosozumab dose of 210 mg SC QM provided greater BMD gains at month 12 compared to the other dosing regimens tested. The following figure 11 illustrates the Sponsor's modeling and simulation of dose-BMD response as a function of romosozumab concentration model.

Figure 11: Sponsor's Simulated BMD Placebo-corrected Percent Change at Lumbar Spine and Total Hip as Function of Romosozumab Dose.



Source: Summary Clinical Pharmacology with reviewer edits.

Reviewer Comments: ***Supportive studies 20060326 and 20101291 demonstrated significant BMD increases and increased BTMs at two romosozumab doses, 140 mg QM and 210 mg QM, while safety and immunogenicity profiles were similar among doses. The Sponsor chose the higher dose, 210 mg QM, for greater increases of BMD and bone formation markers levels which were dose-dependent. Interestingly, bone absorption marker, sCTX was not dose-dependent which implies that romosozumab's dual actions of bone formation and anti-bone resorption react independently to dose so that the balance between bone formation and bone resorption is not the same at different doses.***

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Dosing Duration

The treatment duration in the initial phase 2 Study 20060326 was 24 months. In this study, the rate and magnitude of BMD increases and the degree of bone formation marker elevation indicated that the greatest efficacy occurred during the first 12 months of treatment. In addition, the levels of bone formation markers collected prior to a QM administration of romosozumab returned to baseline values or fell below baseline values between months 2 and 9 (depending on the dose and the marker) and remained there with continued dosing, whereas the bone resorption marker sCTX remained below the original baseline at month 12. Therefore, the duration of treatment chosen for the subsequent phase 2 and phase 3 studies and for the retreatment phase of Study 20060326 was 12 months. The pivotal study limited use of romosozumab to 12 months of treatment.

Reviewer Comments: ***The data from BMD increases and elevation of bone formation markers demonstrates that romosozumab effects taper off during treatment so that the choice of limiting romosozumab treatment to 12 months is appropriate.***

Persistence of Efficacy
The pivotal study 20070337 and supportive study 20060326 studied romosozumab efficacy in the follow-on period with antiresorptive therapy after romosozumab therapy ended.

Fracture Risk Reduction with Follow-on Therapy
The pivotal study 20070337 assessed fracture risk reduction through 24 months (romosozumab or placebo treatment for 12 months followed by denosumab treatment for 12 months). Results demonstrated that fewer fractures occurred during follow-on treatment in subjects who had received romosozumab compared to those who had received placebo in the first year of study (5 versus 25 fractures in the second year, respectively) even though both groups received denosumab during the second year, risk ratio = 0.25 [95% CI: 0.16, 0.40], p<0.001.

BMD with Follow-on Therapy
In the pivotal study 20070337 follow-on therapy period, the initial romosozumab group (followed by denosumab) continued BMD increases at the lumbar spine, total hip, and femoral neck through month 24 when compared to the initial placebo group. Mean differences in percent change from baseline to month 24 in BMD were significantly greater for subjects in the romosozumab/denosumab group compared with the placebo/denosumab group ($p < 0.001$ at each site), 11.1% at the lumbar spine, 5.3% at the total hip, and 4.9% at the femoral neck. These data demonstrate continued BMD increases in the romosozumab group after transitioning to denosumab. The BMD increases in the romosozumab/denosumab group, after both groups transitioned to denosumab, are of the same order of magnitude as those in the control placebo/denosumab group, maintaining the substantial BMD difference that was achieved during the first 12 months of the study.

BMD gains continued in the follow-on therapy groups of the supportive study 20060326 which was consistent with the pivotal study. In this supportive study, two groups of follow-on patients maintained or continued BMD gains at the lumbar spine, total hip, and femoral neck after romosozumab therapy, one group with denosumab follow-on therapy (months 24-36) and another group with zoledronic acid follow-on therapy (months 48-72).

BTMs with Follow-on Therapy
During follow-on anti-resorptive treatment after romosozumab, markers of bone turnover were markedly reduced, as would have been expected from subjects on denosumab or zoledronic acid therapy. In the Bone Turnover Marker and Biomarker substudy of Study 20070337, median percent change in P1NP and sCTX decreased with denosumab treatment during months 12 to 24. In Study 20060326, median percent change in P1NP and sCTX decreased with denosumab treatment during months 24 to 36, regardless of initial treatment, consistent with the known effects of denosumab.

Reviewer Comments: ***Romosozumab's effects on fracture reduction, BMD gains or BTM levels continue in follow-on anti-resorptive therapy from initial romosozumab therapy when compared to initial placebo therapy.***

Resolution of Effect of Romosozumab During Off-treatment Periods
Supportive study 20060326 was the only study to include patient groups off treatment.

BMD in Off-treatment Periods
All patients randomized to initial romosozumab followed by placebo for follow-on therapy, decreased lumbar spine, total hip, and femoral neck BMD gains after discontinuation of active treatment. Subjects randomized to initial therapy with 140 or 210 mg QM doses of romosozumab decreased BMD gains at the lumbar spine, total hip, and femoral neck after romosozumab treatment was discontinued, but remained above baseline for the following 12 months during the placebo phase. In these subjects, percent change from baseline BMD (start of study) at the end of this placebo phase were as follows: 4.3 % (140 mg) and 4.8% (210 mg) at the lumbar spine; 1.3 % (140 mg) and 1.1% (210 mg) at the total hip; and 1.3% (140 mg) and 2.3% (210 mg) at the femoral neck, respectively. For the subjects initially randomized to 70 mg QM, 140 mg Q3M, and 210 mg Q3M doses of romosozumab who received placebo during months 24 to 36, BMD at lumbar spine, total hip and femoral neck were at or near baseline levels by month 36.

BTMs in Off-treatment Periods
P1NP levels in subjects randomized to romosozumab followed by placebo were below baseline at the end of romosozumab therapy which increased towards baseline during off-treatment (placebo). Subjects, randomized to 210 mg QM romosozumab followed by placebo had sCTX values near baseline at the end of romosozumab therapy which increased to above baseline during off-treatment (placebo) and then returned to baseline by 12 months off-treatment.

Reviewer Comments: ***Both BMD gains and BTMs in the off-treatment periods after romosozumab show return towards baseline, indicating reversibility of romosozumab's effects on bone. Higher doses of romosozumab (140 mg QM and 210 mg QM) have slower BMD gains return to baseline, likely because the changes were greater at the higher doses during romosozumab therapy. Of note, sCTX is not affected by dose differences and returned to baseline by 12 months off-treatment.***

Romosozumab Efficacy During Retreatment Periods
Study 20060326 was the only study to assess re-treatment with romosozumab.

BMD During Retreatment Periods
Subjects received romosozumab retreatment from months 36 to 48 after having received either placebo or denosumab from months 24 to 36. After 12 months of placebo (romosozumab/

placebo/ romosozumab or placebo/ placebo/ romosozumab), retreatment with romosozumab showed similar increases in BMD as were seen in response to initial romosozumab treatment. After 12 months of denosumab lumbar spine BMD increased in response to romosozumab between months 36 and 48, but the gains were smaller and increases were seen regardless of whether the initial treatment was placebo or romosozumab (sequence of romosozumab/ denosumab/ romosozumab or placebo/denosumab/romosozumab).

Although the increase in BMD over the months 36 to 48 romosozumab retreatment period was highest in subjects transitioning from placebo, the overall increase in BMD from baseline was higher for subjects who had received an active agent throughout the first 48 months The following table 26 summarizes mean percent increase in lumbar spine BMD retreatment with romosozumab and compares subjects transitioning from placebo or denosumab in the 12 month period before romosozumab retreatment.

Table 26: Lumbar Spine BMD gains in Response to Romosozumab Retreatment.

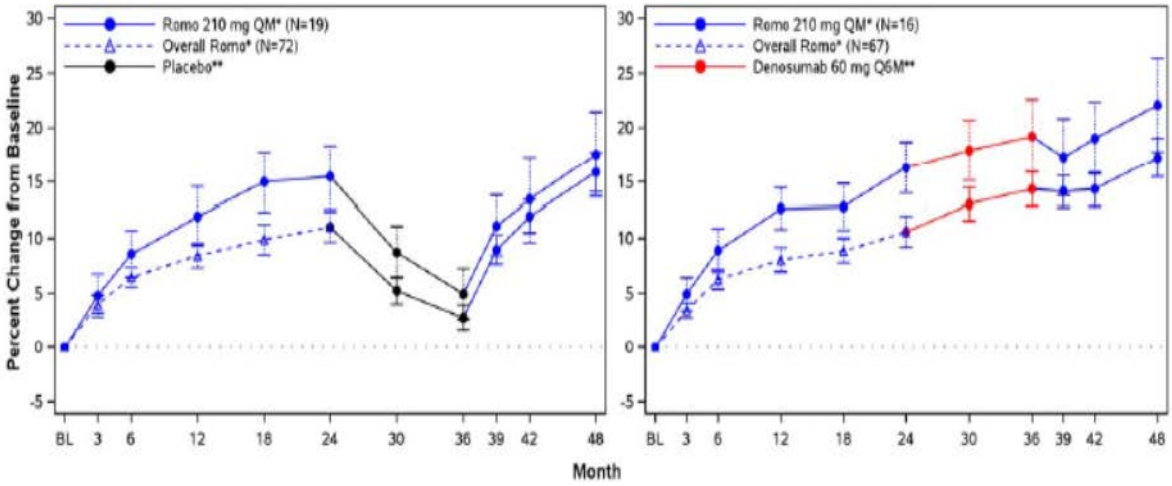
Treatment Group	Mean percent increase in lumbar spine BMD during months 36-48	Total percent increase in lumbar spine BMD from baseline
Subjects transitioning from placebo		
all romosozumab/ placebo/romosozumab	13.1	15.9
romosozumab 210 mg QM/placebo/romosozumab	12.7	17.6
Subjects transitioning from denosumab		
all romosozumab/ denosumab/romosozumab group	2.9	17.3
romosozumab 210 mg QM/denosumab/romosozumab	2.8	22.1

Source CSR 20060326 Table 10-10 with reviewer edits.

The following figure 12 illustrates BMD percent changes (95% CI) from baseline at lumbar spine with romosozumab retreatment in patients transitioning from placebo or denosumab treatment in the preceding 12 months. For the all romo/placebo/romo 210 group, the mean percent increase in lumbar spine BMD from months 36 to 48 was 13.1% (total increase from baseline 15.9%). For the romo 210/placebo/romo 210 group, the mean percent increase from months 36 to 48 was 12.7% (total increase from baseline 17.6%). For the all romo/dmab/ romo 210 group, the mean percent increase in lumbar spine BMD from months 36 to 48 was 2.9% (total increase from baseline 17.3%). For the romo 210/dmab/romo 210 group, the mean percent increase from months 36 to 48 was 2.8% (total increase from baseline 22.1%).

Figure 12: BMD Percent Changes at Lumbar Spine with Romosozumab Retreatment in Patients Transitioning from Placebo or Denosumab.

Placebo Months 24-36: **Denosumab Months 24-36:**



Source: CSR 20060326 Figure 10-14 with reviewer edits.

The same pattern of changes in BMD was seen for total hip and femoral neck during the retreatment period. While the numbers of subjects were small, the mean percent changes from baseline in BMD for the lumbar spine, total hip, and femoral neck at month 48 were comparable for subjects with or without on-study positive antiromosozumab antibodies in most treatment groups.

BTMs During Retreatment Periods

Bone formation markers increased in response to romosozumab retreatment (months 36 to 48) in all groups. For subjects who entered the retreatment phase from a placebo group, the increase in P1NP and decrease in sCTX was rapid and the levels continued to follow a similar profile as seen on initial exposure to romosozumab. For subjects who entered the retreatment phase after denosumab, P1NP and sCTX levels had been diminished during the denosumab treatment period; both P1NP and sCTX gradually increased during the retreatment period, reaching baseline levels by month 42. In these subjects, levels continued to increase above baseline through month 48 (P1NP) or remained at or slightly above baseline at month 48 (sCTX).

Results for other bone formation markers (osteocalcin and BSAP) showed results similar to those for P1NP.

***Reviewer Comments:* Although BMD gains and BTM levels demonstrate that retreatment with romosozumab achieve similar changes when compared to initial 12 months of**

romosozumab therapy, the small number of patients studied (i.e. for romo 210 mg: N=19 for placebo M24-36 group and N=16 for denosumab M24-36 group) limits extrapolation of results into a larger patient population. In these small groups, retreatment after an antiabsorptive, denosumab, showed smaller rate of BMD gains but the overall BMD was higher at the end of 12 months of romosozumab retreatment when compared to placebo. This higher overall gain is due to denosomab's known effects on BMD when compared to placebo during the 12 months transition period before retreatment. The small number of patients studied (n = 19) is inadequate to conclude that romosozumab is effective for retreatment (b) (4)***.***

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The patient population in the pivotal study and supportive studies is representative of the post-menopausal osteoporotic patient in terms of baseline characteristics and entry criteria. The same procedure for drug administration in the healthcare setting by a healthcare provider will be expected for patients prescribed this drug. Healthcare providers will administer the drug to patients in the postmarketing setting which is the same procedure in the clinical studies.

Efficacy was based largely on a foreign population (> 97%) but subgroup analyses did not demonstrate any regional differences for co-primary efficacy endpoints of reduction of vertebral fractures, gains in BMD or changes in BTMs. It is reasonable to expect that efficacy results will be the same in the US postmarket setting.

7.2.2. Other Relevant Benefits

Drug dosing schedule will be 210 mg romosozumab SC QM, given by a healthcare provider. This is a relative benefit as it does not require daily medications and can be given to patients who do not wish to take daily medications such as daily SQ injections (teriparatide), daily medications (some of the bisphosphates), or daily nasal spray (calcitonin).

7.3. Integrated Assessment of Effectiveness

Romosozumab reduced the risk of vertebral fractures and increased BMD in postmenopausal women at an increased risk for fractures based on the totality of the clinical data package which included well- designed, adequately powered, placebo-controlled, and active comparator controlled studies in an appropriate population. The data from the phase 2 and 3 studies in the clinical development program are consistent and can be generalized to the target patient population of postmenopausal women with osteoporosis at increased risk of fracture.

The data support the following key efficacy conclusions for romosozumab:

- Romosozumab significantly reduced the risk of new vertebral fracture by 73% through month 12 compared with placebo. The risk reduction at month 12 persisted through month 24, with a 75% risk reduction after both treatment groups transitioned to antiresorptive therapy (denosumab). Fewer new vertebral fractures occurred during follow-on treatment in subjects who had received romosozumab (5 fractures) compared with subjects who had received placebo (25 fractures) in the first year of study. See section 6.1.2 Study 20070337 Results.

- For new vertebral fracture, the treatment effects were consistent (relative risks favored romosozumab over placebo and romosozumab/denosumab over placebo/denosumab) in all subgroups of baseline characteristics examined, including age, race, geographic region, a range of baseline BMD T-scores, and subjects with a history of prior vertebral, nonvertebral, or fragility fracture. See section 7.1.3 Integrated Subpopulations.

- Although romosozumab significantly reduced the risk of clinical (ie, symptomatic) fractures by 36% through month 12, the following issues negate this clinical fracture claim:
  a) Clinical fracture lacks clinical meaningfulness as defined in the clinical study.
  b) Clinical fracture risk through 24 months was not tested for statistical significance as the fixed-sequence testing ended before this step. See section 6.1.2 Study 20070337 Results.
  c) 85% of clinical fractures is composed of nonvertebral fractures which were not statistically significant at either 12 or 24 months. The remaining 15% of clinical fractures is composed of vertebral fractures which was already counted in the co-primary endpoints of the study (vertebral fractures at 12 and 24 months). See section 6.1.2 Study 20070337 Results.

- The nonvertebral fracture risk reduction with romosozumab was not statistically significant, a result potentially influenced by low nonvertebral fracture rates overall, especially in a high-enrolling region (Central/Latin America). See section 6.1.2. Study 20070337 results.

- The results for other fracture types (major nonvertebral, hip, major osteoporotic) were directionally consistent with the results for new vertebral fracture and clinical fracture (ie, fracture risk appeared lower for romosozumab and romosozumab followed by denosumab than for placebo and placebo followed by denosumab). See section 6.1.2 Study 20070337 Results.

Improvement in BMD

- Results for BMD were consistent across the phase 2 and phase 3 placebo-controlled studies (20070337, 20101291, 20060326, and 20120156). Romosozumab 210 mg QM demonstrated significant increases in BMD at the lumbar spine, total hip and femoral neck, and the effect was seen early with romosozumab treatment (as early as 3 months in Study 20060326). BMD gains were maintained or augmented further in studies that included a transition to antiresorptive therapy after completion of romosozumab. See section 7.1.2 Integrated Secondary Endpoints.

- Romosozumab consistently increased BMD at the lumbar spine and total hip regardless of baseline BMD T-scores, age, and geographic region. When analyzed by region, the percent change in BMD at the lumbar spine and total hip was similar between North America and all other regions, and romosozumab demonstrated statistically significant increases in BMD in all regions. See section 7.1.3 Integrated Subpopulations.

- In subjects who were previously treated with bisphosphonates, BMD gains and strength at the hip as measured by FEA were significantly greater for romosozumab 210 mg QM than for teriparatide at months 6 and 12. See section 6.2.4 Study 20080289 results.

- Retreatment with romosozumab after a treatment-free interval of 12 months showed comparable effects on BMD as those observed after initial exposure to romosozumab, but the results are greatly limited by very small study groups (N<20). See section 7.1.5 Onset, Duration, Durability.

8 Review of Safety

8.1. Safety Review Approach

This safety review focuses on data from 8274 postmenopausal women in the phase 2 and phase 3 studies including 7157 subjects with osteoporosis in the pivotal study (Study 20070337), 218 subjects with osteoporosis who were transitioning from bisphosphonate therapy (Study 20080289), 353 subjects with low bone mass (Study 20060326), 252 Japanese subjects with osteoporosis in a dedicated study in Japan (Study 20101291), and 294 subjects with osteoporosis enrolled in a non-inferiority study (Study 20120156).

This safety review addresses adverse reactions with the following pre-specified categories, listed with their reasons for concern:

1) events causally associated with sclerostin inhibition
    - Hypocalcemia
2) events potentially associated with sclerostin inhibition
    - Hyperostosis

3) events theoretically associated with sclerostin inhibition
   - Osteoarthritis
   - Malignancy
4) adverse events associated with injectable monoclonal antibodies
   - Hypersensitivity events
   - Injection site reactions
5) adverse events associated with anti-resorptive therapies
   - Osteonecrosis of the jaw [ONJ]
   - Atypical femoral fracture [AFF]
6) Adverse events potentially related to tumor necrosis factor-α (TNF-α) mediated inflammatory disease
   - Subjects with or without prior history of TNF-mediated inflammatory disease
7) Adjudicated positive cardiovascular events

When possible, additional adverse event assessments used prespecified standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs). The Sponsor's MedDRA search strategies were used when a SMQ was not available in the categories of hypocalcemia, injection site reactions, hyperostosis, and osteoarthritis.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The following table 27 summarizes overall exposure to romosozumab in the clinical development program:

Table 27: Romosozumab Exposure- Number of Patients by Months of Exposure or Dose

	Placebo			Romosozumab		
	≥ 1 Dose	≥ 6 Months	≥ 12 Months	≥ 1 Dose	≥ 6 Months	≥ 12 Months
Overall total exposure	3791	3508	3305	5478	4273	3879
Phase 1 studies[a]	50	2	0	945	3	0
Postmenopausal osteoporosis studies	3741	3506	3305	4533	4270	3879
Pivotal phase 3 study for postmenopausal osteoporosis[b]	3576	3350	3200	3581	3356	3211
Supportive phase 2 and 3 studies[c]	165	156	105	952	914	668

a Placebo includes studies 20060220, 20060221, 20090153, 20090378; romosozumab includes studies 20060220, 20060221, 20060223, 20090153, 20090378, 20090418, 20101180, 20110227, 20110253, 20120274, 20120277, and 20150197.

b Includes study 20070337 (12 months).
c Placebo includes studies 20060326 (24 months), 20101291 (12 months), and 20120156 (6 months); romosozumab includes studies 20060326 (24 months, 48 subjects who received romosozumab after one year of alendronate are included), 20080289 (12 months), 20101291 (12 months), and 20120156 (6 months).
Source from 2.7.4 Summary of Clinical Safety Table 2 and modified by reviewer

8.2.2. Relevant characteristics of the safety population:

This safety review is primarily based on the 12 month placebo controlled safety analysis set which is based on data from the pivotal study with 3 supportive placebo controlled studies.

- **12-month placebo-controlled postmenopausal osteoporosis (PMO) safety analysis set (also referred to as the 12-month placebo-controlled population)**:
  This population included subjects who were randomized and received at least 1 dose of romosozumab 210 mg QM or placebo in three phase 2 and phase 3 studies (20060326, 20101291, and 20070337).

  Of note, two studies, studies 20080289 and 20120156, are not included in the pooling as these studies involve a different patient population or duration (alendronate pretreatment and only 6 months duration, respectively) but will be considered separately.

8.2.3. Adequacy of the safety database:

Reviewer's comments: Total size and adequacy of the database appears appropriate for the dose of 210 mg monthly with 1 year use as 3879 subjects were exposed at this dose and time period.

However, a significant number of subjects were outside the US and these demographic differences may affect the adequacy of the safety database. The disease of post-menopausal osteoporosis has world-wide prevalence but may have different rates based on many variables such as differences in diet, lifestyles, sun exposure, and access to Vitamin D, etc. The main pivotal trial studied only 2.7% US subjects but included 43% Central/ Latin American subjects and 25% Eastern European subjects.

The Sponsor did make an attempt to reduce variability between demographic regions by inclusion/ exclusion criteria including minimal baseline BMD ratios at the hip, spine, and pelvis, limited vertebral spinal fracture history, and minimal baseline Vitamin D (Vit D) levels. Baseline Vit D bolus was required in some patients along with daily Vit D and calcium supplementation was required for all patients during the pivotal study in order to decrease variability of Vitamin D access. Together, these measures decreased variability in the different patient demographic populations in the studies.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Submission quality is adequate regarding overall organization, ease of finding information, proper location of information and data. There were no data quality and integrity issues identified.

8.3.2. Categorization of Adverse Events

Adverse events coded to previous Medical Dictionary for Regulatory Activities (MedDRA) versions were recoded to MedDRA version 18.1. Only treatment-emergent adverse events were included in the safety analyses.

The Sponsor performed additional safety evaluations, listed in section 8.1, based on the mechanism of action, the pharmacologic profile of romosozumab, potential class effects of bone-forming agents, observations made during the nonclinical and clinical program, and the Division's feedback from the 19 August 2011 EOP2 meeting (14 September 2011 FDA Meeting Minutes). These additional safety analysis and search terms used are the following:

- Hypersensitivity and Malignancy
  - Search terms standardized MedDRA queries (SMQs) (captured by the "unspecified or malignant tumors" SMQ for malignancy)
- Hypocalcemia, Injection Site reactions, Hyperostosis, and Osteoarthritis
  - Internal Amgen search strategies for the events of interest that did not have a MedDRA SMQ.
  - Subject incidences are provided using the 12-month placebo-controlled safety analysis set; Exposure-adjusted incidence rate used the PMO safety analysis set.
- Osteonecrosis of Jaw (ONJ)
  - Predefined search of MedDRA terms were submitted to an independent external adjudication committee for review and adjudication
  - The committee determined whether the event met the case definition criteria for ONJ.
- Atypical Femur Fracture (AFF)
  - Predefined search of MedDRA terms were submitted to an independent external adjudication committee for review and adjudication.
  - The committee determined whether the event met the American Society for Bone and Mineral Research case definition criteria for AFF.

- Tumor necrosis factor-α (TNF-α)-mediated inflammatory disease in subjects with or without a prior history of TNF-mediated inflammatory disease
  - Internal Amgen search strategy using the 12-month placebo-controlled safety analysis set.

Reference ID: 4093382

- Cardiovascular events(Study 20070337)
  - All deaths and serious adverse events deemed by the investigator to be of potential cardiovascular origin or etiology were submitted to an independent committee for adjudication which was blinded to treatment assignment.
  - Classification of each death as cardiovascular-related or non-cardiovascular-related based on predefined criteria in the Clinical Events Classification Charter.
  - Undetermined classification for deaths not classified into either cardiovascular-related or non-cardiovascular related and presumed to be all cardiovascular-related for completeness.
  - Serious adverse events with terms mapping to a predefined preferred term list potentially indicative of cardiovascular etiology were also adjudicated by the cardiovascular adjudication committee.

Reviewer Comment: ***The Sponsor's selections of these specific additional safety evaluations are appropriate and the approach for each category is reasonable.***

Key additional data from individual studies were also included for evaluation below:

- Safety with longer-term exposure and retreatment for the extension phases of the phase 2, dose-finding Study 20060326 (up to year 6)
- Safety with long-term safety follow-up from the pivotal phase 3 study for the PMO indication (Study 20070337, 24-month data)
- Safety after transition to romosozumab from prior bisphosphonate therapy (Studies 20080289 and 20060223)
- Safety of the 90 mg/mL concentration (proposed for commercial use) compared with a 70 mg/mL concentration (used in other phase 3 studies) in Study 20120156
- Device-related safety

Reviewer Comment: ***Inclusion of these key data evaluations from individual studies are reasonable and appropriate.***

Routine Clinical Tests

Routine Clinical Laboratory Data Analysis:

The Sponsor performed analyses of routine clinical laboratory data using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) in the following categories:

1) CTCAE severity grade ≥ 2 using the 12-month placebo-controlled population.
2) Laboratory value shifts from baseline by ≥ 2 CTCAE severity grades using the 12-month placebo-controlled population.
3) Study discontinuation, dose change, or addition of concomitant therapy resulting from shift tables, marked laboratory value abnormality tables for clinically significant findings that are not serious adverse events, and laboratory value changes in the 12-

month placebo-controlled population.

4) Serum calcium changes: actual value (albumin-adjusted, in mg/dL and mmol/L), change from baseline, percentage change from baseline, and maximum decrease of CTCAE ≥ 1 grade shift from baseline using the 12-month placebo-controlled population and PMO population.
5) Calcium substudy (Study 20070337) for hypocalcemia associated with the first romosozumab 210 mg dose along with daily calcium and vitamin D supplementation.
6) Intact parathyroid hormone (iPTH) and urinary calcium substudy (Study 20070337) to characterize serum iPTH concentration and urinary calcium excretion through month 12.
7) Phosphorus and magnesium changes: from baseline and percentage change from baseline across studies using the 12-month placebo- controlled population.
8) Fasting glucose (Study 20070337, 24-month data) changes: with fasting defined as sample collected within 60 minutes of a laboratory blood draw for bone turnover markers.
9) Potential Hy's Law cases as well as serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) > 3 x upper limit of normal (ULN), > 5 x ULN, > 10 x ULN, and > 20 x ULN using the 12-month placebo-controlled population and PMO population.
10) Immunogenicity (formation of anti-romosozumab antibodies):
    - Subject incidence of binding and neutralizing ADA is reported for the 12-month placebo-controlled population.
    - Potential effects of ADA on safety parameters (eg, hypersensitivity, injection site reactions, or autoimmune disorder) from individual studies

Reviewer Comment: ***The selected categories of analysis for routine laboratory values are reasonable and appropriate based on preclinical studies and the molecular basis of romosozumab. The selected population for safety analysis and time for analysis at month 12 are appropriate, given that romosozumab was given to patients for a maximum of 12 months.***

Vital signs, Physical Findings and Other Observations:

The Sponsor analyzed important other observations in the following categories:

1) Vital signs and electrocardiogram (ECG) -absolute values and changes from baseline
    - (ECG) data, when collected, were summarized by study with no integration of data.
2) Audiology substudy (Study 20070337) results on hearing loss
3) Excessive BMD gains: BMD analyses to assess the possibility of excessive BMD gains at lumbar spine, total hip, and femoral neck using the 12-month placebo-controlled population and shift from baseline to the maximum post-baseline (up to month 12) of BMD T-scores.

4) Bone histology for new bone and bone quality in Studies 20070337, 20060326, and 20080289
5) Osteoarthritis substudy (Study 20070337) to assess the effect of romosozumab compared with placebo at month 12 on the progression of osteoarthritis of the knee.
6) Lean body mass changes: percentage changes from baseline at months 6, 12, 18, and 24 in Imaging substudy subjects (Study 20070337)

Reviewer Comment: ***The above categories of vital signs and other observations are reasonable and appropriate given the molecular mechanism and preclinical study results.***

8.3.3. Deaths

53 deaths (0.7% of subjects) in 7384 unique subjects in the 12-month placebo-controlled population were reported.

For romosozumab, 29 deaths (0.8% of subjects) were reported; fatal AEs reported for 2 or more subjects in the romosozumab group included lung neoplasm malignant (4 subjects), myocardial infarction (2 subjects), and death not otherwise specified (5 subjects).

24 deaths (0.7% of subjects) were reported among placebo subjects; fatal adverse events reported for 2 or more subjects included myocardial infarction, angina pectoris, and cerebrovascular accident (2 subjects each) and death not otherwise specified (5 subjects). The following table 28 shows the top fatal adverse events in the Safety population:

Table 28: Treatment-emergent Fatal Adverse Events by Preferred Term (Safety Analysis Set)

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting fatal treatment-emergent adverse events	23 (0.6)	29 (0.8)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (0.7)	29 (0.8)
Death	5 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	5 (0.1)
Lung neoplasm malignant	0 (0.0)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Myocardial infarction	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)
Adenocarcinoma gastric	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Brain contusion	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Breast cancer	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Cardiac arrest	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Cardiac failure congestive	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Cardio-respiratory arrest	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Circulatory collapse	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Congestive cardiomyopathy	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Deep vein thrombosis	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Hepatocellular carcinoma	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Lower gastrointestinal haemorrhage	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Multi-organ failure	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)

Source ISS Table 14-6.2.9 with reviewer edits

Malignant lung neoplasm with fatal outcome was reported for 4 romosozumab subjects (b) (6) dosed at 210 mg QM; all were current or former smokers, 1 subject had a history of basal cell carcinoma, and 1 subject reported a family history of unspecified cancer. The onset ranged from study day 47 to 132 with 2 of the events reported as squamous cell carcinoma stage III at diagnosis, one as stage IV histology not provided, and the fourth unknown stage histology not provided.

Detailed look at all lung neoplasms and not just fatalities demonstrate that the treatment emergent adverse event (TEAE) for lung neoplasm is balanced with 0.2% in romosozumab group and 0.2% in placebo patients. The following table 29 shows the total malignancies and lung neoplasms in the controlled trials.

Table 29: Adverse Events of Lung Neoplasms by Preferred Term

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting treatment-emergent adverse events of malignant or unspecified tumours	69 (1.9)	59 (1.6)	2 (4.0)	1 (2.0)	0 (0.0)	1 (1.6)	71 (1.9)	61 (1.7)
Lung neoplasm malignant	5 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	5 (0.1)
Lung neoplasm	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)
Total Lung neoplasm	6 (0.2)	7 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)	7 (0.2)

Source ISS Table 14-6.8.5 with reviewer edits and modifications.

Reviewer Comment: ***Fatalities due to lung neoplasms during the study have a significant imbalanced of subjects in the romosozumab group (4) versus placebo group (0). All 4 patients had risk for lung neoplasm with smoking history. The days to onset was relatively short from 47-132 days after first treatment of romosozumab. On a detailed look at all lung neoplasms, the groups are well balanced at 0.2% in both the romosozumab and placebo group. Interestingly the deaths from lung neoplasms were detected early in the study.***

A literature search found a paper (Hernandez et al.) which localized sclerostin in non-skeletal tissues including lung. The following quote was from the abstract: "Sclerostin was secreted by bone explants as high molecular weight forms that were reducible to the dimeric form. This dimeric form was detected in sera and in non-skeletal soft tissues specifically kidney, liver, heart and lung." Further literature searches did not reveal any reports of TNF associated diseases or lung cancers with sclerostin.

The current natural course of lung carcinoma can be rapidly fatal and death within the year would not be unexpected in this patient population once a diagnosis is made. There are insufficient cases to determine if the finding of early fatality can be attributed to the drug causing a more rapidly fatal outcome of lung neoplasm but this information would be informative in labeling.

8.3.4. Serious Adverse Events

In the 12-month placebo-controlled population at least 1 serious adverse event was reported for 9.5% of subjects in romosozumab group and 8.8% of subjects in the placebo group. The only serious adverse event occurring in ≥ 0.5% of subjects in the total romosozumab or placebo groups was pneumonia (0.5% romosozumab, 0.3% placebo). Chronic kidney disease (0.0% romosozumab, < 0.1% placebo) was the only preferred term reported for > 1 subject in total romosozumab or placebo treatment groups. The following table 30 summarizes the most frequently reported SAEs in the placebo-controlled safety population.

Table 30: SAEs in the Safety Population

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting serious adverse events	312 (8.7)	344 (9.6)	7 (14.0)	6 (11.8)	4 (6.3)	2 (3.2)	323 (8.8)	352 (9.5)
Pneumonia	10 (0.3)	19 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.3)	19 (0.5)
Hypertension	5 (0.1)	8 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	8 (0.2)
Angina unstable	3 (<0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	3 (<0.1)	7 (0.2)
Cardiac failure congestive	4 (0.1)	7 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	7 (0.2)
Chronic obstructive pulmonary disease	15 (0.4)	6 (0.2)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	15 (0.4)	7 (0.2)
Acute myocardial infarction	4 (0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	6 (0.2)
Atrial fibrillation	4 (0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	6 (0.2)
Osteoarthritis	15 (0.4)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (0.4)	6 (0.2)
Cholelithiasis	8 (0.2)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.2)	5 (0.1)
Cerebrovascular accident	7 (0.2)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.2)	4 (0.1)
Femur fracture	7 (0.2)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.2)	4 (0.1)
Urinary tract infection	7 (0.2)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.2)	4 (0.1)
Femoral neck fracture	8 (0.2)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.2)	3 (<0.1)

Source: Modified ISS Table 14-6.2.2 with reviewer edits

Reviewer Comment: ***SAEs in the 12 month placebo controlled population are relatively***

balanced between the romosozumab and placebo groups. There was a slight inbalance of pneumonia (0.5% (19) romosozumab, 0.3% (10) placebo) favoring romosozumab in both safety populations but the overall rate of pneumonia in both groups is consistent with what is expected in this patient population.

8.3.5. Dropouts and/or Discontinuations Due to Adverse Effects

In the 12-month placebo-controlled population, adverse events leading to discontinuation from study participation were reported for 1.2% (45) of subjects in romosozumab group and 1.4% (50) of subjects in the placebo group. All individual preferred terms were reported for < 0.1% of subjects in total romosozumab and placebo treatment. Table 31 summarizes AEs leading to discontinuation from the study in the placebo-controlled safety population for > 1 subject report by preferred term.

Table 31: AEs Leading to Discontinuation of Study

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting treatment-emergent adverse events leading to discontinuation of study	50 (1.4)	44 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	50 (1.4)	45 (1.2)
Arthralgia	1 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	3 (<0.1)
Musculoskeletal pain	2 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	3 (<0.1)
Pain in extremity	0 (0.0)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)
Abdominal pain	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Back pain	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)
Nausea	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)

Source: ISS 14-6.2.6 with reviewer modifications.

***Reviewer Comment:** Arthralgia (<0.1% (3) romosozumab, < 0.1% (1) placebo) and musculoskeletal pain (< 0.1% (3) romosozumab, < 0.1% (2) placebo were the most frequently reported but the reports are minimal in both groups with no inbalance noted.*

8.3.6. Significant Adverse Events

Adjudicated Positive Atypical Femur Fracture

Atypical Femur Fractures (AFF) has been observed with the use of antiresorptive agents. Because inhibition of bone resorption is a component of the dual effect of romosozumab, there is a potential concern for increased risk of AFF. Nonclinical data did not suggest a plausible mechanism for romosozumab to cause AFF. Aged ovariectomized and adolescent cynomolgus monkey data demonstrate the positive effect of romosozumab on cortical bone by enhancing cortical geometry, increasing mass and strength, and maintaining bone quality. The collective data across studies in ovariectomized monkeys support that romosozumab causes transient increases in intracortical remodeling effecting slight transient reductions in cortical BMD only in the radius. The weight of evidence supports that romosozumab's mode of action on cortical bone would be expected to decrease rather than increase the risk of cortical fractures.

In the 12-month placebo-controlled population (excluding Study 20101291, for which events were not adjudicated [no femur fracture adverse event was reported in Study 20101291]), 1 subject in the romosozumab group and no placebo subject had a positively adjudicated event of AFF.

The following Table 32 summarizes the incidence of adjucated AFF by treatment group in the placebo controlled studies.

Table 32: Adverse Events of Adjudicated Positive Atypical Femoral

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting treatment-emergent adverse events of adjudicated atypical femoral fractures	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Femur fracture	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

Source from ISS Table 14-6.8.8 with reviewer edits.

The following is a summary narrative for the positive AFF patient who was treated with romosozumab in the pivotal study 20070337:
Subject (b) (6) was a 69-year-old Dominican woman with a history of osteoporosis, femur pain, hypertension, and partial hysterectomy. The subject had no prior history of cancer, hip surgery to the affected side, or localized pain to the contralateral proximal lateral femur region. She had no prior use of proton pump inhibitors, bisphosphonates, denosumab, teriparatide, or corticosteroids. Screening X-rays showed 3 spinal fractures (T7, T8, and L4); vitamin D was 19.2 ng/mL (normal range: ≥ 20 ng/mL). BMD T-scores were −3.1 at the hip and −2.8 at the femoral neck. Approximately 3.5 months later on day 101 (after 4 doses of romosozumab 210 mg SC QM), she fell from a standing height and sustained a right femoral

diaphysis fracture. A radiograph indicated the fracture occurred in the sub trochanteric or diaphyseal region of the femur and was a non-comminuted simple transverse or short oblique (< 30 degrees) fracture. Prodromal pain in the affected hip with weight bearing was reported prior to study participation. The subject was hospitalized and underwent osteosynthesis with fixed intramedullary screws. Blinded romosozumab was continued, and the subject continued on to receive open-label denosumab. A follow-up X-ray 3 months after fracture fixation showed intact fracture fixation hardware. The outcome of the event was reported as resolved.

Reviewer Comments: ***This case is concerning for romosozumab actions in the early period of treatment on bone fractures with this positive AFF on day 101. She did have a prodromal pain in the region but the presence of prodromal pain does not alleviate the concern for a romosozumab link to her AFF. The early timing for her fracture after only 4 doses raises concerns for rapid onset of romosozumab effects on bone strength and quality as well as the disparity of balance between bone building and anti-absorption properties of romosozumab in the early treatment period. She had no prior exposure to known products linked to AFF such as bisphosphonate or denosumab therapy. This stand-out case remains concerning for romosozumab effects on bone for AFF. Further discussion of other cases continue in the following section.***

Labeling should reflect the concern that romosozumab may be linked to AFF as a warning to practitioners and patients.

To date in all ongoing and completed studies, there were an additional 5 cases of femur fractures of which 4 cases were adjudicated positive for AFF and was adjudicated as not AFF. All 5 additional cases occurred in the blinded alendronate- controlled Study 20110142 during the open- label phase of follow-on alendronate administration with a time to onset of 502 to 1020 days after initiation of double-blind investigational product. Although the study was blinded at the time of submission for this application, the Division requested unblinded information for the patients in the study who developed AFF. Of the four patients adjudicated for AFF, one subject had been randomized to romosozumab-alendronate roll-over arm and 3 subjects had been randomized to the alendronate-alendronate roll-over arm. The one subject who developed a femur fracture which was NOT adjudicated for an AFF had been randomized to the romosozumab-alendronate roll over arm.

The following are the unblinded abbreviated summary narratives from this study (Study 20110142).

A) Adjudicated Positive for AFF:
   1) Romosozumab-alendronate roll-over arm: 0ne Patient
      - Subject (b) (6): 75-year-old white female with a history of osteoporosis, hypertension, fall, atherosclerosis, chronic heart failure, and an

upper left leg middle shaft fracture in (b) (6) caused by "lower" force treated by osteosynthesis. She had no prior history of cancer, localized pain to the contralateral proximal femur region, or hip surgery to the affected side. She had no prior use of corticosteroids, bisphosphonates, teriparatide, proton pump inhibitors, or denosumab. Screening spine X-ray showed fractures at L1 and L4, vitamin D was 21.6 ng/mL, and BMD T-scores were −3.80 at the hip and −3.26 at the femoral neck. The subject received romosozumab for 1 year then rolled over to receive open-label alendronate. One year and 9 months after initiating open label alendronate (Month 33), the subject experienced a right femur shaft fracture while walking. She was admitted to the hospital and underwent osteosynthesis with intramedullary nail. The investigator assessed the event as not related to blinded therapy or open-label alendronate. A follow up X-ray showed that the fracture was resolved.

2) Alendronate-Alendronate Roll-Over Arm: 3 Patients

- Subject (b) (6) was in the alendronate-alendronate roll over arm: 72-year-old female with a history of osteoporosis, left femur fracture due to a traffic accident treated with osteosynthesis, pain in right thigh following left femur fracture (started 2004), back osteoarthritis, ex-smoker, stomatitis, polyuria, right upper limb pain, right lower limb pain, varicose veins, and measles. The subject had no prior use of corticosteroids, bisphosphonates, teriparatide, or denosumab. Screening spine X-rays showed fractures at T4 and L2, vitamin D was 23 ng/mL and BMD T-scores were −3.90 at the hip and −3.21 at the femoral neck. The subject received 1 year of alendronate followed by open label alendronate. During study Month 5, the prodromal pain in right thigh that was present before study initiation intensified following a non-serious event of ankle joint injury. During study Month 16, she fell and sustained a right femur shaft fracture. She was admitted to the hospital and femoral fracture osteosynthesis was performed. The investigator assessed the event as related to blinded therapy and open-label alendronate. The event was reported as resolved; the subject was walking with a cane and undergoing ongoing physical therapy.

- Subject (b) (6) was in the alendronate-alendronate roll over arm. 58-year-old female with a history of lower leg (not knee or ankle) fracture and forearm fracture after a fall from her own height. Her last date of menstrual cycle was in 1999. She had no known history of cancer, hip surgery to the affected side, or localized pain to the contralateral proximal lateral femur region. She had no prior use of corticosteroids, bisphosphonates, teriparatide, proton pump inhibitors, or denosumab. Screening spine X-rays showed fractures at T5 and T10, vitamin D was 18.2 ng/mL and BMD T-scores

were −3.0 at the hip and −3.57 at the femoral neck. The subject received alendronate for 1 year then rolled over to receive open-label alendronate. Approximately 5 months after rolling over to the open label alendronate (Month 17), she tripped over a separator on the street and sustained a left femur sub trochanteric fracture. She was admitted to the hospital, and sub trochanteric fracture osteosynthesis with intramedullary nail was performed. The investigator assessed the event as not related to blinded therapy or open-label alendronate. The event was reported to be resolved, and the subject was walking without assistance.

- Subject (b) (6) was in the alendronate-alendronate roll over arm. 78-year-old female with a history of osteoporosis, varicose veins, and osteoarthritis. She had no prior history of corticosteroid use, hip surgery to affected area, or localized pain in the contralateral femur region; prodromal pain over the fracture site was reported during weight bearing. Screening x-rays showed a Grade 3 vertebral fracture at T7, vitamin D was 25.9 ng/mL, and BMD T-scores were −4.33 at the hip and −3.85 at the femoral neck. The subject received alendronate for 1 year then rolled over to receive open-label alendronate. One year and 4 months after rolling over to the open label alendronate (Month 28), the subject stumbled while walking on unstable ground, fell from her own height, and experienced a femur shaft fracture. She was admitted to the hospital and underwent osteosynthesis surgery. The investigator assessed the event as not related to blinded therapy or open-label alendronate. The event was reported as resolved and the subject was walking without assistance.

B) Femur Fracture Adjudicated as NOT AFF: One patient

Subject (b) (6) was in the romosozumab-alendronate roll over arm.

- 72-year-old female with a history of osteoporosis, acid peptic disease, hysterectomy, thrombocytopenia, cystopexy, club foot correction, hypertension, dyslipidemia, chronic obstructive pulmonary disease, asthma, allergic rhinitis, and chronic back pain. The subject did not have a history of cancer or hip surgery to the affected side. She had no prior use of corticosteroids and no prodromal symptoms over the fracture site. Screening spine X-ray showed a fracture at T5, vitamin D was 17.9 ng/mL, and BMD T-scores were −2.78 at the hip and −2.36 at the femoral neck. Two weeks after initiating romosozumab, the subject underwent unspecified foot surgery. She received romosozumab for 1 year and then rolled over to receive open-label alendronate. Approximately 1 year and 4 months after initiating open-label alendronate (Month 28), she stumbled and fell from her own height while

wearing shoes bigger than her size. She sustained a right femur fracture and was admitted to the hospital. She was treated with skeletal traction, analgesics, sedation, and internal fixation of the fracture. A postoperative X-ray showed adequate reduction of the right femur shaft fracture and a new right intertrochanteric femur fracture with a cephalomedullary pin in place. The subject was reported as not having had a fall, injury, or prodromal symptoms that may have led to the right intertrochanteric femur fracture. The event of intertrochanteric femur fracture was adjudicated and did not meet criteria for atypical femur fracture. The investigator assessed the events of femur shaft fracture and intertrochanteric femur fracture as not related to blinded therapy but related to open-label alendronate. The event of femur shaft fracture was reported as resolved with sequelae and the event of femur intertrochanteric fracture was ongoing. The subject was ambulating with a cane and receiving ongoing physical therapy.

Reviewer Comments: ***Summary of these additional case narratives from unblinded data from the alendronate-controlled trial:***

- ***1 case: on Romo-alendronate, AFF at month 33 (after 21 months on alendronate)***
- ***1 case: on Romo-alendronate, femur fx NOT adjudicated as AFF at month 28 (after 16 months on alendronate)***
- ***3 cases: on alendronate-alendronate arm, AFF after 16, 17, and 28 months on alendronate***

Of note is that the baseline BMD for all subjects who developed AFF in this study exceeded the exclusion criteria in the pivotal study 20070337 of -3.5 SD BMD at either hip of femoral neck. The exception was the one case of femur fracture not adjudicated as an AFF who had higher baseline BMD (-2.78 SD hip and -2.38 SD femoral neck).

The presence of AFF or femur fractures in this clinical study does not alleviate concerns that romosozumab is linked to these fractures although these AFF cases are confounded by alendronate treatment as all subjects presented during alendronate treatment which is known to increase risks of AFF but usually after extensive long-term treatment (3 years or more). These subjects were at baseline at high risk for fractures; given their baseline BMD values exceeded -3.50 SD.

Bone Quality:

Bone Biopsy Substudy in Pivotal Study 20070337:
The Sponsor submitted results of the bone biopsy substudy in the original application and then submitted additional information under Module 1.11.3 on February 14, 2017.

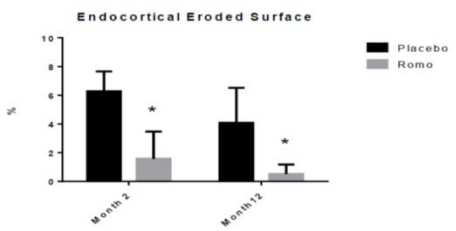
As described in the Bone Biopsy Substudy submitted in the original BLA twenty-nine subjects (15 romosozumab, 14 placebo) with quadruple fluorochrome labeling (double fluorochrome

labeling at baseline and before month 2) were evaluated for histomorphometry at month 2. Within-subject comparisons showed significant stimulation of bone formation in the romosozumab group between baseline and month 2 in the cancellous and endocortical compartments, as demonstrated by significant increases in single-labelled, double-labelled, and mineralizing surfaces and surface- based bone formation rates (BFR/BS) in the romosozumab group. No significant changes were seen in mineral apposition rates (MAR) in the romosozumab group. In the placebo group, no significant changes were noted for any of these histomorphometry parameters in the within-subject comparisons.

At month 2, romosozumab significantly increased osteoid thickness and osteoid volume compared with placebo. As a consequence of the increased cancellous bone formation rate, the calculated parameter activation frequency (derived from BFR/BS) was also significantly increased. Consistent with the dual effect of romosozumab, a reduction in bone resorption was also evident at month 2, as indicated by significantly lower median eroded surface in the cancellous (romosozumab, 1.810%; placebo, 3.370%) and endocortical compartments (romosozumab, 1.580%; placebo, 6.270%) and a significantly lower median osteoclast surface in the cancellous compartment (romosozumab, 0%; placebo, 0.095%) in the romosozumab group. In contrast to the increase in bone formation parameters observed at month 2, dynamic and static formation parameters at month 12 demonstrated a decrease in bone formation secondary to the decrease in the rate of bone remodeling in the cancellous compartment, consistent with self-regulation of bone formation. The MAR, adjusted apposition rate, single-labelled, double-labelled, and mineralizing surfaces, surface- and volume-based bone formation rates, activation frequency, and osteoid volume were significantly lower and mineralization lag time and formation period were significantly greater in the romosozumab group compared with the placebo group. Similar to month 2, eroded surface and osteoclast surface on both cancellous and endocortical surfaces were significantly lower in the romosozumab group, indicating sustained inhibition of bone resorption.

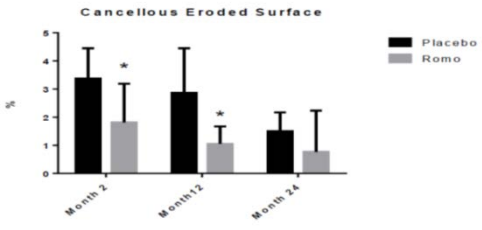
The following figures (Figures 13 and 14) graphs endocortical (Figure 13) and cancellous (Figure 14) eroded surface percentiles comparing the two groups of romosozumab treated and placebo patients at month 2 and month 12.

Figure 13: Endocortical Eroded Surface Bone Substudy Analysis Set



Source: Module 1.11.13: Table 14fm-8.2.3

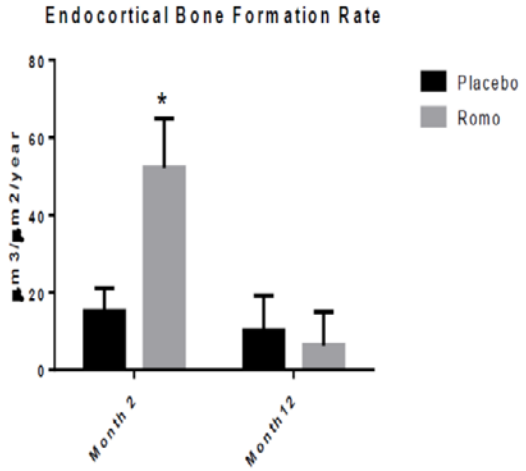
Figure 14: Cancellous Eroded Surface



Source: Module 1.11.13: Table 14fm-8.2.3

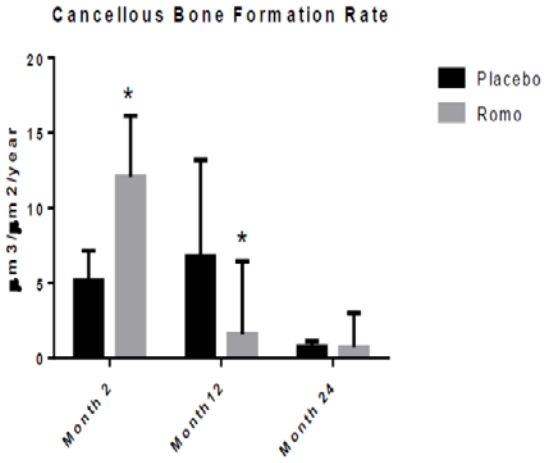
The following figures (Figure 15 and 16) graph endocortical (Figure 15) and cancellous (Figure 16) bone formation rates comparing romosozumab-treated group to placebo at months 2, 12, and 24 (for cancellous bone only).

Figure 15: Endocortical Bone Formation Rate (Bone Biopsy Substudy Analysis Set)



Source: Module 1.11.13: Table 14fm-8.2.3

Figure 16: Cancellous Bone Formation Rate



Source: Module 1.11.13 Table 14fm-8.2.3

As discussed in section 6.1.2, all biopsies evaluable for histology at months 2, 12, and 24 showed normal lamellar bone, normal mineralization, and osteoid.

In contrast to an increase in bone formation parameters observed at month 2, dynamic and static formation parameters at month 12 demonstrated a decrease in bone formation secondary to the decrease in the rate of bone remodeling in the cancellous compartment. Similar to month 2, eroded surface and osteoclast surface were significantly lower in the romosozumab group than in the placebo group, indicating sustained inhibition of bone resorption.

These findings were consistent with those seen in the two other bone biopsy substudies (Study 20060326 [months 6 and 12, n = 32] and 20080289 [month 12, n = 4]).

Reviewer Comments: ***The Sponsor postulates that the bone biopsy data decrease the biological plausibility of a potential relationship of the antiresorptive properties of romosozumab to AFF. While the bone biopsy results may support this postulate at the end of treatment at month 12, the disparate rate of bone formation compared to bone erosion is most prominent early in treatment at month 2. Early in treatment may be the time range where romosozumab's antiabsorptive mechanism increases risks of AFF. Bone formation***

marker, N1P1, and absorption marker, sCTX, support rapid action by romosozumab within 2 weeks of the first dose and they both taper towards baseline by month 12. Early risk for fracture is supported by the only case in the pivotal trial where the patient sustained her AFF on day 101.

Taken in totality, the clinical data supports concern for romosozumab as a risk for AFF in this patient population. This concern should be included in the labeling as a warning.

Adjudicated Positive Osteonecrosis of the Jaw

Osteonecrosis of the Jaw (ONJ) has been observed with the use of antiresorptive agents. Nonclinical data findings suggest that dental disease and inflammation in rats with a lifetime exposure to romosozumab is not associated with ONJ-like findings such as exposed necrotic bone. Sclerostin antibody treatment causes greater alveolar crest height and bone mass in an ovariectomized rat model of localized periodontitis. In fracture repair models, local osteoclastic activity in response to injury is better maintained with sclerostin antibody treatment when contrasted with bisphosphonates and RANKL inhibitors.

In the 12-month placebo-controlled population (excluding Study 20101291, for which events were not adjudicated), 1 subject in the romosozumab group and no placebo subject had a positively adjudicated case of ONJ. This case was confounded by continuous use of a maladaptive fitting denture. The following Table 33 summarizes ONJ incidence in the placebo controlled portion of the study:

Table 33: Adjudicated Positive Osteonecrosis of the Jaw by Preferred Term

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting treatment-emergent adverse events of adjudicated osteonecrosis of the jaw	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Impaired healing	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

Sourced from ISS: Table 14-6.8.9 with reviewer edits.

One additional positively adjudicated case of ONJ was identified in the romosozumab group of Study 20070337 after the double-blind period (subject was taking denosumab at the time). This case occurred after the administration of 1 dose of denosumab in a subject who had a prior non-serious adverse event of periodontitis. No initial placebo patients developed ONJ in the studies.

The following are abbreviated summary narratives for these two patients from Study 2007003:

A) ONJ during placebo-controlled period

Subject (b) (6):

67-year-old woman (randomized to romosozumab) with osteoporosis and dentures who had a nonserious, unrelated, grade 1 adverse event of tooth fracture on day 109. The subject had no prior bisphosphonate use, no cancer history, no chemotherapy, and no radiation. The fracture of 2 teeth was without significant trauma, and required placement of a new removable partial maxillary denture at month 7, as well as extraction of 4 teeth at month 8. Approximately 13 months after the initial dose of investigational product (day 363), a grade 1, serious adverse event of delay of gum healing was reported as a not-related event The subject had exposed bone of the hard palate at the right maxilla, medial jaw at an extraction site different from the 4 extracted teeth mentioned above. The case was adjudicated positive for ONJ. Follow-up information revealed that the denture was not fitted properly and it was in contact with the exposed bone; however the subject continued to wear dentures during the adverse event of delayed gum healing. The case was readjudicated and remained positive for ONJ. The subject underwent gum cauterization and the event resolved on day 435.

B) ONJ during denosumab follow-on period after 12 months romosozumab

Subject (b) (6)

65-year-old woman with osteoporosis, diabetes mellitus, and dentures, who completed a year of romosozumab 210 mg SC QM and received 1 dose of denosumab 60 mg SC. The subject had no prior bisphosphonate use, no cancer history, no chemotherapy, and no radiation. On day 393, approximately 1 month after the first denosumab dose, the subject had nonserious; grade 2 acute apical periodontitis of the right maxillary canine tooth with subsequent need for multiple root canals and tooth extraction a few weeks later. She then developed delayed healing of the tooth socket and exposed bone which was noted at month 15 for 15 days and then again at approximately month 17. The case was adjudicated positive for ONJ. At month 22, the subject had resolution of the apical
periodontitis. The magnetic resonance imaging report of the head and neck showed low intensity area and high intensity area in T1-weighted images and short time inversion recovery, respectively, and was suspicious for osteomyelitis. The subject subsequently developed the serious, grade 2 adverse event of right maxillary jawbone necrosis on day 435. Readjudication following the additional information maintained the positive adjudication classification. As of the cutoff date for this study, the event was ongoing.

Reviewer Comments: ***These two cases during the pivotal trial are concerning for a risk of ONJ with romosozumab, one during the placebo controlled portion and one just after a first dose of denosumab. Both cases were adjudicated positively for ONJ. No cases were identified in the placebo group either during the placebo controlled portion of the trial or during denosumab extension. Given these findings, there is a concern for ONJ development with romosozumab, especially with maladaptive dentures. This concern should be placed in the labelling as a warning and in the med guide.***

To date in all ongoing and completed studies, there were 2 additional cases of positively adjudicated ONJ. Both additional cases were found in the blinded alendronate-controlled Study 20110142, where the positively-adjudicated ONJ occurred at months 22 and 28 during the open-label phase of alendronate administration. Although the study was blinded at the time of submission for this application, the Division requested unblinded information for the patients in the study who developed ONJ along with information for AFF.
The following are abbreviated summary narratives from these two patients, one was randomized to romosozumab and then rolled-over to alendronate while the other one was randomized to alendronate and rolled-over to the same alendronate:

Study 20110142: Positively Adjudicated ONJ:

A) Randomized to romosozumab for 12 months and rolled-over to alendronate:
Subject (b) (6)
70-year-old female from Norway with a past medical history of cardiac arrhythmia who had no prior treatment with glucocorticoids, immunosuppressants, or IV bisphosphonate, and who was a current smoker (200 pack-years). The subject was reported to have a history of dental abscess, osteomyelitis, root canal in the affected area; and dental treatment 4-6 months prior to the onset of the oral lesion. She completed 1 year of romosozumab and was then rolled over to open-label alendronate. She developed an oral infection in Month 27. In Month 28, the subject had a non-serious adverse event of ONJ, which was adjudicated as positive for ONJ. The subject wore upper dentures, and the area of lesion was at or near the contact point.

B) Randomized to alendronate for 12 months and rolled-over to alendronate:
Subject (b) (6)
84-year-old Asian female from Hong Kong with a past medical history of osteoporosis, spine fracture, and hypertension. The subject had no prior treatment with denosumab, bisphosphonate, steroids, or immunosuppressants. She completed 1 year of alendronate and was rolled over to open-label alendronate. She developed a non-serious event of osteonecrosis of the jaw in Month 21. The non-serious event of ONJ was adjudicated as negative for ONJ. Despite local debridement and treatment with antibiotics, nasopharyngolaryngosocopy suggested a non-healing wound with granulation tissue, and an imaging study with a CT suggested ONJ. The event was upgraded to serious by the investigator. Due to persistent symptoms leading to hospitalization for treatment of the event, the case was sent for re-adjudication, and was re-adjudicated as positive. The event of ONJ was reported as ongoing.

***Reviewer Comment*: For ONJ, 2 cases (1 randomized to Romo-alendronate and 1 to alendronate-alendronate), both also appearing over 1 year after alendronate exposure.**

- ***1 case: on Romo-alendronate, ONJ at month 27 (after 15 months on alendronate)***
- ***1 case: on alendronate-alendronate, ONJ at month 21 on alendronate.***

These two cases were found in the alendronate controlled trial and unblinded at FDA request. Both cases occurred during the alendronate roll-over period but one case of each for a patient randomized to initial romosozumab treatment and placebo treatment. Alendronate treatment confounds the results as the antiabsorptive properties of the bisphosphonates are linked to both ONJ and AFF. The concern that romosozumab increases the risk of ONJ is supported by the fact that one of the patients positive ONJ patients had received romosozumab for one year prior to roll-over to alendronate.

In totality, given the results from the pivotal trial and this alendronate-controlled trial, there is data to support that romosozumab can be linked to ONJ in this patient population, especially those with maladaptive dentures during treatment. The labeling and med guide should provide this information to providers and patients as a warning.

8.3.7. Treatment Emergent Adverse Events and Adverse Reactions

In the 12-month placebo-controlled population, 78.4% of subjects in the romosozumab group and 79.6% of subjects in the placebo group had adverse events.

The most frequent adverse events (≥ 10%) in total romosozumab or placebo treatment groups were nasopharyngitis (13.2% romosozumab, 12.3% placebo), arthralgia (12.7%, 11.8%), and back pain (10.3%, 10.5%). In general, the frequency of adverse events was similar between treatment groups; no adverse event preferred term was reported at a ≥ 2% higher incidence in the romosozumab group compared with the placebo group.
Table 34 summarizes the rate of AEs (below):

Table 34: Adverse Events in Romosozumab 210 mg QM and Placebo

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting adverse events	2850 (79.7)	2806 (78.4)	45 (90.0)	43 (84.3)	43 (68.3)	47 (74.6)	2938 (79.6)	2896 (78.4)
Nasopharyngitis	438 (12.2)	459 (12.8)	7 (14.0)	9 (17.6)	8 (12.7)	20 (31.7)	453 (12.3)	488 (13.2)
Arthralgia	429 (12.0)	467 (13.0)	3 (6.0)	2 (3.9)	2 (3.2)	0 (0.0)	434 (11.8)	469 (12.7)
Headache	205 (5.7)	233 (6.5)	8 (16.0)	5 (9.8)	1 (1.6)	2 (3.2)	214 (5.8)	240 (6.5)
Muscle spasms	140 (3.9)	163 (4.6)	0 (0.0)	3 (5.9)	2 (3.2)	0 (0.0)	142 (3.8)	166 (4.5)
Cough	117 (3.3)	129 (3.6)	2 (4.0)	5 (9.8)	0 (0.0)	0 (0.0)	119 (3.2)	134 (3.6)
Spinal osteoarthritis	87 (2.4)	86 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.3)	87 (2.4)	90 (2.4)
Oedema peripheral	67 (1.9)	86 (2.4)	1 (2.0)	0 (0.0)	1 (1.6)	0 (0.0)	69 (1.9)	86 (2.3)
Asthenia	79 (2.2)	83 (2.3)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	80 (2.2)	83 (2.2)
Dyslipidaemia	72 (2.0)	81 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	72 (2.0)	81 (2.2)
Neck pain	54 (1.5)	80 (2.2)	1 (2.0)	1 (2.0)	1 (1.6)	0 (0.0)	56 (1.5)	81 (2.2)
Paraesthesia	61 (1.7)	72 (2.0)	1 (2.0)	2 (3.9)	0 (0.0)	0 (0.0)	62 (1.7)	74 (2.0)

Source: Modified from ISS Table 14a-6.1.1 with reviewer edits

Reviewer Comment: ***The AEs were well balanced between romosozumab and placebo and no dose related trends were observed in the exposure-adjusted rate of AEs. There were no categories of AEs ≥ 2% of difference between romosozumab and placebo. The most frequent emergent AEs were nasopharyngitis (13 % romosozumab, 12 % placebo), arthralgia (13 %, 12 %), and back pain (10 %, 11 %) and these items should be included in the label.***

AEs of special interest will be discussed in Section 8.4 and include the following:

- Injection site reactions (based on the narrow search term strategy for injection site reactions),
- Hypersensitivity (based on the narrow search term strategy for hypersensitivity)
- Hypocalcemia (defined as albumin adjusted serum calcium that was below the lower limit of normal)

8.3.8. Laboratory Findings

Laboratory data analyses used the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3.0). The number of subject incidences for ≥ Grade 3 CTCAE findings are listed in Appendix 13.7 and discussed in the following section.

In general, clinical laboratory evaluations (eg, serum chemistry, hematology) demonstrated no clinically significant effect of romosozumab.

For the 12-month placebo-controlled population, the subject incidence of laboratory test results with CTCAE grade ≥ 2 was 19 % in the romosozumab group and 19 % in the placebo group. No clinically important trends were noted. Specific laboratory findings for calcium, magnesium, phosphorus, and creatinine are shown in the following table 35.

Table 35: Subject Incidence of Laboratory CTCAE Grade ≥ 2 in the Placebo Control Period

			20070337		20060326		20101291		Total	
Laboratory Parameters	Relationship to Normal	Grade	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM (N = 3695) n (%)
Calcium (Corrected)	Above	Grade 2	7 (0.2)	5 (0.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.2)	5 (0.1)
	Below	Grade 2	1 (<0.1)	7 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	7 (0.2)
		Grade 4	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Magnesium	Above	Grade 3	2 (<0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	4 (0.1)
	Below	Grade 2	9 (0.3)	6 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.2)	6 (0.2)
Phosphorus	Below	Grade 2	4 (0.1)	16 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	16 (0.4)
	Below	Grade 3	4 (0.1)	5 (0.1)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	4 (0.1)	6 (0.2)
Creatinine	Above	Grade 2	17 (0.5)	19 (0.5)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	17 (0.5)	20 (0.5)

Source: Modified from ISS Table 14-7.1.508 with reviewer edits.

Calcium: Hypocalcemia

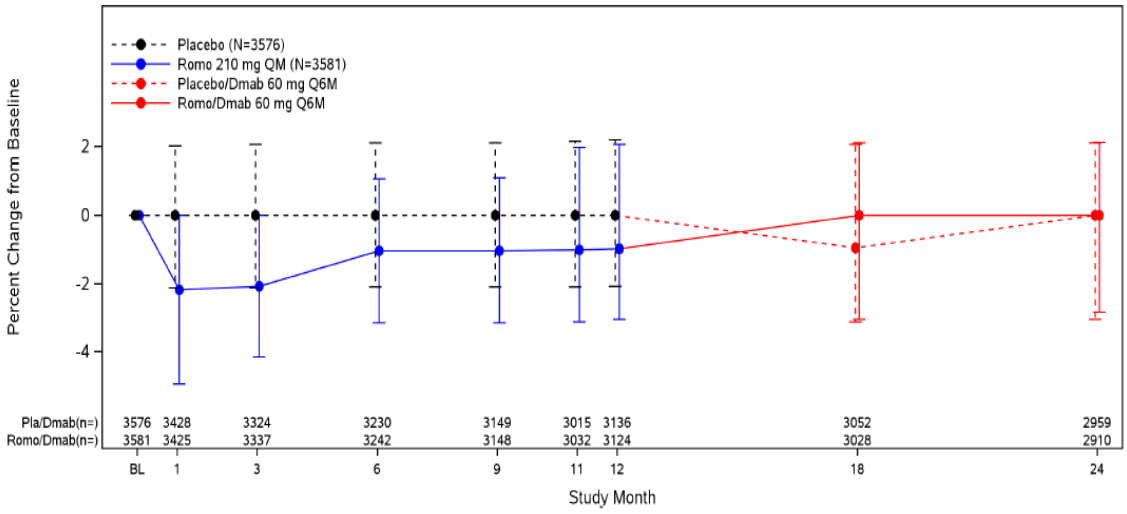
The mechanism of action of romosozumab suggests that administration of romosozumab may be associated with decreases in serum calcium as a result of increased bone formation and increased demands for calcium for matrix mineralization.

The subject incidence of CTCAE grade 2 decreases in serum calcium was 0.2% in the romosozumab group and < 0.1% in the placebo group (see Table 35). No subject in the romosozumab group had a grade 3 or 4 decrease in serum calcium although 1 subject in the placebo group had a grade 4 decrease in serum calcium. No subject with a CTCAE ≥1 grade decrease from baseline also had a hypocalcemia adverse event.

Adverse events of hypocalcemia were reported for < 0.1% (1) of subjects in the romosozumab treatment group and no subject in the placebo group in the placebo-controlled safety population; no serious adverse events of hypocalcemia were reported.

Corrected serum calcium levels decreased the most at month 1, the median percent change from baseline was -2.2% for subjects who received romosozumab and 0.0% for subjects who received placebo. Calcium levels normalized over time as demonstrated in the following Figure 17, such that at month 12, the median percent change from baseline was -1.0% for the romosozumab group and 0.0% for the placebo group, and was 0.0% for both groups at month 24.

Figure 17: Percent Change from Baseline in Calcium Corrected by Albumin



Source: 20070337 CSR Figure 14-7.5 with reviewer edits

Study 20070337 included a calcium substudy which characterized hypocalcemia (defined as albumin-corrected serum calcium level < 7.5 mg/dL) with the first 210 mg dose of

romosozumab and found that no patients had hypocalcemic values as defined.

Reviewer's Comments: ***No SAEs for hypocalcemia was found in the safety population and only 1 patient (< 0.1%) had an AE related to hypocalcemia. As expected, calcium levels decreased with the first dose of romosozumab but normalized over time, to within 1% of baseline at month 12 and to baseline by month 24 on denosumab. Of note, all patient were supplemented with calcium and vitamin D during the studies and some patients were bolused with vitamin D for low baseline vitamin D.***

Calcium in Renal Failure:

In study 20110227, patients with renal failure were compared to healthy patients when exposed to romosozumab. All patients were supplemented with calcium and vitamin D in the study. The study found that only patients with stage 4 renal insufficiency (RI) or stage 5, end stage renal disease (ESRD) developed AEs of hypocalcemia while no healthy subjects developed hypocalcemia. No subject in the study developed a SAE or fatal hypocalcemia. Stage 5, ESRD patients had more incidences (total AEs =4) and more severe grades (total AEs = 4: grade 1= 1, grade 2 = 2, and grade 3 =1) of hypocalcemia than stage 4, RI patients (total AEs =1: grade 1 = 1). The following table 36 summarizes the number of renal insufficiency (RI) or chronic kidney disease (CKD) patients who presented with hypocalcemia by grade of presentation.

Table 36: Subject Incidence of Hypocalcemia by CTCAE Grade in Study 20110227

Preferred Term	Group 1 Stage 4 RI (N = 8) n (%)	Group 2 ESRD (N = 8) n (%)	Group 3 Healthy Subjects (N = 8) n (%)	Total (N = 24) n (%)
Number of subjects reporting treatment emergent hypocalcemia events	1 (12.5)	4 (50.0)	0 (0.0)	5 (20.8)
Hypocalcaemia	1 (12.5)	4 (50.0)	0 (0.0)	5 (20.8)
Grade 1	1 (12.5)	1 (12.5)	0 (0.0)	2 (8.3)
Grade 2	0 (0.0)	2 (25.0)	0 (0.0)	2 (8.3)
Grade 3	0 (0.0)	1 (12.5)	0 (0.0)	1 (4.2)

Source: CSR 20110227 Table 14-6.2.1.2 with reviewer edits.

Reviewer Comments: ***This study demonstrates that patients with more severe renal failure had higher incidences and greater severity of hypocalcemia compared to stage 4 RI patients where only 1 AE for hypocalcemia was reported and healthy patients where none developed hypocalcemia. These findings support the use of romosozumab in renal failure patients but calcium serum calcium and vitamin D status should be monitored closely during therapy, especially in patients with ESRD which should be included in the labeling.***

Phosphorus:
Because romosozumab increases bone formation, there is an increased demand for phosphorus, in addition to calcium, to support bone matrix mineralization. For the 12-month placebo-controlled population, mild decreases in phosphorus with romosozumab were observed. The subject incidence of CTCAE grade 2 decreases in phosphorus was 0.4% in the romosozumab group and 0.1% in the placebo group (grade 3: 0.2%, 0.1%) see Table 36 above. There were no AEs reported for hypophosphatemia.

Median percent change from baseline at month 12 was -5.4% in the romosozumab group and -2.3% in the placebo group.

Reviewer Comments: ***As expected, phosphorus decreased during romosozumab treatment. There were slightly higher rates of CTCAE grade 2 in phosphorus levels in the romosozumab group compared to placebo (0.4% in the romosozumab group and 0.1% in the placebo group) but CTCAE grade 3 changes were relatively balanced. Overall, phosphorus rates decreased as expected for romosozumab and the rate of severe decreases was minimal and acceptable for the mechanism of action for romosozumab. No safety issue identified.***

Magnesium:
Because romosozumab increases bone formation, there may be an increased demand for magnesium, in addition to calcium and phosphorus, to support bone matrix mineralization and for its role in the calciotropic hormone axis.

For the 12-month placebo-controlled population, no change in magnesium was observed in either group. The subject incidence of CTCAE grade 2 decreases in magnesium was 0.2% in both the romosozumab and placebo groups; no grade 3 or 4 changes were reported. See table 36. There were no reported AEs associated with hypomagnesia.

Reviewer Comments: ***Changes in magnesium were balanced for CTCAE grade 2 decreases between romosozumab and placebo groups and there were no severe grade changes of 3 or 4. Given these findings, magnesium changes are expected for this patient population and no safety issues have been identified.***

Fasting glucose
Several studies in rodents indicate a potential role of bone in regulation of glucose metabolism, although a clinically meaningful translation of this effect in humans is unclear. In Study 20070337, romosozumab treatment did not demonstrate an effect on fasting glucose. Table 37 below shows glucose abnormalities ≥ 2 CTCAE in the placebo controlled studies. Patients with diabetes were not excluded from the studies.

Reference ID: 4093382

Table 37: Glucose CTCAE Grade ≥ 2 in the Placebo Control Period

			20070337		20060326		20101291		Total	
Laboratory Parameters	Relationship to Normal	Grade	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM (N = 3695) n (%)
Glucose	Above	Grade 2	171 (4.8)	178 (5.0)	1 (2.0)	1 (2.0)	0 (0.0)	2 (3.2)	172 (4.7)	181 (4.9)
		Grade 3	71 (2.0)	55 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	71 (1.9)	55 (1.5)
		Grade 4	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Glucose	Below	Grade 2	12 (0.3)	24 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (0.3)	24 (0.6)

Source: Modified from ISS Table 14-7.1.508 with reviewer edits.

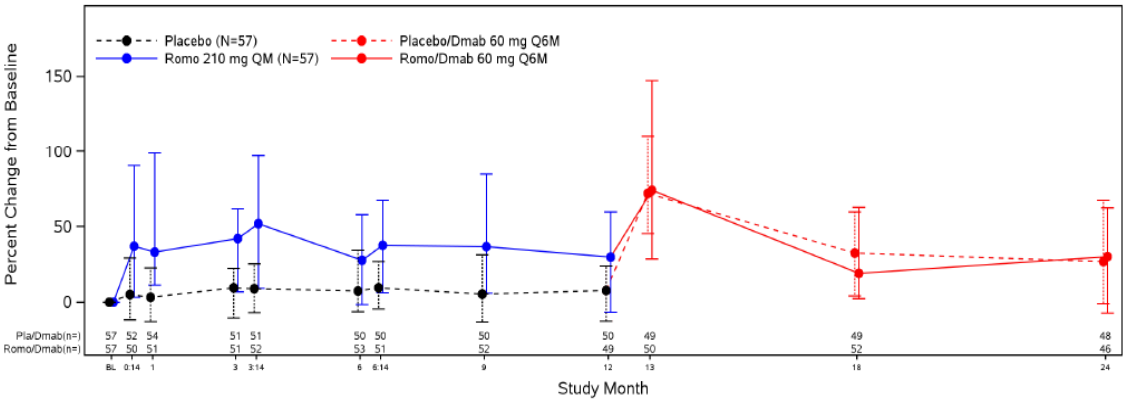
Reviewer Comments: ***Glucose values are similar between groups and glucose changes from CTCAE levels are relatively balanced between romosozumab and placebo groups. Despite preclinical concerns, glucose does not appear to be a safety issue for romosozumab.***

iPTH

Because romosozumab increases bone formation, there may be compensatory responses in iPTH as a result of bone matrix mineralization. Study 20070337 included an iPTH and urinary calcium substudy comprising 656 subjects to characterize serum iPTH concentration and urinary calcium excretion through month 12. AEs related to iPTH elevations such as hypocalcemia were balanced between romosozumab and placebo groups.

The median percentage change from baseline in iPTH was 29% in the romosozumab group and 4% in the placebo group at month 6 and 27% in the romosozumab group and 8% in the placebo group at month 12. Differences between romosozumab and placebo were statistically significant at both timepoints (nominal p-value < 0.001 from Wilcoxon rank-sum test without multiplicity adjustment). Figure 18 below graphs the mean increases in iPTH compared to placebo in this iPTH substudy of 20070337. Patients are randomized to romosozumab or placebo for 12 months (in blue) and all patients follows with denosumab treatment for 12 additional months (in red).

Figure 18: Intact Parathyroid Hormone Percent Change From Baseline by Visit iPTH substudy



N = Number of randomized subjects enrolled in the BTM and biomarker substudy, received at least one dose of investigational product with a baseline and at least one post-baseline reported result for the parameter of interest
Baseline to month 12: n = Number of subjects who received at least one dose of investigational product in the 12-month double-blind period with observed data
Post month 12 to month 24: n = Number of subjects who received at least one dose of denosumab at month 12 or 18 with evaluable data at the time point of interest
Subjects start to receive denosumab 60mg Q6M at month 12

Source: *Figure 14b-7.1 with reviewer edits.*

Reviewer Comments: ***iPTH rose in response to romosozumab as expected and although levels fell over time; it was still statistically elevated compared to levels in placebo patients. The rise in iPTH levels on romosozumab may be due to the anti-absorptive mechanism, similar to denosumab. iPTH levels all elevated and were balanced between the treatment groups once all patients were on denosumab in the follow-on period by month 24.***

The rise in iPTH levels in romosozumab patients support the importance of calcium and vitamin D supplementation.

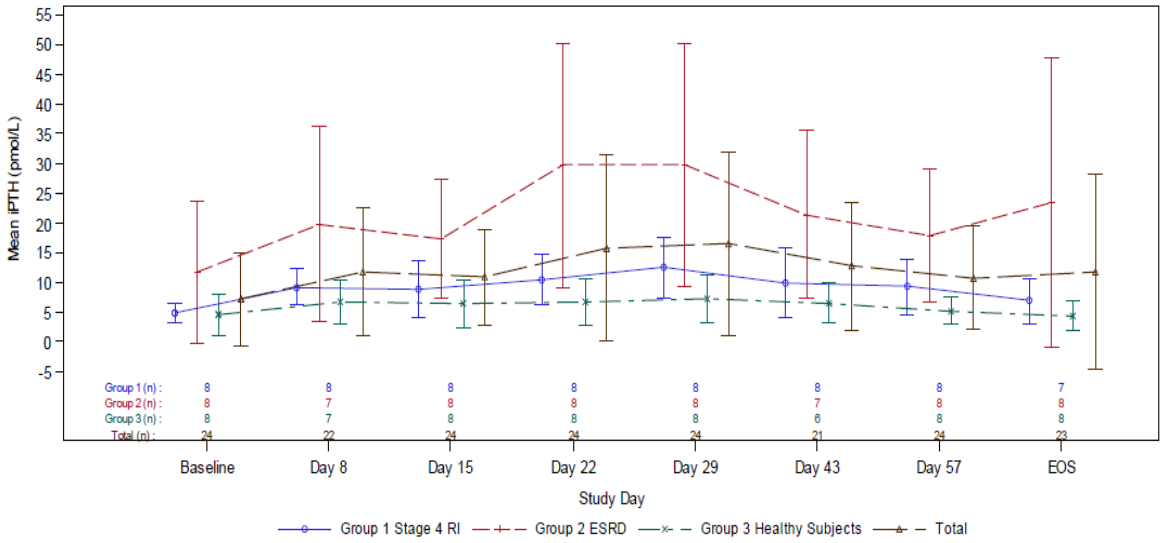
iPTH in renal failure: In Phase 1 Study 20110227, the administration of romosozumab resulted in a greater increase in iPTH in subjects with stage 4 RI and stage 5 CKD requiring hemodialysis than in healthy subjects.

In this study, at baseline, the mean (SD) iPTH levels were higher for subjects with end stage renal disease (ESRD) (11.77 [12.0] pmol/L] compared with subjects with stage 4 RI (5.01 [1.6] pmol/L) and healthy subjects (4.68 [3.4] pmol/L). After the administration of the single SC dose of romosozumab on day 1, serum iPTH levels increased among all treatment groups. The observed mean (SD) iPTH values and the mean (SE) percent increase from baseline in iPTH were greater for subjects with ESRD and subjects with stage 4 RI than for healthy subjects.

At day 29, mean percent increases from baseline in iPTH were 150% in subjects with stage 4 RI, 287% in subjects with ESRD, and 94% in healthy subjects. After this time point, iPTH levels returned towards baseline levels.

By day 57, mean percent change from baseline was 80% in subjects with stage 4 RI, 97% in subjects with ESRD, and 32% in healthy subjects. By the end of study, iPTH levels returned further towards baseline for subjects with stage 4 RI and healthy subjects, but trended upwards for subjects with ESRD (mean percent change from baseline was 41% for subjects with stage 4 RI, 119% for subjects with ESRD, and 13% for healthy subjects). Figure 19 (below) graphs the mean level of iPTH in the three populations, healthy, stage 4 RI, and ESRD at baseline and time after dosing.

Figure 19: Mean Intact Parathyroid Hormone (iPTH) by Time CRF study 20110227



Source: Clinical Study Report: 20110227 Figure 14-7.1.3 with reviewer edits

Reviewer Comments: ***Although renal failure patients had higher baseline iPTH, all patients reacted with compensatory increases in iPTH after romosozumab dosing which is consistent with the mechanism of action of romosozumab on bone mineralization. ESRD patients had much greater compensatory increase in iPTH (287%) versus (150%) in stage 4 CKD or (94%) in healthy subjects by day 29 and had slower return towards baseline at the end of study.***

This study supports the use of romosozumab in renal failure patients but supports the importance of monitoring for hypocalcemia in these renal failure patients on therapy along with daily supplementation.

Urinary Calcium:
Corresponding median percentage change from baseline in estimated 24-hour urinary calcium excretion values were −16.8% in the romosozumab group and 3.0% in the placebo group at month 6, and −15.9% in the romosozumab group and −7.6% in the placebo group at month 12. Differences between romosozumab and placebo for urinary calcium excretion were statistically

significant at 6 months (nominal p-value < 0.001 from Wilcoxon rank-sum test without multiplicity adjustment) but not at 12 months (nominal p-value = 0.10 from Wilcoxon rank-sum test without multiplicity adjustment).

As additional sensitivity analyses to support the endpoint of estimated 24-hour urine calcium excretion, percent changes in estimated 24-hour urine calcium and urine calcium to creatinine ratio were further analyzed in subjects having 24-hour urine volume between 500 mL or 3500 mL or having 100% increase in their estimated 24-hour urine calcium excretion from baseline at month 6 or 12. In subjects with a 24-hour urine volume between 500 mL and 3500 mL, results were similar to those obtained for all subjects who participated in the substudy, with statistically significant differences between groups at month 6, but not at month 12. For subjects with a ≥ 100% increase in urinary calcium at months 6 and 12, no statistically significant differences between romosozumab and placebo groups were observed for estimated 24-hour urinary calcium percentage change from baseline. No AEs were identified related to hypouricalcemia or hyperurocalcemia. The changes from baseline in urinary calcium in the romosozumab group compared to placebo at 6 months and 12 months in the study 20070337 substudy for urinary calcium is summarized in Table 38 below:

Table 38: 24 Hour Urinary Calcium Excretion Percent Change From Baseline at 6 months and 12 months (Serum Intact Parathyroid Hormone and Urinary Calcium Substudy of 20070337).

	Placebo (N = 318)	Romosozumab 210 mg QM (N = 285)	Difference from Placebo
Urine calcium (24hr)			
Month 6			
n	275	259	
Mean	177.3	41.9	
SD	1413.9	329.5	
Median	3.0	-16.8	
Q1, Q3	-40.9, 84.4	-53.7, 33.4	
Min, Max	-100.0, 19297.2	-99.8, 4416.4	
p-value			0.001[a]
Month 12			
n	281	255	
Mean	42.6	39.5	
SD	234.7	292.5	
Median	-7.6	-15.9	
Q1, Q3	-45.8, 57.2	-49.2, 32.1	
Min, Max	-99.8, 3017.6	-99.7, 3479.3	
p-value			0.10[a]

Source CSR 20070337 substudy Table 14u-7.3.2 with reviewer edits.

Reviewer Comments: ***Urinary calcium results demonstrate greater conservation of calcium during the early months (up to month 6) and statistically significant decreases in urinary calcium loss when comparing the romosozumab treated group to placebo which is consistent with romosozumab's mechanism of action and increased demand for bone mineralization***

early. By month 12, the differences in urinary calcium normalizes which support limited treatment with romosozumab.

Potential Hy's Law cases:

Hy's Law is used to detect drugs that can cause serious liver injury. Briefly, Hy's Law cases have the following three components:

1. > 3 X ULN of ALT or AST than placebo
2. Total bilirubin >2X ULN, without initial findings of cholestasis (defined as elevated serum alkaline phosphatase)
3. No other reason can be found to explain the combination of increased ALT or AST and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

At baseline: The subject incidence of elevated baseline ALT and elevated baseline AST of > 3 x ULN and > 5 x ULN was lower in the romosozumab group than the placebo group, and similar between treatment groups for elevations > 10 x ULN and > 20 x ULN. Overall, the subject incidence of elevated baseline AST and ALT > 3 x ULN was lower in the romosozumab group than the placebo group (AST: romosozumab 3 subjects [< 0.1%], placebo 6 [0.2%]; ALT: 2 [< 0.1%], 10 [0.3%]). The subject incidence of elevated baseline AST > 5 x ULN was lower in the romosozumab group than the placebo group, and elevated baseline ALT > 5 x ULN was similar between groups (AST: 0 [0.0%], 1 [<0.1%]; ALT: 1 [<0.1%], 2 [<0.1%]). No subject in either group had elevated baseline transaminases > 10 x ULN or > 20 x ULN.

During Study: The subject incidence of on-study elevation of AST and ALT > 3 x ULN and > 5 x ULN was lower in the romosozumab group than the placebo group (AST > 3 x ULN: romosozumab 15 subjects [0.3%], placebo 29 subjects [0.8%]; AST > 5 x ULN: 3 [< 0.1%], 6 [0.2%]; ALT > 3 x ULN: 23 [0.5%], 31 [0.9%]; ALT > 5 x ULN: 6 [0.1%], 11 [0.3%]). On-study elevations of AST > 10 x ULN were similar between treatment groups (both 2 subjects [< 0.1%]), while on-study elevation of ALT > 10 x ULN were lower in the romosozumab group than the placebo group (2 [<0.1%], 4 [0.1%]). No subject in the romosozumab group and 1 subject in the placebo group had an on-study elevation of AST or ALT > 20 x ULN.

Two tables below (Table 39 and Table 40) summarizes the incidence of baseline and on study AST (Table 39) and ALT (Table 40) elevations across the 12 month placebo controlled studies based on 3X, 5X, 10X, or 20X > ULN.

Table 39: **Subject Incidence of Serum Aspartate Aminotransferase (AST) Elevations**

	20070337		20060326		20101291		Total	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
> 3 x ULN (n/N1(%))								
Baseline	6/3574 (0.2)	2/3579 (<0.1)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	6/3687 (0.2)	2/3693 (<0.1)
On study	28/3501 (0.8)	9/3495 (0.3)	1/49 (2.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	29/3612 (0.8)	9/3608 (0.2)
> 5 x ULN (n/N1(%))								
Baseline	1/3574 (<0.1)	0/3579 (0.0)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	1/3687 (<0.1)	0/3693 (0.0)
On study	6/3501 (0.2)	3/3495 (<0.1)	0/49 (0.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	6/3612 (0.2)	3/3608 (<0.1)
>10 x ULN (n/N1(%))								
Baseline	0/3574 (0.0)	0/3579 (0.0)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	0/3687 (0.0)	0/3693 (0.0)
On study	2/3501 (<0.1)	2/3495 (<0.1)	0/49 (0.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	2/3612 (<0.1)	2/3608 (<0.1)
>20 x ULN (n/N1(%))								
Baseline	0/3574 (0.0)	0/3579 (0.0)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	0/3687 (0.0)	0/3693 (0.0)
On study	1/3501 (<0.1)	0/3495 (0.0)	0/49 (0.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	1/3612 (<0.1)	0/3608 (0.0)

Source: Modified from ISS Table 14-7.1.501 with reviewer edits.

Table 40: Subject Incidence of Serum Alanine Aminotransferase (ALT) Elevations

	20070337		20060326		20101291		Total	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
> 3 x ULN (n/N1(%))								
Baseline	9/3576 (0.3)	2/3580 (<0.1)	0/50 (0.0)	0/51 (0.0)	1/63 (1.6)	0/63 (0.0)	10/3689 (0.3)	2/3694 (<0.1)
On study	30/3502 (0.9)	16/3495 (0.5)	1/49 (2.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	31/3613 (0.9)	16/3608 (0.4)
> 5 x ULN (n/N1(%))								
Baseline	2/3576 (<0.1)	1/3580 (<0.1)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	2/3689 (<0.1)	1/3694 (<0.1)
On study	10/3502 (0.3)	5/3495 (0.1)	1/49 (2.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	11/3613 (0.3)	5/3608 (0.1)
>10 x ULN (n/N1(%))								
Baseline	0/3576 (0.0)	0/3580 (0.0)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	0/3689 (0.0)	0/3694 (0.0)
On study	4/3502 (0.1)	2/3495 (<0.1)	0/49 (0.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	4/3613 (0.1)	2/3608 (<0.1)
>20 x ULN (n/N1(%))								
Baseline	0/3576 (0.0)	0/3580 (0.0)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	0/3689 (0.0)	0/3694 (0.0)
On study	0/3502 (0.0)	0/3495 (0.0)	0/49 (0.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	0/3613 (0.0)	0/3608 (0.0)

Source: ISS: Table 14-7.1.509 with reviewer edits.

Reviewer Comments: ***The subject incidences for elevated AST and ALT > 3X and > 5X ULN were lower in the romosozumab than in the placebo group at both baseline and in study. During the study, the AST elevations > 10X ULN was balanced with 2 subjects (<0.1%) in each group while ALT > 10X ULN remained lower for romosozumab subjects than for placebo (2 [<0.1%], 4 [0.1%]). No subjects had AST or ALT elevations > 20 X ULN during the studies. Overall, from this summary data, romosozumab does not appear to increase AST or ALT levels greater than in placebo patients.***

Patient level review of the elevated AST and ALT data:
Of the romosozumab subjects with elevated transaminases > 3 x ULN, over half had elevated transaminases at baseline (16 of 28 subjects), and the majority had confounding factors. The confounders included past medical history, such as alcoholic liver damage, hepatic steatosis, cholelithiasis, and use of concomitant medications known to cause increases in transaminases such as acetaminophen, statins, antihypertensives, and methotrexate. The transaminases trended to normal or baseline for the majority of subjects (18 of 29 [64%]). The one romosozumab subject without confounding factors (b) (6) had an increase of ALT (170 U/L) on study day 28 to > 3 x to ≤ 5 x ULN with an AST (84 U/L) of > 1 x to ≤ 3 x ULN. This subject completed a year of romosozumab, and the transaminases trended down to > 1 x to ≤ 3 x ULN by study day 365 (ALT 42 U/L, AST 34 U/L).

Two subjects in the romosozumab arm had on-study elevations of AST and ALT > 10 x ULN. One subject (b) (6), with a history of transaminase elevation following use of Augmentin, had elevations of transaminase following treatment of bronchiectasis during study with Augmentin; she completed a year of romosozumab, and LFTs normalized by the end of year one. The other subject (b) (6) developed elevated transaminases in the setting of suspected type A viral hepatitis; romosozumab was discontinued, and LFTs trended down by the time of drug withdrawal.

In the first-in-human phase 1 Study 20060220, 1 subject in the single-dose romosozumab 10 mg/kg SC group with normal baseline liver function tests developed nausea, vomiting, and diarrhea following a meal on the evening that the study drug was administered. AST and ALT increased to > 5 x ULN on study day 4 while bilirubin levels remained normal. Over the next several days, the subject's liver function tests normalized without any treatment. The following Table 41 summarizes the subject demographics and treatment (romosozumab) group.

Table 41: Selected subject with elevated AST and ALT > 5 x ULN on study 20060220

Subject Number	Treatment Group	Sex	Age (Years)	Preferred Term / Verbatim Term	Event Onset (Study Day)	Duration (Days)	Withdrawn Due to Event	Serious	Severity	Related
(b) (6)	AMG 785 10 mg/kg SC (cohort 6a)	F	53	Hepatitis / Non Specific Hepatitis	2	25	No	Yes	Severe	Yes

Source Appendix 11, CSR 20060220 with reviewer edits and modification

Subject (b) (6) brief SAE narrative: This 53-year-old Hispanic or Latino woman (no. (b) (6)) enrolled in cohort 6a (10 mg/kg SC AMG 785) of AMG 785 first-in-human study and developed elevated liver function tests (ALT and AST). Past medical history did not include liver disease, gallstones, or peptic ulcer. Concomitant medications included acetaminophen.

Baseline AST (day -1) was 22 U/L, ALT 22 U/L, alkaline phosphatase 75 U/L, and bilirubin normal.

The subject received the single dose of blinded investigational product on study day 1. On the evening of study drug administration, the subject developed nausea and vomiting after the meal and 1 episode of watery diarrhea. On study day 2, the subject vomited after lunch. The AST was 47 U/L, ALT 52 U/L, alkaline phosphatase 66 U/L, and bilirubin normal. On study 3, the subject experienced nausea after breakfast and lunch; dinner was tolerated well. On study day 4 no gastrointestinal symptoms were observed; AST was 216 U/L, ALT 530 U/L, alkaline phosphatase 188 U/L, and bilirubin normal. On study day 5, gastrointestinal symptoms resolved; no intervention was required. Study day 6: AST was 88 U/L, ALT 314 U/L, alkaline phosphatase 195 U/L, and bilirubin 0.4 mg/dL. During the next 3 days, study days 7-10, AST decreased from 93 to 38 U/L, ALT decreased from 261 to 136 U/L, alkaline phosphatase ranged between 155 and 171 U/L, and bilirubin remained normal. Hepatitis panels were nonreactive, and abdominal ultrasound was unremarkable. On (b) (6) (study day 26), AST and ALT were 20 and 23 U/L, respectively, and alkaline phosphatase was 121 U/L; the adverse event was considered resolved. By study day 108, AST and ALT were 17 and 20 U/L, respectively, alkaline phosphatase 71 U/L, and bilirubin normal.

Reviewer Comment: ***The symptoms and laboratory findings are consistent with hepatitis and timely related to study drug day 1 but this subject did not meet Hy's law as bilirubin was not elevated despite elevations of both AST and ALT. Her symptoms resolved by day 4 of the study with concurrent decreases towards normal of her LFTS. No subjects in phase 1 studies met Hy's Law criteria.***

The following Table 42 provides the subject incidence of potential Hy's law cases (ie, cases that met the Hy's law laboratory criteria) for the 12-month placebo-controlled population.) The number of subjects meeting the criterion of ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN was 1 (< 0.1%) subject in the romosozumab group and 1 (< 0.1%) subject in the placebo group. Of note, the sponsor noted that one patient had an error in total bilirubin levels entered into the database which made that patient meet Hy's Law criteria. Once that error was corrected, the patient (b) (6) no longer met Hy's Law criteria. The sponsor stated the following:

> *" an After the database snapshot, but prior to the investigator unblinding, the total bilirubin level that met Hy's Law criteria for Subject (b) (6) was reassessed and amended as total bilirubin was erroneously entered as elevated by the site. Following this correction, the subject no longer met the criteria for Hy's law. Therefore, only 1 subject met the criteria for Hy's law in the romosozumab group."*

Reviewer Comment: ***The correction of the error in total bilirubin dropped the number of cases of potential Hy's Law cases to 1 in the romosozumab group and 1 in the placebo group. Details for these potential cases are discussed in detail below.***

Table 42: Potential Hy's Law Cases

	20070337		20060326		20101291		Total	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
ALT or AST > 3 x ULN (n/N1(%))								
Baseline	12/3576 (0.3)	3/3580 (<0.1)	0/50 (0.0)	0/51 (0.0)	1/63 (1.6)	0/63 (0.0)	13/3689 (0.4)	3/3694 (<0.1)
On study	41/3502 (1.2)	19/3495 (0.5)	1/49 (2.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	42/3613 (1.2)	19/3608 (0.5)
Total bilirubin > 2 x ULN (n/N1(%))								
Baseline	1/3576 (<0.1)	0/3580 (0.0)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	1/3689 (<0.1)	0/3694 (0.0)
On study	7/3503 (0.2)	4/3495 (0.1)	0/49 (0.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	7/3614 (0.2)	4/3608 (0.1)
ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN and ALP < 2 x ULN (n/N1(%))								
Baseline	0/3539 (0.0)	0/3544 (0.0)	0/50 (0.0)	0/51 (0.0)	0/63 (0.0)	0/63 (0.0)	0/3652 (0.0)	0/3658 (0.0)
On study within 7 days	1/3501 (<0.1)	2/3495 (<0.1)[a]	0/49 (0.0)	0/50 (0.0)	0/62 (0.0)	0/63 (0.0)	1/3612 (<0.1)	2/3608 (<0.1)[a]

Source: *ISS Table 14-7.2*

Two cases met Hy's Law criteria, one placebo and one romosozumab treated group. A further review of the cases showed alternate medical etiology for the laboratory abnormalities.

Subject [redacted] (b) (6) was in the romosozumab arm:
A 71-year-old subject [redacted] (b) (6)) received 210 mg romosozumab on days 1, 36, 67, 98, and 133. Following day 36 administration of romosozumab (the second dose), she had a serious adverse event of grade 1 "diffuse liver fatty deposit." Laboratory results that day were ALT: 103 U/L (3 x ULN), AST: 102 U/L (3 x ULN), and total bilirubin: 70.11 µmol/L (normal range: 3 to 21 µmol/L; 3 x ULN). On day 42, AST was 55 U/L, ALT was 46 U/L, and total bilirubin was 14 µmol/L. Concomitant adverse events were non-serious cholelithiasis (grade 2) on day 44, non-serious diabetes mellitus (grade 1) on day 49, non-serious bile duct stone (grade 2) on day 358, and serious gastric adenocarcinoma on day 127 which led to death on day 545.

Subject [redacted] (b) (6) was randomized to the placebo arm.
An 88-year-old subject [redacted] (b) (6) with a medical history of cholecystectomy, dyslipidemia, hypertension, osteoarthritis, diabetes mellitus, and elevated liver function tests received placebo. On day 279, the subject had a grade 3, serious adverse event of transaminases

increased. Previous laboratory results at month 9 were AST: 109 U/L (3 x ULN); ALT: 11 x ULN, and total bilirubin: 1.3 µmol/L (ULN: 1.2 µmol/L). Laboratory results all normalized in the same month. The event resolved without treatment on day 290. Concomitant medications were lovastatin and glucosamine at the time of the event.

Reviewer Comments: ***There is no data to support Hy's Law cases with the use of romosozumab in these clinical studies. The only subject in the romosozumab arm who met Hy's law criteria had confounding reasons for elevated AST, ALT. and total bilirubin including cholelithiasis temporarily related to her elevated AST, ALT, and total bilirubin just 7 days after her elevated LFTs were noted at her second dose on study day 36. Furthermore, her case is confounded by her gastricarcinoma diagnosis on day 145 which lead to her death on study day 545. The second case is in a placebo patient and also confounded by her history of cholelithiasis/ cholecystectomy.***

8.3.9. Vital Signs

Analysis of vital signs (systolic and diastolic blood pressures, pulse rate, body temperature, body weight, and BMI) and electrocardiograms in individual studies demonstrated no clinically important effect of romosozumab.

Reviewer Comments: ***Romosozumab would not be expected to cause changes in these vital signs and there is no data to support any changes.***

8.3.10. Electrocardiograms (ECGs)

EKG data are provided in individual clinical study reports and were not pooled for integrated analyses. Analysis of EKGs in individual studies demonstrated no clinically important effect of romosozumab.

Reviewer Comments: ***Because of its large physical size and low potential for interfering with cardiac channel repolarization, romosozumab would not be expected to affect ECG changes. The studies did not identify ECG changes to support a safety concern.***

8.3.11. QT

There is a low likelihood for delayed cardiac repolarization due to hERG channel blockade with romosozumab, primarily based on its physical size of approximately 150 kD and the low potential for large protein therapeutics (especially monoclonal antibodies) to interfere with cardiac ion channels in vivo, including hERG-mediated current.

In pre-clinical studies in conscious telemetry-instrumented cynomolgus monkeys following single IV doses up to 300 mg/kg followed by 14 days of monitoring, there was no evidence for

romosozumab –related EKG change. AUC and Cmax exposure margins achieved were up to 32-fold and 210-fold, respectively, to clinical exposures at 210 mg QM. Additionally, there were no romosozumab-related electrocardiographic or blood pressure changes in the 1-month and 6-month repeat-dose toxicology studies in monkeys at doses up to 300 mg/kg IV.

In the first-in-human study (Study 20060220), single SC doses of romosozumab (0.1 to 10 mg/kg) or placebo or single IV doses of romosozumab (1 to 5 mg/kg) or placebo were administered to healthy men (N = 16) and postmenopausal women (N = 56). A total of 54 subjects received romosozumab, and 18 subjects received placebo. Electrocardiogram evaluations included assessments for all 72 subjects. No patterns or trends in ECGs occurred that were considered to be clinically relevant.

In the phase 1b, multiple-dose study (Study 20060221), SC administration of 6 doses of 1 mg/kg romosozumab every 2 weeks (Q2W), or 3 doses of 3 mg/kg romosozumab every 4 weeks (Q4W) were evaluated in healthy men or postmenopausal women with low bone mass, and 3 doses of 2 mg/kg romosozumab Q4W or 6 doses of 2 mg/kg romosozumab Q2W were evaluated in healthy postmenopausal women with low bone mass. A total of 36 subjects received romosozumab, and 12 subjects received placebo. EKG evaluations included assessments for all 48 subjects. No subject had a maximum post dose Fridericia's corrected QTc (QTcF) or Bazett's corrected QTc (QTcB) value > 480 msec or a maximum change in QTcF or QTcB (compared to baseline) that was > 60 msec. Maximum QTcF and QTcB changes from baseline of > 30 to 60 msec were observed for 7 of 36 subjects (19%) and 7 of 36 subjects (19%), respectively, who received romosozumab and 2 of 12 subjects (17%) and 1 of 12 subjects (8%), respectively, who received placebo. No patterns or trends in ECGs occurred that were considered to be clinically relevant.

In the phase 1b Study 20060223, postmenopausal women with low bone mass who had been receiving alendronate (70 mg QW) for at least 1 year were randomized to continue receiving alendronate (group A, n = 10) or discontinue alendronate and receive a single 3 mg/kg SC dose of romosozumab (group B, n = 24). In addition, a group of treatment- naïve subjects received a single 3 mg/kg SC dose of romosozumab (group C, n = 6). No subject had a maximum post dose QTcF or QTcB value > 480 msec. Maximum QTcF and QTcB changes from baseline of > 60 msec were observed for no subjects and 1 of 10 subjects (10%), respectively, in group A; 1 of 24 subjects (4%) and 1 of 24 subjects (4%), respectively, in group B; and 1 of 6 subjects (17%) and 1 of 6 subjects (17%), respectively, in group C. Maximum QTcF and QTcB changes from baseline of > 30 to 60 msec were observed for 3 of 10 subjects (30%) and 4 of 10 subjects (40%), respectively, in group A; 4 of 24 subjects (17%) and 7 of 24 subjects (29%), respectively, in group B; and 1 of 6 subjects (17%) and 1 of 6 subjects (17%), respectively, in group C. No patterns or trends in ECGs occurred that were considered to be clinically relevant.

In the phase 1b Study 20090153, SC administration of 3 doses of 3 mg/kg romosozumab or placebo Q4W was evaluated in 24 healthy postmenopausal women with low bone mass. A total of 12 subjects received romosozumab and 12 subjects received placebo. Electrocardiogram evaluations included assessments for all 24 subjects. No subject had a maximum post dose QTcF or QTcB value > 480 msec or a maximum QTcF or QTcB change from baseline of > 30 msec. No patterns or trends in ECGs occurred that were considered to be clinically relevant.

In the phase 1 Study 20090378, SC administration of single doses of 1, 3, and 5 mg/kg romosozumab or placebo were evaluated in healthy postmenopausal Japanese and non-Japanese women. A total of 22 subjects received romosozumab, and 8 subjects received placebo. Electrocardiogram evaluations included assessments for all 30 subjects. No subject had a maximum post dose QTcF or QTcB value > 480 msec or maximum QTcF or QTcB changes from baseline of > 30 msec. No patterns or trends in ECGs occurred that were considered to be clinically relevant.

The phase 2a Study 20060326 evaluated the safety and efficacy of multiple doses and frequencies of romosozumab monotherapy for postmenopausal osteoporosis (data from the 12-month primary analysis). A total of 255 subjects were treated with romosozumab in this study. No subject had a QTcF > 500 msec. Three subjects in the romosozumab groups (1 subject in the 210 mg QM group and 2 subjects in the 70 mg QM group) had QTcB > 500 msec. None of these subjects had adverse events of cardiac arrhythmia, hypocalcemia, hypokalemia, or hypomagnesia, and all of these subjects had a cardiac history that could potentially account for these findings.

One subject in the 210 mg QM group had a QTcB of 509 msec at month 9. This subject had a screening QTcB of 491 msec; day 1 QTc of 478 msec, 463 msec, and 363 msec; month 1 QTc of 468 msec; month 3 QTc of 485 msec; and month 12 QTc of 479 msec. Month 9 QTcB and QTcF changes from baseline were > 60 msec (74 msec and 64 msec, respectively) and decreased at month 12 (44 msec and 46 msec, respectively). The subject's medical history included hypertension and asthma, and no on-study cardiac adverse events were reported. One subject in the 70 mg QM group had a QTcB at month 12 of 506 msec. This subject had a screening QTc of 422 msec; day 1 QTc of 436 msec, 441 msec, and 460 msec; month 1 QTc of 413 msec; month 3 QTc of 445 msec; and month 9 QTc of 486 msec. Month 12 QTcB was 60 msec above baseline, and QTcF was 47 msec above baseline. The subject had a medical history of cardiac discomfort and had adverse events of aortic stenosis and hypercholesterolemia on study day 49 and hypertension on study day 268. One subject in the 70 mg QM group had a QTcB of 504 msec at month 12. This subject had a day 1 QTc of 453 msec, 454 msec, and 462 msec; month 1 QTc of 476 msec; month 3 QTc of 485 msec; and month 9 QTc of 498 msec. The subject had a history of hypertension, depression, bipolar disorder, chronic obstructive pulmonary disease, hypercholesterolemia, Parkinsonian rest tremor, and environmental allergies. The subject's

Reference ID: 4093382

concomitant medications that could be associated with QT prolongation included fluoxetine (started prior to study entry in 2004) and azithromycin (study days 51 to 55 for an adverse event of bronchitis, study days 331 to 335 for and adverse event of upper respiratory tract infection).

Changes from baseline in QTcB and QTcF > 60 msec occurred in 4 subjects in the romosozumab groups: 3 subjects in the 210 mg QM group and 1 subject in the 210 mg Q3M group. One subject in the 210 mg QM group had 2 ECGs done at month 1 that showed different QTc changes from baseline. One ECG for this subject showed changes from baseline in QTcB and QTcF of < 60 msec (31 msec for each), and the other ECG showed changes from baseline in QTcB and QTcF of > 60 msec (68 msec and 67 msec, respectively). Except for the subject in the 210 mg QM group described above who had a month 9 ECG with QTc > 500 msec and a change from baseline QTc > 60 msec, all other subjects did not have corresponding changes in QTc intervals > 500 msec. No associated cardiac events were reported.

Reviewer Comments: ***In phase 1 and 2 romosozumab studies, no EKG change patterns could be identified. In the small number of patients who had QT abnormalities, their clinical course was confounded by concurrent medications which are known to prolong QT or past medical history with baseline high QT.***

The one subject in phase 2a Study 20060326 who had month 9 QTC > 500 and change from baseline QTc> 60 msec had a high screening QTcB of 491 msec day 1 QTc of 478 msec, 463 msec, and 363 msec; month 1 QTc of 468 msec; month 3 QTc of 485 msec; and month 12 QTc of 479 msec. Month 9 QTcB and QTcF changes from baseline were > 60 msec (74 msec and 64 msec, respectively) and decreased at month 12 (44 msec and 46 msec, respectively). Her past medical history included asthma and hypertension which could have contributed to her high baseline QTc values. She had no on-study cardiac event.

No on-study cardiac changes could be attributed to romosozumab use. These studies support that romosozumab does not induce EKG changes.

8.3.12. Immunogenicity

The pharmacokinetic exposure, safety (eg, hypersensitivity, injection site reactions, or autoimmune disorder), and efficacy (changes in BMD) profiles of the subjects who tested positive for binding ADA were found to be consistent with the profiles of ADA negative Subjects. In the phase 2 and phase 3 studies included in this marketing application, the incidence of ADA was approximately 20% (852 of 4289), and the incidence of neutralizing antibodies was 1.1% (46 of 4289). The earliest onset of ADA was 3 months after first dose of romosozumab. ADA appears to have an effect on pharmacokinetics with a moderate decrease in exposure (up to 25% in mean values) observed during months 3 and 9 in subjects with binding ADA and a larger decrease for subjects with neutralizing ADA. The exposures were

similar (< 10% in mean values) at month 12.

For the 12-month placebo-controlled population, 17.8% (656 of 3689) of subjects in the romosozumab group were positive at any time for binding ADA, and 0.2% (6 of 3689) were positive at any time for neutralizing ADA. The following table 43 shows the number and percentages of subjects who had binding and/or neutralizing antibodies at baseline and at any time during each placebo-controlled study.

Table 43: Anti-Romosozumab Antibody Summary (Safety Analysis Set)

	20070337		20060326		20101291		Total	
	Placebo (N = 3576)	Romosozumab 210 mg QM SC (N = 3581)	Placebo (N = 50)	Romosozumab 210 mg QM SC (N = 51)	Placebo (N = 63)	Romosozumab 210 mg QM SC (N = 63)	Placebo (N = 3689)	Romosozumab 210 mg QM SC (N = 3695)
Subjects with an on-study result[a]	0	3575	29	51	0	63	29	3689
Total antibody incidence - n (%)								
Binding antibody positive at anytime	0 (0.0)	634 (17.7)	0 (0.0)	8 (15.7)	0 (0.0)	14 (22.2)	0 (0.0)	656 (17.8)
Neutralizing antibody positive at anytime	0 (0.0)	5 (0.1)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Subjects with a result at baseline	0	3406	0	51	0	63	0	3520
Pre-existing antibody incidence - n (%)								
Binding antibody positive at or before baseline	0 (0.0)	22 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (0.6)
Neutralizing antibody positive at or before baseline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Sourced from ISS: Table 14-8.1. with reviewer edits

Reviewer Comments: ***17.8% (656 of 3689) of subjects in the romosozumab group were positive at any time for binding ADA, and 0.2% (6 of 3689) were positive at any time for neutralizing ADA. Although subjects were romosozumab naïve upon entrance to the pivotal study 20070337, the assay identified 22 (0.6%) patients with pre-existing antibody positive at baseline. This assay positive identification is dependent on the cut-point of the assay and this low level of positive assay at baseline is acceptable.***

Pharmacokinetics values decreased by approximately 25% for subjects who turned positive for ADA in-study. There are no safety concerns for this decrease in exposure for patients who turn ADA positive. Only 6 (0.2%) of patients developed neutralizing antibodies and this low percentage of patients developing neutralizing antibodies is not a safety concern.

Binding and neutralizing antibody status was assessed in relationship to hypersensitivity, injection site reactions, and autoimmune disorders. Adverse events potentially related to hypersensitivity and autoimmune disorders were generally similar for subjects who received romosozumab, regardless of binding or neutralizing ADA status, as well as for subjects who received placebo. Injection site reaction adverse events were reported more frequently in the romosozumab group, regardless of ADA status, than in the placebo group.

The following two tables (Table 44 and Table 45) show the incidences of injection site reactions, hypersensitivity and autoimmune disorders by ADA status (Table 44 – binding antibody status, Table 45-neutralizing antibody status) through month 15 for subjects treated with romosozumab 210 mg QM or placebo. The collections of search terms used to identify adverse events potentially related to hypersensitivity were based on standardized MedDRA queries (SMQs).

Table 44: Incidence of Injection Site Reaction, Hypersensitivity and Autoimmune Disorder by Binding Anti-Romosozumab Antibody Status

		All Romosozumab 210mg QM Subjects			
			Binding Antibody Positive		
Adverse Event of Interest Preferred Term	Placebo Total (N = 3689) n (%)	Antibody Negative (N = 2821) n (%)	Pre-existing (N = 22) n (%)	Developing (N = 669) n (%)	Total (N = 691) n (%)
Number of subjects reporting treatment emergent adverse events	374 (10.1)	337 (11.9)	2 (9.1)	90 (13.5)	92 (13.3)
Hypersensitivity (SMQ)	253 (6.9)	197 (7.0)	1 (4.5)	48 (7.2)	49 (7.1)
Injection site reactions (EOI)	107 (2.9)	141 (5.0)	1 (4.5)	46 (6.9)	47 (6.8)
Autoimmune disorders	33 (0.9)	26 (0.9)	0 (0.0)	5 (0.7)	5 (0.7)

Source: ISS Table 14-8.2.1 modified by reviewer

Table 45: Incidence of Injection Site Reaction, Hypersensitivity and Autoimmune Disorder by Neutralizing Anti-Romosozumab Antibody Status

		All Romosozumab 210mg QM Subjects			
		Neutralizing	Neutralizing Antibody Positive		
Adverse Event of Interest Preferred Term	Placebo Total (N = 3689) n (%)	Antibody Negative (N = 649) n (%)	Pre-existing (N = 0) n (%)	Developing (N = 27) n (%)	Total (N = 27) n (%)
Number of subjects reporting treatment emergent adverse events	374 (10.1)	87 (13.4)	0 (0.0)	3 (11.1)	3 (11.1)
Hypersensitivity (SMQ)	253 (6.9)	47 (7.2)	0 (0.0)	1 (3.7)	1 (3.7)
Injection site reactions (EOI)	107 (2.9)	44 (6.8)	0 (0.0)	2 (7.4)	2 (7.4)
Autoimmune disorders	33 (0.9)	5 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Table 14-8.2.2 modified by reviewer

Reviewers Comments: ***For patients who develop AEs, the rates for hypersensitivity and autoimmune disorders is balanced between patients who develop either binding ADA or neutralizing ADA when compared to placebo patients who do not develop antibodies.***

Injection site reaction is higher for patients on romosozumab regardless of ADA status when compared to placebo patients (7% romosozumab versus 3% placebo patients). ADA status does not appear to affect hypersensitivity or autoimmune disorders. Injection site reactions are higher (7%) in romosozumab treated patients regardless of ADA status but maybe more reflective of the specific drug product and application procedure, using two syringes per dose.

BMD gains and BTMs were not affected by binding or neutralizing ADA status as discussed in section 4.5, Clinical Pharmacology.

ADA Status During Re-treatment:
Study 20060326 evaluated ADA status during romosozumab re-treatment. During the 12-month romosozumab retreatment period (months 36 to 48) of, 2 of 139 subjects (1.4%) developed positive binding ADA during the retreatment phase having been previously ADA negative. Eight subjects were binding ADA positive at their month 36 visit, of which 5 were positive during re-treatment. Two subjects were neutralizing ADA positive at month 36, of whom 1 remained positive during retreatment. No subject developed positive neutralizing ADA during the retreatment phase having been previously antibody negative. The frequency of overall adverse events by antibody status was comparable between antibody positive and antibody negative subjects (73.7% and 84.8%, respectively).

<u>Reviewers Comments:</u> In totality, this data supports the safety of re-treatment in this patient population but there is evidence that neutralizing ADA patients can have rapid declines of romosozumab levels to immeasurable levels on re-treatment. Study 20060326 demonstrated that ADA status can convert to a positive status upon re-treatment but at much lower rates (1.4%) than the initial exposure. Importantly, no patient develop neutralizing ADA who were previously antibody negative. Furthermore, of the two subjects who had developed neutralizing ADA, one lost her neutralizing ADA status.

In reviewing the antibody data, one patient who developed neutralizing ADAs on first exposure was found to have inadvertently been re-dosed and developed immeasurable levels of romosozumab. The case was as follows (from Clin Pharm review, section 4.4.2):

> ***"one of the neutralizing antibody positive subjects (Subject (b) (6)) from Phase 1 study 20060220 was inadvertently enrolled and dosed in a subsequent ascending multi-dose pharmacology/pharmacodynamic study 20060221. A rapid decline in romosozumab serum concentrations was observed in this subject after the first dose in study 20060221, and serum concentrations were not measurable after day 6, despite continued dosing once every two weeks. unexpected case provides evidence that neutralizing ADA positive patients can have much reduced concentrations of romosozumab on re-exposure. "***

8.4. Analysis of Submission-Specific Safety Issues

8.4.1. Adverse Events Potentially Related to Hypersensitivity

All monoclonal antibodies could potentially be associated with hypersensitivity reactions. In the 12-month placebo-controlled population, adverse events potentially related to hypersensitivity based on the standardized MedDRA queries (SMQs) search strategy, were reported for 6.7% of subjects in the romosozumab treatment group and 6.9% of subjects in the placebo group; serious adverse events were reported for 0.2% (all in Study 20070337). The following Table 46 summarizes the numbers and percentages of AEs and SAEs potentially related to hypersensitivity in the placebo-controlled trials.

Table 46: Summary Adverse Events of Hypersensitivity

	20070337		20060326		20101291		Total	
	Placebo (N = 3576)	Romosozumab 210 mg QM SC (N = 3581)	Placebo (N = 50)	Romosozumab 210 mg QM SC (N = 51)	Placebo (N = 63)	Romosozumab 210 mg QM SC (N = 63)	Placebo (N = 3689)	Romosozumab 210 mg QM SC (N = 3695)
Potentially related to hypersensitivity								
Adverse events	245 (6.9)	242 (6.8)	4 (8.0)	4 (7.8)	4 (6.3)	3 (4.8)	253 (6.9)	249 (6.7)
Serious adverse events	0 (0.0)	7 (0.2)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	7 (0.2)

Source: Modified from ISS Table 14-6.8.1 with reviewer edits and modification

SAEs:
The 7 SAEs potentially related to hypersensitivity all occurred in the pivotal study 20070337and a detailed breakdown of each SAE by preferred term is listed in the following Table 47.

Table 47: SAEs of Hypersensitivity in Subjects Receiving Romosozumab (Study 20070337)

Preferred Term	Study Day Start	Study Day End	Days Since IP	Outcome	Causality	Action Taken with IP
Hypersensitivity	3	7	3	Resolved	Related	Withdrawn
Dermatitis allergic	140	153	19	Resolved	Related	Withdrawn
Alveolitis allergic[a]	267	NP	26	Not resolved	Not related	Withdrawn from study
Immune thrombocytopenic purpura[b]	35	458	1	Resolved	Not related	None
Dermatitis	166	317	17	Resolved	Related	Dose altered or withheld
Circulatory collapse[c]	345	365	9	Fatal	Not related	No action taken[d]
Rash macular[e]	3	10	3	Resolved	Related	Withdrawn
Angiodema[e]	28	31	28	Resolved	Not related	NA[f]
Dermatitis exfoliative[e]	28	31	28	Resolved	Not related	NA[f]
Rash macular[e]	134	148	134	Resolved	Related	NA[f]

IP = investigational product; NP = not provided; NA = not applicable
[a] The event was considered not related to romosozumab. Per the investigator, a potential cause is that the subject had been engaged in greenhouse cultivation.
[b] The verbatim term was idiopathic thrombocytopenia. Other adverse events included hepatic steatosis, portal hypertension, and liver disorder. Concomitant medications included naproxen.
[c] Subject with a medical history of current tobacco abuse. There were no reports of pruritus, flush, or urticaria for this subject.
[d] Fatal event.
[e] All 4 events occurred in the same subject.
[f] Not applicable; IP was withdrawn after the adverse event of rash macular in the subject.

Source: SummClinSafety Appendix 8.2 with reviewer modification

The following are summary narratives of these SAEs all from the pivotal study 20070337 potentially related to hypersensitivity with romosozumab:

1) Subject (b) (6) had a fatal event of circulatory collapse on study day 365. This 78-year-old subject with a medical history of tobacco use developed unspecified cardiovascular disease and was hospitalized on study day 345, 8 days after receiving her twelfth dose of romosozumab. She was hospitalized in the ICU and died from cardiovascular collapse on day 365. The patient had negative antibody status (ADA negative) and negative neutralizing ADA status during the study.
2) subject (b) (6) had dyspnea, cough, and wheezing approximately 24 hours after receiving the first dose of romosozumab. This 74-year-old with a relevant medical history of allergic respiratory disease, allergies to Rulide (roxithromycin) and codeine, aspergillosis, asthma, bronchiectasis, gastroesophageal reflux disease, hypercholesterolemia, osteoporosis, and nephrolithiasis (all of which were ongoing at baseline) had dyspnea, cough, and wheezing approximately 24 hours after receiving the first dose of romosozumab. Two days later (day 3), she presented to the general practitioner with a rash on her chest and back. A serious, grade 4 adverse event of acute allergic reaction with unknown etiology (on chest and back) was reported. The rash resolved after treatment with hydrocortisone, and the subject was sent home with prednisolone. The event was reported as resolved on day 7. The investigator was unaware of exposure to any other antigens, and investigational product was withdrawn. The patient subsequently tested positive for antibodies (ADA positive) for months 3, 6, and 12 after the first dose but tested negative at month 15 after the first dose. Neutralizing antibody status remained negative.
3) Subject (b) (6) with SAE dermatitis.
A 64-year-old with a medical history of COPD and eczema had grade 3 adverse events of eczema 9 days after first dose and was hospitalized for a serious adverse event of dermatitis on study day 166; the subject received intravenous steroids and intravenous antihistamines, and the dermatitis resolved. The subject tested positive for ADA status months 6, 12, 15, and 24 and was neutralizing antibody negative.
4) Subject (b) (6) with SAE dermatitis allergic
A 65-year-old with a medical history of allergic rhinitis and a milk allergy had non-serious adverse events of skin tingling for 2 days after the first 3 doses of romosozumab. Approximately 3 weeks after the fifth dose, the subject developed facial edema and generalized rash. The subject was hospitalized with a serious adverse event of dermatitis allergic and received intravenous corticosteroids and topical steroids, intravenous fluids, and oral antihistamine. Study drug was discontinued; the event resolved. The patient remained ADA and neutralizing ADA status negative.
5) Subject (b) (6) 4 SAEs of dermatitis exfoliative, angioedema, rash macular

A 75-year-old with a medical history of childhood asthma developed nausea, ill being, chills, and burning sternal pressure 8 hours after the initial romosozumab dose. On study day 3, a serious adverse event of macular rash on trunk was reported and a skin biopsy revealed "unspecific superficial dermatitis with urticarial components, drug reaction cannot be excluded." Study drug was withdrawn, and the event resolved on study day 10. On study day 28, the subject was hospitalized with a serious adverse event of dermatitis exfoliative and angioedema. A skin biopsy showed discrete superficial perivascular dermatitis. The subject was treated with topical steroids and creams, and the events resolved on study day 31. On study day 135, the subject was hospitalized for a macular rash and treated with topical steroid creams and oral antihistamines; the event resolved on study day 148. The patient was reported to be ADA negative at months 12, 15, and 24.

Reviewers Comments: ***Analysis of the narratives for the SAEs in the romosozumab group for the pivotal study 20070337 is concerning for hypersensitivity in some patients with romosozumab use. Regardless of investigator determination of drug-related reaction or not, these SAEs are concerning for hypersensitivity in some patients. For example, patient (b) (6) developed an acute reaction with dyspnea, wheezing, and coughing within 24 hours after the first dose which is concerning for an hypersensitivity reaction to romosozumab. She subsequently turned ADA positive at month 3 through month 12 before turning negative by month 15.***

For patient (b) (6), she had a difficult course after receiving only one dose but developed repeated episodes of macular rash and an episode of dermatitis exfoliative and angioedema which required hospitalization. She tested ADA negative. It is unclear if patient (b) (6) who had a fatal coronary SAE was a hypersensitivity reaction as she developed cardiovascular event 8 days after her 12th dose of romosozumab. She was negative for ADA during the course of her treatment.

In summary, there is concern for hypersensitivity reactions with romosozumab use in some patients based on the data and narratives from the pivotal study. This concern should be included in the med guide and in labeling.

AEs:
For adverse events (AEs), the only preferred term reported for ≥ 1.0% of subjects in either treatment group was rash (1.1%, 0.9%). The incidence of recurrent adverse events potentially related to hypersensitivity was 0.6% and 0.5%, respectively. The incidence of adverse events potentially related to hypersensitivity leading to discontinuation of investigational product was 0.3% and 0.2%, respectively. The incidence of adverse events potentially related to hypersensitivity leading to discontinuation from study participation was < 0.1% in both groups. Adverse events potentially related to hypersensitivity occurred within ≤ 2 days after

administration of investigational product for 1.3% and 0.9%, respectively, and within > 2 to ≤ 7 days after administration of investigational product for 1.5% and 1.0%, respectively. Adverse events potentially related to hypersensitivity that were reported at a slightly greater rate in the romosozumab group than the placebo group included injection site rash (0.3%, < 0.1%), generalized rash (0.1%, 0.0%), erythematous rash (0.1%, < 0.1%), macular rash (0.1%, 0.0%), and injection site urticaria (< 0.1%, 0.0%).

Erythema multiforme (< 0.1%, 0%) developed in 1 subject (b) (6) 1 day after receiving romosozumab. Adverse events of face edema (0.1%, 0.1%), eyelid edema (0.1%, < 0.1%), and allergic edema (< 0.1%, < 0.1%) were generally similar between the romosozumab and placebo groups. Although adverse events of urticaria (0.5%, 0.6%), bronchospasm (< 0.1%, < 0.1%), and angioedema (< 0.1%, < 0.1%) were reported at a slightly greater rate in the placebo group than the romosozumab group, case level details indicated potential causal relationship due to romosozumab with a lack of other confounder for urticarial and angioedema. The subject incidences with percentages of hypersensitivity events that are considered to have a causal association to romosozumab are shown below in Table 48.

Table 48: Hypersensitivity Events Considered being Causally Related to Romosozumab

Umbrella Term (If Applicable) Preferred Term	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Rash	33 (0.9)	54 (1.5)
Rash	32 (0.9)	41 (1.1)
Rash macular	0 (0.0)	4 (0.1)
Rash generalized	0 (0.0)	5 (0.1)
Rash erythematous	1 (< 0.1)	4 (0.1)
Dermatitis	60 (1.6)	41 (1.1)
Dermatitis	28 (0.8)	15 (0.4)
Dermatitis allergic	32 (0.9)	26 (0.7)
Dermatitis exfoliative	0 (0.0)	1 (< 0.1)
Urticaria	23 (0.6)	20 (0.5)
Erythema multiforme	0 (0.0)	1 (< 0.1)
Angioedema	3 (< 0.1)	1 (< 0.1)

Source: ISS Table 14-6.2.1 with reviewer edits

Adverse events potentially related to hypersensitivity that were reported ≤ 2 days after administration of investigational product and at a greater rate in the romosozumab group included injection site rash (0.3%, < 0.1%), rash (0.2%, 0.1%), and injection site hypersensitivity (0.1%, < 0.1%). Adverse events potentially related to hypersensitivity that were reported ≤ 2

days after administration of investigational product and only in the romosozumab group included injection site urticaria, dermatitis, acneiform dermatitis, erythema multiforme, eyelid edema, face edema, gingival swelling, hypersensitivity, injection site dermatitis, lip swelling, generalized rash, and face swelling (all < 0.1%, 0.0%). Adverse events potentially related to hypersensitivity that were reported > 2 to ≤ 7 days after administration of investigational product and only in the romosozumab group included eczema (0.2%, 0.0%); and erythematous rash, macular rash, face edema, injection site rash, generalized rash, application site dermatitis, drug eruption, hypersensitivity, face swelling, and swollen tongue (all < 0.1%, 0.0%). Results for the PMO population were generally similar to the 12-month placebo- controlled population.

Reviewer Comments: ***Review of the data confirms the concern for hypersensitivity in some patients with romosozumab. In addition to the concern with SAEs present only in romosozumab patients in the pivotal study (discussed earlier), the subject incidence for AEs for injection site urticaria, dermatitis, acneiform dermatitis, erythema multiforme, eyelid edema, face edema, gingival swelling, hypersensitivity, injection site dermatitis, lip swelling, generalized rash, and face swelling (all < 0.1%, 0.0%) was only found in romosozumab patients ≤ 2 days after dosing. For AEs reported > 2 to ≤ 7 days after drug, the following incidences were only found in romosozumab patients: eczema (0.2%, 0.0%); erythematous rash, macular rash, face edema, injection site rash, generalized rash, application site dermatitis, drug eruption, hypersensitivity, face swelling, and swollen tongue (all < 0.1%, 0.0%). One subject developed an AE of erythema multiforme in the romosozumab group and no subject in the placebo group. Together this data reinforces the concern for hypersensitivity reaction for some patients with romosozumab and this concern should be reflected in the med guide and labeling.***

In Study 20070337, potential anaphylactic events were identified using the 2012 World Allergy Organization Guidelines and used to further assess the anaphylactic reactions using the Anaphylaxis Reaction SMQ algorithm. The subject incidence of potential anaphylactic reactions was generally similar between both treatment groups and both study periods. The majority of subjects had confounding factors that could potentially explain their adverse events. Based on review of the cases, no anaphylactic reactions associated with romosozumab use were reported.

Adverse events potentially related to hypersensitivity were generally similar regardless of ADA status and was discussed in section 8.3.8 above.

Reviewer Comments: ***There is no data to support anaphylaxis in the pivotal study, 20070337. AEs do not appear to be related to ADA status in patients.***

8.4.2. Injection Site Reactions

In the 12-month placebo-controlled population, adverse events of injection site reactions were reported for 5.2% of subjects in the romosozumab group and 2.9% of subjects in the placebo group; no serious adverse events of injection site reactions were reported. Table 49 below summarizes these findings for AEs of injection site reaction in the placebo-controlled studies.

Table 49: Adverse Events Injection site reactions (Safety Analysis Set)

	20070337		20060326		20101291		Total	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Injection site reactions								
Adverse events	104 (2.9)	187 (5.2)	2 (4.0)	3 (5.9)	1 (1.6)	2 (3.2)	107 (2.9)	192 (5.2)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Modified from ISS Table 14-6.8.1 with reviewer edits

Preferred terms reported for ≥ 1% of subjects in either treatment group were injection site pain (1.7%, 1.2%) and injection site erythema (1.4%, 0.2%). Most adverse events of injection site reactions were mild or moderate; the only severe events reported were injection site pain (1 each romosozumab and placebo). The incidence of adverse events of injection site reactions leading to discontinuation of investigational product was 0.1% and < 0.1, respectively. The subject rate of adverse events of injection site reactions leading to study discontinuations was <0.1% for romosozumab and placebo treatment groups. The median time to onset of the first injection site reaction adverse event was 91.0 days for romosozumab and 62.0 days for placebo. The median duration of injection site reaction adverse events was 3.0 days for romosozumab and 6.0 days for placebo. The incidence of concurrent injection site reactions (ie, > 1 type of injection site reaction on the same investigational product administration date with overlapping start and resolution dates) was 1.0% and 0.1%, respectively; the incidence of recurrent injection site reactions (ie, > 1 injection site reaction on 2 or more different investigational product administration dates) was 1.6% and 0.4%.

Injection site reaction adverse events were reported more frequently in the romosozumab group, regardless of ADA status, than in the placebo group.

Drug product composition consisted of (b) (4), (b) (4)

(b) (4) The placebo is the same except for romosozumab.

Reviewer Comments: ***Patients injected 3 separate injections of 1 cc injections for each dose which could account for the relatively high number of injection site AEs for both placebo and romosozumab but there were no SAEs reported for either group. All excipients in the drug product formulation are standard components, thus the relatively high rate of injection site AEs in both groups might be related to 3 injections for each dose during the study.***

The rates of injection site reactions for romosozumab patients is mildly inbalanced in favor of romosozumab when compared to placebo. On the other hand, mean time for the appearance of injection site reaction AE s was longer for romosozumab compared to placebo (91 days versus 62 days) and shorter in duration (3 days versus 6 days). Most injection site reactions were low grade AE. Given these findings, there is no concern for excessive injection site reactions with romosozumab but there is evidence of mild reactions at the injection site to romosozumab. There is evidence that injection site reactions might be due to the number (3) injections required per dose. In the final commercial product, each dose will consist of two injections which will be expected to decrease injection site reactions.

8.4.3. Malignancy (Malignant or Unspecified Tumor)

Although sclerostin expression has been reported in a limited number of soft tissue and bone tumors, there is no current evidence that the presence or absence of sclerostin is related to malignant potential. There are no reports of an increased cancer incidence in patients with sclerosteosis or van Buchem disease. In the 12-month placebo-controlled population, adverse events of malignant or unspecified tumors were reported for 1.7% of subjects in the romosozumab treatment group and 1.9% of subjects in the placebo group; serious adverse events were reported for 1.1% and 1.2%, respectively. Preferred terms reported for ≥ 0.2% of subjects in either treatment group were basal cell carcinoma (0.2%, 0.5%) and thyroid neoplasm (0.2%, 0.3%). Table 50 below summarizes the incidence of malignant or unspecified tumors in the placebo-controlled studies.

Table 50: AE of Malignant or Unspecified Tumors by Preferred Term

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting treatment-emergent adverse events of malignant or unspecified tumours	69 (1.9)	59 (1.6)	2 (4.0)	1 (2.0)	0 (0.0)	1 (1.6)	71 (1.9)	61 (1.7)
Basal cell carcinoma	16 (0.4)	7 (0.2)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (0.5)	7 (0.2)
Thyroid neoplasm	10 (0.3)	7 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.3)	7 (0.2)
Lung neoplasm malignant	5 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	5 (0.1)
Squamous cell carcinoma of skin	1 (<0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	4 (0.1)
Breast cancer	2 (<0.1)	1 (<0.1)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.6)	2 (<0.1)	3 (<0.1)
Invasive ductal breast carcinoma	0 (0.0)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)
Colon cancer	0 (0.0)	2 (<0.1)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)
Lung neoplasm	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)
Non-Hodgkin's lymphoma	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Pancreatic carcinoma	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Squamous cell carcinoma	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)
Pancoast's tumour	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

Source: ISS Table 14-6.8.5 with reviewer modification and edits.

Non-Hodgkin's lymphoma was reported for 2 romosozumab subjects dosed at 210 mg QM and 1 placebo subject (both treatment groups < 0.1 events per 100 subject-years) of which 1 in each treatment group was serious . Events reported under the high- level group term of leukemias were reported for 2 romosozumab subjects dosed at 210 mg QM (1 each acute lymphocytic leukemia and myeloid leukemia) and 1 placebo subject (chronic lymphocytic leukemia) (both treatment groups < 0.1 per 100 subject-years) of which both events in the romosozumab group were serious.

Reviewer Comments: ***Recent comments by Koda et al (Nature 2014; 506(7487):240–244) raise concerns that genetic alteration of osteoblasts in the bone marrow microenvironment can induce an aggressive AML in clinical studies as was seen in mice studies where transplanted bone marrow cells from Ctnnb1CAosb leukaemic mice into lethally irradiated wild-type recipients induced all features of haematopoietic dysfunction and AML and early lethality. The clinical studies did not support an increased rate of AML or other hematopoietic malignancies for romosozumab.***

Malignant lung neoplasm with fatal outcome was reported for 4 romosozumab subjects (b) (6) dosed at 210 mg QM and discussed under section 8.3.3 deaths. Pancoast's tumor was reported on study day 254 for 1 romosozumab subject (b) (6) who was dosed at 210 mg QM. The subject was a former smoker and had a history of asthma, chronic obstructive pulmonary disease, and lung abscess.

Reviewer Comments: ***There does not appear to be a clear signal for malignancy with romosozumab. As discussed in section 8.3.3, the inbalance of fatal lung carcinoma in the romosozumab group, (4 romo, 0 placebo) is tempered by a balanced incidence of lung neoplasms between romosozumab and placebo groups (5, 5). Although the small numbers of lung neoplasm found in the study limits our ability to interpret the inbalance for fatalities between groups, the total incidence of lung neoplasm in each group is consist with what is expected for this patient population with a smoking history.***

8.4.4. Hyperostosis and Audiology Substudy

Hyperostosis with adverse neurological consequences is a feature of sclerosteosis and van Buchem disease. It is not a feature of individuals heterozygous for the respective mutations. In the 12-month placebo-controlled population, adverse events of hyperostosis were reported for 0.5% of subjects in the romosozumab treatment group and 0.8% of subjects in the placebo group; serious adverse events in this category were reported for < 0.1% and 0.1%, respectively. Adverse event preferred terms for hyperostosis were similar between treatment groups, as were events under the high level group terms of spinal cord and nerve root disorders, cranial nerve disorders, and hearing disorders. The following Table 51 summarizes AE and SAE rates related to hyperostosis in the placebo-controlled studies.

Table 51: Summary of AE and SAE for Hyperostosis

	20070337		20060326		20101291		Total	
	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Hyperostosis								
Adverse events	27 (0.8)	19 (0.5)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (0.8)	19 (0.5)
Serious adverse events	5 (0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	1 (<0.1)

Modified from Summary of Clin Safety Table 17 with reviewer edits.

Table 52 details and summarizes component preferred terms in the search for hyperostosis.

Reference ID: 4093382

Table 52: Adverse Events of Hyperostosis by Preferred Term

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM SC (N = 3581) n (%)	Placebo (N = 50) n (%)	Romosozumab 210 mg QM SC (N = 51) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3689) n (%)	Romosozumab 210 mg QM SC (N = 3695) n (%)
Number of subjects reporting treatment-emergent adverse events of hyperostosis	27 (0.8)	19 (0.5)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (0.8)	19 (0.5)
Lumbar spinal stenosis	8 (0.2)	9 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.2)	9 (0.2)
Exostosis	11 (0.3)	6 (0.2)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (0.4)	6 (0.2)
Spinal column stenosis	7 (0.2)	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.2)	3 (<0.1)
Cervical spinal stenosis	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)

Source: ISS Table 14-6.8.6. with reviewer edits

A potential consequence of hyperostosis is nerve compression which may include facial drooping, numbness, or changes in hearing or vision. Study 20070337 included an audiology substudy of 498 subjects to assess the effect of romosozumab treatment for 12 months compared with placebo on the incidence of hearing loss (defined as subjects meeting the American Speech-Language-Hearing Association criteria for ototoxicity), and mean change from baseline in hearing threshold (assessed as change from baseline in pure tone average; defined as [1] loss of ≥ 20 dB at any single frequency or [2] loss of ≥ 10 dB at any 2 adjacent frequencies or [3] loss of response at 3 consecutive frequencies where responses were previously obtained). The subject incidence of hearing loss at baseline was similar between romosozumab and placebo groups, and no significant difference in average change in hearing threshold was observed between the romosozumab and placebo groups at month 12 as assessed by the mean change from baseline in pure tone average.

Reviewer Comments: ***Auditory substudy demonstrated no significant difference in changes of auditory hearing between study groups. Fewer patients presented with AEs consistent with hyperostosis when compared to placebo patients. Thus, the AE data from the clinical studies did not support hyperostosis with romosozumab use.***

8.4.5. TNF-mediated Inflammatory Conditions

For the 12-month placebo-controlled population, the subject incidence of treatment-emergent TNF-mediated inflammatory adverse events was 0.2% in the romosozumab group and 0.4% the placebo group. No subject in the romosozumab group had a treatment-emergent adverse event of rheumatoid arthritis. The subject incidence rate was also lower in the romosozumab group than placebo group independent of a prior history of a TNF-mediated inflammatory disease

(prior history of TNF-mediated inflammatory disease; no prior history of TNF-mediated inflammatory disease).

The following two tables summarize TNF mediated inflammatory AEs by preferred term for patients with prior history of TNF mediated inflammatory disease (Table 53) and without a prior history of TNF mediated inflammatory disease (Table 54).

Table 53: TNF Mediated Inflammatory Adverse Events for Subjects with Prior History

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 59) n (%)	Romosozumab 210 mg QM SC (N = 64) n (%)	Placebo (N = 3) n (%)	Romosozumab 210 mg QM SC (N = 1) n (%)	Placebo (N = 0) n (%)	Romosozumab 210 mg QM SC (N = 0) n (%)	Placebo (N = 62) n (%)	Romosozumab 210 mg QM SC (N = 65) n (%)
Number of subjects reporting treatment-emergent TNF-mediated inflammatory adverse events	8 (13.6)	5 (7.8)	0 (0.0)	0 (0.0)	0 (-)	0 (-)	8 (12.9)	5 (7.7)
Psoriasis	6 (10.2)	5 (7.8)	0 (0.0)	0 (0.0)	0 (-)	0 (-)	6 (9.7)	5 (7.7)
Multiple sclerosis	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (-)	0 (-)	1 (1.6)	0 (0.0)
Psoriatic arthropathy	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (-)	0 (-)	1 (1.6)	0 (0.0)

Source: Modified from ISS Table 14-6.4.500 with reviewer edits.

Table 54: TNF Mediated Inflammatory Adverse Events for Subjects without Prior History

	20070337		20060326		20101291		Total	
Preferred Term	Placebo (N = 3517) n (%)	Romosozumab 210 mg QM SC (N = 3517) n (%)	Placebo (N = 47) n (%)	Romosozumab 210 mg QM SC (N = 50) n (%)	Placebo (N = 63) n (%)	Romosozumab 210 mg QM SC (N = 63) n (%)	Placebo (N = 3627) n (%)	Romosozumab 210 mg QM SC (N = 3630) n (%)
Number of subjects reporting treatment-emergent TNF-mediated inflammatory adverse events	5 (0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	6 (0.2)	2 (<0.1)
Psoriasis	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (<0.1)	1 (<0.1)
Seronegative arthritis	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Colitis ulcerative	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Rheumatoid arthritis	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)

Sourced from modified ISS Table 14-6.4.501 with reviewer edits.

In addition, the following 2 events of palindromic rheumatism reported in subjects dosed with romosozumab are not included in the TNF-mediated search strategy: 1 subject (b) (6) in phase 1 study 20150197 had a serious adverse event of palindromic rheumatism reported on study day 10; and 1 subject (b) (6) in study 20070337 with a medical history of

palindromic rheumatism had a non-serious adverse event of worsening palindromic rheumatism on study days 76 to 128.

Reviewer Comments: ***The TNF mediated AE rates for romosozumab group are lower than for placebo regardless of prior history of TNF mediated inflammatory disease. In addition, no romosozumab patient develop rheumatoid arthritis. The data supports the use of romosozumab in the targeted patient population regardless of prior history with TNF mediated inflammatory disease.***

8.4.6. Osteoarthritis

Study 20070337 included an osteoarthritis substudy of 343 subjects to assess the effect of romosozumab compared with placebo at month 12 on the progression of osteoarthritis of the knee (defined as an increase in total Western Ontario and McMaster Universities Arthritis Index [WOMAC] score of at least 10 points on a scale normalized to 100 points). Additional assessments included change from baseline in WOMAC subscale scores for pain and physical function, patient global assessment of change from baseline measured by the EuroQoL-5 Dimensions-5 Levels Health Survey (EQ-5D-5L VAS), and adverse events of osteoarthritis utilizing the events of interest search strategy through month 12.

No significant progression of osteoarthritis of the knee was observed for subjects in the romosozumab group compared with the placebo group at month 12, as assessed by the change from baseline in the WOMAC total and subscale scores. The subject incidence of worsening knee osteoarthritis (defined as > 10-point increase in WOMAC total score) was also similar between the romosozumab and placebo groups at month 12. For subjects' self-assessment of health status via the EQ-5D-5L VAS, the romosozumab group had a mean increase of 2.09 units from baseline, and the placebo group had a mean increase of 1.10 units, with a higher score indicating better overall health.

Reviewer Comments: ***The osteoarthritis WOMAC results showed similarities between the two study groups in the pivotal study and indicates no increase in osteoarthritis with romosozumab. In addition, the EQ-5D-5L VAS results actually showed romosozumab patients reported better overall health than placebo patients. There are no concerns for osteoarthritis from romosozumab in this patient population based on these results.***

8.4.7. Safety Analyses by Demographic Subgroups

Age

The patient population was analyzed by age groups to determine if there are AE differences by age. Overall, results of the subgroup analysis do not indicate an altered safety profile of romosozumab by age subgroup. The overall subject incidence of adverse events was similar across age subgroups and between the romosozumab and placebo treatment groups. Of

adverse events that were reported more frequently for romosozumab in an older age subgroup, incidences in the placebo subgroup for that age were also higher.

The following table 55 summarizes the most frequently reported AEs, stratified by age group in the placebo-controlled clinical studies.

Table 55: Adverse Events by Age Group and Preferred Term

	< 65 years		≥ 65 years		< 75 years		≥ 75 years	
Preferred Term	Placebo (N = 803) n (%)	Romosozumab 210 mg QM SC (N = 802) n (%)	Placebo (N = 2886) n (%)	Romosozumab 210 mg QM SC (N = 2893) n (%)	Placebo (N = 2552) n (%)	Romosozumab 210 mg QM SC (N = 2562) n (%)	Placebo (N = 1137) n (%)	Romosozumab 210 mg QM SC (N = 1133) n (%)
Number of subjects reporting adverse events	619 (77.1)	632 (78.8)	2319 (80.4)	2264 (78.3)	2025 (79.3)	1995 (77.9)	913 (80.3)	901 (79.5)
Nasopharyngitis	103 (12.8)	128 (16.0)	350 (12.1)	360 (12.4)	316 (12.4)	363 (14.2)	137 (12.0)	125 (11.0)
Arthralgia	86 (10.7)	111 (13.8)	348 (12.1)	358 (12.4)	289 (11.3)	324 (12.6)	145 (12.8)	145 (12.8)
Back pain	83 (10.3)	90 (11.2)	303 (10.5)	291 (10.1)	264 (10.3)	276 (10.8)	122 (10.7)	105 (9.3)
Pain in extremity	57 (7.1)	53 (6.6)	249 (8.6)	232 (8.0)	200 (7.8)	180 (7.0)	106 (9.3)	105 (9.3)

Source: Modified from ISS: Table 14-6.3.2 with reviewer edits.

***Reviewer Comments:* Analysis of the commonly presented AEs demonstrated no significant differences between age groups when comparing romosozumab and placebo groups. Based on this data, there is minimal concern for AE differences by age in this patient population.**

Race

Analysis of adverse events by race (white, non-white) using the 12-month placebo-controlled population was performed to determine if there are differences in AE rates based on race for romosozumab. Overall, results of the subgroup analysis do not indicate an altered safety profile of romosozumab by race subgroup. The overall subject incidence of adverse events was similar across race subgroups and between the romosozumab and placebo treatment groups. Individual adverse event preferred terms were generally reported more frequently in the non-white subgroup for both romosozumab and placebo groups. The following table 56 summarizes the sub analysis for AE differences between romosozumab and placebo by race and preferred term in the placebo controlled studies:

Table 56: Adverse Events by Race and Preferred Term

Preferred Term	White		Non-white	
	Placebo (N = 2084) n (%)	Romosozumab 210 mg QM SC (N = 2101) n (%)	Placebo (N = 1605) n (%)	Romosozumab 210 mg QM SC (N = 1594) n (%)
Number of subjects reporting adverse events	1697 (81.4)	1646 (78.3)	1241 (77.3)	1250 (78.4)
Nasopharyngitis	258 (12.4)	258 (12.3)	195 (12.1)	230 (14.4)
Arthralgia	206 (9.9)	231 (11.0)	228 (14.2)	238 (14.9)
Back pain	160 (7.7)	155 (7.4)	226 (14.1)	226 (14.2)
Pain in extremity	118 (5.7)	129 (6.1)	188 (11.7)	156 (9.8)

Source: Modified from ISS Table 14-6.3.3 with reviewer edits.

Reviewer Comments: ***AEs by race appears well balanced between romosozumab and placebo groups. Interestingly, non-whites had higher rates of AEs in both placebo and romosozumab groups which were balanced. The pivotal study had a great portion (97.5%) of the study completed outside the US and it is possible practice differences affect the rate of AEs reported in these other countries. Because the numbers are balanced between romosozumab and placebo groups, there is no concern for racial differences with romosozumab in this patient population.***

Body Mass Index

A sub analysis was conducted to determine if different weight affected AE rates with romosozumab. The overall subject incidence of adverse events was similar across BMI subgroups and between the romosozumab and placebo treatment groups. Cataract was reported more frequently in subjects with lower BMI in both the romosozumab and placebo groups (≤22.5 kg/m2: 2.3% romosozumab, 1.6% placebo; > 22.5 to ≤ 26 kg/m2: 2.0%, 1.1%; > 26 kg/m2: 1.6%, 1.7%). Peripheral edema was reported more frequently in subjects with higher BMI in both the romosozumab and placebo groups (≤ 22.5 kg/m2: 1.4% romosozumab, 1.2% placebo; > 22.5 to ≤26 kg/m2: 2.0%, 2.2%; > 26 kg/m2: 3.5%, 2.2%). The following table 57 summarizes AEs by BMI tertile using preferred terms in the placebo controlled clinical studies.

Table 57: Adverse Events by BMI Tertile and Preferred Term

Body Mass Index	<= 22.5		> 22.5 to <= 26		> 26	
Preferred Term	Placebo (N = 1235) n (%)	Romosozumab 210 mg QM SC (N = 1245) n (%)	Placebo (N = 1237) n (%)	Romosozumab 210 mg QM SC (N = 1227) n (%)	Placebo (N = 1212) n (%)	Romosozumab 210 mg QM SC (N = 1216) n (%)
Number of subjects reporting adverse events	952 (77.1)	979 (78.6)	992 (80.2)	964 (78.6)	989 (81.6)	947 (77.9)
Nasopharyngitis	166 (13.4)	179 (14.4)	153 (12.4)	163 (13.3)	133 (11.0)	144 (11.8)
Arthralgia	125 (10.1)	150 (12.0)	145 (11.7)	156 (12.7)	163 (13.4)	160 (13.2)
Back pain	120 (9.7)	117 (9.4)	138 (11.2)	129 (10.5)	127 (10.5)	132 (10.9)
Pain in extremity	73 (5.9)	85 (6.8)	116 (9.4)	97 (7.9)	115 (9.5)	103 (8.5)
Cataract	20 (1.6)	29 (2.3)	13 (1.1)	25 (2.0)	20 (1.7)	19 (1.6)
Oedema peripheral	15 (1.2)	18 (1.4)	27 (2.2)	25 (2.0)	27 (2.2)	43 (3.5)

Source: Modified from ISS Table 14-6.3.5. with reviewer edits.

Reviewer Comments: ***Overall the AE rates appear balanced between placebo and romosozumab groups at the different weight groups. There is a slight inbalance of cataract in the low weight group (≤ 22.5 BMI) favoring romosozumab versus placebo (2.3%, 1.6%) and inbalance for peripheral edema in the high weight group (>26 BMI) favoring romosozumab versus placebo (3.5%, 2.2%). The overall incidences of these AE are low and the small differences could be within the realm of chance findings. Thus, the risks for these AEs with romosozumab is acceptable. There is minimal concern that weight is a risk factor for romosozumab based on this data.***

Geographic Region

97.5% of the pivotal study was conducted outside the US. A sub analysis was conducted to determine if geographical regional differences affected AEs and romosozumab use. A subgroup analysis of adverse events by geographic region (Western Europe and Australia/ New Zealand, Central and Eastern Europe, Asia Pacific, North America, and Central/Latin America) using the 12-month placebo-controlled population was performed. Subjects in Western Europe and Australia/New Zealand had the highest incidence of adverse events (87.6% romosozumab, 89.0% placebo), followed by North America (84.8%, 81.1%), Asia Pacific (83.9%, 80.2%), Central/Latin America (76.2%, 77.6%), and Central and Eastern Europe (73.9%, 77.6%). Numeric differences were noted across regions in the incidence of certain adverse events. However, no consistent pattern of numeric differences for romosozumab was apparent across regions. Despite regional differences in the incidence of individual adverse events, the incidence of individual adverse events was similar between treatment groups within a region (≤ 5% difference for nearly all adverse events and regions).

The following table 58 summarizes AEs by geographic regions overall and using the preferred term in the most commonly reported AEs in the placebo-controlled study populations.

Table 58: Adverse Events by Geographic Regions and Preferred Term Overall and by Commonly Reported Preferred Term

	Western Europe and Australia/New Zealand		Central and Eastern Europe		Asia Pacific		North America		Central/Latin America	
Preferred Term	Placebo (N = 519) n (%)	Romo 210 mg QM SC (N = 502) n (%)	Placebo (N = 1039) n (%)	Romo 210 mg QM SC (N = 1043) n (%)	Placebo (N = 481) n (%)	Romo 210 mg QM SC (N = 471) n (%)	Placebo (N = 111) n (%)	Romo 210 mg QM SC (N = 125) n (%)	Placebo (N = 1539) n (%)	Romo 210 mg QM SC (N = 1554) n (%)
Number of subjects reporting adverse events	462 (89.0)	440 (87.6)	806 (77.6)	771 (73.9)	386 (80.2)	395 (83.9)	90 (81.1)	106 (84.8)	1194 (77.6)	1184 (76.2)
Nasopharyngitis	68 (13.1)	91 (18.1)	164 (15.8)	144 (13.8)	75 (15.6)	96 (20.4)	15 (13.5)	14 (11.2)	131 (8.5)	143 (9.2)
Arthralgia	56 (10.8)	64 (12.7)	95 (9.1)	105 (10.1)	35 (7.3)	48 (10.2)	12 (10.8)	16 (12.8)	236 (15.3)	236 (15.2)
Back pain	65 (12.5)	59 (11.8)	48 (4.6)	42 (4.0)	40 (8.3)	53 (11.3)	10 (9.0)	8 (6.4)	223 (14.5)	219 (14.1)
Pain in extremity	32 (6.2)	42 (8.4)	45 (4.3)	52 (5.0)	19 (4.0)	19 (4.0)	6 (5.4)	11 (8.8)	204 (13.3)	161 (10.4)

Source: Modified from ISS Table 14-6.3.4 with reviewer edits.

Reviewer Comments: ***Overall reporting of AEs appear balanced between romosozumab and placebo groups but the rate of reporting differs among individual regions and individual preferred term AE. Although the Sponsor indicated that individual regional differences that were 5% or greater when comparing romosozumab group to placebo were affected by low number of subjects with the particular AE, that may not be the case. For instance, looking at nasopharyngitis in Western Europe/New Zealand/ Australia and Asia Pacific, there is an inbalance of AEs for nasopharyngitis between romosozumab and placebo (91 patients(18 %) vs 68 patients (13 %)) and (96 patients (20 %) vs 75 patients (16 %)) respectively. Yet, Central America which had more subjects had a comparable AE rate between romosozumab and placebo of 143 patients (9 %) vs 131 patients (9 %).***

This reviewer agrees with the Sponsor in that other findings such as for hypersensitivity had such low numbers for each individual AE term. Table 59 below summarizes the AEs for hypersensitivity and it is difficult to interpret the differences because of the infrequency of reports.

The overall balance of AEs reported between romosozumab and placebo groups in each individual region lessen concerns about regional differences. On the other hand, > 90 % of subjects were recruited from outside the US, and differences within regions for individual preferred terms such as noted in the example above for nasopharngyitis AEs do not alleviate

concerns about different practices, reporting, and procedures in these countries as they relate to the US population.

The following Table 59 summarizes AE by geographic regions for the preferred term for hypersensitivity in the placebo controlled study populations.

Table 59: Adverse Events by Geographic Regions and Preferred Term for hypersensitivity.

	Western Europe and Australia/New Zealand		Central and Eastern Europe		Asia Pacific		North America		Central/Latin America	
Preferred Term	Placebo (N = 519) n (%)	Romo 210 mg QM SC (N = 502) n (%)	Placebo (N = 1039) n (%)	Romo 210 mg QM SC (N = 1043) n (%)	Placebo (N = 481) n (%)	Romo 210 mg QM SC (N = 471) n (%)	Placebo (N = 111) n (%)	Romo 210 mg QM SC (N = 125) n (%)	Placebo (N = 1539) n (%)	Romo 210 mg QM SC (N = 1554) n (%)
Injection site pain	4 (0.8)	12 (2.4)	13 (1.3)	17 (1.6)	8 (1.7)	9 (1.9)	3 (2.7)	6 (4.8)	18 (1.2)	19 (1.2)
Injection site erythema	0 (0.0)	10 (2.0)	1 (<0.1)	12 (1.2)	0 (0.0)	14 (3.0)	1 (0.9)	2 (1.6)	4 (0.3)	15 (1.0)
Pruritus	11 (2.1)	12 (2.4)	11 (1.1)	13 (1.2)	6 (1.2)	2 (0.4)	1 (0.9)	2 (1.6)	19 (1.2)	16 (1.0)
Rash	5 (1.0)	14 (2.8)	10 (1.0)	7 (0.7)	7 (1.5)	9 (1.9)	2 (1.8)	1 (0.8)	8 (0.5)	10 (0.6)
Eczema	6 (1.2)	0 (0.0)	2 (0.2)	5 (0.5)	16 (3.3)	13 (2.8)	1 (0.9)	0 (0.0)	3 (0.2)	7 (0.5)

Source: Reviewer modified from ISS Table 14-6.3.4

8.5. Specific Safety Studies/Clinical Trials

8.5.1. Hepatic Impairment

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

<u>Reviewer Comments:</u> Because romosozumab is not eliminated through the hepatic pathway, it is acceptable for the Sponsor not to have conducted clinical studies in patients with hepatic impairment for this application.

8.5.2. Subjects Transitioned from Bisphosphonate Therapy

The Sponsor studied patients who transitioned from bisphosphonate therapy in two studies, study 20090289 and study 20060223, to understand safety and efficacy parameters in this patient population.

Study 20080289

Study 20080289 was a multicenter, randomized, open-label, teriparatide (TPTD)-controlled study in 436 postmenopausal women with osteoporosis (safety analysis set of 432 subjects) who were transitioning from bisphosphonate therapy. Subjects needed to have received at

least 3 years of oral bisphosphonate therapy prior to screening and alendronate in the year immediately prior to screening, with a baseline T-score ≤ −2.5 at the lumbar spine, total hip, or femoral neck and history of nonvertebral fracture after the age of 50 or vertebral fracture. This study was designed to evaluate the responses in BMD through 12 months of treatment with romosozumab 210 mg QM, compared with 12 months of treatment with TPTD.

The percentages of subjects reporting adverse events were generally similar between the TPTD group (148 of 214 subjects [69 %]) and the romosozumab group (164 of 218 subjects [75 %]). The incidences and types of events reported were those that would be expected in the population studied and were generally similar between the TPTD and romosozumab groups. Injection site reactions were observed more frequently with romosozumab (8 %) compared with TPTD (3 %), which led to study drug discontinuation for 1 subject in the romosozumab group. Of the subjects who reported injection site reactions, the median time to the first adverse event was 92.0 days in the romosozumab group and 36.5 days in the TPTD group. The median duration of injection site reaction adverse events was 2.0 days in the romosozumab group and 5.5 days in the TPTD group. The safety findings in this study of subjects transitioning from at least 3 years of oral bisphosphonate therapy and alendronate in the year immediately prior were consistent with the overall safety profile of romosozumab.

Reviewer Comments: ***The safety findings in this study are consistent with the findings in the romosozumab placebo controlled studies. The results from this study do not raise any safety concerns for patients who transition to romosozumab from long-term (>3 years) bisphosphonate therapy.***

Study 20060223

Study 20060223 was a multicenter, randomized, open-label, single-dose study in 40 postmenopausal women with low bone mass who had been receiving alendronate for at least 1 year and in postmenopausal women with low bone mass who were treatment naive (ie, had not received alendronate, other bisphosphonates, or other treatments for osteoporosis/bone loss). Subjects who had been receiving alendronate were randomized to continue alendronate treatment or transition to romosozumab; treatment-naive subjects received romosozumab. Adverse events were similar across all 3 groups in this study.
Overall, adverse events were reported for 5 of 10 subjects (50%) who received alendronate only; 10 of 24 subjects (42%) who received romosozumab after previous alendronate treatment; and 5 of 6 subjects (83%) who received romosozumab and were previously treatment naive. These differences may be attributed to the small number of subjects in each group. Adverse events were reported as treatment related for 1 subject (4%) who received romosozumab after previous alendronate treatment (injection site reaction) and for 3 subjects (50%) who received romosozumab and were previously treatment naive (injection site erythema, injection site reaction, and nausea); all of these events were reported as mild in severity.

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Reviewer Comments: ***The low numbers of patients (40) in this study limits interpretation of the results of this study. At best, this study demonstrates that romosozumab is relatively well tolerated as all AEs were reported to be mild in severity.***

8.5.3. Drug Drug Interactions

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

Reviewer Comments: ***Based on the properties of romosozumab as a sclerostin-specific monoclonal antibody, it is acceptable for the sponsor not to conduct clinical studies for drug-drug interactions.***

8.6. Additional Safety Explorations

8.6.1. Human Carcinogenicity or Tumor Development

This drug will be short-term use, up to 1 year prior to transitioning to another osteoporosis drug. Pre-clinical rat studies included a rat lifetime pharmacology (carcinogenicity) study at doses up to 50 mg/kg QW and results did not raise concern for carcinogenicity.

Reviewer Comments: ***Malignancy and tumor development concerns were discussed in Section 8.3.3 for lung neoplasms and section 8.4.3 for malignancy and unknown tumors. There is no clear signal for tumor or malignancy with romosozumab from results of the clinical studies.***

8.6.2. Human Reproduction and Pregnancy

No clinical data are available from pregnant or lactating women who have received romosozumab. No studies of romosozumab have been conducted in pregnant women. All studies in this marketing application were conducted in postmenopausal women, and no pregnancy has been reported across the romosozumab development program. Also, no studies have been conducted to determine whether romosozumab is present in breast milk or to assess the effects of romosozumab in breast-fed infants.

Reproductive and developmental effects of romosozumab were assessed in the rat in both a preliminary and definitive embryo-fetal development study, a combined fertility and embryo-development study, and a pre-and postnatal development study. At the highest dose level tested (300 mg/kg), skeletal abnormalities (fused and extra digits) were seen in 1/75 litters, but based on the weight of evidence (including single litter incidence, below group mean exposure to romosozumab, the presence of antiromosozumab antibodies in the dam, and

absence of skeletal malformations at substantially higher maternal and fetal exposures), these observations were concluded to be unrelated to romosozumab.

Across all embryo-fetal development studies, romosozumab-related effects were limited to a slight increase in the incidence of reduced ventral processes on the sixth cervical vertebrae at 300 mg/kg in rats. This single variation represented a slight delay in normal development of the rat skeleton, occurred in a skeletal process not found in humans, and was seen at maternal rat exposures at least 30 times higher than those observed in human subjects receiving romosozumab at 210 mg SC QM.

These data indicate that romosozumab presents a low risk to the developing human fetus.

No studies have been conducted on the potential for romosozumab to be transferred via semen or its effect on sperm. Based on studies conducted on other monoclonal antibodies, the likelihood of romosozumab being transferred via seminal fluid and its effect on sperm is expected to be low.

Reviewer Comments: ***The target patient population in this application is in post-menopausal women who are not of reproductive age. From preclinical studies, romosozumab appears to be low risk for fetal development. It is acceptable for the Sponsor not to conduct any clinical studies for romosozumab as that is not the targeted patient population.***

8.6.3. Pediatrics and Assessment of Effects on Growth

This drug is indicated for postmenopausal women and is not expected to be used for a pediatric indication. Full pediatric waiver obtained.

Reviewer Comments: ***Full pediatric waiver is appropriate for the targeted patient population of post-menopausal women with osteoporosis.***

8.6.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

Neither the effects of overdose of romosozumab nor an antidote to overdose are known. Data from completed phase 1 clinical studies demonstrate that romosozumab has an acceptable safety profile up to the highest dose tested (doses up to 10 mg/kg SC and 5 mg/kg IV).

Reviewer Comments: ***Romosozumab will be injected by clinical practitioners in office setting which will decrease risks for abuse. There is no clear benefit to patients to seek additional doses of romosozumab.***

Drug Abuse

There is no evidence that romosozumab is habit forming or could lead to dependence.

8.6.5. Withdrawal and Rebound

Retreatment efficacy results are discussed in section 7.1.5 Onset Duration and Durability of Efficacy Effects. This section discusses safety with withdrawal and rebound.

Off-treatment
Off-treatment is defined as a period when subjects transitioned off romosozumab to a period of no active study medication.

Study 20060326 was designed to study the persistence of romosozumab effects on BMD and bone turnover markers during off-treatment. In this study, subjects who had received either 24 months of romosozumab treatment or 12 months of alendronate followed by romosozumab were randomized to either 12 months of placebo or denosumab treatment (months 24-36). In addition, those groups that received active treatment for the first 48 months (romosozumab from months 0 to 24, denosumab for months 24 to 36 and romosozumab 210 mg QM from month 36 to 48) were assigned to the "no intervention" group from months 48 to 72. Subjects assigned to no intervention had no indication of rebound or withdrawal effects in clinical laboratory values. The summary of the significant finds are the following:

- median percent change in albumin-corrected calcium from month 48 to month 72 was 0.0%
- median iPTH level decreased through month 60, then returned to above month 48 level by month 72
- mean phosphorus level increased slightly at month 51, then returned to approximately the month 48 level by month 72
- mean GFR decreased through month 51, then increased to above month 48 levels by month 72.

Retreatment
Study 20060326 also studied retreatment after subjects had been off-treatment. In this study, the retreatment phase was from months 36 to 48, during which time all participating subjects received romosozumab 210 mg QM regardless of their initial treatment.

The safety of romosozumab in the retreatment phase (month 36 to 48) was generally consistent with results seen up to 24 months of romosozumab treatment and in line with expectations based on previous clinical study findings.

Reviewer Comments: ***As noted in section 7.1.5, although BMD gains and BTM levels demonstrate that retreatment with romosozumab achieve similar changes when compared to initial 12 months of romosozumab therapy, the small number of patients studied (i.e. for***

romo 210 mg: N=19 for placebo M24-36 group and N=16 for denosumab M24-36 group) limits extrapolation of results into a larger patient population. This study found no new safety concerns for patients off-study and with retreatment with romosozumab.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

No postmarketing data are available because romosozumab has not been marketed in any geographic region.

8.7.2. Expectations on Safety in the Postmarket Setting

There has been no postmarket experience with this drug as it is a new molecular entity.

The clinical studies used practitioners who injected romosozumab in the office setting and the post market setting will be expected to be the same. There is a safety concern that each dose requires two syringes injected and new practitioners and patients will need guidance and information to insure proper dosing. Such information should be included in the labeling and med guide.

There are no additional safety concerns for patients in subpopulations such as older patient populations, different weight status, and different race etc. from the results of the clinical data.

There are no concerns for abrupt stoppage or discontinuation for romosozumab. Romosozumab has not been studied in other clinical population so there is little information for off-label use.

There is an increased concern for hypocalcemia in patients with severe renal failure and these patients should be monitored for hypocalcemia during therapy.

For the targeted patient population from these clinical studies, the following are safety concerns for romosozumab in the post market setting:

- Increase risk for AFF, especially in early treatment with romosozumab
- Increase risk for ONJ
- Increased risk for hypocalcemia in patients with renal failure
- Risk of hypersensitivity reactions

8.8. Additional Safety Issues From Other Disciplines

Not Applicable

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8.9. Integrated Assessment of Safety

Review and analysis of the safety data support the following conclusions:

- The overall subject incidence of adverse events, serious adverse events, fatal adverse events, and adverse events leading to withdrawal of investigational product or study were similar between the romosozumab and placebo groups across the phase 2 and 3 studies. The subject incidence of adverse events was similar between treatment groups in the 12-month placebo-controlled population except for injection site reactions (5 % for romosozumab and 3 % for placebo) and serious adverse events of hypersensitivity.

- The subject incidences of adverse events and serious adverse events were generally balanced between the romosozumab and teriparatide groups in Study 20080289 that enrolled subjects previously treated with bisphosphonate. The types of events reported were those that would be expected in the population studied. Injection site reactions were observed more frequently with romosozumab compared with teriparatide. Most adverse events related to injection site reactions were reported as mild in severity and none was reported to be serious.

The safety data demonstrated the following key risks:

- **AFF**: Since romosozumab has antiresorptive activity, as demonstrated by BTM profiles and histomorphometry data from bone biopsies, AFF is an important potential risk for romosozumab. Atypical low-energy or low trauma fractures of the femoral shaft have been reported in patients receiving romosozumab See section 8.3.6 Significant Adverse Events. Labeling can manage this risk as the number of AFF cases observed to date is low and all cases had confounding factors.

- **ONJ**: Since romosozumab has antiresorptive activity, as demonstrated by BTM profiles and histomorphometry data from bone biopsies, ONJ is an important potential risk for romosozumab. Osteonecrosis of the jaw, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving romosozumab. See section 8.3.6 Significant Adverse Events. Labeling can manage this risk as the number of ONJ cases observed to date is low and all cases had confounding factors.

- **Hypersensitivity:** Like other monoclonal antibodies, romosozumab could be associated with hypersensitivity reactions. Based on medical review of the integrated safety data, hypersensitivity is considered an important identified risk with romosozumab. Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria, occurred in the romosozumab group. See sections 8.4.1 hypersensitivity.

Labeling can manage this risk.

- **Hypocalcemia:** Inhibition of sclerostin by romosozumab leads to rapid bone mass accrual at initiation of treatment and an increased demand for bone-building substrates such as calcium. Based on the clinical trial data, hypocalcemia is considered an important identified risk. Mild and transitory decreases in albumin- corrected calcium and a compensatory increase in iPTH were observed after initiation of romosozumab Based on the totality of data, the risk of hypocalcemia is manageable with appropriate monitoring recommended for patients with stage 5 CKD. See sections 8.3.8 Laboratory evaluations. Labeling can manage this risk.

- **Hyperostosis:** The intended pharmacologic effect of romosozumab is an increase in BMD and bone strength; however, hyperostosis (excessive bone growth) may be a potential risk with romosozumab administration. The current data, including the audiology substudy, do not support a safety risk of hyperostosis with romosozumab use; however, given the mechanism of action for romosozumab, it is considered a potential risk. See section 8.4.4 Hyperostosis. The data does not support a safety risk for hyperostosis with romosozumab.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held or is planned.

10 Labeling Recommendations

10.1. Prescribing Information

1 INDICATIONS AND USAGE
Sponsor Proposed Indication:
"EVENITY is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. (b) (4)

(b) (4)

Recommended Modifications: Delete (b) (4) from the indication.

(b) (4)

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(b) (4)

2 DOSAGE AND ADMINISTRATION

Sponsor Proposed:

(b) (4)

Recommended Modification:

- Two separate syringes (and injections) are needed to administer the total dose of 210 mg of EVENITY. Inject two 105 mg/1.17 mL prefilled syringes, one after the other.

- EVENITY should be administered by a healthcare provider.

Reviewer Comments: ***A single monthly dose consists of two full syringes; both injected one after the other. Each monthly dose will be injected by healthcare provider.***

4 CONTRAINDICATIONS

Reviewer Comments: ***Categories of hypocalcemia and hypersensitivity are acceptable.***

5 WARNINGS AND PRECAUTIONS

Reviewer Comments: ***Warning categories of hypocalcemia, hypersensitivity, osteonecrosis of the jaw and atypical femur fractures are acceptable. Recommend additional language to match other osteoporosis medications with similar warnings and precautions.***

6 ADVERSE REACTIONS

Sponsor Proposed:

– ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hypocalcemia *[see Contraindications (4) and Warnings and Precautions (5.1)]*
- Hypersensitivity *[see Contraindications (4) and Warnings and Precautions (5.2)]*

Recommended Modifications:
Include the following adverse reactions:

- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.3)]*
- Atypical Subtrochanteric and Diaphyseal Femoral Fractures *[see Warmings and Precautions (5.4)]*

Reviewer Comments: ***Recommend adding osteonecrosis of the jaw and atypical femur fracture to the adverse reactions as these were found in the pivotal study. See section 8.3.6 Significant Adverse Events.***

6.1 CLINICAL TRIAL EXPERIENCE
Sponsor Proposed:
Adverse Reactions in Pooled 12-Month Placebo-controlled Population
No information on ONJ or AFF

Proposed Modification: Add the following information:
Osteonecrosis of the Jaw
ONJ has been reported in the osteoporosis clinical trial program in patients treated with EVENITY [*see Warnings and Precautions (5.3)]*.

Atypical Subtrochanteric and Diaphyseal Fractures
In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with EVENITY. The duration of EVENITY exposure to time of atypical femoral fracture diagnosis was as early as 3.5 months *[see Warnings and Precautions (5.4)].*

Reviewer Comments: ***Both ONJ and AFF were found in the pivotal trial and should be noted in the section under adverse reactions. See section 8.3.6***

7 DRUG INTERACTIONS

Reviewer Comments: ***No drug interaction issues.***

8 USE IN SPECIFIC POPULATIONS

Reviewer Comments: ***No significant modification recommendations.***

12 CLINICAL PHARMACOLOGY

Reviewer Comments: ***Recommended modifications by Clin Pharm reviewer to add information on bone turnover markers and add detail to clinical study information. This reviewer agrees with Clin Pharm recommendations. See Clin Pharm review.***

Reference ID: 4093382

14 CLINICAL STUDIES

Sponsor Proposed:

(b) (4)

Sponsor Proposed:

(b) (4)



Modification Recommended: Delete section and add language to state that the incidences of nonvertebral fractures were NOT statistically significant at either 12 months or 24 months for romosozumab compared to placebo.

Reviewer Comments: ***This reviewer recommends that the sponsor clarify the language or delete the section. Both nonvertebral fracture endpoints, at 12 months and 24 months, were NOT statistically significant when adjusted for multiplicity. The sponsor did a post hoc analysis and determined that regional variations in South America (43% of study population) had lower than expected rates of nonvertebral fractures which affected these fracture endpoints. See section 6.1.2 Study 20070337 results.***

17 PATIENT COUNSELING INFORMATION

Modification Recommended: Add patient information on ONJ such as the following:

Osteonecrosis of Jaw

Advise patients to practice good mouth care during treatment with EVENITY and tell your dentist that you are receiving EVENITY before you have dental work.

Reviewer Comments: ***There is no current patient counseling information on ONJ. Recommend counseling information language to inform patients and health care providers.***

10.2. Patient Labeling

Medication guide will be incorporated into the labeling as this drug is intended for injection by healthcare providers only.

10.3. Nonprescription Labeling

Not Applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

Drug risks appear to be manageable with labeling and medication guidelines and will not need a

REMS in the post marketing setting.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

None Identified

11.2. Conditions of Use to Address Safety Issue(s)

Drug will be administered in the healthcare setting by healthcare providers. Labeling and medication guide can manage risks for this drug and there are no anticipated risks requiring REMS.

11.3. Recommendations on REMS

Recommendation: No REMS required as drug will be administered by healthcare provider.

12 Postmarketing Requirements and Commitments

Possible PMC pending, awaiting information request response. An update will be filed to this review if needed.

13 Appendices

13.1. References

Balasubramanian A, Tosi LL, Lane JM, et al. Declining rates of osteoporosis management following fragility fractures in the U.S., 2000 through 2009. J Bone Joint Surg Am. 2014; 96:e52.

Bonafede MM, Shi N, Bower AG, et al. Teriparatide treatment patterns in osteoporosis and subsequent fracture events: a US claims analysis.
Osteoporos Int. 2015; 26:1203-1212.

Burge R, Dawson-Hughes B, Solomon DH, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025.
J Bone Miner Res. 2007; 22:465-475.

Colón-Emeric C, Kuchibhatla M, Pieper C, et al. The contribution of hip fracture to risk of subsequent fractures: data from two longitudinal studies.
Osteoporos Int. 2003; 11:879-883.

Diez-Perez A, Hooven FH, Adachi JD, et al. Regional differences in treatment for osteoporosis. The Global Longitudinal Study of Osteoporosis in Women (GLOW). Bone. 2011; 49:493-498.

Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res. 2004; 19:745–751.

Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013; 8:136

Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001; 285(3):320-323.

Miller PD, Delmas PD, Lindsay R, et al. Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. J Clin Endocrinol Metab. 2008; 93(10):3785-3793.

National Osteoporosis Foundation (NOF) Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation. 2014.

Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res. 2008 Oct; 23(10):1591-1600.

Office of the Surgeon General. Bone Health and Osteoporosis: A Report of the Surgeon General. Public Health Service, U.S. Department of Health and Human Services, Washington, DC, 2004.

Sarpong EM. The impact of obesity on medication use and expenditures among nonelderly adults with asthma. J Health Care Poor Underserved. 2014; 25:1245-1261.

van Geel TA, van Helden S, Geusens PP, et al. Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis. 2009; 68:99-102.

van Helden S, Cals J, Kessels F, et al. Risk of new clinical fractures within 2 years following a fracture. Osteoporos Int 2006; 17:348–354.

Wade SW, Strader C, Fitzpatrick LA, et al. Estimating prevalence of osteoporosis: examples from industrialized countries. Arch Osteoporos. 2014; 9:182.

Wade SW, Strader C, Fitzpatrick LA, Anthony MS. Sex- and age-specific incidence of non-traumatic fractures in selected industrialized countries. Arch Osteoporos. 2012; 7:219-227.

World Health Organization. WHO Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level (Summary Meeting Report, Brussels, Belgium, 5-7 May 2004). Geneva, Switzerland: WHO Press; 2007.

Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res 2014; 29:2520-6.

13.2. Financial Disclosure

In compliance with 21 CFR Part 54, Amgen forwarded a Certification/ Disclosure Form to the clinical investigators and sub-investigators who participated in covered clinical studies for romosozumab. The investigators were requested to certify to the absence of certain financial interests or arrangements or to disclose, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(iv). Investigators were asked to provide this information for the period covering the dates of their participation in the clinical studies. In addition, investigators were requested to notify Amgen if there is any change to the information given for up to one year after the study ended. No clinical investigators and/or sub-investigators who participated in the studies listed are full or part-time employees of Amgen.
Amgen also certifies that it has not entered into any financial arrangements with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), and that these investigators were not the recipients of significant payments of other sorts as defined in 21 CFR 54.2(f).

Reasons for not providing information upon request by Amgen include the following:

- Investigator did not respond to at least two requests by the Sponsor to provide financial disclosure information
- Investigator was no longer affiliated with the clinical site and therefore did not complete/return a financial disclosure form
- Investigator was incorrectly listed on the Form 1572
- Investigator was new since the primary analysis
- Investigator never signed the disclosure or completed the disclosure incorrectly

Sponsor Efforts to Minimize Bias

In order to adequately protect against potential bias created by a disclosable financial interest and/or arrangements, Amgen employed the following steps to minimize bias of the clinical study results:

- Use of multiple clinical sites
- Clinical site monitoring
- Clinical site audits
- Independent and centralized assessment of efficacy response data

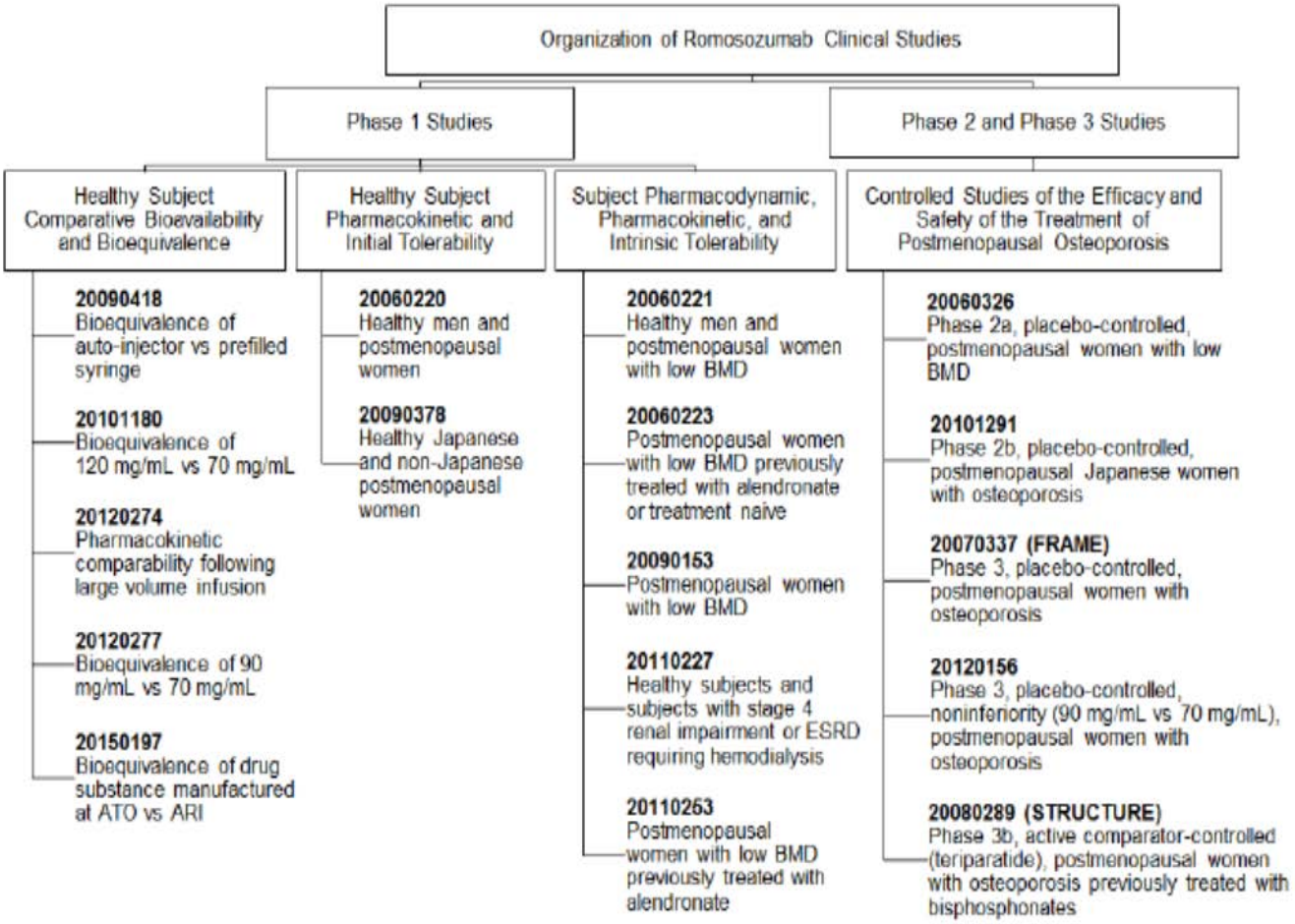
Covered Clinical Study (Name and/or Number): 20070337

Was a list of clinical investigators provided:	✓ Yes	No ☐ (Request list from Applicant)
Total number of investigators identified: 222 centers		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	✓ Yes	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	✓ Yes	No ☐ (Request information from Applicant)

Reference ID: 4093382

Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	✓ Yes	No ☐ (Request explanation from Applicant)

13.3. All Clinical Studies in Romosozumab Clinical Development



ARI = Amgen Rhode Island; ATO = Amgen Thousand Oaks; BMD = bone mineral density; ESRD = end-stage renal disease

13.4. Protocol Study Schedules

13.4.1. Study 20070337

Study 20070337 Study Schedule: Page 1

Procedure	SCR[1]	D 1 /Baseline	D 14[4,22]	M 1	M 2	M 3	M 3 + 14 days[5]	M 4	M 5	M 6	M 6 + 14 days[5]	M 7	M 8	M 9	M 10	M 11	M 11 + 14 days[12]	M 12/ET[16]	M12 + 10 days	M 13[4,5]	M 15	M 18	M 24/ET[16]	M 30[18]	M 36/EOS/ET[7, 16]
Informed Consent	X																								
Medical, Fracture and Medication History	X																								
Instructions for daily vitamin D and calcium supplementation	X																X								
Physical Exam	X																X					X		X
Vital Signs (blood pressure, temperature, pulse)	X			X						X							X				X	X	X	X
Height and Weight	X									X							X				X	X	X	X
Serum 25 (OH) Vitamin D	X																								
Serum protein electrophoresis to assess multiple myeloma or related lymphoproliferative disorder	X[21]																								
Serum Chemistry/Hematology	X	X		X		X				X				X				X				X	X	X	X
Serum Calcium																X	X		X						
Anti-romosozumab antibody		X		X		X				X								X[7]			X		X[7]		
Anti-denosumab antibody																		X[7]					X[7]		X
Self-Report Measures for Predicting Periodontitis		X																							
Lateral Spine x-rays (lumbar and thoracic)[9]	X									X								X[14]					X[14]		X[14]
Proximal Femur DXA	X																	X[14]					X[14]		X[14]
Lumbar Spine DXA[11]		X																X[14]					X[14]		X[14]
PROs/ClinRO (OPAQ, EQ-5D-5L, LAD, and BPI worst pain)[2]		X								X								X				X	X		
Reporting of nonvertebral fractures and suspected clinical vertebral fractures				X	X	X		X	X	X		X	X	X	X	X		X			X	X	X	X	X
Post-fracture PROs/ClinRO: OPAQ, EQ-5D-5L, LAD, and BPI worst pain[10]				X	X	X		X	X			X	X	X	X	X									
Tooth count		X																							
Assessment of tooth loss																		X					X		
Adverse Event/Concomitant Medication data collection	X[1]	X		X	X	X		X	X	X		X	X	X	X	X		X			X	X	X	X	X
If applicable: Vitamin D loading dose (at least 50,000 to 60,000 IU, preferably by the oral route)		X[6]																							
IP (romosozumab/placebo) injection[2]		X		X	X	X		X	X	X		X	X	X	X	X									
IP (denosumab) injection[2, 13]																		X				X	X[18]	X	

Source: CSR 20070337 with reviewer edits

Study 20070337 Study Schedule Page 2:

Procedure	SCR	D 1 /Baseline	D 14[3,4,5]	M 1	M 2	M 3	M 3 + 14 days[5]	M 4	M 5	M 6	M 6 + 14 days[5]	M 7	M 8	M 9	M 10	M 11	M 11 + 14 days[11]	M 12/ET 21	M12 + 10 days	M 13[4]	M 15	M 18	M 24/ET[22]	M 30	M 36/EOS/ET[23]
PK Sub-study (approximately 560 subjects)																									
Romosozumab levels[19]		X	X	X		X				X				X				X		X					
BTM and Biomarker Sub-study (subset of approximately 150 subjects participating in the PK-sub-study)																									
Romosozumab levels							X				X														
P1NP, sCTX, Sclerostin,iPTH[9]		X	X	X		X	X			X	X			X				X		X		X	X		X
Serum Calcium and Phosphate			X				X				X									X					
BSAP, OC, TRAP 5b		X	X	X		X	X			X	X			X											
Novel Biomarker Development (serum and plasma sample)		X	X	X		X	X			X	X			X				X		X		X	X		X
Timed Overnight Urine Sample		X								X								X							
Forearm and Total Body DXA and HR-pQCT Sub-study (Imaging Sub-study I, subset of approximately 200 subjects)																									
DXA (Forearm[16]/Total Body)		X[18]								X								X[14]				X	X[14]		
HR-pQCT /(Distal Radius/Distal Tibia)		X								X								X				X	X		
Lumbar Spine and Proximal Femur DXA Sub-study (Imaging Sub-study II, subset of approximately 120 subjects)																									
DXA (Lumbar Spine/Proximal Femur)										X												X			
Bone Biopsy Sub-study (subset of approximately 40 subjects for Month 2 biopsies, approximately 60 subjects for Month 12 biopsies, and approximately 40 subjects for Month 24 biopsies)																									
Romosozumab levels, P1NP, sCTX, Sclerostin, iPTH[19]		X	X																						
Iliac Crest Bone Biopsy - Month 2 cohort					X[18]																				
Iliac Crest Bone Biopsy - Month 12 cohort[17]																		X[18]							
Iliac Crest Bone Biopsy - Month 24 cohort[17]																							X[18]		
Calcium Sub-study (subset of approximately 920 subjects)																									
Serum Calcium			X																						
Audiology Sub-study (subset of approximately 400 subjects)																									
Medical history related to hearing disorders	X[20]																								
Otoscopic evaluation	X[20]																	X							
Audiogram	X[20]																	X							
Osteoarthritis Sub-study (subset of approximately 300 subjects)																									
Signal knee x-ray (anterior/posterior and lateral view)	X[20]																								
WOMAC		X[20]																X							
Pharmacogenetics Sub-study (subset: all subjects who sign separate Pharmacogenetics consent)																									
Blood draw for pharmacogenetics assessment		X																							
Serum iPTH and Urinary Calcium Sub-study (subset of approximately 450 subjects)																									
iPTH		X								X								X							
Timed Overnight Urine Sample		X								X								X							

Source: CSR 20070337 with reviewer edits

13.4.2. Supportive Study 20060326 Schedule Assessments

Schedule of Assessments (1/5): AMG 785 Treatment + Denosumab Extension Phase Screening to Month 36

Assessment	Screening	D1	D1 plus 1wk[2]	M 1[2]	M 2[2]	M 3	M 4[1]	M 5[1]	M 6	M 7[1]	M 8[1]	M 9	M 10[1]	M 11[1]	M 12/EOI/ET	M 12 plus 1wk	M 13	M 14	M 15	M 16[1]	M 17[1]	M 18	M 19[1]	M 20[1]	M 21	M 22[1]	M 23[1]	M 24	M 24 plus 10d [14]	M 27/ET	M 30 [14]	M 36/ET/EOS[14]
Informed Consent	X																											X				
Medical/Medication History	X																															
Physical Exam	X														X													X		X[13]		X
Vital Signs	X			X		X			X			X			X		X[9]		X			X			X			X		X	X	X
Height & Weight	X			X		X			X			X			X		X[9]		X			X			X			X		X[13]	X	X
ECG	X	X[11]		X		X						X			X		X[9]		X[9]						X[9]			X		X[13]		
24-hr Urine Collection[7]				X																												
Heme/Chem plus IPTH/vit D[10]	X	X		X		X			X			X			X		X[9]		X			X			X			X		X	X	X
Serum Calcium																													X			
AMG 785 levels		X[2]	X[2]	X[2]	X[2]				X[2]			X[2]			X[4]	X	X	X	X			X			X			X		X		
BTMs & Sclerostin[3]		X	X	X	X	X			X			X			X	X	X	X	X			X			X			X		X	X	X
Anti-AMG 785 antibody		X		X		X			X			X			X[4]		X[9]		X			X			X			X		X		
Anti-denosumab antibody																												X[14]				X
Biomarker Development		X													X													X		X[14]	X	X
DXA (Spine/Femur)[5]	X					X			X						X				X[9]			X						X		X[13]	X	X
DXA (Radius)		X													X													X				X
QCT (Femur and/or spine)[12]		X													X																	
Bone Biopsy Sub-study									X[6]						X[6]													X[9]				
AE/Con Med Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Injection[8]		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X[14]			X	
IP Dispensation(ALN/TPTD only)		X				X			X			X																				

1 - Subjects in the QM dose groups only
2 - Subjects in AMG 785/ placebo groups only
3 - BTMs at all visits: P1NP, CTX, OC, BSAP. Sclerostin only at Day 1
4 - At M12 PK & antibody to also be done in ALN group
5 - To be done in duplicate at Screening and M12
6 - Subset of approximately 25 subjects (AMG 785/ placebo)
7 - Subset of approximately 70 subjects (AMG 785/ placebo)
8 - When applicable, based on dose group - refer to specific schedules
9 - Subjects formerly on ALN only
10 - Vitamin D only at Screening
11 - At Day 1, ECGs to be done in triplicate
12 - Subset from AMG 785/ placebo & TPTD
13 - only for subjects not participating in the 12 month extension period (ET at M27)
14 - only for subjects participating in the 12 month extension phase (M24 to M36)

Schedule of Assessments (2/5): AMG 785/ Placebo Treatment (Groups A and B)

24-month AMG 785 treatment phase only, refer to overall schedule of assessment for 12-month denosumab extension phase

Assessment	SCR	Day 1	D1 plus 1wk	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12/ET	M 12 plus 1wk	M 13	M 14	M 15	M 16	M 17	M 18	M 19	M 20	M 21	M 22	M 23	M 24	M 27/ET
Groups Required	*All*	*All*	*All*	*All*	*All*	*All*	*A*	*A*	*All*	*A*	*A*	*All*	*A*	*A*	*All*	*All*	*All*	*All*	*All*	*A*	*A*	*All*	*A*	*A*	*All*	*A*	*A*	*All*	*All*
Informed Consent	X																											X	
Medical/Medication History	X																												
Physical Exam	X														X													X	X
Vital Signs, Height & Weight	X			X		X			X			X			X				X			X			X			X	X
ECG	X	X		X		X						X			X													X	X
24-hr Urine Collection (subset)				X																									
Heme/Chem plus IPTH	X	X		X		X			X			X			X				X			X			X			X	X
Serum Calcium																													
AMG 785 levels		X	X	X	X	X			X			X			X	X	X	X	X			X			X			X	X
BTM		X	X	X	X	X			X			X			X	X	X	X	X			X			X			X	X
Anti-AMG 785 antibody		X		X		X			X			X			X				X			X			X			X	X
Biomarker Development		X													X													X	
DXA (Spine/Femur)	X					X			X						X							X						X	X
DXA (Radius)		X													X													X	
QCT (Femur and/or spine) subset		X													X														
Bone Biopsy Sub-study									X						X													X	
AE/Con Med Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Injection		All		A	A	All	A	A	All	A	A	All	A	A	All		A	A	All	A	A	All	A	A	All	A	A		

Schedule of Assessments (3/5): ALN Treatment (Group D) and TPTD Treatment (Group E)

24-month AMG 785 treatment phase only, refer to overall schedule of assessment for 12-month denosumab extension phase

ALN

Assessment	SCR	D1	M 3	M 6	M 9	M 12/ET	M 12 plus 1wk	M 13	M 14	M 15	M 16	M 17	M 18	M 19	M 20	M 21	M 22	M 23	M 24	M 27/ET
Informed Consent	X																		X	
Medical/Medication History	X																			
Physical Exam	X					X													X	X
Vital Signs, Height & Weight	X		X	X	X			X		X			X			X			X	X
ECG	X	X	X		X	X		X		X						X			X	X
Heme/Chem plus IPTH	X	X	X	X	X	X		X		X			X			X			X	X
AMG 785 levels						X	X	X	X	X			X			X			X	X
BTM		X	X	X	X	X	X	X	X	X			X			X			X	X
Anti-AMG 785 antibody						X		X		X			X			X			X	X
Biomarker Development		X				X													X	
DXA (Spine/Femur)	X		X	X		X				X			X						X	X
DXA (Radius)		X				X													X	
AE/Con Med Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Injection						X		X	X	X	X	X	X	X	X	X	X	X		
IP Dispensation		X	X	X	X															

TPTD

Assessment	SCR	D1	M 3	M 6	M 9	M 12/EOS/ET
Informed Consent	X					
Medical/Medication History	X					
Physical Exam	X					X
Vital Signs, Height & Weight	X		X	X	X	X
ECG	X	X	X		X	X
Heme/Chem plus IPTH	X	X	X	X	X	X
BTM		X	X	X	X	X
Biomarker Development		X				X
DXA (Spine/Femur)	X		X	X		X
DXA (Radius)		X				X
QCT (Femur and/or Spine) subs	X					X
AE/Con Med Assessment		X	X	X	X	X
IP Injection		X				
IP Dispensation		X	X	X	X	

Schedule of Assessments (4/5): 12-Month AMG 785 Retreatment Phase (Group G)

Assessment	M36 [1]	M 37	M 38	M 39	M 40	M 41	M 42	M 43	M 44	M 45	M 46	M 47	M 48/ET	M 51/EOS
Informed Consent	X													
Medical/Medication History														
Physical Exam													X	
Vital Signs		X		X			X			X			X	
Height & Weight		X		X			X			X			X	
Heme/Chem plus IPTH		X		X			X			X			X	
AMG 785 levels	X	X	X				X			X			X	
BTMs [2]		X		X			X			X			X	
Anti-AMG 785 antibody	X	X		X			X			X			X	X
Biomarker Development		X	X										X	
DXA (Spine/Femur)				X			X						X	
DXA (Radius)													X	
Pharmacogenetics	X													
Vitamin D loading dose	X													
AE/Con Med Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X
IP Injection (AMG 785) [3]	X	X	X	X	X	X	X	X	X	X	X	X		

1 - All M36 procedures as part of the extension phase should also be completed
2 - BTMs at all visits: P1NP, CTX, OC, BSAP
3 - IP injection must be the last procedure at each applicable visit

Schedule of Assessments (5/5): 24-Month Follow-on Phase (Group H)

Assessment	M 48 [1]	M 48 plus 14 days	Phone call 12 days after ZOL infusion	M 51	M 54	M 60	M 66	M 72/EOS/ET
Visit windows	±7d	-7/+28d	±3d	±14d	±14d	±14d	±14d	-14/+7d
Subjects completing the visit	All	ZOL group only		All	All	All	All	All
Informed consent	X							
Evaluation of M48 lumbar spine and proximal femur DXA scan to determine eligibility	X							
Instructions for daily calcium and vitamin D supplementation	X							
Physical examination								X
Height & weight								X
Serum chemistry				X				X
Serum calcium						X		
IPTH				X		X		X
Anti-AMG 785 antibodies				X				
BTMs (CTX, P1NP, BSAP, OC)				X	X	X	X	X
DXA (lumbar spine/proximal femur)					X	X	X	X
Adverse Event / Concomitant medication assessment		X	X	X	X	X	X	X
IP Infusion		X						

1 - Listed are only procedures unique to the month 48 visit of the 24-month follow-on phase. All procedures defined for the month 48 visit of the 12-month AMG 785 re-treatment phase must also be completed.

13.4.3. Study 20101291 Schedule Assessments

Study Assessments: for Study 20101291

Procedure	SCR	D 1 /Baseline	D1 plus 1 wk	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12/ET	M 15/EOS
Informed Consent	X															
Medical, Fracture & Medication History	X															
Instructions for daily vitamin D and calcium supplementation	X															
Physical Examination	X														X	
Vital Signs (blood pressure, temperature, pulse)	X			X		X			X			X			X	
Height & Weight	X					X			X			X			X	
25 (OH) Vitamin D, FSH[1], Estradiol[1], TSH	X															
Serum Chemistry/Hematology	X	X	X	X		X			X			X			X	
Serum Calcium					X											
iPTH	X	X	X	X	X	X			X			X			X	
Romosozumab levels, P1NP, sCTX, BSAP, OC		X	X	X	X	X			X			X			X	
Anti-**romosozumab** antibody		X		X		X			X			X			X^2	X^2
DXA (spine/proximal femur)[5]	X								X						X	
Adverse Event/Concomitant Medication data collection	X^3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP (**romosozumab**/Placebo) Injection[4]		X		X	X	X	X	X	X	X	X	X	X	X		

Notes:

a) To maintain the blind of the study, the following on-study (after Day 1/baseline) data will not be reported to any study-related personnel: serum calcium, albumin-adjusted calcium, phosphorus, alkaline phosphatase, **romosozumab** levels, BTMs, iPTH, anti-**romosozumab** antibodies, and DXA results. However, in the case of a panic value for either serum calcium, albumin-adjusted calcium, phosphorus or alkaline phosphatase the central laboratory will notify the study site.

b) Visit windows are: +/- 7 days for QM visits up to M12, +/- 3 days for the D1 plus 1 week visit, and +/- 14 days for the M15 visit.

c) If a subject terminates early from the study between Day 1 and Month 12, the Month 12 procedures are to be completed at that time.

1 - FSH and Estradiol only if applicable (see section 4.1.1, for women age 55-59 if there is uncertainty regarding menopausal status)

2 - Blood draws will continue every three months for subjects testing positive for neutralizing antibodies, up to 12 months after last dose of IP

3 - During Screening, serious adverse event reporting only

4 - IP injection must be the last procedure at each applicable visit

5 - To be done in duplicate at Screening and M12

13.4.4. Study 20120156 Schedule Assessments

	Screening		Treatment							Follow-up
Visit	Screening	Rescreening	Study day 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6/Early termination	Month 9/ End of study
Window (days)	35	35	-[1]	±7	±7	±7	±7	±7	±7	±14
General & Safety Assessments										
Informed consent	X									
Demography (sex, date of birth, age, race, and ethnicity)	X									
Determination of hepatitis B and C status	X									
Medical history	X									
Instructions for daily calcium and vitamin D supplementation	X									
Physical examination (standard of care)	X								X	
Vital signs (blood pressure, heart rate, and temperature)	X								X	
Height and weight	X								X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments										
Serum chemistry	X		X	X		X			X	
Hematology	X		X	X		X			X	
If applicable: hepatitis B and hepatitis C laboratory testing	X									
Serum 25 (OH) vitamin D	X	X								
Romosozumab levels			X	X		X			X	
Anti-romosozumab antibody			X	X		X			X	X[2]
Bone turnover markers			X	X		X			X	
Imaging Assessments										
Dual-energy X-ray absorptiometry scan of the lumbar spine (in duplicate)	X								X	
Dual-energy X-ray absorptiometry scan of the proximal femur	X								X	
Dosing										
Romosozumab injection (must be the last procedure at each dosing visit)			X	X	X	X	X	X		
If applicable: vitamin D loading dose (50,000 to 60,000 IU, preferably oral route)			X[3]							

1 –The first dose of IP should preferably be given on the day of randomization. If not possible, the first dose of IP must be given within 72 hours of randomization.
2 – Blood draws will continue every 3 months for subjects testing positive for neutralizing antibodies at their ET or EOS study visit
3 – Is to be administered within 1 week of the day 1 visit. However, if the window is missed, the vitamin D loading dose should be given as soon as possible thereafter.

13.5. Key Regulatory FDA Interactions

Event and Date	Key Points of Guidance Provided
Interactions with US FDA	
EOP2, 19 August 2011 (14 September 2011, Reference ID: 3014899) and Advice, 07 October 2011 (Reference ID: 3026648)	FDA agreed the intended patient population, women between the ages of 60 and 90 with osteoporosis and a T-score ≤ -2.5 at the total hip or femoral neck, appeared to be an acceptable study population for Protocol 20070337. FDA agreed that 12 month duration of dosing with AMG 785 is acceptable, as long as a clear detailed definition of vertebral fracture with qualitative and quantitative criteria be provided. FDA requested, at minimum, 24 months of fracture efficacy data. FDA also stated 12 months of safety data is of concern, especially for assessment of bone quality. Amgen agreed to a 24 month phase 3, placebo-controlled study with co-primary endpoints at months 12 and 24. Successful outcome would require a positive outcome at both time points.
Final CAC Report to the Carcinogenicity SPA Request (rat), 13 October 2011 (Reference ID: 3028223)	Executive CAC recommendations and conclusions received, confirming acceptability of the proposed rat lifetime pharmacology study.
Type C Clinical Data Package Meeting, 10 November 2014 (Reference ID: 3656395)	FDA agreed that the proposed clinical data from the phase 3 study with a complete study report from Study 20070337 appeared adequate to support submission of an initial marketing application for romosozumab for osteoporosis in postmenopausal women , and noted that filing will be determined after submission of the application. FDA stated that for a single, multicenter, pivotal trial, the level of efficacy evidence must be more persuasive ($p < 0.01$) and supported by efficacy data from other non-pivotal studies
Type C Structure and Format Meeting, 28 July 2015 (19 August 2015, Reference ID: 3808438)	FDA agreed with Amgen's proposal not to include safety data from the ongoing studies 20110142, 20110174, or the extension phase of 20070337 (post-month 24). Additionally, the Agency indicated they would like to see the following for Study 20060326 (and possibly 20101291): 1. A comprehensive discussion of how Amgen reached the dose used in the phase 3 trial 2. What happens when treatment with romosozumab ends ("off treatment") 3. What happens with retreatment with romosozumab
Pre-BLA Meeting 18 May 2016	Study 20070337 can serve as a single pivotal trial to support BLA filing. The BLA should provide in-depth justification as to why the data from trial 20070337 are applicable to the intended U.S. population and U.S. medical practice.

Source: Clinical Overview Appendix 1 with reviewer edits.

Reference ID: 4093382

13.6. Study 20070337 Substudy Details

13.6.1. Bone Turnover Marker and Biomarker Sub-study

Central laboratories and vendors were used to analyze all screening and on-study samples for serum chemistry, hematology, biomarker and BTMs (P1NP, osteocalcin [OC], bone-specific alkaline phosphatase [BSAP], serum Type I collagen C-telopeptide [sCTX], tartrate-resistant acid phosphatase 5b [TRAP 5b]), 25 (OH) vitamin D, PK, and antiromosozumab antibodies, and antidenosumab antibodies for this study.

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period

- To assess the effect of romosozumab treatment for 12 months compared with placebo on percent changes in bone formation markers (P1NP, BSAP, and OC) and bone resorption markers (sCTX and TRAP 5b)
- To assess the effect of romosozumab treatment for 12 months compared with placebo on percent change in serum sclerostin level
- To enable exploratory assessments of novel biomarkers through prospective collection of blood samples

For the 24-month study period (12-month double-blind placebo-controlled study period followed by the 12-month open-label denosumab follow-up study period)

- To assess the effect of romosozumab treatment for 12 months followed by denosumab treatment for 12 months compared with placebo followed by denosumab treatment on percent changes in the bone formation marker P1NP and the bone resorption marker sCTX
- To assess the effect of romosozumab treatment for 12 months followed by denosumab treatment for 12 months compared with placebo followed by denosumab treatment on percent change in serum sclerostin level
- To enable exploratory assessments of novel biomarkers through prospective collection of blood samples

2. RATIONALE

Romosozumab neutralizes the bone formation inhibitor sclerostin and stimulates bone formation without stimulating bone resorption as demonstrated in preclinical and clinical studies (Padhi et al, 2011; Ominsky et al, 2010; Li et al, 2009). More specifically, romosozumab has been shown to increase markers of bone formation (P1NP, OC, and BSAP) and to decrease the bone resorption marker sCTX compared with placebo. Data from the phase 1 ascending multiple dose study indicated a peak in P1NP around day 15 to 22 with both 2 and 3 mg/kg doses of romosozumab. The phase 2 data confirmed that for all romosozumab doses tested, the bone formation markers increased from baseline at Week 1, achieved peak levels by Month 1 and returned to baseline between Month 2 and Month 9 for P1NP and OC, or by Month 12 for BSAP. For the 210-mg QM dosing regimen, P1NP levels returned to baseline around Month

6. From Month 6 to Month 12, levels of bone formation decreased below baseline indicating a decrease in bone remodeling. However, it is not known whether bone formation marker levels transiently increase after repeated dosing between Month 2 and Month 12 as P1NP, OC, and BSAP were measured at the end of the dosing interval (ie, before the next monthly injection) in the phase 2 dose-ranging study. From Week 1 to Month 12, sCTX decreased from baseline for all romosozumab doses tested in the phase 2 dose-ranging study, confirming the inhibition of bone resorption observed in the phase 1 studies. Still, the dynamic effects of romosozumab on bone formation and bone resorption are not fully understood. This sub-study will allow further characterization of the effect of romosozumab on bone formation and resorption over time, by assessing the following BTMs:

- P1NP - a marker of the conversion of procollagen to collagen
- BSAP - an indicator of osteoblast activity
- OC - an indicator of osteoblast activity
- SCTX - a marker of collagen breakdown
- TRAP 5b - an indicator of osteoclast numbers

Sclerostin levels and iPTH will be assessed as biomarkers to gain additional insights into the effect of romosozumab. Results of iPTH will be analyzed as part of the Serum iPTH and Urinary Calcium sub-study. In addition, blood samples will be collected to support the development of potential novel biomarkers of bone metabolism and PMO.

The effect of transitioning from romosozumab/placebo treatment to denosumab treatment will be studied by assessing BTMs and biomarkers during the 12-month open-label denosumab follow-up study period.

In combination with the PK sub-study, the PK/PD relationship will be studied in a broader population.
A timed urine collection will be performed in subjects participating in the BTM and biomarker sub-study. Results will be analyzed with the Serum iPTH and Urinary Calcium sub-study

3. SUB-STUDY DESIGN

Enrollment in the PK sub-study is a prerequisite for participation in the BTM and Biomarker sub-study. Eligible subjects at all centers may be enrolled into the BTM and Biomarker sub-study: up to approximately 150 subjects (approximately 75 per arm).

4. ENDPOINTS

During the 12-month double-blind placebo-controlled study period

- Percent change from baseline at Day 14, Month 1, Month 3, Month 3 plus 14 days, Month 6, Month 6 plus 14 days, Month 9, and Month 12 in P1NP, and sCTX
- Percent change from baseline at Day 14, Month 1, Month 3, Month 3 plus 14 days, Month 6, Month 6 plus 14 days, and Month 9 in BSAP, OC, and TRAP 5b

• Percent change from baseline at Day 14, Month 1, Month 3, Month 3 plus 14 days, Month 6, Month 6 plus 14 days, Month 9, and Month 12 in sclerostin

During the 24-month study period (12-month double-blind placebo-controlled study period followed by the 12-month open-label denosumab follow-up study period)
• Percent change from baseline at Month 13, Month 18, and Month 24 in P1NP, and sCTX
• Percent change from baseline at Month 13, Month 18, and Month 24 in sclerostin

5. ELIGIBILITY

Inclusion
• Subject has provided informed consent for participation in this sub-study
• Subject is enrolled in the PK sub-study

Exclusion
• Subject has experienced a nonvertebral fracture or clinical vertebral fracture within 6 months prior to enrollment
• Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge
• Subject participating in the Serum iPTH and Urinary Calcium sub-study

6. PROCEDURES

Study visits for the BTM and Biomarker sub-study are Day 1, Day 14, Month 1, Month 3, Month 3 plus 14 days, Month 6, Month 6 plus 14 days, Month 9, Month 12, Month 13, Month 18, and Month 24**.**

7. STATISTICAL CONSIDERATIONS

It is expected that 150 subjects (75 subjects per arm) will provide stable estimates for the BTMs. Considering 7.5% drop out during the 12-month double-blind placebo-controlled study period, 75 subjects per arm will provide an estimate for the percent change from baseline in P1NP with a 9.4% of the half-width of the 95% CI assuming a 40% standard deviation and an estimate for the percent change from baseline in sCTX with an 8.2% of the half-width of the 95% CI assuming a 35% standard deviation.

BTMs and biomarkers will be analyzed using non-parametric methodology since it is anticipated that the distribution of these parameters will deviate markedly from normality. Rank tests will be used to compare between treatment groups.

Reference ID: 4093382

13.6.2. Forearm and Total Body Dual-energy X-ray Absorptiometry and Hi Resolution Peripheral Quantitative Computed Tomography Sub-study (Imaging Sub-study I)

Lateral spine X-rays, DXA images, and HR-pQCT images were acquired according to specific instructions provided by the central imaging vendor who analyzed the radiographs per the central imaging charter.

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period
To assess the effect of romosozumab treatment for 12 months compared with placebo on:

- Percent changes in DXA BMD at the radius and total body
- Percent changes in failure load estimated by FEA at the distal radius and the distal tibia as evaluated by HR-pQCT (XtremeCT®)
- Percent changes in other HR-pQCT outcomes at the distal radius and the distal tibia

For the 24-month study period (12-month double-blind placebo-controlled study period followed by the 12-month open-label denosumab follow-up study period)

To assess the effect of romosozumab treatment for 12 months followed by denosumab treatment for 6 months and for 12 months compared with placebo followed by denosumab treatment on:

- Percent changes in DXA BMD at the radius and the total body
- Percent changes in failure load estimated by FEA at the distal radius and the distal tibia as evaluated by HR-pQCT (XtremeCT®)
- Percent changes in other HR-pQCT outcomes at the distal radius and the distal tibia

2. RATIONALE

Romosozumab stimulates bone formation and reduces bone resorption. This unique effect on bone turnover results in marked increase in BMD at the lumbar spine and hip as shown in phase 1 and 2 studies. Yet, the effects of romosozumab on more cortical sites like the radius are not fully elucidated. Preclinical studies with romosozumab at cortical sites in non-human primates showed an increase in periosteal and endosteal bone formation with no increase in cortical porosity (Ominsky et al, 2010). A phase 1b study using peripheral QCT indicated a trend to increase Polar Moment of Inertia (PMI), an estimate measure of strength, but did not show major changes in cortical bone area and cortical bone mineral content with 3 mg/kg of romosozumab every 4 weeks over 169 days. Phase 2 data indicated that compared with placebo, there was no statistically significant change in the distal 1/3 radius BMD at Month 12 in any of the romosozumab arms. At Month 12, the percent changes from baseline in distal 1/3

radius BMD in the control arms were -0.9% (placebo), -0.3% (alendronate) and -1.7% (teriparatide); the mean change 210 mg romosozumab QM was -1.2%. DXA BMD measures as well as bone strength are influenced by the bone size and the bone geometric distribution; and neither can be accurately assessed by DXA.

APPEARS THIS WAY ON ORIGINAL

The proposed DXA and HR-pQCT Imaging sub-study will enhance the understanding of the effects of romosozumab on cortical bone. In addition, the characterization of the effects of romosozumab on bone geometry variables and bone-micro-architecture available from this sub-study will further inform the potential impact of romosozumab on cortical bone strength. For this purpose, in addition to forearm DXA assessments, HR-pQCT (XtremeCT) scans with ar isotropic resolution of 82 allowing for longitudinal evaluations of bone structure and micro-architecture parameters (Genant et al, 2008). This sub-study will allow the evaluation of the bone density and structural changes in total, cortical and trabecular compartments and relate them to changes in strength estimated by FEA.

Additionally, to further evaluate the effect of romosozumab as compared with placebo on cortical bone, which comprises 80% of the skeleton, total body BMD with whole body DXA scanning will be assessed.

The effect of romosozumab treatment for 12 months, followed by denosumab treatment for 12 months will also be studied.

3. SUB-STUDY DESIGN

A subset of centers with access to XtremeCT® scanners will participate in the Imaging sub-study I. At those centers, all eligible subjects may be enrolled into the sub-study: up to approximately 200 subjects (approximately 100 per arm).
Forearm DXA scans, total body DXA scans, and HR-pQCT scans of the distal radius and the distal tibia will be performed at the Day 1, Month 6, Month 12, Month 18, and Month 24 study visits.

4. ENDPOINTS

During the 12-month double-blind placebo-controlled study period

- Percent change from baseline in radius (1/3, ultradistal and total) DXA BMD at Month 6 and Month 12
- Percent change from baseline in total body (without head) DXA BMD at Month 6 and Month 12
- Percent change from baseline in ultimate load at the distal radius and the distal tibia as measured by FEA from HR-pQCT scans at Month 6 and Month 12
- Percent change from baseline in HR-pQCT parameters (eg, bone volume/total volume, total volumetric BMD, cortical volumetric BMD, trabecular volumetric BMD, cortical thickness, trabecular thickness, and trabecular separation) at the distal radius and the distal tibia at Month 6 and Month 12

During the 24-month study period (12-month double-blind placebo-controlled study period followed by the 12-month open-label denosumab follow-up study period)

- Percent change from baseline in radius (1/3, ultradistal and total) DXA BMD at Month 18 and Month 24
- Percent change from baseline in total body (without head) DXA BMD at Month 18 and Month 24
- Percent change from baseline in ultimate load at the distal radius and the distal tibia as measured by FEA from HR-pQCT scans at Month 18 and Month 24
- Percent change from baseline in HR-pQCT parameters (eg, bone volume/total volume, total volumetric BMD, cortical volumetric BMD, trabecular volumetric BMD, cortical thickness, trabecular thickness, and trabecular separation) at the distal radius and the distal tibia at Month 18 and Month 24

5. ELIGIBILITY

Inclusion

- Subject is enrolled at a center participating in the Imaging sub-study I
- Subject has provided informed consent for participation in this sub-study

Exclusion

- Subjects with neither wrist evaluable by DXA (ie, bilateral wrist replacement/fractures)
- Subjects with metal prosthesis or significant artifacts affecting the total body DXA scan (eg, hip or knee replacement, pacemaker)
- Subject is enrolled in the Lumbar Spine and Proximal Femur DXA sub-study (Imaging sub-study II)
- Subject will not be available for protocol-required study visits or procedures, to the best of the subject's and investigator's knowledge.

6. PROCEDURES

Study visits for the Imaging sub-study I are on Day 1, Month 6, Month 12, Month 18, and Month 24.

7. STATISTICAL CONSIDERATIONS

It is expected that 200 subjects will provide stable estimates for the percent change in DXA BMD. Considering 7.5% dropout during the 12-month double-blind placebo-controlled study period, 100 subjects per arm will provide an estimate for the percent change from baseline in total body BMD without head with a 0.49% of the half-width of the 95% CI assuming a 2.4% standard deviation and an estimate for the percent change from baseline in distal 1/3 radius BMD with an 0.69% of the half-width of the 95% CI assuming a 3.4% standard deviation.

Percent change from baseline at Month 12 in the failure load at the distal radius was observed in a denosumab study (4.6% mean increase with a 5.3% standard deviation in the denosumab

Reference ID: 4093382

group and 0.94% mean increase with a 7.8% standard deviation in the placebo group; Amgen data on file). If the same increase is assumed in the Imaging sub-study II, 200 subjects (100 subjects per arm) will provide a 95% power to detect a significant difference between the treatment groups, considering a 7.5% dropout during the 12-month double-blind placebo-controlled study period. If a 4.0% increase is assumed in the romosozumab group, 200 subjects will provide an 87% power to detect a significant difference between the treatment groups at Month 12.

Percent changes from baseline at Month 12 in DXA BMD will be compared between treatment groups using an ANCOVA model with treatment group, baseline BMD, machine type and interaction of baseline BMD and machine type as independent variables. Any missing value during the 12-month double-blind placebo-controlled study period will be imputed by carrying forward the last non-missing post baseline value prior to the missing value.

Percent change from baseline at Month 12 in the failure load will be compared between treatment groups using an ANCOVA model with treatment group and baseline value of ultimate load as independent variables. Percent change from baseline at Month 6 in the failure load will be analyzed using same approach.

Percent change from baseline at Month 24 in the failure load and the other HR-pQCT parameters at Month 24 will be analyzed using the same ANCOVA approach as for the failure load at Month 12. Any missing value during the 12-month open-label denosumab follow-up study period will be imputed by carrying forward the last non-missing post-Month 12 value prior to the missing value.

13.6.3. Lumbar Spine and Proximal Femur Dual energy X-ray Absorptiometry Sub-study (Imaging Sub-study II)

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period

- To assess the effect of romosozumab treatment for 6 months compared with placebo on percent changes in BMD at the lumbar spine, total hip and femoral neck

For the 24-month study period (12-month double-blind placebo-controlled study period followed by the 12-month open-label denosumab follow-up study period)

- To assess the effect of romosozumab treatment for 12 months followed by denosumab treatment for 6 months compared with placebo followed by denosumab treatment on percent changes in BMD at the lumbar spine, total hip and femoral neck
neck

2. RATIONALE

This sub-study will allow evaluation of the time course of the effect of romosozumab treatment for 12 months and of romosozumab treatment for 12 months followed by denosumab treatment for 12 months on BMD at the spine and proximal femur.

3. SUB-STUDY DESIGN

Eligible subjects at all centers may be enrolled into the Imaging sub-study II: up to approximately 120 subjects (approximately 60 per arm). Subjects have to provide sub-study specific informed consent to participate. Lumbar spine and proximal femur DXA scans will be performed at the Month 6 and Month 18 study visits.

4. ENDPOINTS

During the 12-month double-blind placebo-controlled study period

- Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Month 6

During the 24-month study period (12-month double-blind placebo-controlled study period followed by the 12-month open-label denosumab follow-up study period)

- Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck at Month 18

5. ELIGIBILITY

Inclusion

- Subject has provided informed consent for participation in this sub-study

Exclusion

- Subject is enrolled in the Forearm and Total Body DXA and HR-pQCT sub-study (Imaging sub-study I)
- Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge

6. PROCEDURES

Study visits for the Imaging sub-study II are on Month 6, and Month 18.

7. STATISTICAL CONSIDERATIONS

Percent change from baseline at Month 6 in the DXA BMD endpoints will be compared between treatment groups using an ANCOVA model with treatment group, baseline value of BMD, machine type and interaction of baseline BMD value and machine type as independent variables. Percent change from baseline at Month 18 in the DXA BMD endpoints will be analyzed using same approach.

13.6.4. Bone Biopsy Sub-study

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period
- To assess the effect of romosozumab treatment for 2 months compared with placebo on parameters of bone histology, and bone histomorphometry
- To assess the effect of romosozumab treatment for 12 months compared with placebo on parameters of bone histology, histomorphometry, and micro-CT

For the 24-month study period (12-month double-blind placebo-controlled study period followed by the 12-month open-label denosumab follow-up study period)
- To assess the effect of romosozumab treatment for 12 months followed by denosumab treatment for 12 months compared with placebo followed by denosumab treatment on parameters of bone histology, histomorphometry, and micro-CT treatment on parameters of bone histology, histomorphometry, and micro-CT.

2. RATIONALE

Romosozumab is a bone forming agent that is currently being studied as an investigational therapy for postmenopausal women with osteoporosis at increased risk for fracture. Bone forming agents can promote larger improvements in bone mass and bone strength compared with antiresorptives and in addition can restore bone architecture. Analogs of parathyroid hormone (PTH 1-34 [teriparatide] and PTH 1-84) increase bone remodeling with greater osteoblast than osteoclast activity, resulting in marked improvement in BMD, as well as indices of bone microstructure that are associated with improved mechanical strength (Lindsay et al, 2006; Lindsay et al, 2003; Jiang et al, 2003). Romosozumab is a humanized monoclonal antibody that binds and inhibits sclerostin, thereby promoting osteoblast differentiation/activity, leading to an increase in bone formation, BMD, and bone strength (Ominsky et al, 2010).This bone biopsy sub-study is designed to evaluate the effect of romosozumab treatment on bone histomorphometry in the first two months after initiation of treatment when biochemical markers of bone formation are at their peak. In the phase 2 dose-ranging study (Study 20060326), markers of bone formation showed increases from baseline at Week 1 and achieved peak levels by Month 1. After the first month, markers of bone formation decreased from their peak, gradually approaching baseline levels. For the romosozumab 210-mg SC QM dosing regimen, median P1NP and OC levels remained above baseline through months 6 and 9, respectively, and median BSAP levels remained above baseline through month 12.

Biopsies at approximately the Month 2 study visit will be used to evaluate the effect of romosozumab treatment as early as 4 to 6 weeks after initiation of treatment, ie, during a period of robust bone formation, and will be used to explore the modeling and remodeling mechanism of bone formation. The use of a quadruple label procedure permits a comparison of

dynamic bone formation indices at baseline and after administration of romosozumab by measuring characteristics of each set of double labels separately and comparing them to each other in a single biopsy specimen.

In addition, this bone biopsy sub-study will assess bone microarchitecture and geometry after romosozumab treatment for 12 months and will evaluate if the newly formed bone has normal structure, normal mineralization characteristics and normal marrow. Similarly, long term bone safety will be assessed after romosozumab treatment for 12 months followed by denosumab treatment for 12 months.

3. SUB-STUDY DESIGN

Biopsy procedures using tetracycline quadruple-labeled is discussed in section 6.1.2 under study 20070337 study results. Biopsies will be performed at 3 different time points in the study. Early biopsies to assess short-term changes will be performed after up to 2 months of treatment with romosozumab/placebo. Late biopsies will be performed at the end of the 12-month double-blind placebo-controlled study period and at the end of the 12-month open-label denosumab follow-up study period.
A subset of centers will participate in the bone biopsy sub-study. At those centers, all eligible subjects may be enrolled into the sub-study: up to approximately 40 subjects into the early biopsy (Month 2) cohort, up to approximately 60 subjects into the late biopsy Month 12 cohort, and up to approximately 40 subjects into the late biopsy Month 24 cohort. Subjects have to provide sub-study specific informed consent to participate. Subjects providing consent for and undergoing a Month 2 biopsy will not be permitted to enroll in the Month 12 biopsy cohort or the Month 24 biopsy cohort. Subjects providing consent for and undergoing a Month 12 biopsy may also enroll in the Month 24 biopsy cohort.

To participate in the Month 2 early biopsy cohort, subjects must be enrolled into the sub-study and start the first cycle of labeling during the screening period for the main study. Subjects may be enrolled into the Month 12 biopsy cohort at any time during the study up to the Month 11 visit. Subjects may be enrolled into the Month 24 biopsy cohort at any time during the study up to the Month 23 visit.

4. ENDPOINTS

During the 12-month double-blind placebo-controlled study period

- Modeling and remodeling parameters, bone histology, and bone histomorphometry parameters at Month 2
- Bone histology and histomorphometry parameters and micro-computer tomography parameters at Month 12

During the 24-month study period (12-month double-blind placebo-controlled study period followed by the 12-month open-label denosumab follow-up study period)

- Bone histology and histomorphometry parameters and micro-computer tomography parameters at Month 24

5. ELIGIBILITY

Inclusion

- Subject has provided informed consent for participation in this sub-study

Exclusion

- Contraindicated or intolerant to doxycycline or tetracycline or its derivatives
- Contraindicated to an iliac crest bone biopsy
- Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge.

6. PROCEDURES

The Month 2 quadruple labeling procedure, tetracycline double-labeling procedure, and bone biopsy is described in the bone biopsy manual excerpted as follows:

LABELLING PROCEDURES

To participate in the Month 2 early biopsy cohort, subjects must be enrolled into the bone biopsy sub-study and start the first cycle of labelling during the screening period for the main study. Subjects may be enrolled into the Month 12 biopsy cohort at any time during the study up to the Month 11 visit. Subjects may be enrolled into the Month 24 biopsy cohort at any time during the study up to the Month 23 visit.

Subjects will follow a quadruple (Month 2) or double (Month 12 and 24) labelling procedure prior to undergoing the biopsy.

LABELLING COMPOUNDS

For determination of the level of bone turnover, bone formation rates, and mineralization defects, labelling of the bone with tetracycline compounds is required before proceeding with the bone biopsy. Tetracycline compounds chelate calcium on bone surfaces and are deposited within the bone at sites of active mineralization. The "labels" can then be visualized in fluorescent light during histomorphometric evaluation.

Tetracycline, demeclocycline and doxycycline are the most commonly used compounds; tetracycline hydrochloride and demeclocycline are the preferred labelling compounds for this sub-study. In regions where neither tetracycline hydrochloride nor demeclocycline is available, the use of doxycycline is acceptable. In such instances, **the investigator must seek Amgen approval of doxycycline confirm the recommended dose and schedule prior to initiating the labelling procedure**.

The following tetracycline derivatives are recommended for the purposes of this study:

Oral Demeclocycline

Oral demeclocycline should be used for the first administration cycle for those subjects enrolled into the Month 2 bone biopsy cohort. Oral demeclocycline may also be used as a labelling compound for those subjects enrolled in the Month 12 or Month 24 bone biopsy cohort. If subjects have consented to both Month 12 and Month 24 biopsies, tetracycline should be utilized for Month 12 procedures, and demeclocycline used for Month 24. This is to facilitate distinguishing the labels during analysis.

The dosage of demeclocycline is 600 mg daily given orally either as 300 mg twice daily regimen or 150 mg four times daily dosing. Each labelling 'cycle' consists of **3** days of demeclocycline 600 mg given daily followed by a 10 day break, then a further 3 days of treatment. Either the 150 mg or 300 mg preparation may be used.

Oral tetracycline

Oral tetracycline should be used for the second labelling cycle for those subjects enrolled into the Month 2 bone biopsy cohort. Oral tetracycline should also be used as the labelling compound for those subjects enrolled in the Month 12 or Month 24 bone biopsy cohort. If a subject has consented to both Month 12 and Month 24 biopsies, tetracycline should be used for Month 12 labelling procedures. To facilitate distinction of labels during analysis, in those subjects that have consented to both the 12 and 24 month biopsies, demeclocycline is the preferred labelling compound for month 24.

For Month 2

Oral tetracycline should be used for the second labelling cycle for those subjects enrolled into the Month 2 bone biopsy cohort. Each 'cycle' consists of an oral dose of 1000 mg daily given for **2** days followed by a 10 day break, then a further **2** days of treatment.

For Month 12 or Month 24

Each 'cycle' of treatment consists of an oral dose of 1000 mg daily given for **3** days followed by a 10 day break, then a further **3** days of treatment. Either the 250 mg or the 500 mg preparation may be used.

Oral Doxycycline

For Month 2

When demeclocycline is not available, oral doxycycline may be used for the first labelling cycle for those subjects enrolled into the Month 2 bone biopsy cohort.

For Month 12 or Month 24

For 12 and 24 month biopsies in regions where neither tetracycline nor demeclocycline is available, ***the investigator must seek Amgen approval for the usage of doxycycline prior to initiating the labelling procedure***.

Each 'cycle' of treatment consists of an oral dose of doxycycline 300 mg daily given for **4** days followed by a 10 day break, then a further **4** days of administration.

Concomitant Therapy
Absorption of tetracycline derivatives is impaired by antacids containing aluminum, calcium, or magnesium, and by iron- containing preparations. Foods and some dairy products also interfere with absorption. As described above, oral forms of tetracycline should be given at least 1 hour before or 2 hours after meals.

All subjects are required to take calcium and vitamin D supplementation daily during the study. However, subjects enrolled in the bone biopsy sub-study should be instructed not to take their daily calcium supplement on days they are taking oral tetracycline, demeclocycline or doxycycline. Subjects should not take any other tetracycline derivatives prior to the bone biopsy being performed.

Unused samples from bone biopsy specimens may be utilized to support the development of potential novel biomarkers of bone metabolism and PMO.

For subjects in the Month 2 early biopsy cohort, romosozumab levels, BTMs (P1NP, sCTX), sclerostin and iPTH will be assessed at the Day 1 and at the Day 14 visits.

7. STATISTICAL CONSIDERATIONS
This sub-study study is not powered for any specific measured parameter. Sample size has been estimated based on previous bone biopsy studies with teriparatide, the only currently approved bone forming agent, as well as regulatory considerations. Subjects in the placebo group will serve as the control group.

Bone histomorphometric parameters and parameters derived from micro-computer tomography of the transiliac biopsies will be summarized descriptively by actual treatment received. Bone histologic findings by actual treatment group will also be summarized.

13.6.5. Calcium Sub-study

1. OBJECTIVES
For the 12-month double-blind placebo-controlled study period
- To characterize the subject incidence of hypocalcemia (albumin-corrected serum calcium level < 7.5 mg/dL) associated with the first romosozumab 210-mg dose along with daily calcium and vitamin D supplementation for treatment of PMO

2. RATIONALE

Reference ID: 4093382

Based on the well-known importance of calcium in mineralizing newly formed bone and the unique mechanism of action of romosozumab to increase bone formation, decreases in serum calcium may be seen in subjects treated with romosozumab.

Phase 1 data indicates that the nadir in serum calcium is expected around Day 14 after the first dose of romosozumab on Day 1. Decreases in serum calcium were less pronounced following subsequent dosing visits. Therefore, in this sub-study, the risk of hypocalcemia will be assessed following the first dose of 210 mg romosozumab while subjects are receiving daily calcium and vitamin D supplementation.

3. SUB-STUDY DESIGN

Eligible subjects at all centers may be enrolled into the Calcium sub-study: up to approximately 920 subjects (approximately 460 per arm). Subjects have to provide sub-study specific informed consent to participate. A balanced regional and racial distribution is targeted for enrollment. As mandated by the main study, all subjects will receive daily calcium and vitamin D supplementation that at a minimum is in a range of 500 to 1,000 mg of elemental calcium and 600 to 800 IU of vitamin D from screening to end of study. In addition, subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening will receive an initial loading dose of 50,000 to 60,000 IU of vitamin D, preferably by the oral route. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may also receive the vitamin D loading dose at the principal investigator's discretion.

4. ENDPOINTS

During the 12-month double-blind placebo-controlled study period

- Subject incidence of hypocalcemia at Day 14, defined as albumin-corrected serum calcium level < 7.5 mg/dL

5. ELIGIBILITY

Inclusion Criteria

- Subject has provided informed consent for participation in this sub-study

Exclusion Criteria

- Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge

6. PROCEDURES

This sub-study requires one additional study visit at Day 14 (± 3 days).

7. STATISTICAL CONSIDERATIONS

It is expected that a sample size of 920 subjects will provide stable estimates of the absolute incidence of hypocalcemia. The absolute incidence of hypocalcemia will be considered low (<

Reference ID: 4093382

2%), provided that the upper limit of the 95% 1-sided CI for event rate is < 2%. Assuming that the rate of hypocalcemia is 0.5% in the romosozumab arm, 460 subjects randomized to the romosozumab group will provide 90% power for demonstrating that the absolute incidence of hypocalcemia is < 2%.

Subject incidence of hypocalcemia at Day 14 will be calculated and the associated upper limit of 95% 1-sided CI will be estimated based on a binomial distribution.

13.6.6. Audiology Sub-study

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period
To assess the effect of romosozumab treatment for 12 months compared with placebo on:

- Subject incidence of hearing loss
- Change in hearing threshold

2. RATIONALE

Romosozumab is a humanized monoclonal antibody against sclerostin which is being evaluated as a bone forming agent for the treatment of postmenopausal osteoporosis. Sclerosteosis is an autosomal-recessive disorder caused by absence of the *SOST* gene which encodes sclerostin (Brunkow et al, 2001). Patients with sclerosteosis develop deafness in early childhood in part due to impingement of the vestibulocochlear nerve (cranial nerve VIII) caused by hyperostosis (Hamersma et al, 2003). Because romosozumab is a bone forming agent, it may theoretically cause clinical hyperostosis in the vestibulocochlear nerve foramina which could affect the nerve and cause changes in audiometry parameters. In preclinical studies with romosozumab, rats and cynomolgus monkeys treated with supratherapeutic doses developed histologically detectable hyperostosis (Amgen, data on file). To date, clinical studies of romosozumab have not detected an imbalance in incidence of hearing adverse events. The primary purpose of this sub-study is to measure potential changes in hearing during the 12-month double-blind placebo-controlled study period. Approximately 20% of the postmenopausal osteoporosis study population is expected to have baseline incidence of hearing deficit (Cruickshanks et al, 2010).

Pure-tone average (PTA) is the average of hearing sensitivity at 500, 1,000, and 2,000 Hz. This average should approximate the speech reception threshold, within 5 dB, and the speech detection threshold, within 6 to 8 dB. The speech reception threshold is the softest intensity spondee words that an individual can repeat at least 50% of the time. Spondees are bisyllabic words equally emphasizing both syllables. In some cases (eg, for patients with poor word recognition) a limited set of words may be used. The speech detection threshold, also termed the speech awareness threshold, is the lowest intensity speech stimulus that an individual can detect at least 50% of the time.

Reference ID: 4093382

3. SUB-STUDY DESIGN

A subset of centers with access to specialized audiology labs meeting the standards defined in the audiology manual will participate in the Audiology sub-study. At those centers, all eligible subjects may be enrolled into the Audiology sub-study; up to approximately 400 subjects (approximately 200 per arm). Subjects have to provide sub-study specific informed consent to participate. Assessments for the Audiology sub-study will be performed at the Screening and Month 12 study visits.

4. ENDPOINTS

During the 12-month double-blind placebo-controlled study period

- Subject incidence of hearing loss in either ear through Month 12
- Change from baseline in hearing threshold at Month 12

5. ELIGIBILITY

Inclusion Criteria

- Subject has provided informed consent for participation in this sub-study
- Symmetric hearing with air-conduction thresholds no worse than 55 dB hearing level for the test frequencies of 250 Hz through 4,000 Hz
- Symmetric hearing with air-conduction thresholds no worse than 65 dB hearing level for the test frequencies of 6,000 through 8,000 Hz
- Pure tone air conduction thresholds must replicate within 5 dB for 1,000 and 2,000 Hz

Exclusion Criteria

- Threshold asymmetry ≥ 20 dB at any test frequency, including all test frequencies from 250 Hz through 8000 Hz
- Significant air-bone gaps, defined as exceeding 15 dB at ≥ 2 bone conduction test frequencies
- Abnormal otoscopic findings
- History of fluctuant hearing
- History of otologic surgery
- Tumor of the head, neck, or auditory system that, in the opinion of the investigator, may affect the ability to perform assessments required by the sub-study protocol or that may interfere with the interpretation of the results
- Head injury that, in the opinion of the investigator, may affect the ability to perform assessments required by the sub-study protocol or that may interfere with the interpretation of the results
- Meniere's disease
- Autoimmune inner ear disease
- Perilymphatic fistula

- Exposure to IV antibiotics such as aminoglycosides or macrolides within 6 months prior to randomization
- Unwilling or unable to avoid excessive noise exposure during the 24 hours prior to protocol-mandated audiology assessments at baseline and Month 12 (eg, musical concerts, the use of personal stereos with earphones)
- Subject will not be available for protocol-required study visits or procedures, to the best of the subject's and investigator's knowledge

6. PROSCRIBED THERAPIES

- Aminoglycoside or macrolide antibiotics
- Chemotherapy with carboplatin, cisplatin, vincristine, or vinblastine

7. PROCEDURES

Assessments for the Audiology sub-study are performed at Screening and at the Month 12 study visit. Screening assessments are to be performed after eligibility for the main study has been confirmed and may be completed up to 14 days after the first dose of IP has been received.

8. STATISTICAL CONSIDERATIONS

Sample Size

The sample size of 400 provides at least 90% power for testing non-inferiority of romosozumab and placebo on the endpoint of change from baseline in PTA at Month 12. The power is under the assumptions of 7.5% drop-out over the 12-month double-blind placebo-controlled study period and a standard deviation of PTA change from baseline ≤ 26 dB. The non-inferiority testing is based on a 2-sided 95% CI for the treatment difference in mean PTA change from baseline and a 10 dB margin.

Statistical Methods (Rauch et al, 2011)

Subject incidence of hearing loss in either ear through Month 12 will be compared between treatment groups using logistic regression model with treatment group indicator, baseline average hearing threshold for the subject and age as independent variables. The hearing loss is defined as 1) loss of ≥ 20 dB at any single frequency or 2) loss of ≥ 10 dB at any 2 adjacent frequencies or 3) loss of response at 3 consecutive frequencies where responses were previously obtained.

The change from baseline in hearing threshold at Month 12 will be compared between treatment groups using a mixed effect model with treatment, test frequency, interaction between treatment and test frequency, baseline hearing threshold, and age as fixed effects and ear as random effect. The treatment effect on hearing threshold for each test frequency will be estimated, and the Tukey's procedure will be used to adjust for multiple comparisons.

13.6.7. Osteoarthritis Sub-study

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period

- To assess the effect of romosozumab treatment for 12 months compared with placebo on the progression of osteoarthritis of the knee

2. RATIONALE

Romosozumab is a humanized monoclonal antibody against sclerostin, which is being evaluated as a bone forming agent for treatment of postmenopausal osteoporosis. Sclerosteosis is an autosomal-recessive disorder caused by an absence or deficiency of the *SOST* gene which encodes sclerostin (Brunkow et al, 2001). *SOST* is expressed in articular chondrocytes and may be focally increased in cartilage of patients with osteoarthritis (Chan et al, 2011). To date, clinical studies of romosozumab have not detected an imbalance in the incidence or progression of osteoarthritis.

The purpose of this sub-study is to evaluate the clinical effect of romosozumab on knee osteoarthritis in patients with clinical history of osteoarthritis. The knee has been selected for evaluation as it represents an anatomic location where osteoarthritis results in significant morbidity, and because the WOMAC PRO instrument has been well-validated to assess clinical progression of the disease (Tubach et al, 2005).

3. SUB-STUDY DESIGN

Eligible subjects (ie, history of osteoarthritis at the knee) at all centers may be enrolled into the Osteoarthritis sub-study: up to approximately 300 subjects (approximately 150 per arm). Subjects have to provide sub-study specific informed consent to participate. Assessments for the Osteoarthritis sub-study will be performed at the Screening, the Day 1 and the Month 12 study visits.

4. ENDPOINTS

During the 12-month double-blind placebo-controlled study period

- Change from baseline in WOMAC total score at Month 12
- Subject incidence of worsening osteoarthritis of the knee, as measured by the WOMAC, through Month 12

5. ELIGIBILITY

Inclusion Criteria

- Subject has provided informed consent for participation in this sub-study
- Signal knee pain due to osteoarthritis on most days for at least 1 month within 3 months prior to randomization
- Morning stiffness lasting < 30 minutes

- Presence of knee crepitus
- Signal knee osteoarthritis confirmed by knee x-ray within the past 12 months, to be read and interpreted by principal investigator or qualified delegate

Exclusion Criteria

- History of knee arthroplasty (either knee) or expected to require knee arthroplasty due to symptoms of osteoarthritis within 12 months of randomization
- History of inflammatory arthritis including rheumatoid arthritis or psoriatic arthritis
- History of pseudogout or gouty arthropathy
- History of meniscal or gouty arthropathy within 12 months prior to randomization
- History of knee fracture or other clinically significant trauma or knee surgery to the index knee
- Body mass index of > 40 kg/m2
- Intraarticular knee injection of corticosteroids or hyaluronan preparations within 3 months prior to randomization
- Any other medical condition which in the opinion of the investigator could confound evaluation of the index knee
- Subject is unable to complete the WOMAC
- Subject will not be available for protocol-required study visits or procedures, to the best of the subject's and investigator's knowledge

6. PROCEDURES

Assessments for the Osteoarthritis sub-study are performed at Screening, at the Day 1 study visit and the Month 12 study visit. Screening assessments are to be performed after eligibility for the main study has been confirmed, and Screening and Day 1 assessments may be completed up to 14 days after the first dose of IP has been received.

7. PROSCRIBED THERAPIES

- Intraarticular knee injection of corticosteroids or hyaluronan preparations

8. STATISTICAL CONSIDERATIONS

Sample Size

The sample size of 300 subjects provides at least 90% power for testing non-inferiority of romosozumab and placebo on the WOMAC total score change from baseline at month 12. The power is under the assumptions of 7.5% drop-out over the 12-month double-blind placebo-controlled study period and a 23 point standard deviation of WOMAC total score change from baseline. The non-inferiority testing is based on a 2-sided 95% CI for the treatment difference in the mean WOMAC total score change from baseline and a 10 point margin.

Statistical Methods

Change from baseline in WOMAC total score at month 12 will be compared between treatment groups using analysis of covariance (ANCOVA) with treatment group indicator, baseline WOMAC total score and age as independent variables. The 95% CI for treatment effect on WOMAC total score change will be presented and compared with the value of 10 point.

Subject incidence of worsening osteoarthritis of the knee will be compared between treatment groups using logistic regression with baseline WOMAC total score and age as independent variables.

13.6.8. Serum Intact Parathyroid Hormone and Urinary Calcium Sub-study

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period

- To characterize the serum iPTH concentration (at baseline, 6 months and 12 months)
- To characterize urinary calcium excretion (at baseline, 6 months and 12 months)

2. RATIONALE

Based on the well-known importance of calcium in mineralizing newly formed bone and the unique mechanism of action of romosozumab to increase bone formation, decreases in serum calcium with expected changes in serum intact parathyroid hormone are expected in subjects treated with romosozumab. Sclerostin, the biologic target of romosozumab, is not known to be a regulator of the well described processes of parathyroid cell proliferation or PTH secretion (Kumar, 2011; Naveh-Many, 2010; Akerström, 2005; Kifor, 2002). In addition, patients with sclerosteosis and lifelong deficiency of sclerostin are not known to have abnormalities in basal secretion of parathyroid hormone or calcitonin secretion (Epstein, 1979).

In patients treated with Teriparatide (a PTH analog and bone anabolic agent), increases in serum calcium lead to increased filtered loads of calcium in the kidney and increased urinary calcium excretion rates. The increase urinary calcium excretion increases the risk of urinary calcium supersaturation and therefore nephrolithiasis. The mechanism of action of romosozumab is distinct from teriparatide; romosozumab is also a bone anabolic agent, but, since it is not a PTH analog, it does not have the calcemic actions of teriparatide. In the Phase 2 study of romosozumab in post-menopausal osteoporosis women (Protocol 20060326), no significant difference, compared to placebo, was observed in the 24 hour urinary calcium excretion 1 month after initiation of romosozumab.

Because romosozumab is a bone forming agent associated with compensatory increases in serum iPTH following reductions in serum calcium, this sub-study is designed to measure and better characterize changes in serum iPTH during the 12-month double-blind placebo-

controlled study period. Urinary calcium excretion will also be monitored because of the observation of nephrolithiasis with teriparatide.

3. SUB-STUDY DESIGN

Eligible subjects at all centers may be enrolled into the Serum iPTH and Urinary Calcium sub-study: up to approximately 450 subjects (approximately 225 per arm). Subjects have to provide sub-study specific informed consent to participate. A balanced regional and racial distribution is targeted for enrollment. As mandated by the main study, all subjects will receive daily calcium and vitamin D supplementation that at a minimum is in a range of 500 to 1,000 mg of elemental calcium and 600 to 800 IU of vitamin D from screening to end of study. In addition, subjects with a serum 25 (OH) vitamin D level of ≥ 20 ng/mL and ≤ 40 ng/mL at screening will receive an initial loading dose of 50,000 to 60,000 IU of vitamin D, preferably by the oral route. Subjects with a serum 25 (OH) vitamin D level of > 40 ng/mL at screening may also receive the vitamin D loading dose at the principal investigator's discretion. There was no standardization of calcium or 25 (OH) vitamin D levels for this substudy.

4. ENDPOINTS

During the 12-month double-blind placebo-controlled study period

- Percent change from baseline in serum iPTH at Month 6 and Month 12
- Change from baseline in serum iPTH at Month 6 and Month 12
- Percent change from baseline in estimated 24 hour urinary calcium excretion at Month 6 and Month 12
- Change from baseline in estimated 24 hour urinary calcium excretion at Month 6 and Month 12

These results are discussed in section 8.3.8 for serum iPTH levels and urinary calcium.

5. ELIGIBILITY

Inclusion Criteria

- Subject has provided informed consent for participation in this sub-study

Upon agreement with the Sponsor, subjects may be consented following Day 1. Back-up samples collected for other testing may be analyzed for any PK timepoint that may have been missed due to later consent.

Exclusion Criteria

- Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge
- Subjects participating in the BTM and Biomarker sub-study

6. PROCEDURES

This sub-study requires no additional study visits.

7. STATISTICAL CONSIDERATIONS

Serum iPTH and urinary calcium data will be collected from the BTM and Biomarker sub-study (approximately 150 subjects) and the Serum iPTH and Urinary Calcium sub-study (approximately 450 subjects). Analysis will be using data pooled from these two sub-studies (approximately 600 subjects in total) for serum iPTH and urinary calcium at Month 6 and Month 12. It is expected that a sample size of 600 subjects (approximately 300 subjects per arm) will provide stable estimates of the changes in serum iPTH and urinary calcium excretion over time. Considering a 7.5% drop out during the 12-month double-blind placebo-controlled study period, 300 subjects per arm will provide an estimate for the percent change from baseline in serum iPTH with 5.9% of the half-width of the 95% CI, assuming a 50% standard deviation. This sample size will provide an estimate for 24-hour urine calcium with 0.24 mmol/d of the half-width of the 95% CI, assuming a 2 mmol/d standard deviation.

Change and percent change in serum iPTH and urine calcium will be summarized by visit and non-parametric methodology will be used to compare between treatment groups.

13.6.9. Pharmacokinetics Sub-study

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period

- To characterize the serum romosozumab concentration

2. RATIONALE

This sub-study will allow studying the PK of romosozumab in a broader population and enable a population PK analysis. In conjunction with the BTM and Biomarker sub-study and DXA results, the PK/PD relationship will also be studied in a broader population.

The effect of transitioning from romosozumab/placebo treatment to denosumab treatment will be studied during the 12-month open-label denosumab follow-up study period by assessing PK and the PK/PD relationship (in conjunction with the BTM and Biomarker sub-study and DXA results).

3. SUB-STUDY DESIGN

Eligible subjects at all centers may be enrolled into the PK sub-study: up to approximately 600 subjects (approximately 300 per arm) will be enrolled. Subjects have to provide sub-study specific informed consent to participate. A balanced regional and racial distribution is targeted for enrollment.

4. ENDPOINTS

- Romosozumab serum concentrations at Day 1, Day 14, Month 1, Month 3, Month 6, Month 9, Month 12, and Month 13

5. ELIGIBILITY

Inclusion

- Subject has provided informed consent for participation in this sub-study

Upon agreement with the Sponsor, subjects may be consented following Day 1. Back-up samples collected for other testing may be analyzed for any PK timepoint that may have been missed due to later consent.

Exclusion

- Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge

6. PROCEDURES

Study visits for the PK sub-study are Day 1, Day 14, Month 1, Month 3, Month 6, Month 9, Month 12, and Month 13.

7. STATISTICAL CONSIDERATIONS

Enrollment of 600 subjects represents approximately a 10% sampling and as such is expected to be representative of the overall study population. A population PK and PK/PD analysis will be performed and reported separately.

13.6.10. Pharmacogenetics Sub-study

1. OBJECTIVES

For the 12-month double-blind placebo-controlled study period

- To prospectively collect materials suitable for evaluating the influence of genetic variation on individual drug response

2. RATIONALE

As the genetic basis for sclerosteosis forms the target validation for romosozumab, the exploration of potential pharmacogenetic associations may be important.

3. SUB-STUDY DESIGN

Pharmacogenetic material will be collected from all subjects providing sub-study specific informed consent at their Day 1 visit, ie, prior to first dose.

4. ENDPOINTS

The collection of pharmacogenetic material in this study does not have a pre-defined endpoint.

5. ELIGIBILITY

Inclusion

Subject has provided informed consent for participation in this sub-study

Exclusion
No sub-study specific exclusion criteria apply

6. PROCEDURES

A separate blood sample will be drawn for the Pharmacogenetics sub-study.

7. STATISTICAL CONSIDERATIONS

The degree to which genetic variation may influence a subject's therapeutic response is unknown but potentially rare, suggesting the collection of genetic material from all subjects would be ideal.

13.7. Adverse Events Toxicity Grading CTCAE ≥ Grade 3 for Study 20070337

The following table 61 outlines grade 3 or higher laboratory results in Study 20070337. Details are discussed within section 8.3.8 Laboratory Findings:

Table 60: AE CTCAE ≥ Grade 3 in Study 20070337 in the Double-Blind Period.

Laboratory Parameters	Relationship to Normal	Grade	Placebo (N = 3576) n (%)	Romosozumab 210 mg QM (N = 3581) n (%)
No. of subjects with CTCAE grade ≥ 3 laboratory result			141 (3.9)	151 (4.2)
Sodium	Above	Grade 3	1 (<0.1)	2 (<0.1)
	Below	Grade 3	30 (0.8)	39 (1.1)
Potassium	Above	Grade 3	4 (0.1)	4 (0.1)
		Grade 4	0 (0.0)	1 (<0.1)
	Below	Grade 3	4 (0.1)	9 (0.3)
		Grade 4	0 (0.0)	1 (<0.1)
Magnesium	Above	Grade 3	2 (<0.1)	4 (0.1)
Calcium	Below	Grade 4	1 (<0.1)	0 (0.0)
Calcium (corrected)	Below	Grade 4	1 (<0.1)	0 (0.0)
Phosphorus	Below	Grade 3	4 (0.1)	5 (0.1)
Aspartate aminotransferase	Above	Grade 3	5 (0.1)	3 (<0.1)
		Grade 4	1 (<0.1)	0 (0.0)
Alanine aminotransferase	Above	Grade 3	10 (0.3)	5 (0.1)
Alkaline phosphatase	Above	Grade 3	1 (<0.1)	0 (0.0)
Total bilirubin	Above	Grade 3	3 (<0.1)	4 (0.1)
Albumin	Below	Grade 3	2 (<0.1)	1 (<0.1)
Glucose	Above	Grade 3	71 (2.0)	55 (1.5)
		Grade 4	0 (0.0)	2 (<0.1)
Hemoglobin	Below	Grade 3	4 (0.1)	4 (0.1)
		Grade 4	0 (0.0)	1 (<0.1)
Platelets	Below	Grade 3	0 (0.0)	1 (<0.1)
White blood cells	Below	Grade 3	2 (<0.1)	2 (<0.1)
Total neutrophils	Below	Grade 3	8 (0.2)	9 (0.3)
		Grade 4	0 (0.0)	2 (<0.1)
Lymphocytes	Below	Grade 3	6 (0.2)	12 (0.3)

CTCAE = Common Terminology Criteria for Adverse Events

Source: CSR20070337 Table 14-7.5.3 with reviewer edits.

Adverse Event Toxicity Grading Scale

For grading of adverse events, the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 is to be used.

Grade	CTCAE version 3.0
1	MILD AE
2	MODERATE AE
3	SEVERE AE
4	LIFE-THREATENING OR DISABLING AE
5	DEATH RELATED to AE

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/s/

T D CHANG
05/03/2017

THERESA E KEHOE
05/03/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	**BLA # 761062**
Supporting document/s:	SD 1 (SN 0001)
Applicant's letter date:	07/19/2016
CDER stamp date:	07/20/2016
Product:	Romosozumab (IgG2 sclerostin antibody)
Indication:	Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Applicant:	Amgen Inc, Thousand Oaks, CA
Review Division:	Division of Bone, Reproductive and Urologic Products
Reviewer:	Gemma Kuijpers, Ph.D.
Supervisor/Team Leader:	Kimberly Hatfield, Ph.D.
Division Director:	Hylton Joffe, M.D., M.M.Sc.
Project Manager:	Samantha Bell, B.S., B.A.

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Reference ID: 4081796

1 Executive Summary

1.1 Introduction

Amgen seeks to market EVENITY (romosozumab), a humanized anti-sclerostin IgG2 antibody, for the treatment of osteoporosis in postmenopausal women at increased risk for fracture. AMG785 (romosozumab) inhibits the effects of sclerostin and has both anabolic and anti-catabolic effects on bone.

1.2 Brief Discussion of Nonclinical Findings

Pharmacology

Sclerostin is an extracellular inhibitor of the canonical Wnt signaling pathway. It is produced by the osteocyte, a bone mineral-embedded cell derived from the osteoblast, and is involved in para- and autocrine signaling in bone tissue. AMG785, by neutralizing the actions of sclerostin, can transiently stimulate bone formation and inhibit bone resorption, resulting in increases in bone mass and strength. These effects are achieved through time-dependent transcriptional changes in Wnt target genes in cells of the osteoblast lineage (osteocyte, osteoblast, and bone lining cell). The bone formation response appears to be self-regulated, possibly due to an osteocyte-mediated inhibition of osteoprogenitor cell proliferation.

AMG785 blocked the sclerostin-mediated inhibition of matrix mineralization in an in vitro osteoblast cell-based mineralization assay.

In 12-month bone quality studies in ovariectomized (OVX) rats and monkeys, at doses equivalent to **1-19x and 1-22x** human AUC(0-τ) of 12888 μg.h/mL at the monthly subcutaneous dose of 210 mg, respectively, AMG785 increased bone mass and strength of lumbar spine, tibia, femur, and radius in a dose- and time-dependent manner. Bone formation and resorption markers were rapidly and transiently increased. The bone changes consisted of increases in trabecular thickness in vertebrae and long bone metaphyses, and increases in cortical thickness in long bone meta- and diaphyses. These effects were due to stimulation of bone formation concomitant with suppression of bone resorption mostly at trabecular and endosteal bone surfaces. AMG785 caused slight transient increases in cortical bone porosity.

Increases in bone strength in the OVX animals were demonstrated by positive effects on whole bone and material strength parameters at all skeletal sites evaluated (vertebral bodies and cores, femoral shaft and femoral neck). Humerus bone material strength was not significantly affected. Based on bone mass vs. strength correlations, bone quality was maintained at all evaluated sites. An improvement in bone quality was observed in the vertebrae of rats and monkeys at **19-22x** human exposure multiples. Evaluations of selected bone quality parameters did not show any negative effects.

In human studies, the AMG785-induced increase in bone mass was accompanied by an increase in bone formation and a decrease in bone resorption markers. The increase in resorption markers in animals was probably due to the more pronounced increase in serum PTH causing increased bone turnover at Haversian and possibly periosteal surfaces.

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General toxicity
Toxicity studies of up to 6-month duration were conducted in rats and monkeys. The main findings were related to the pharmacologic effect of AMG785 and included RBC, WBC and platelet decreases, serum calcium and phosphorus decreases, and extramedullary hematopoiesis. The effects were associated with hyperostosis and increases in bone formation and densitometric parameters. Exposure multiples in the 6-month studies ranged from **1-38x** and **1-93x** human exposure, in rats and monkeys, respectively. Assessments of local tolerance did not reveal significant concerns.

Carcinogenicity
A carcinogenicity study was conducted in Sprague Dawley rats. The rats were dosed for up to 98 weeks with 0, 3, 10, 50 mg/kg/week, equivalent to **1-19x** human exposure. The study did not show any significant increases in tumor incidences. A low incidence of osteosarcoma (2/54) was observed in high dose males at 19x human exposure. However, the lack of statistical significance of this finding and the large exposure multiple suggests that AMG785 is unlikely to increase the human risk of osteosarcoma.

Osteosarcoma and other bone tumors have previously been observed in rats treated for 2 years with PTH or PTHrP analogues at low human exposure multiples. The absence of bone tumors in the AMG785 study may be related to the self-regulatory nature of the osteoblast bone formation response.

Reproductive toxicity
Reproductive toxicity was evaluated in rat fertility and early embryonic development (FEED), embryofetal development (EFD) and pre- and postnatal development (PPND) studies. Findings in the definitive FEED and EFD studies included reduced ventral processes of the 6th cervical vertebrae at doses of 100 and 300 mg/kg (**17-56x** human exposure). However, this anatomical structure is not present in humans and the finding is not considered clinically relevant. Fetal poly- and syndactyly were observed in the definitive EFD study at **32x** human exposure, consistent with syndactyly that has been observed in sclerostosis patients and SOST knockout mice. Although it may have been treatment-related, the finding is considered of low clinical relevance based on the exposure multiple, and the timing of digit formation in the first trimester in humans, when placental transfer of immunoglobulins is limited. In the PPND study, there were small decreases in bone mass and size in the F1 offspring at **1.5-56x** human exposure of unclear biological significance. None of these findings are considered relevant for the postmenopausal indication.

Theoretical safety issues
Sponsor evaluated multiple potential clinical safety concerns based on the weight of evidence from nonclinical studies, clinical studies and published literature. From a nonclinical perspective there are no indications that AMG75 would increase the risks for osteoarthritis, vascular calcification, increased longitudinal bone growth, hyperostosis, hypercementosis, altered hematopoiesis, sarcopenia, altered glucose metabolism, and exacerbation of TNFα-mediated inflammation. Based on nonclinical pharmacology and toxicology data, the concern about tumor induction or promotion due to activation of Wnt signaling is not considered to be substantial.

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Nonclinical perspective on clinical bone AEs
There is some clinical concern about two different skeletal adverse events, atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ), one case of which each was observed in the romosozumab treatment group in the pivotal Phase 3 study. The concern was intensified by the identification of romosozumab's antiresorptive properties. However, the nonclinical bone safety evaluations were not suggestive of significant negative effects on bone strength or quality. Although the predictive value of the evaluated nonclinical parameters for these events is not entirely clear, this is at least partially reassuring.

Conclusion
The nonclinical pharmacology and toxicology studies were adequately conducted. The submitted data support the marketing of AMG785 for the postmenopausal osteoporosis indication. The basis of the recommendation to approve is outlined in section 1.3.

1.3 Recommendations

1.3.1 Approvability

Based on the lack of significant concerns about bone quality and the paucity of non-pharmacology related toxicities in animal studies of up to 2-year duration at adequate human exposure multiples, and also based on the lack of significant clinical safety concerns from a nonclinical perspective, the submitted nonclinical data support the use of romosozumab in postmenopausal women at the recommended subcutaneous dose of 210 mg once monthly for 12 months.

1.3.2 Additional Non-Clinical Recommendations

No additional nonclinical assessments are needed for approval of the application.

Recommendation to the clinical review team:
If the clinical team has concerns regarding the ability of romosozumab to cause osteonecrosis of the jaw (ONJ), a nonclinical study could be conducted to examine the effects of r13c7 in a rat surgical ONJ model (refer to Kim et al., Bone 81:442-448, 2015). Adequate dose selection and inclusion of a bisphosphonate control arm would be recommended for such a study.

1.3.3 Labeling

At the time of this review, the following initial edits were proposed by the pharmacology/toxicology team for the nonclinical sections of the Sponsor's proposed labeling. This content was also sent to the Sponsor in the first round of labeling negotiations on 3/29/17. A final labeling review will be conducted under separate cover following negotiations with the sponsor. Proposed additions are underlined, while proposed deletions are ~~strikethrough~~.

Reference ID: 4081796

EVENITY™ (romosozumab) for injection, for subcutaneous use
Initial U.S. Approval: 20yy

----------INDICATIONS AND USAGE----------
EVENITY is a sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. (1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

Data

Animal Data
Reproductive and developmental effects of romosozumab were assessed in the rat in a preliminary and definitive embryo-fetal development study, a combined fertility and embryo-development study, and a pre- and post-natal study.

(b) (4)

Skeletal malformations (b) (4) (including syndactyly and polydactyly), occurred in 1 out of 75 litters across all rat reproductive toxicity studies. The abnormalities were observed in the litter of a dam given weekly subcutaneous doses during organogenesis of 300 mg/kg (equivalent to at least 32 times the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg, based on AUC comparison). (b) (4)

(b) (4)

In the offspring of female rats given weekly doses from 6 weeks before cohabitation and mating through lactation, bone density or size were minimally or slightly decreased at doses of 10, 60 or 300 mg/kg (equivalent to 1.5, 19, or 56 times the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg, based on AUC comparison). Other (b) (4) adverse effects on postnatal growth and development were not observed.

(b) (4)

8.2 Lactation

Risk Summary
EVENITY is not indicated for use in females of reproductive potential. There is no information on the presence of romosozumab in human milk, the effects on the breastfed infant, or the effects on milk production. (b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

In a rat carcinogenicity study, once-weekly doses of 3, 10 or (b) (4) 50 mg/kg (b) (4) were administered by subcutaneous injection to Sprague-Dawley (b) (4) rats from 8 ~~weeks~~ (b) (4) up to 98 weeks of age, (b) (4) resulting in systemic exposures that were up to 19 times (b) (4) the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison). Romosozumab caused a dose-dependent increase in bone mass with (b) (4) trabecular and cortical bone thickening at all doses. There were no effects of romosozumab on mortality and romosozumab did not cause significant increases in (b) (4) tumor incidence in male or female rats.

Mutagenicity

Mutagenesis has not been evaluated, as monoclonal antibodies are not expected to alter DNA or chromosomes.

Impairment of Fertility

No effects on fertility were observed in male and female rats (b) (4) given subcutaneous doses up to 300 mg/kg (up to 56 times the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab, based on AUC comparison). (b) (4) No effects were noted in reproductive organs in rats and cynomolgus monkeys dosed (b) (4) subcutaneously for 6 months with weekly doses up to 100 mg/kg (b) (4) exposures up to 38 and 93 times (b) (4), respectively, (b) (4) the systemic exposure observed in humans administered monthly subcutaneous doses of 210 mg, (b) (4) based on AUC comparison).

13.2 Animal Toxicology and/or Pharmacology

No adverse effects were noted in rats and monkeys after 26 once-weekly subcutaneous injections at doses up to 100 mg/kg, equivalent to (b) (4) systemic exposures of 38 and 93 times (b) (4), respectively, (b) (4) the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison).

(b) (4)

(b) (4) Bone safety studies of up to 12 month duration were conducted in ovariectomized (OVX) rats and monkeys, with once-weekly (b) (4) (b) (4) doses yielding exposures ranging from 1 to 22 times the

systemic exposure in humans given monthly doses of 210 mg, based on AUC comparison. Romosozumab increased (b) (4) (b) (4) bone mass and (b) (4) improved cancellous bone microarchitecture and cortical bone geometry by enhancing bone formation and suppressing bone resorption (b) (4) at trabecular and endocortical surfaces. The increases in bone mass were significantly correlated with increases in (b) (4) bone strength. (b) (4) (b) (4) (b) (4) In rats and monkeys, bone quality was maintained at all skeletal sites at doses ranging from 1 to 22 times human exposure, and slightly improved in vertebrae at 19 to 22 times human exposure (b) (4) (b) (4) There was no evidence of mineralization defects, osteoid accumulation (b) (4) or woven bone formation.

1.4 Abbreviations

GENERAL

2QW	twice every week
3D	three-dimensional
ADA	anti-drug antibody
AFF	atypical femoral fracture
ALN	alendronate
AMG 785	romosozumab
AUC	area under the curve
$AUC_{(0\text{-tau})}$	AUC from beginning to end of the dosing period
BAP/BSAP	bone-specific alkaline phosphatase
BMC/vBMC	bone mineral content/volumetric bone mineral content
BMD/vBMD	bone mineral density/volumetric bone mineral density
BMDD	bone mineral density distribution
BMU	bone multicellular unit
BRU	bone remodelling unit
bSEM	backscattered scanning electron microscopy
C0	initial concentration
C6	sixth cervical vertebra
Cmax	maximum concentration
CTx	carboxy-terminal crosslinked telopeptide of type I collagen
DKK1	Dickkopf Wnt signaling pathway inhibitor 1
DNA	deoxyribonucleic acid
DPD	deoxypyridinoline
DXA	dual-energy x-ray absorptiometry
ECD	extracellular domain
ECM	extracellular matrix
EFD	embryo-fetal development
F	female
Fab	fragment antigen-binding fragment of antibody

Fc	fragment crystallizable region of antibody
FEA	finite-element analysis
FEED	fertility and early embryonic development
FTIRM	Fourier-transform infrared microspectroscopy
Fu	ultimate load
GD	gestation day
HRpQCT	high-resolution peripheral quantitative computed tomography
hERG	human ether-a-go-go-related gene
IV	intravenous(ly)
Kd	equilibrium dissociation constant
KinExA	kinetic Exclusion Assay technology
L2	second lumbar vertebra
L3	third lumbar vertebra
L4	fourth lumbar vertebra
LD	lactation day
LRP	low-density lipoprotein receptor-related protein
M	male
m13c7	mouse 13c7, a mouse version of romosozumab
mRNA	messenger ribonucleic acid
microCT or μCT	micro-computed tomography
NA	Not applicable
ND	no data
NOAEL	no observable adverse effect level
NTx	amino-terminal cross-linked peptide of type I collagen
OA	osteoarthritis
OC	osteocalcin
ONJ	osteonecrosis of the jaw
OPG	osteoprotegerin
OVX	ovariectomized
P1NP	procollagen type 1 N-terminal propeptide
PPND	pre- and postnatal development
pQCT	peripheral quantitative computed tomography
PTH	parathyroid hormone
Q4W	every 4 weeks
QM	once monthly
QW	once weekly
r13c7	rat 13c7, a rat version of romosozumab
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
RT-PCR	reverse transcription-polymerase chain reaction amplification
SC	subcutaneous
Scl-Ab	sclerostin antibody
SD	Sprague Dawley
SD	standard Deviation
SEM	standard Error of Mean
SOST	sclerostin gene

Tb	trabecular
tBMD	tissue mineral density
TNF	tumor necrosis factor
TRACP 5b or TRAP5b	tartrate acid phosphatase 5b

HISTOLOGY

BS	bone surface
BV	bone volume
Ec	endocortical
Ic	intracortical
LE	lining cell
Ma.OP	marrow osteoprogenitors
Ma.Op.N	marrow osteoprogenitor number
MBF	modeling-based bone formation
Me.Ar	medullary area
OB or Ob	osteoblast(s)
OCy	osteocytes
Ob.N	osteoblast number
Ob.N/Ob.S	osteoblast density per unit of osteoblastic surface
Ps	periosteal
RBF	remodeling-based bone formation
Tb	trabecular

HISTOMORPHOMETRY

Cancellous bone compartment:

STATIC	DYNAMIC
Tissue area (T.Ar)	Mineralizing surface/bone surface (MS/BS)
Bone volume (BV/TV)	Mineralizing surface/osteoid surface (MS/OS)
Mineralized volume (Md.V/TV)	Single label surface (sLS/BS)
Osteoid volume (OV/BV)	Double label surface (dLS/BS)
Trabecular thickness (Tb.Th)	Mineral apposition rate (MAR)
Trabecular separation (Tb.Sp)	Adjusted apposition rate (Aj.AR)
Trabecular number (Tb.N)	Osteoid maturation rate (Omt)
Osteoid thickness (O.Th)	Mineralization lag time (Mlt)
Osteoid surface (OS/BS)	BFR*, surface referent (BFR/BS)
Osteoblast surface (Ob.S/BS)	BFR*, volume referent (BFR/BV)
Osteoclast surface (Oc.S/BS)	Activation frequency (Ac.f)
Eroded surface (ES/BS)	Formation period (FP)
Wall thickness (W.Th)	Formative surface (FoS/BS)
	Quiescent surface (QS/BS)

Cortical bone compartment:

STATIC	DYNAMIC
Total tissue area (Tt.T.AR)	Periosteal single label surface (Ps.sL.Pm/Ps.Pm)
Cortical area (Ct.Ar)	Periosteal double label surface (Ps.dL.Pm/Ps.Pm)
Medullary area (Me.Ar)	Periosteal labeled surface (Ps.L.Pm/Ps.Pm)
Cortical area, relative (%Ct.Ar)	Periosteal MAR (Ps.MAR)
Medullary area, relative (%Me.Ar)	Periosteal BFR, surface referent (Ps.BFR/BS)
Cortical width (Ct.Wi)	Endocortical single label surface (Ec.sL.Pm/Ec.Pm)
Periosteal perimeter (Ps.Pm)	Endocortical double label surface (Ec.dL.Pm/Ec.Pm)
Endocortical perimeter (Ec.Pm)	Endocortical labeled surface (Ec.L.Pm/Ec.Pm)
Percent porosity area (%Po.Ar)	Endocortical mineral apposition rate (Ec.MAR)
Endocortical eroded perimeter (Ec.E.Pm/Ec.Pm)	Endocortical BFR, surface referent (Ec.BFR/BS)
	Endocortical quiescent surface (Ec.Q.Pm/Ec.Pm)
	Endocortical formative surface (Ec.Fo.Pm/ Ec.Pm)
	Haversian single label surface (H.sL.Pm/H.Pm)
	Haversian double label surface (H.dL.Pm/H.Pm)
	Haversian labeled surface (H.L.Pm/H.Pm)

2 Drug information

2.1 Drug

Generic Name
- Romosozumab

Code Names
- AMG785

CAS Registry Number:
- 909395-70-6

Protein sequence/molecular weight
- Approx. 146 kDa

Heavy Chain

```
  1 EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYNMHWVRQA PGQGLEWMGE
 51 INPNSGGAGY NQKFKGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARLG
101 YDDIYDDWYF DVWGQGTTVT VSSASTKGPS VFPLAPCSRS TSESTAALGC
151 LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSNFG
201 TQTYTCNVDH KPSNTKVDKT VERKCCVECP PCPAPPVAGP SVFLFPPKPK
251 DTLMISRTPE VTCVVVDVSH EDPEVQFNWY VDGVEVHNAK TKPREEQFNS
301 TFRVVSVLTV VHQDWLNGKE YKCKVSNKGL PAPIEKTISK TKGQPREPQV
351 YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPML
401 DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK
```

Light Chain

```
  1 DIQMTQSPSS LSASVGDRVT ITCRASQDIS NYLNWYQQKP GKAPKLLIYY
 51 TSRLLSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GDTLPYTFGG
101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
201 LSSPVTKSFN RGEC
```

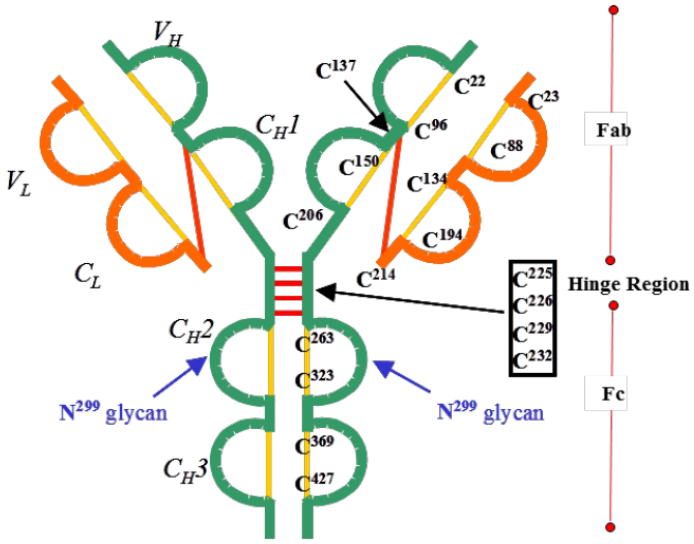
Blue Cysteines in intrachain disulfide bonds
Red Cysteines in Heavy-Heavy interchain disulfide bonds
Magenta Cysteines in Heavy-Light interchain disulfide bonds
NST N-linked glycosylation site

Reference ID: 4081796

Structure or Biochemical Description

- AMG785 (humanized m13c7) is a monoclonal anti-sclerostin IgG2 antibody. It is a recombinant product expressed in CHO cells.
-

Figure 1. Schematic of Romosozumab Structure



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

V_H is the variable domain of the heavy chain

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

V_L is the variable domain of the light chain

C_L is the constant domain of the light chain

Pharmacologic Class

- Sclerostin inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 100391 (AMG785, romosozumab; Amgen)
IND 103077 (AMG785, romosozumab; Amgen)

2.3 Drug Formulation

The antibody is provided in a sterile solution for SC injection, at strength of **90 mg/mL**. The product contains the excipients sucrose (b) (4) polysorbate (b) (4) acetate (b) (4) calcium (b) (4) and NaOH (b) (4) at pH 5.2. One dose of 210 mg is administered by injection of 2 x 1.17 mL from a single-use (b) (4) prefilled syringe.

2.4 Comments on Novel Excipients

The product contains no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

Product related impurities do not have properties comparable to those of the product. Additionally, their low levels preclude a significant cause for concern. Since romosozumab is a

biotechnology-derived product, the impurity qualification requirements as described in ICH Q3A/B guidances are not applicable.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is postmenopausal women with osteoporosis. The proposed dosing regimen is 210 mg once monthly administered by subcutaneous injection.

2.7 Regulatory Background

AMG785 was developed under IND100391 by Amgen Inc. for the osteoporosis indication. The IND was first submitted on October 26, 2006.

The EOP2 meeting was held on August 19, 2011. The Division recommended that Sponsor conduct a 2-year rodent bioassay to evaluate the carcinogenic potential of AMG785 based on activation of Wnt signaling and the potential implication of the Wnt pathway in tumorigenicity. The Division stated that a 12-month monkey study may be adequate to support a 12-month clinical treatment duration.

The protocol for a rat carcinogenicity ('life time pharmacology') study was submitted by Sponsor on September 2, 2011, and was reviewed by the Executive Carcinogenicity Assessment Committee (ECAC) on October 11, 2011.

At the Type B pre-BLA meeting on May 18, 2016, no major issues regarding the adequacy of the nonclinical program for romosozumab were identified or discussed.

3 Studies submitted/reviewed

3.1 Studies Reviewed

Pivotal pharmacology and toxicology studies submitted to the BLA were reviewed in detail. This included the OVX monkey bone pharmacology study, repeat dose toxicity studies in rats and monkeys, rat carcinogenicity study and rat reproductive toxicity studies. The results of several other pharmacology, toxicity, PK and genotoxicity studies were reviewed and presented in written and/or tabular summaries. Some of the studies described in this review were previously reviewed for IND 100391 or IND 103077, both for AMG785.

3.2 Studies Not Reviewed

A number of pharmacology, toxicology and PK/ADME studies were not reviewed or not reviewed in detail. Those studies were considered not to be of immediate or signficant relevance to the safety assessment of the product for the postmenopausal osteoporosis indicaton. The PK/assay validation studies were not reviewed.

3.3 Previous Reviews Referenced

Several studies submitted to the BLA had been reviewed for IND 100391 and 103077, including the 1-month and 6-month toxicity studies in rats and monkeys and the dose range finding and definitive embryofetal development (EFD) studies.

Dr. Gemma Kuijpers reviewed the pivotal pharmacology studies in detail as well as several other pharmacology and toxicology studies submitted to the BLA, and integrated the findings in studies previously reviewed for IND 100391 or 103077 in the BLA review.

Dr Andrea Benedict reviewed the report of the monkey PK comparability study for Process 1 and Process 2 drug products (Study 113155). The review was filed in DARRTS for BLA 761062 (SD1) on March 2, 2017.

Dr. Eric Andreased reviewed the 1-month and 6-month rat and monkey toxicity studies and the definitive embryofetal development study, submitted to AMG785 IND 100377. The review was filed in DARRTS for IND 103077 (SD4) for AMG785-IND 103077 on June 18, 2009.

Dr. Miyun Tsai-Turton reviewed the final report of the rat carcinogenicity study report (Study 107895). The results were discussed with the Executive Carcinogenicity Assessment Committee (ECAC) on February 14, 2017. The study review was filed in DARRTS for BLA 761062 (SD1) on March 27, 2017. The statistical review of the carcinogenicity study data was conducted by Dr. Hepei Chen and Dr. Feng Zhou (Division of Biometrics VI) and the review was filed in DARRTS for BLA 761062 (SD1) on March 24, 2017. The Meeting Minutes of the February 14, 2017, ECAC meeting were filed in DARRTS for BLA 761062 by Dr. Leuenroth-Quinn on February 17, 2017. The Minutes are attached to this review (APPENDIX 2).

Dr. Laurie McLeod-Flynn reviewed the reports of the rat embryofetal development study (EFD Study 108057) and the rat fertility and early embryonic development study (FEED Study 108061). The review was filed in DARRTS for BLA 761062 (SD1) on March 29, 2017. Dr. Miyun Tsai-Turton reviewed the report of the rat pre- and postnatal development study (PPND Study 108062). The review was filed in DARRTS for BLA 761062 (SD1) on March 27, 2017.

Information request were sent to Sponsor on February 15, February 21, March 6 and March 10, 2017. The responses submitted by Sponsor to the BLA resolved the issues.

Reference ID: 4081796

4 Pharmacology

4.1 Mechanism of Action

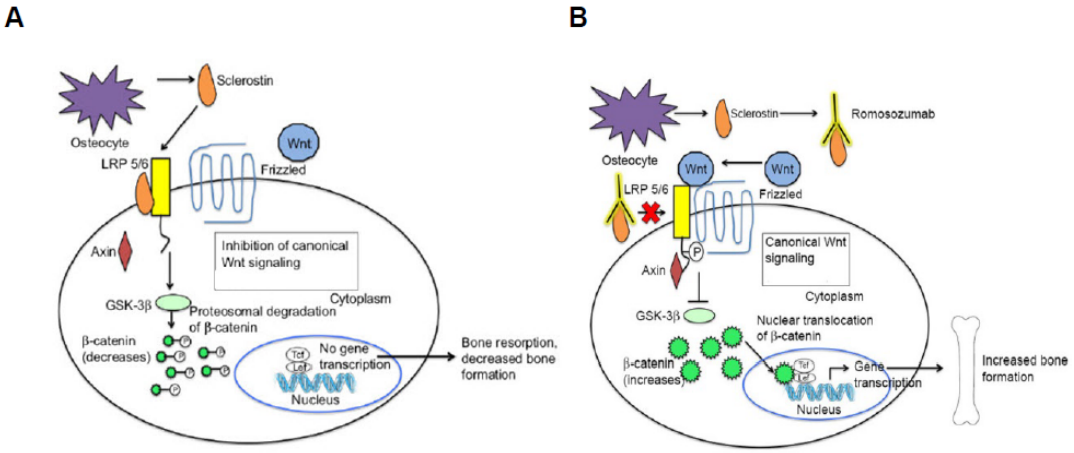
Romosozumab (AMG785) is a humanized IgG2 monoclonal antibody against sclerostin. Sclerostin (Scl) is a cysteine-knot glycoprotein factor produced by osteocytes which plays an important role in the regulation of bone metabolism. Sclerostin was first identified through the discovery of the human genetic high bone mass disorders sclerosteosis and Van Buchem disease (VBD) where sclerostin is absent or subject to decreased expression. The increased bone mass in these populations is thought to be due to the loss of sclerostin's inhibitory effect on bone formation.

The discovery of sclerostin led to the development of sclerostin antibodies (Scl-Ab) to increase bone mass for therapeutic purposes. The treatment was initially considered anabolic since the antibodies were known to increase bone mass by increasing bone formation. However, it later became evident that sclerostin does not only inhibit bone formation but also activates bone resorption, and Scl-Ab has both anabolic and antiresorptive effects. The Sponsor's nonclinical and clinical studies in this application provide evidence of both actions.

Sclerostin produced by the osteocyte binds to LRP4, LRP5 and/or LRP6 receptors, which are parts of Wnt receptor complexes, thereby inhibiting Wnt/β-catenin signaling and downstream transcriptional events (Figure 1, below). Studies with Scl-Ab in OVX rats have shown complex, time-dependent effects on Wnt target gene expression, mainly in osteocytes but also in osteoblasts and bone lining cells. The targets are directly or indirectly linked to osteoblast and osteoclast generation, differentiation and/or function. The gene transcription changes are most conspicuous in the osteocyte, the cell which is ultimately responsible for the anabolic effect of Scl-Ab. Delayed downregulation of pro-mitotic factors in the osteocyte appears to limit osteoblastic cell proliferation, consistent with the transient or 'self-regulatory' nature of the bone formation response to Scl-Ab. Suppression of bone resorption appears to be at least partly due to blockade of osteocytic RANKL production and stimulation of osteocyte or osteoblast OPG production, while the increase in bone formation involves differentiation of lining cells or osteoprogenitor cells resulting in increased numbers of active osteoblasts.

It has been suggested that the anabolic effect of intermittent PTH administration occurs at least in part through inhibition of sclerostin which would explain the common anabolic effect of PTH and Scl-Ab treatment. However, PTH can increase bone mass also in the absence of sclerostin, contradicting this hypothesis. The MOA's of these treatments, both probably mediated principally by the osteocyte, have only partly been elucidated.

Figure 1. Effects of Sclerostin and Romosozumab on Canonical Wnt Signaling and Bone Formation and Resorption.



Sclerostin, predominantly secreted by osteocytes, is a negative regulator of the canonical Wnt pathway that inhibits the interaction of selected Wnt ligands with LRP coreceptors (A). Romosozumab is a humanized monoclonal antibody against sclerostin that inhibits the sclerostin-LRP5/LRP6 interaction thereby allowing Wnt ligand engagement by LRP5/LRP6 and subsequent activation of canonical Wnt signaling (B).

Modified from (Shah et al, 2015)

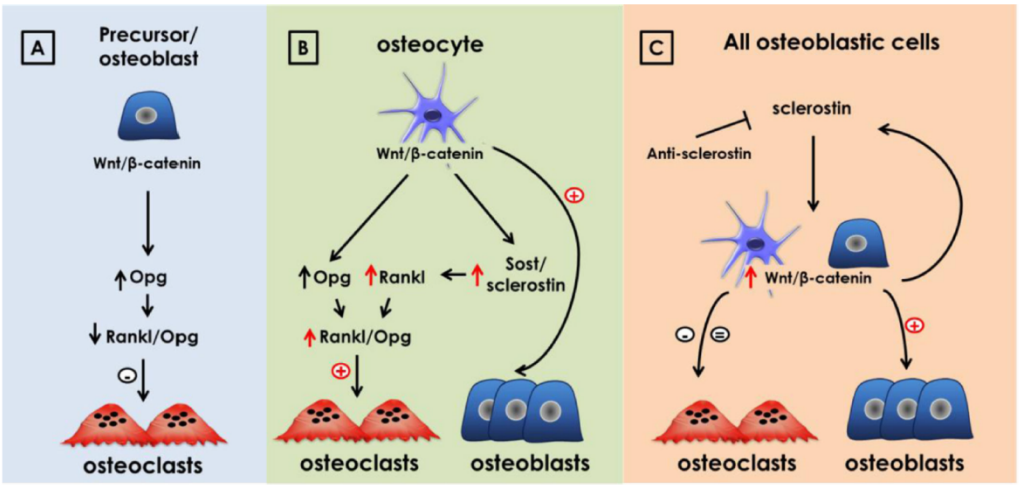


Figure 1. Activation of Wnt-βcatenin signaling in osteocytes has an anabolic effect in bone
(A) Activation of Wnt/βcatenin in osteoblasts/osteoblast precursors increases bone mass by increasing OPG production, which reduces bone resorption, without apparent effect on osteoblast production. **(B)** Activation of Wnt/βcatenin signaling in osteocytes increases both bone formation and bone resorption, with a positive balance that results in bone gain. **(C)** Activation of Wnt signaling in all osteoblastic cells induced by neutralizing antibodies to sclerostin increases bone formation and initially decreases the serum levels of the bone-resorption marker CTX in both mouse and clinical models, that eventually come back to control levels. These findings suggest that osteocytes, rather than less-differentiated cells in the osteoblastic lineage, might mediate anabolism induced by systemic activation of the Wnt/βcatenin pathway, with neutralizing antibodies of sclerostin.

From: Delgado-Calle and Bellido, *Curr Mol Biol Rep*, 2015

4.2 Primary Pharmacology

The sponsor conducted in vitro and in vivo pharmacology studies with sclerostin-antibodies. The antibodies used in the in vivo studies included rat or mouse Scl-Ab (rat studies) or AMG785 (rat and monkey studies).

In vitro studies showed high affinity binding of AMG785 to sclerostin, which led to blockade of the sclerostin-mediated inhibition of bone matrix mineralization in a mouse calvarial cell line.

In vivo bone effects

Long term bone pharmacology studies ('bone quality studies') of up to 12-month duration were conducted with AMG785 in OVX rats and monkeys (Studies 107899 and 107903), at doses up to 50 mg/kg in rats and 30 mg/kg in monkeys (up to 19x and 22x human exposure at the monthly 210 mg dose, based on AUC comparison), respectively. Studies were also conducted in rats and monkeys to evaluate the mechanisms involved in the effects of AMG785 on bone metabolism.

In both OVX rats and monkeys, AMG785 caused a rapid and dose-related increase in osteoblastic bone formation. Bone marker data also showed increases in osteoclastic bone resorption, which was probably due to PTH-induced stimulation of Haversian and possibly periosteal remodeling. In monkeys, both formation and resorption responses were transient and peaked at 10 weeks.

The dynamic events led to marked dose-related increases in bone mass and size, evidenced by increases in densitometric and geometric parameters (BMD, BMC, area, perimeter, thickness) , at all evaluated skeletal sites. The increases in bone mass and size were largest in the first 6 months but continued at a slower rate thereafter. Changes occurred at all doses ≥3 mg/kg, with parameters in the mid and/or high dose groups (10-50 mg/kg in rat, 30 mg/kg in monkey) exceeding those in the sham control groups.

Histomorphometry of cancellous and cortical bone sites showed enhanced bone formation predominantly at trabecular and endocortical surfaces, and increases in trabecular and cortical thickness. Cortical thickening in both species was mostly due to increased endosteal bone apposition, although there was also a periosteal component. In OVX monkeys, the bone formation increases were most pronounced after 3 months of dosing and declined to control levels at 12 months. Bone resorption indices (eroded surface fractions) at these surfaces were reduced in the AMG785-treated OVX monkeys, particularly at 3 months in rib but were still observed at 12 months in femur. The resorption effect was not significant in the OVX rat. In OVX monkeys, increased bone modeling was evidenced by a reduction in quiescent surface and an increase in formative surface fraction due to activation of bone lining cells.

In cortical bone, AMG785 also increased periosteal and intracortical ("Haversian") bone formation rates in rats and/or monkeys. Based on lack of significant changes in bone width and porosity in monkeys, resorption at these two surfaces was probably also increased. This was most likely due to the AMG785-induced increase in serum PTH.

Bone strength was increased in conjunction with bone mass, and there were positive effects on extrinsic as well as intrinsic (geometry-corrected) biomechanical parameters at both cancellous and cortical bone sites. Based on the positive and statistically significant correlations between bone mass and whole bone strength parameters, and between bone density and intrinsic strength parameters, adverse effects on bone quality were not identified in the 12-month studies. In both monkeys and rats, an apparent improvement of vertebral bone quality was seen at the high doses of 30 and 50 mg/kg, respectively.

Data from a high dose recovery group in the 12-month OVX monkey study with treatment discontinued after 6 months showed that all or most effects of AMG785 reversed towards OVX control levels, including BMD/BMC, trabecular and cortical thickness, and strength parameters. One exception was the reduction in endocortical eroded perimeter fraction in femur shaft, which was still significantly decreased vs OVX control at end of recovery.

In another 6-month study in OVX monkeys (Study 118025) at a clinically equivalent dose of 3 mg/kg dose, a detailed evaluation of changes in radius and tibia was performed. AMG785 caused an increase in intracortical bone turnover mainly in radius but also in tibia. Slight decreases in diaphyseal pQCT-vBMD were also observed in radius in tibia, as seen in the 12-month OVX monkey study. However, DXA-BMD of all radius regions was increased. Histomorphometry showed slight increases in cortical porosity which may have contributed to the decreases in pQCT-vBMD. However, BMC and cortical thickness of both radius and tibia were slightly increased and there were no decreases in diaphyseal and metaphyseal strength of the radius at 3 and/or 6 months.

Tissue BMD (bone without soft tissue) was minimally but significantly decreased by AMG785 in vertebrae, radius and tibia (cortical and/or cancellous bone) of OVX monkeys. The significance of the tissue BMD effect was not clear.

Kinetics of remodeling

While AMG785 induces modeling-based bone formation and suppresses bone resorption, residual resorption followed by formation continues to contribute to the bone remodeling process. A reconstruction of the kinetics of the vertebral remodeling cycle was performed using histomorphometry in a 28-week study in aged male monkeys (Study R20150071). Vertebral bone volume and formation were increased, and an increase in MS/OS reflected improved osteoblast efficiency. The kinetic analysis showed decreased resorption and reversal periods, a decrease in erosion depth, an increase in wall thickness and no significant effect on formation period. This resulted in a positive bone balance in the individual bone remodeling units. A reduction of resorption and reversal periods was also observed in iliac cancellous bone after 3 months of treatment in the 12-month study (107903) and explains the decrease in eroded bone surface fractions (ES/BS) in both the 28-week and the 12-month study.

Exploratory analyses

Detailed exploratory analyses of bone structural units (BSUs) in intact vertebral and femoral bone using bSEM and FTIRM, and an analysis of Modeling Bone Formation (MBF) and Remodeling Bone Formation (RBF) were included in a 10-week fibula fracture healing study in adolescent male monkeys with 30 mg/kg AMG785 (Study 108088). AMG785 showed positive

effect on bone healing in this study. MBF was increased and RBF was unaffected at vertebral trabecular and femoral endocortical surfaces. The exploratory analyses showed a very slight shift in vertebral BMDD towards lower values, and a decrease in vertebral BMDD standard deviation suggesting an increase in the homogeneity of trabecular bone with respect to mineral density. There were no global mineralization effects. Matrix and mineral properties were not affected in any bone compartment, but intracortical mineralization appeared temporarily accelerated. Evaluation of MBF and RBF suggested that increases in both modeling and remodeling based bone formation likely contribute to the bone efficacy of AMG785. The data were generally supportive of preservation of bone quality upon AMG785 treatment and did not suggest significant bone safety concerns.

Mechanistic studies

Mechanistic studies provided information about gene transcription in vertebral osteocyte, osteoblast and lining cells in response to acute and chronic Scl-Ab dosing (Studies 105877 and 115777). After initial stimulation of osteoblast number and activity, there was a delayed induction of p53 and an inhibition of mitogenesis and cell cycle progression signaling pathways in the mature osteocyte. This was likely limiting the proliferation of cells in the osteoblast lineage (steoprogenitors) and related to the 'self-regulation' (transient increase) of bone formation. Transcriptional activation of genes involved in osteoclastogenesis and resorption were less clearly self-regulated. The MOA of Scl-Ab appears to include stimulation of osteoblast OPG production, and inhibition of osteocyte RANKL production, together causing a suppression of osteoclast generation and/or function. The sponsor suggested that in contrast to Scl inhibition, activation of bone formation by PTH is not tightly self-regulated, which may explain the pronounced bone tumorigenicity of PTH(rP) analogues (Study 115776).

Species differences

In general, the effects of AMG785-induced sclerostin inhibition on bone turnover, mass, structure, and strength were similar in OVX rats, OVX monkeys and postmenopausal women, suggesting broad cross-species similarity in the role of sclerostin in bone metabolism. The main difference between animals and humans was the decrease in resorption markers in postmenopausal women vs. the increase in resorption markers in animals. This was probably related to the larger increases in serum PTH observed in animals who did not receive dietary Ca supplementation, causing more stimulation of intracortical and possible also of periosteal bone remodeling. Nonetheless, histologic bone resorption indices at trabecular and endocortical surfaces were reduced in OVX monkeys (Study 107903), an effect that was also observed in humans, and in rats treated with rat Scl-Ab, r13c7 (Study R20110286). The apparent lack of such an effect in the AMG785-treated OVX rats may have been due to the fact that resorption indices were measured only after 12 months of dosing in the pivotal OVX rat study.

In vitro studies

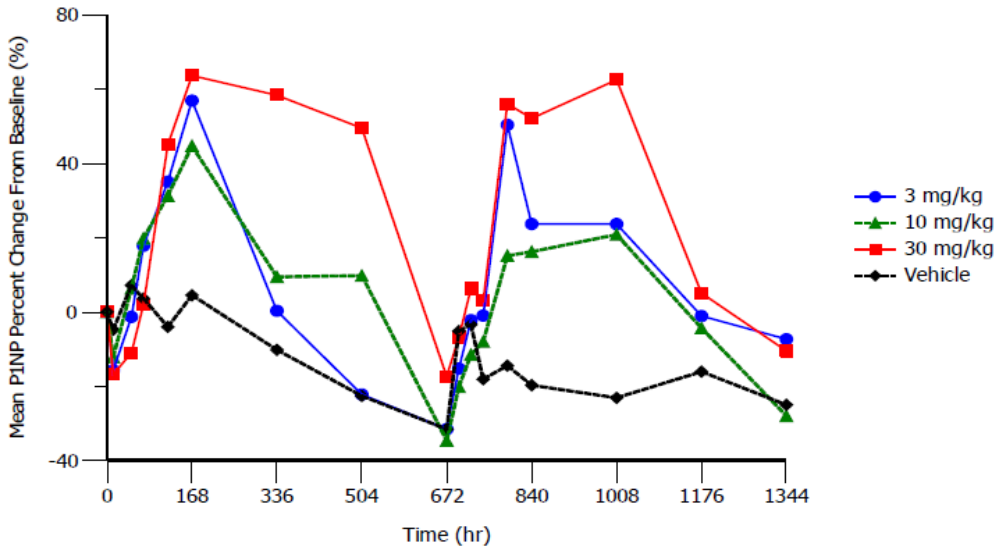
Study Number	Type of Study	Methods	Findings
R2006058	Binding affinity of romosozumab to sclerostin	Kinexa equilibrium binding assay to determine the binding affinity of romosozumab, r13C7, and m13C7 binding to human, cynomolgus monkey, mouse and/or rat sclerostin.	Romosozumab binds to human, cynomolgus monkey, and rat sclerostin with Kd of 11 pM, 23 pM, and 3 pM, respectively. Antibody r13C7 binds rat sclerostin with Kd of 6 pM. Antibody m13C7 binds to human, mouse, and rat sclerostin with Kd of 9 pM, 1 pM, and 3 pM, respectively.
R20130040	Effects of romosozumab on sclerostin binding to LRP4, LRP5, and LRP6	Human sclerostin was incubated with or without romosozumab prior to incubation and immunoprecipitation with recombinant ECDs of human LRP4, LRP5 and LRP6. Western blotting was used to evaluate the effect of romosozumab on LRP-sclerostin binding.	Romosozumab did not block the binding of sclerostin to the ECD of the facilitator protein LRP4. AMG785 did block the binding of sclerostin to the ECDs of the key Wnt signaling co-receptors, LRP5 and LRP6. *Reviewer Comment: Sponsor's in vivo data showed that romosozumab suppressed bone resorption in all species studied (rat, monkey, human). It has been suggested in the literature that binding of sclerostin to LRP4 plays a role in Scl-mediated stimulation of osteoclast activity. The data from Study R20130040 suggest that the osteoclast stimulating effect of sclerostin is either not mediated by LRP4, or the ECD binding site of LRP4 is not involved in this effect.*
R2006057	Effects of romosozumab in an osteoblast-lineage cell-based mineralization bioassay	This bioassay was conducted in MC3T3-E1-BF cells, a mouse calvaria-derived osteoblast-lineage cell line. Romosozumab (0, 10, 20 and 40 μg/mL) was pre-incubated with 1 μg/mL of sclerostin and this mixture was added to the MC3T3-E1-BF cells. The extent of mineralization was measured by solubilizing the precipitated calcium phosphate after 12 days and measuring total calcium.	Recombinant sclerostin from 4 species (human, cynomolgus, rat, and mouse) dose-dependently inhibited matrix mineralization by MC3T3-E1-BF cells. Romosozumab blocked the inhibitory effect on mineralization of all 4 sclerostins.

In vivo studies

An 8-Week Compound Section Dose Range-Finding and Pharmacokinetic Study in the Cynomolgus Monkey
(Study 105876) (non-GLP)
This was an 8-week study in intact female cynomolgus monkeys with AMG785 doses of 0, 3, 10, 30 mg/kg once monthly.

- Serum OC and P1NP were dose-dependently increased. Tmax of P1NP was 7-14 days (Figure 3, below).
- CTx was increased only at the high dose of 30 mg/kg

Figure 3. Mean P1NP Percent Change From Baseline in Female Cynomolgus Monkeys (Study 105876)



A 52 Week Bone Quality Study to Determine the Effects of Weekly Subcutaneous Injection of AMG 785 on the Primary Pharmacodynamics of Aged Ovariectomized Cynomolgus Monkey
(Study Nr. 107903)
(b) (4)
(Study treatment period Jan 2012 – Jan 2013)
(GLP/QA Dec 17, 2014)

A detailed review of this study is located in APPENDIX 1.

Monkeys were sham-operated or OVX-ed and after a 4-month bone depletion period they were treated for 12 months, QW, with 0, 3, or 30 mg/kg AMG785 (1.3x, or 22x human AUC), or with 30 mg/kg followed by vehicle for 6 months each (recovery group). ADA+ animals were excluded from analyses.

Reference ID: 4081796

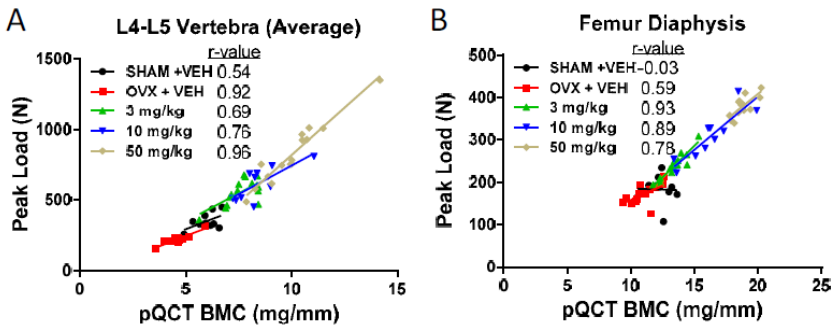
- AMG785 treatment transiently increased bone formation and resorption markers. Effect on formation and resorption markers peaked at 3 months, but were 2.5-fold larger for formation marker P1NP vs resorption marker CTx.
- AMG785 caused increases in PTH and Vitamin D that remained above OVX levels at 12 months. Serum Ca was slightly decreased.
- Densitometry (DXA) showed increases in BMD and/or BMC and Area in spine, tibia, femur, and distal radius. Increases were most prominent in the first 6 months, and at 12 months levels often exceeded those in sham controls at both 3 and 30 mg/kg.
- PQCT showed increases in cortical thickness in tibia and radius diaphysis due to slight increase in bone width and/or decrease in medullary area. Cortical BMD was transiently decreased in tibia (minimally) and radius (slightly), but BMC was slightly increased.
- AMG785 increased bone strength of femur diaphysis and did not affect intrinsic cortical bone strength. Bone strength parameters in spine and femur neck were increased consistent with densitometry results.
- Correlations between bone mass and strength were positive and suggested maintenance or improvement of bone quality.
- Histomorphometry was performed for ilium, vertebrae and femoral neck (cancellous bone), and for rib and femur diaphysis (cortical bone), at interim time points and/or end of study.
    - Data clearly showed progressive increases in trabecular and cortical thickness over time, and increases in bone formation indices including BFR/BS at trabecular, endocortical, periosteal and Haversian (intracortical) bone surfaces, particularly at the earlier biopsy time points (Wk 13), consistent with the transient nature of the increases in bone formation markers.
    - Cortical thickness increases in rib and femur were mainly due to endosteal bone apposition consistent with pQCT densitometry.
    - Numerically, BFR/BS in OVX controls was largest at Haversian > endocortical ≈ trabecular >> periosteal surfaces.
    - The increase in trabecular and endocortical bone formation was due to an increase in formative vs quiescent fractional bone surface (i.e. bone modeling). Wall thickness was increased in cancellous bone.
    - The slight increase in cortical porosity at 6-12 months suggested a concomitant increase in Haversian resorption. Similarly, the lack of change in total bone area suggested a concomitant increase in periosteal resorption.
    - In cancellous bone, eroded surface % was decreased only at Wk 13 in ilium. Endocortical eroded surface % was markedly reduced in rib, mostly in Wk 13, to below OVX and sham control levels. However, it was also markedly suppressed in femur diaphysis at 12 months, and was not reversed in the recovery group. Data suggested that at the endocortical surface AMG785 initially causes a marked stimulation of bone formation ("modeling") and a marked and continued reduction in osteoclastic bone resorption.
- The increases in systemic resorption markers (reflecting all skeletal surfaces) were probably due to increases in Haversian resorption and to a minor extent to periosteal resorption, outweighing reductions in resorption localized to trabecular and endocortical surfaces. This enhanced resorption was probably related to the AMG785-induced PTH increase, protecting against hypocalcemia.

Reference ID: 4081796

- The animal data support the appropriateness of the proposed clinical treatment period of 12 months.

A 12-Month Bone Quality Study to Determine the Effects of Weekly Subcutaneous Injection of AMG 785 in the Ovariectomized Sprague Dawley Female Rat
(Study Nr. 107899)
(b) (4)
(Study treatment period Aug 2011- Aug 2012)
(GLP/QA May 16, 2014)

Methods	Animals	Sprague Dawley rats. Animals were sham-operated or OVXed at 6 months of age, and then underwent a 2-month bone depletion period.
	Doses (AMG785)	Sham group: 0 mg/kg, once weekly, SC injection OVX groups: **0, 3, 10, 50 mg/kg**, weekly, SC injection ($AUC_{(0\text{-}1mo)}$ multiples of approximately **0.6x, 4.3x, 19x** the human AUC(0-τ) at 210 mg q4w) (Sponsor multiples: 0.6x, 3.9x, 19.2x) Treatment was started after the 2-mo bone depletion period.
	Group size	N/grp was initially 20, 20, 50, 35, 35 F/grp, but after exclusion of ADA-positive animals or animals with confounding necropsy findings, group size for analysis of findings was reduced to: **N= 10, 15, 15, 10, 15**. A baseline group terminated after bone depletion (N=10/gr) was also included in study.
	Endpoints/ Methods	Mortality, clinical observations, body weight/food consumption, Cpl (predose, in Wks 9, 17, 25, 33, 41, 49, and 52; by ELISA) bone markers (OC, ALKP, CTx, urine DPD), ADA, DEXA and pQCT (in vivo, necropsy, organ weight, histology, DEXA/pQCT/uCT (ex vivo), histomorphometry (Wk 52 ONLY), biomechanical testing.
Results (AMG785 effects)	Observations/ Pathology	No Tx-related deaths or observations, no significant effect on BW or FC
	Cpl AUC	Minimal and maximal mean Cpl in retained rats suitable for bone quality assessment (some of whom were binding ADA-positive) ranged from 21.4 to 44.3 ug/mL, 169 to 242 ug/mL, and 793 to1190 ug/mL between weeks 9 to 52, in 3, 10, and 50 mg/kg AMG 785 dosed groups, respectively. The AUC multiple calculation for 3, 10, 50 mg/kg was based on data from the 2-year carcinogenicity study which used the same doses as this 12-mo bone quality study.
	Bone markers	AMG785 increased bone formation marker osteocalcin (OC) throughout treatment with maximal effect of +30% (vs OVX control) at Wk 11. AMG also increased serum resorption marker CTx in Wks 11-39 with maximal effect of +36% vs control at Wk 39). However, AMG had no effect on urine resorption marker DPD.

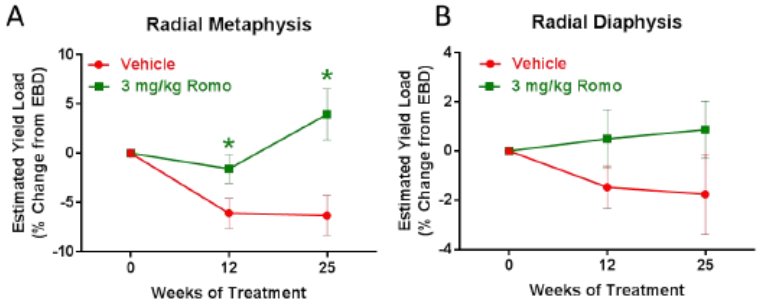
	Histomorph-ometry	At 52 weeks, trabecular thickness was increased dose-dependently in cancellous bone of L3 vertebrae and proximal tibia metaphysis. This was associated with increases in static and dynamic formation parameters. Wall thickness in L3 was increased dose-dependently at all doses. Also after 52 weeks, cortical thickness and cortical area in tibia diaphysis were increased, associated with non-dose-related increases in endocortical bone formation/apposition at all doses. While Ps.BFR/BS was smaller than Ec.BFR/BS, periosteal BFR was increased by a larger % than Ec.BFR by AMG treatment, also in non-dose-related manner. There was a non-dose-related ca. 2x INCREASE in Oc.S/BS in L3 vertebra but this was not significant. Cancellous ES/BS was not measured. A small non-dose-related DECREASE in resorption index Ec.E.Pm/Ec.Pm (up to -20%) was observed in the tibial diaphysis, at all doses, at 52 weeks. Intracortical bone remodeling (a minor process in rats) was not assessed. There was no impairment of bone mineralization, i.e., no changes in O.Th and Mlt.
	Densitometry	AMG increased BMC and BMD (DXA and pQCT) at cancellous bone sites (spine, proximal tibia metaphysis). BMD increases in lumbar spine were +19%, +34%, +48% at Wk 51/52 vs Wk 1 AMG also increased cortical BMC, BMD, and cortical area/thickness (by pQCT) in the proximal tibia diaphysis, due to increased periosteal circumference and decreased endosteal circumference. AMG treatment resulted in values often exceeding sham levels at higher dose levels. Ex vivo DXA and pQCT data were basically similar to in vivo data. Micro-CT also showed increased bone mass and minimally reduced tissue BMD in cancellous and cortical bone (latter also seen in 12-mo OVX monkey study but may be an artifact)
	Mechanical testing	Bone mass and geometry changes resulted in increased bone strength parameters in vertebrae, femur neck and femur diaphysis. Peak load (Fu) increased up to 121% (femur diaphysis), +46% (FN), +270% (LV), compared to OVX controls by Wk 52. Bone mass and bone strength positively and significantly correlated at all doses. Based on increased slope of regression line at 50 mg/kg (L4+L5), there were increases in calculated material properties, indicating improvement of vertebral bone quality due to either beneficial micro-architectural properties (most likely) or increases in intrinsic bone material strength. **Figure 4. Maintenance or Improvement of Bone Mass-strength Relationship Aft Romosozumab Treatment for 52 Weeks in OVX Rats** 

Reviewer Comments		• Data from rats were consistent with data from the 12-month monkey bone efficacy/quality study. • In another study in OVX rats with Scl-Ab r13c7 (26-week Study R20110286), static histomorphometric resorption indices in both cancellous and cortical bone were clearly decreased by r13c7 (as in humans treated with AMG785). • The OVX rat study was an adequate nonclinical bone efficacy/safety assessment.

A 6 Month Subcutaneous Pharmacodynamic Repeated-dose Toxicity Study in the Aged Ovariectomized Cynomolgus Monkey
(Study Nr. 118025)
(b) (4)
(GLP/QA Dec 23, 2015)

Goal of study was to measure bone mass and strength in radius (vs tibia) specifically, in aged OVX monkeys, at clinical exposure (3 mg/kg).

Methods	Animals	Cynomolgus monkeys (OVX only), 9-16 yrs, 3-5.7 kg
	Treatment/ Group size	AMG785 doses: 0 and 3 mg/kg, QW, SC (3 mg/kg ≈ 1.3x human AUC) N= 12/grp (ctrl) N= 32/grp (3 mg/kg) initial group size, reduced to N=19/grp after exclusion
	Treatment duration	6 months, Tx started after 4-mo bone depletion period
	Methods/ endpoints	Cpl, ADA, Bone markers, Hormones, Densitometry (DXA/pQCT), ExtremeCT (HR-pQCT), Mechanical testing (at 6 months), Histomorphometry (labeling at 8 time points), finite element analysis (FEA).
Results (AMG785 effects)	Observations/ Pathology	Several treated animals developed ADAs and were excluded from analyses
	Markers/ Hormones	Increased formation and resorption markers CTx and P1NP, and increased serum PTH/VitD
	Densitometry	Increase in BMC in spine, proximal tibia, distal radius metaphysis and ultradistal radius due to increased trabecular thickness. Increase in cortical thickness (proximal tibia and distal radius diaphysis) due to increase in periosteal circumference (radius and tibia) and decrease in endosteal circumference (tibia). Small decrease in cortical pQCT-BMD in radius meta- and diaphysis, but not in tibia. Increases in pQCT total and cortical area, thickness and BMC, at tibia > radius.
	ExtremeCT (HRpQCT)	Increase in BMC at radius meta- and diaphysis. Decrease in tissue BMD (tBMD, or TMD) in radius meta- and diaphysis at Mo 6, possibly related to increased intracortical remodeling

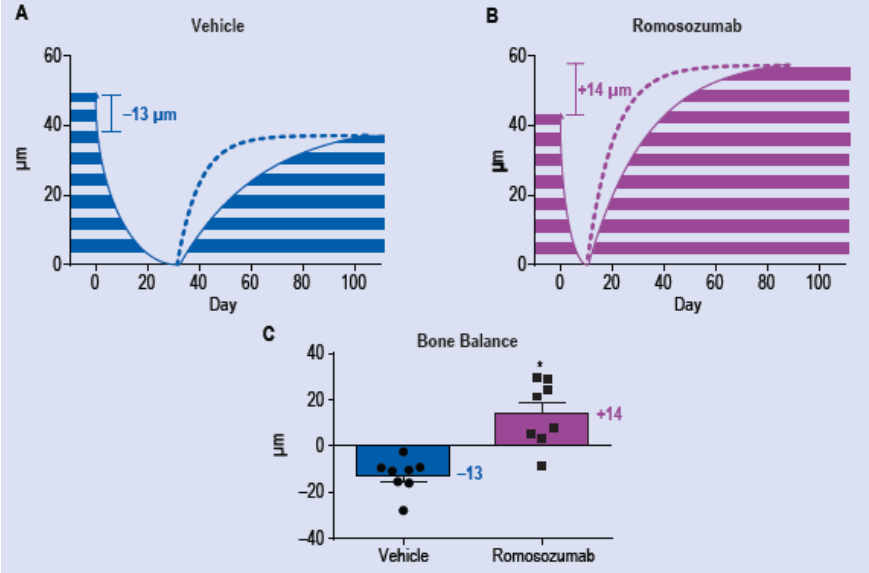
	Histomorph-ometry (cortical radius/tibia)	Transient stimulation of intracortical remodeling from Wk 12-Wk25 (max at Wk 16), in radius>>tibia, based on evaluation of fluorochrome-labelled bone at several time points At 6 months, BFR/BS increased (n.s.) at endosteal and periosteal surfaces, similar to 12-mo study 107903. Significant increase in Haversian BFR/BS was consistent with increased intracortical remodeling and small nonsignificant 40% increase in porosity in radius. No significant change in cortical geometry (thickness, area) in tibia and radius. Decrease in Ec.E.Pm mainly in tibia.
	Mechanical testing	Radial diaphysis was weaker in AMG treated group (consistent with BMD data) but that appeared due to fact that 3 mg/kg animals had lower BMC at start of Tx (possibly due to exclusion of several ADA+ animals). This was confirmed by observed increases in peak load, yield load and stiffness when using pre-Tx BMC as covariate, and also by the lack of effects on intrinsic strength parameters, except for a small but significant decrease in radius diaphyseal yield stress (-8%). Correlations between radius meta- and diaphyseal BMC and Fu or AUC were unchanged by 3 mg/kg AMG. FEA confirmed lack of an adverse effect on yield load (Fig. 8). **Figure 8. Romosozumab Improved Finite Element-estimated Strength at the Radius in OVX Cynomolgus Monkeys** 
Reviewer Comments		Study provided detailed information on bone efficacy/safety of tibia and radius. Decrease in radius cortical bone BMD may have been due to increased intracortical modeling, but slightly increased cortical thickness due to bone apposition at both outer and inner surfaces appeared to compensate for potential negative strength effect. Decrease in tissue BMD of radial shaft may have contributed to the decrease in yield stress at 6 months. Cause of effect on bone tissue BMD (BMD of bone material), also observed in other studies, is unclear and may be an artifact. There was no clear signal of adverse effects on bone material strength by AMG (eg increased brittleness). Correlations between BMC and extrinsic (corrected) strength parameters, or BMD and intrinsic strength parameters, respectively, were not affected, suggesting the same.

Effect of Romosozumab on Bone Remodeling Kinetics in the Cynomolgus Monkey
(Study Nr.20150071)
(Amgen, Inc)(Non-GLP, Report date Jan 26, 2016)

The study objective was to determine the effects of romosozumab on trabecular (vertebral) bone remodeling using a kinetic reconstruction analysis and examination of resorption depth in monkey lumbar vertebrae. The tissues used in this study were from a study to investigate the effects of romosozumab and two other drug treatments for 28 weeks on fracture repair in a critical gap defect model in the monkey ulna.

Procedure	Animals	Cynomolgus monkeys (males, 10-12 years old) (aged/mature)
	Doses	AMG785: 0 and 30 mg/kg, Q2W, (30 mg/kg = 22x human AUC)
	Group size	10-12/ group
	Duration	28 weeks
	Procedure	Densitometry (DXA, uCT) Histomorphometry: o Fluorochrome labels were administered periodically over the time course. o L3 vertebral bodies from N= 9/grp were analyzed by histomorphometry. Kinetic reconstruction of remodeling process was performed. Remodeling formative sites were defined by an underlying scalloped cement line. o Final W.Th was measured in completed packets that contained any label to provide an average effect across the treatment duration; those that contained tetracycline labels, administered early in the treatment period, were separately evaluated to capture the early treatment effect. Final W.Th was also projected for packets near completion at the end of the study to reflect the treatment effect after 28 weeks. o Resorption depth was measured in packets at the reversal line without osteoid with pre-osteoblasts, by counting lamellae from the deepest point outward along the surface until a quiescent surface was reached. After animal exclusions, final N analyzed was 8/grp.
Results	Densitometry (DXA, uCT)	Densitometric parameters BMD, BMC, area, and BV/TV were increased in the healed gap defects in AMG vs vehicle-treated
	Histomorph-ometry	AMG caused a ca. 2X increase in W.Th in active BMUs, which was associated with an increase in MS/OS reflecting improved osteoblast efficiency. Ob.S/BS was not measured. Romosozumab reduced eroded surface % (ES/BS) significantly by ca. 70%, explained by a marked reduction (ca. 66%) in the length of the resorption (i.e. resorption + reversal) period. Formation period FP was unaffected. Romosozumab reduced final resorption depth by 13%, and together with the increase in W.Th, this resulted in a positive bone balance (+14 μm), in contrast to the negative bone balance observed in controls (-13 μm) (diagram below). Despite the decrease in erosion depth, the rate of osteoclastic resorption appeared to be increased during the shortened resorption period (diagram below). Vertebral trabecular bone BFR/BS (surface referent) was increased. This was also observed in 12-month OVX monkey study (107903), in cancellous bone of vertebrae and femur neck (at 52 wks), and ilium (at 13-27 wks), at QW doses of 3 or 30 mg/kg.

Reference ID: 4081796

		This diagram shows the positive bone balance in remodeling sites in vertebra of monkeys treated with (A) vehicle or (B) 30mg/kg AMG785. Bone balance in BRU is shown in (C).  *Solid lines outline the resorption and formation phases of the bone remodeling cycle, with the dashed lines representing the thickness of osteoid overlaying mineralized bone. Colored and white lines represent lamellae with a thickness of 3.2 µm. Bone balance, representing the difference between resorption depth and final W.Th, was negative in the vehicle control group (blue) and positive in the romosozumab (purple) group. Data are mean ± SEM. *P < 0.05 vs vehicle by t-test. n = 9/group.*
Conclusions		Romosozumab increased wall thickness and decreased final resorption depth, yielding a positive bone balance that probably contributes to the increased bone volume and mass. RsP+RvP were decreased and FP increased which explains reduction in eroded surface at trabecular surfaces.
Reviewer Comments		Study provided detailed information on the dynamic events in a bone remodeling unit (BRU) in monkey vertebra, specifying the MOA of anti-Scl Ab AMG785 at the tissue level. Sponsor did not distinguish resorption from reversal period, and the calculated 'resorption period' was in fact the combination of resorption and reversal periods. According to Reviewer's analysis of histomorphometry data from Study 107903 (cancellous ilium at 13 wks, and femoral neck at 12 months), AMG785 caused a larger reduction in reversal ("resting") period than in resorption period. The positive bone balance in the bone remodeling unit may also be achieved during modeling-based bone formation (MBF) at the various bone surfaces

The Effects of AMG 785 in a 10-Week Bone Healing Study Following Osteotomy of the Fibula in Young Male Cynomolgus Monkeys
(Study Nr.108288)
(b) (4)
(Non-GLP, 2015)

Study goal was to evaluate effects of romosozumab on diaphyseal bone healing, but also on bone modeling/ remodeling, tissue composition/mineralization and microarchitecture.

Reviewer comment:
The original study report only describes data on the effects of AMG785 on fibula fracture healing. Subsequent amendments to the report included three types of exploratory analyses (Appendices 36/37, 38/39, and 40). The latter two were evaluations of bone matrix quality (App 38/39) and of tissue-level mechanisms of Scl-Ab-mediated bone formation (App 40). The data were previously published (Ross et al, JBMR 29: 1597, 2014; and Ominsky et al, JBMR 29: 1424, 2014, respectively). App 36/37 included 3D histomorphometry data (C. Hernandez, Cornell Univ)

Methods	Animals	Male monkeys (4-5 yrs old, adolescent). Animals underwent bilateral fibular osteotomy with internal stabilization with pin.
	Doses	AMG785: 0 and 30 mg/kg, Q2W (not weekly), SC 30 mg/kg = 22x human AUC (data from Study 107903 in OVX females)
	Treatment duration	10 weeks, starting day after surgery
	Group size	Initial size: N= 21 control and N=22 AMG785. N =4 AMG-treated were excluded from analyses due to undetectable serum levels in Wk 6. Final group size: N=21 control and N=18 AMG785. Further exclusions reduced grp size for biomechanical testing to N=12/grp, and for histomorphometry to N=9, 10 (ctrl, AMG).
	Methods/ Endpoints	DXA (in vivo), biomarkers, PK, radiography, ex vivo DXA/pQCT, histomorphometry (HMM), biomechanical testing of fibula, vertebrae and femur Additional analyses: o 3D-histomorphometry (vertebral cores) o Histomorphometric characterization of Modeling Bone Formation (MBF) (formation on quiescent surfaces) and Remodeling Bone Formation (RBF) (formation on eroded surfaces) (L2 and femur diaphysis) o Backscattered scanning electron microscopy (bSEM) (mineralization kinetics) (vertebra L2 and femur midshaft); Fourier transform infrared microspectroscopy (FTIRM) (mineral/matrix properties) (endocortical and intracortical BSUs/compartments of femur diaphysis; trabecular BSUs of L2 vertebra)
Results	Observations/ Pathology	After 10 weeks of healing, fibula fractures in AMG group had less callus cartilage, smaller fracture gaps, and contained more bone and less fibrovascular tissue.
	Markers, DXA, pQCT,	Increase in P1NP and CTx, and significant increases in bone mass and bone strength in AMG-treated male monkeys in both non-fractured and healed bone.

Reference ID: 4081796

	HMM, strength testing	Non-fractured bone: Increases in DXA/pQCT BMC and BMD of lumbar spine and cortical thickness of distal radius, and increased bone formation indices at endocortical and periosteal surfaces in femoral shaft and neck. Increase in bone mass in spine and proximal femur were due to greater trabecular thickness in cancellous bone (vertebrae and femur neck). Spine strength was increased along with mass. Fibula: Increased callus BMC, torsional bone strength and better fibula fracture healing in AMG-treated male monkeys. Improved correlation between BMC and max torque for fractured/healed fibula in AMG-treated vs controls.
	Exploratory analyses	3D histomorphometry: AMG caused no new trabeculae, but did cause trabecular thickening and converted rod-like trabeculae into plate-like trabeculae.
		Histomorphometry to determine "tissue level mechanisms" responsible for AMG785-induced bone formation (Ominsky et al 2014): o Marked increase in extent of MBF on trabecular and endocortical surfaces by AMG. o No significant effect on extent of RBF despite decreased eroded surface (ES/BS and ES/OS) on trabecular and endocortical surfaces; this was explained by likely increase in formation and total remodeling periods concomitant with increase in wall thickness (based on extent of observed fluorescent label) o Increase in proportion of RBF and MBF containing sequential labels from week 2 indicated increase in lifespan of formative site.
		Bone matrix quality determination (Ross et al 2014): Mineralization kinetics (BSEM) (L2, femur shaft) o Mean global mineralization of trabecular and cortical bone (vertebra L2, femur) relatively unaffected o Small increase in the number of trabecular bone pixels with a low mineralization value, and modest decrease in the standard deviation of BMDD distribution in LV2. The latter made trabecular bone slightly less heterogeneous. Matrix/mineral properties (FTIRM) (bone age-specific measurements in L2 and femoral shaft compartments) o No effect of AMG785 on mineral-to-matrix ratio, crystallinity, or collagen cross-linking, in endocortical, intracortical, or trabecular compartments (labelled BSUs). o Non-significant trend toward accelerated mineralization intracortically (temporarily increased mineral:matrix ratio in intracortical compartment at 0.5-2 wks ie young bone-tissue age), but not in endocortical or trabecular compartments. o Significant 10% increase in carbonate substitution for tissue older than 2-weeks in the trabecular compartment (mechanical significance unlikely).
Reviewer Comments		The small BMDD decrease in trabecular bone may be related to the slight tissue BMD decrease measured by microCT and HRpQCT in trabecular bone in other monkey studies. However, there was no effect on BMDD in cortical bone in which tissue BMD decreases had also been seen. The significance of the decrease in trabecular bone mineralization heterogeneity is unclear. The Sponsor indicated that the effect was a result of the increase in number of pixels in the 5%-95% range (sharper peak). Decreased heterogeneity has been observed in long term bisphosphonate treated bone. However this is reflected by a shift and a narrowing of the distribution curve towards higher

Reference ID: 4081796

		BMDD values. It is not clear how the decrease in heterogeneity with AMG785 could affect bone quality. A temporary increase in mineralization in intracortical bone may be adverse (increased brittleness), however biomechanical measurements and calculation of bone material (intrinsic) properties did not reveal adverse effects on bone strength in any of Sponsor's animal studies. However, these measurements were made after prolonged dosing and may not show early effects. Reviewer concludes that there were slight changes in bone properties that signal some minor concerns about bone quality

AMG785 and hPTH(1-34): Exploratory 26-Week Subcutaneous Toxicology Study in the Sprague Dawley Rat
(Study 115776)
(Amgen, Inc) (Non-GLP mechanistic study)

Methods	Animals	Sprague Dawley rats, 8-wks old, dosed with vehicle, AMG785 (3 or 50 ug/kg/wk) or human PTH1-34 (75 ug/kg/day) for 4 or 26 wks.
	Group size	N=10/s/g after exclusion of AMG785-ADA-positive animals
	Endpoints/ Methods	Assessments included bone mass and histomorphometry parameters (vertebrae, femur). Also performed were immunostaining (Runx2, nestin) and cell histology evaluation to distinguish osteoprogenitor (Opg) from osteoblasts and lining cells (various bone sites).
Results	Bone markers	Scl-Ab: Early increase in formation markers declining markedly after 4 wks with little effect on resorption markers; PTH: more sustained increases in formation and resorption markers.
	Histomorph-ometry/ histology	Greater increases in cancellous and cortical bone mass in AMG785 vs PTH treated animals, correlating with higher BFR in AMG785 vs PTH treated animals in spine/mid-femur at 4 wks. Attenuation of BFR/BS after 4 wks was larger in AMG785 than in PTH group. Increase in resorption indices Oc.S/bS in vertebrae by PTH but not AMG785. Similar increases in Ob.N and Ob.N/Ob.S at 4 wks in AMG785 and PTH treated animals. However, larger MAR at 4 wks in AMG785 vs PTH-treated animals suggested increased individual Ob cell activity At Wk 26, increase in BFR/BS by AMG785 was maintained by lower Ob.N, lower Ob.N/ObS (ie higher bone surface area occupied per osteoblast) and higher MAR vs. PTH. At Wk 26, the lower Ob.N/Ob.S was associated with lower number of Opg cells (Opg.N); Opg.N generally correlated with Ob.N. Lower Ob.N at 26-vs-4 wks in AMG vs PTH groups possibly reflected larger degree of self-regulation of bone formation.
Reviewer Comments/ Conclusions		Compared to PTH, Scl-Ab can cause increases in cancellous bone mass with same/fewer number of osteoblasts, by increasing the osteoblast "footprint" and increasing individual osteoblast activity. This is coordinated with less stimulation of pre-progenitor cells and progenitor cells by Scl-Ab vs PTH, ie, more 'self-regulation'. These differences may be related to the pronounced osteosarcoma development by PTH but not AMG785 in rats.

Temporal effects of r13c7 on bone; effects of withdrawal or transition to OPG-Fc
(Study Number. R20110286)
(Amgen; non-GLP)

Methods	Animals	Female Sprague Dawley rats were sham-operated or OVXed at 4 months of age, and underwent a 2-month bone depletion period.
	Doses	After bone depletion, rats were treated SC, QW, with vehicle or **25 mg/kg** r13c7 for **6, 12, or 26 weeks** (n=12/group). Additional groups of OVX rats were treated for 6 weeks with 25 mg/kg r13c7 (SC Q1W, n=12) followed by 20 weeks of VEH (SC, 2QW, n=12), 10 mg/kg OPG-Fc (SC, 2QW, n=16), or 25 mg/kg r13c7 Q4W (n=12). Sham-operated rats were terminated at baseline (n=10) and after 6, 12, and 26 (n=12 each).
	Group size	N=12 or 16/grp
	Endpoints/ Methods	Endpoints included in vivo longitudinal assessment of DXA BMD and serum biomarkers; ex vivo microCT (Wks 6, 26), bone strength (Wks 6 and 26), histomorphometry (Wks 6, 12 and 26), osteoclastogenesis assay (Wks 6, 12, 26) and vertebra and tibia gene expression.
Results (r13c7 effects)	Observations /Pathology	Reduced ex vivo osteoclastogenesis in bone marrow collected from femur at Wk 6 and 12. Increases in gene expression of Wnt inhibitors SOST and DKK1 at the vertebra through Wk 26.
	Bone markers	Increases in bone formation markers OC and P1NP, which peaked early and returned toward control levels over time. Transient mild decrease in bone resorption biomarker TRACP-5b.
	Histomorph-ometry	At week 6, histologic bone formation rate (BFR/BS) was significantly increased on trabecular surfaces in the vertebra and proximal tibia, and on periosteal and endocortical surfaces of the tibia diaphysis. The increase in BFR/BS attenuated over time, remaining elevated on tibial, endocortical and trabecular surfaces, but approaching control levels by Wk 26 on tibial, periosteal and vertebral trabecular surfaces. R13c7 clearly **decreased bone resorption** as reflected by decreases in resorption indices in cancellous bone of L3 and proximal tibia (ES/BS, QS/BS, OcS/BS) and in tibial cortex (Ec.ES/BS – **marked** effects) at Wks 6, 12 and 26. This resulted in increases in trabecular thickness (spine and tibia) and cortical thickness (tibia), the latter mainly due to endocortical bone accretion. This was reflected by DXA and uCT data on bone mass.
	Densitometry	Progressive increase in bone mass at the lumbar spine and whole hindleg (in vivo DXA). Increased bone mass was also identified by ex vivo microCT analysis of several bone sites.
	Mechanical testing	Increase in bone strength (extrinsic/whole bone) of L5, femur shaft and femur neck at Wk 6 and 26. Neutral-to-positive effect on calculated intrinsic strength parameters for L5 and femoral shaft. Bone mass (uCT-vBMC) and bone strength (Fu and AUC) were positively correlated, similarly for all groups.

Reference ID: 4081796

	Other findings	Discontinuation of Scl-Ab treatment at week 6 caused loss of bone mass and strength over time. This reversal was prevented by transition to rat OPG-Fc. Transition to once-monthly r13c7 dosing after Wk6 preserved previous bone mass and strength gains, but did not achieve the increases observed with continued once weekly dosing.
Reviewer Comments/ Conclusions		• Neutralization of Scl in OVX rats by rat-specific Scl-Ab r13c7 (weekly dosing) caused increases in trabecular, endocortical and periosteal bone FORMATION, more prominently in Wk 6 than in Wks 12 and 26. • Scl-Ab r13c7 also caused marked sustained suppression of trabecular and endocortical bone resorption (this is unlike effect of AMG785 which did not clearly affect resorption markers or histologic indices in OVX rat). • This dual effect led to increases in bone mass and strength at various skeletal sites. Bone quality (correlation BMC vs strength) was maintained. This effect was more similar to the effect of AMG785 in postmenopausal women than that of AMG785 in the OVX rat. • After dose discontinuation, treatment with RANKL inhibitor (OPG) or less frequent treatment with r13c7 preserved the gains in bone mass and strength. This correlates with the proposed clinical use of romosozumab for 12 months, followed by a change to treatment with denosumab (Prolia; a RANKL inhibitor).

r13C7: Exploratory Single Dose Subcutaneous Toxicology Study in the Aged Ovariectomized Female Sprague Dawley Rat
(Study 105877)
(Amgen, Inc) (Non-GLP mechanistic study)

- 6-month old OVX rats were treated with a single dose of rat Scl-Ab r13c7 (100 mg/kg) (N=20F/grp) which caused strikingly similar transcriptional profiles across all 3 osteoblastic cell types (lining cells, osteoblasts, osteocytes) in lumbar vertebrae.
- Only a relatively small number of genes associated with canonical Wnt signaling was activated, particularly Wisp1 and Twist1.
- ECM genes were also upregulated consistent with bone modeling.
- Scl-Ab also regulated a limited number of genes related to cell cycle arrest and B cell development.

r13C7: 26-week Subcutaneous Toxicology Study in the Aged Ovariectomized Female Sprague Dawley Rat With an 18-week Recovery
(Study 115777)
(Amgen, Inc) (Non-GLP mechanistic study)
(Taylor et al, Bone 84: 148-159, 2016)

- 8-month old OVX rats were treated with rat Scl-Ab r13c7 (0, 50 mg/kg), once weekly for 26 weeks, followed by an 18-wk recovery period.
- Methodologies included histomorphomtery, pQCT, stereologic analysis, LCM (laser capture microdissection) to separate bone cells, RNA extraction, microarray, and Taqman, and gene network/function analysis.

- Data showed a rapid and marked increase in BFR/BS and Ob.N with maximal BFR/BS on Day 29, followed by a progressive decline in BFR/BS and Ob.N through dosing Day 183. During recovery, BFR/BS was initially suppressed and then returned to control levels.
- Bone resorption (OcS/BS) was dose-dependently decreased from Wk 4-26, ie during the entire dosing period.
- Transcriptional changes in Wnt and mitotic cell genes occurred according to specific time patterns in the three dfferent types of bone cells (OB=osteoblasts, LE=lining cells, Ocy=osteocytes) (Fig. 5, below)
- Reduction in osteoprogenitors preceded the reduction in osteoblasts and bone formation and correlated with significant transcriptional changes in the osteocyte (Fig. 5A).
- Transcriptional changes included induction of signaling pathways that are known to regulate Wnt signaling and suppress mitogenesis and cell cycle progression.
- The data suggested that regulation of canonical Wnt signaling is complex and multifactorial and involves (a) induction of pathways such as TGF-β1, Hippo, and noncanonical Wnt that are recognized to modulate the output of canonical Wnt signaling, and (b) induction of extracellular inhibitors such as Sost and Dkk1. However, the most significant signaling changes occurred in pathways that would limit cell cycle progression (Fig. 5B, below).
- The temporal relationship between these transcriptional changes and changes in BFR/BS suggests that suppression of mitogenesis and cell cycle progression may contribute to the self-regulation of bone formation observed with long-term Scl-Ab treatment.
- The induction of p53 and other tumor suppressor signaling would be expected to limit mitogenesis and reduce the potential for bone carcinogenicity.
- RANKL/OPG ratio was suppressed during the 26-week dosing phase, consistent with the effects on bone resorption parameters.
- Trabecular bone mass progressively increased through Day 183, and declined during recovery. Oc.S/BS (% osteoclast covered surface) was decreased during the dosing and increased in the recovery period, with corresponding changes in expression of major regulators of osteoclastogenesis. Changes of genes important for osteoclastogenesis regulation mirrored the histologic changes in bone resorption.
- The potential MOA of acute and chronic Scl-Ab exposure is presented in Fig.9 below.

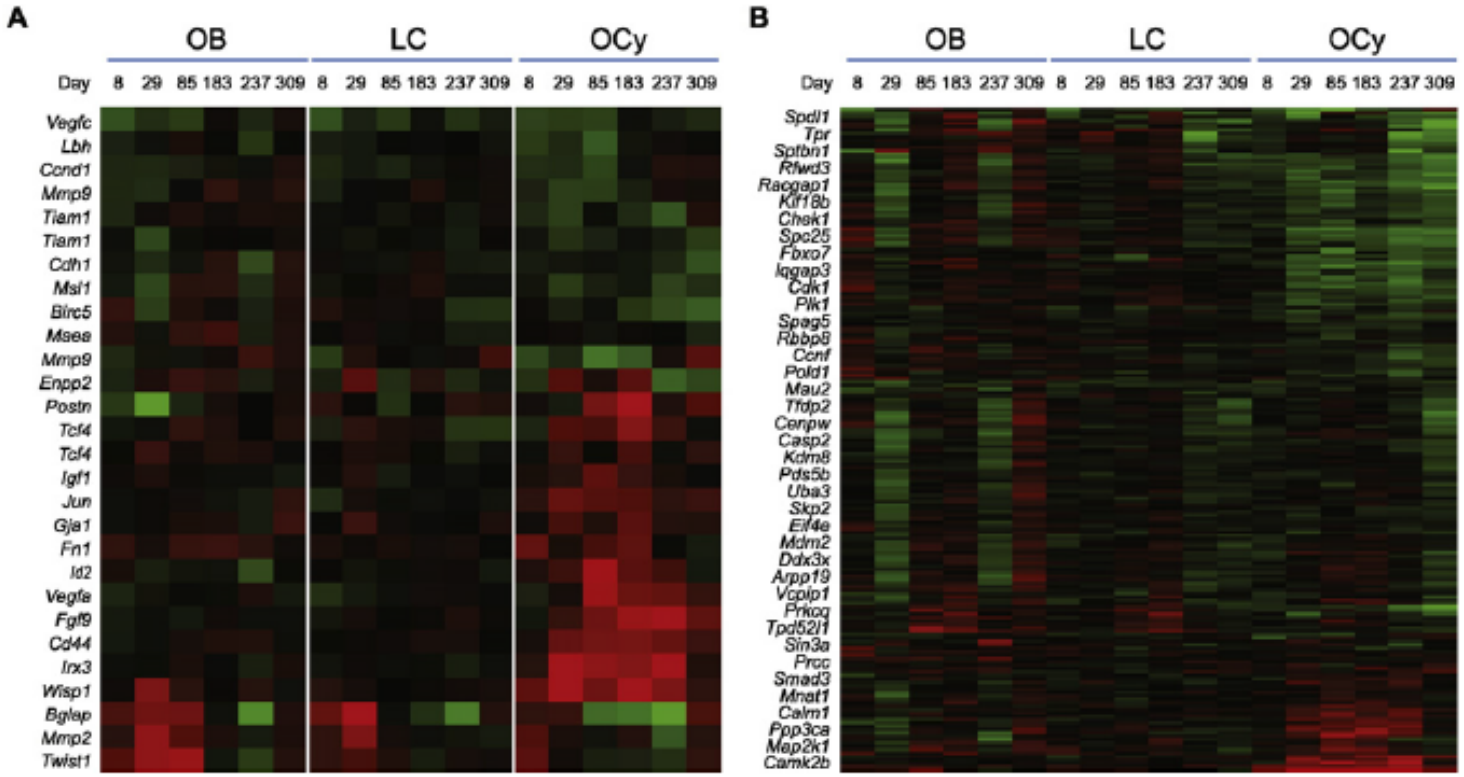


Fig. 5. Time-dependent gene expression patterns in the different OB lineage cell types at 50 mg/kg Scl-Ab. (A) Canonical Wnt target genes (Nusse list). (B) Mitotic cell cycle genes (GO:0000278). Columns represent groups of biological replicates at each time point and rows represent specific genes (~35% of genes labeled in panel B). Each cell contains color-coded $\log_2$ ratios (treated group mean/time-matched VEH group mean).

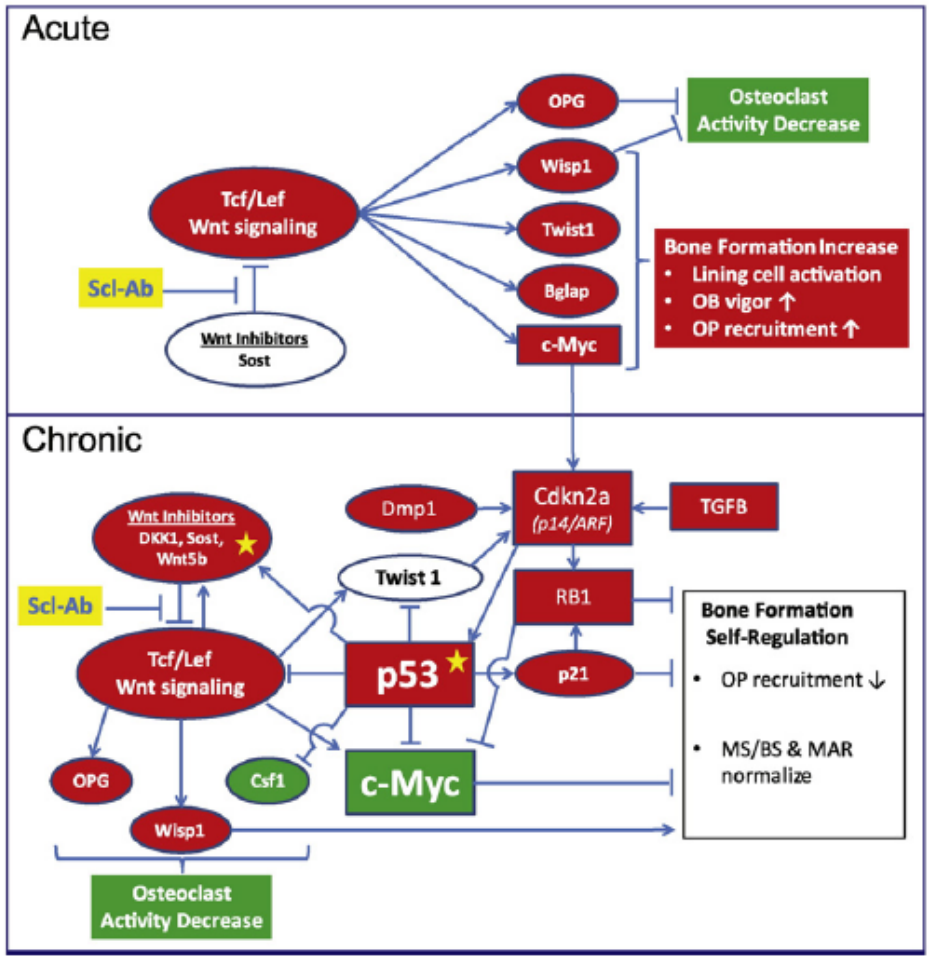


Fig. 9. Potential mechanism of action of Scl-Ab with acute and chronic administration. DEGs (ovals), upstream regulators (rectangles), and histomorphometry data from the osteocyte-enriched laser capture microdissection samples from ovariectomized rat vertebra treated with Scl-Ab for up to 183 days were incorporated into a hypothetical gene network. Associations between genes that were increased (red) or decreased (green) are illustrated. Pathways that have been reported to respond to skeletal loading are annotated with a star. Within the first week of treatment, Scl-Ab activated canonical Wnt signaling, activating a defined set of Wnt target genes that have been associated with increased bone formation and decreased bone resorption. With extended treatment, the nature of Wnt signaling changed, likely driven by increased p53 (and decreased c-Myc) signaling as well as by increased Wnt inhibitor synthesis, resulting in attenuation of the bone-forming response.

Clinical Histomorphometry
(Bone Biopsy Substudy of Phase 3 Study 20070337)

> *This information was informally reviewed in order to better interpret animal findings and their potential relevance to clinical outcomes. Please refer to the clinical review for additional information and interpretation of clinical findings.*

In postmenopausal women treated with SC romosozumab 210 mg QM vs placebo for 12 months (Study 20070337), histomorphometric analysis of iliac biopsies (2 and 12 months) showed the following effects of romosozumab:

- Significant decreases in erosion surface ES/BS% and Oc.S/BS at the cancellous surface (Effect at Month 12 larger than at Month 2) and decrease in endocortical Ec.ES/BS (Month 2 data only), consistent with the decrease in systemic resorption markers (e.g. serum CTx).
- Significant increases in Tb.Th (35%) and W.Th (ca. 10%).
- Increase in cortical thickness (Ct.Th) (ca. 10%) at Month 12 but not Month 2.
- Increases in MS/BS and BFR/BS at cancellous and endocortical surfaces at Month 2, consistent with the (transient) bone formation marker P1NP increase. At Month 12, cancellous BFR/BS was similar to placebo (cortical Month 12 data not available).
- Increase in intracortical/Haversian bone formation based on ca. 2X increase in MS/BS (% mineralizing surface) (statistically significant) and intracortical BFR/BS (not-statistically-significant), but no change in MAR (osteoblast activity parameter).
- No effect on cortical porosity, thus intracortical resorption was likely increased too.
- Marked decrease in Ps.BFR/BS (due to decreases in MS/BS and MAR) at Month 2 (change from baseline) that was marginally significant (p=0.08), in a small number of biopsies. However, there was no change in average Ps.BFR/BS at Month 2 in a larger study group. Data on Ps.BFR/BS at 12 months were not available.
- Mlt increase in cancellous bone at Month 12, and slight significant O.Th increase at Month 2 but not Month 12. However, in light of normal bone histology, the data did not appear to indicate a significant mineralization defect.

Denosumab (Dmab, 60 mg SC, once every 6 months) administered in the 12-24 month period, after placebo or 210 mg/mo romosozumab, had the following effects:

- Increase or maintenance of the romosozumab-induced increase in bone mass (i.e. BV/TV, Tb.Th).
- Decreases in cancellous ES/BS and Oc.S/BS, as compared to placebo (0-12 mo). The decreases appeared to be smaller than those caused by romosozumab, indicated by increases in these parameters as compared to those in romosozumab-treated (0-12 mo). Data on effect of Dmab on Ec.ES/BS were not available.
- Reversal of increase in W.Th in romosozumab-treated, at 24 vs 12 months.
- Decrease in cancellous MS/BS and BFR/BS at 24 vs 12 months, in both groups, as expected based on anti-resorptive effects of Dmab; values at Month 24 were similar in both groups.
- Decreased AcF in both groups at Month 24 vs Month 12.
- No effect on Co.Po% at Month 24 vs 12; no difference between groups.
- No effect on O.Th or Mlt at Month 24 vs 12 and no difference between the 2 groups.

- Data on Ps.BFR/BS in Dmab-treated were not available.

Reviewer's Comment:
The bone histomorphometry data from rat, monkey and human studies suggests that the bone effects of romosozumab are similar across species. This supports the clinical relevance of the information from the animal studies about the effects of romosozumab at various skeletal sites and surfaces.

		Postmenopausal Women*			OVX Monkey**	
		Resorption markers/indices	**Formation markers/indices**		**Resorption markers/indices**	**Formation markers/indices**
Markers	Formation		↑↑			↑↑
	Resorption	↓			↑	
HMM indices	Trabecular	↓	↑↑		↓	↑↑
	Endosteal	↓	↑↑		↓	↑↑
	Intracortical	ND (↑)	↑		ND (↑-↑↑)	↑
	Periosteal	ND (↑)	↑		ND (↑↑-↑↑↑)	↑↑↑

* Study 20070337 (Phase 3)
** Studies 107903 and 118025
HMM= histomorphometry
ND = No Data
( ) Effects in parentheses are extrapolated by the reviewer based on effects on formation markers/indices and structural parameters

Primary pharmacology studies not reviewed

The following studies were not considered critically relevant for the BLA application and were not reviewed:

Study Number	**Title**
R20110286	Treatment with Sclerostin Antibody Followed by an Anti-Resorptive Agent in Ovariectomized Rat Model
R20070773	Effects of Subcutaneously Administered Ratized Sclerostin Antibody (r13C7) Alone or in Combination With Alendronate on Bone in Ovariectomized (OVX) Rats With or Without Alendronate Pretreatment
R2006054	Dose-dependent Effects of Subcutaneous Administration of Murine Sclerostin Antibody (m13C7) on Bone Formation and Bone Mass in Ovariectomized Sprague Dawley Rats
R20120173	Effects of Sclerostin Antibody Retreatment on Bone in Ovariectomized Rats
R20150070	Retreatment with Scl-Ab in Combination with OPG-Fc in OVX Rats

4.3 Other Pharmacology

Summary

Quantitative RT-PCR analyses of human tissues showed SOST expression at ≥ 1 copy/cell (based on 30 pg RNA/cell) in pulmonary artery, left atria, and kidney. Another study showed consistent expression across species in bone and aorta (not rat aorta), with expression in kidney limited to humans.

Testing in animal models relevant for the target patient population was also performed. Scl-Ab was shown to increase bone mass in the fracture callus, resulting in improvements in functional strength in a rodent fracture repair model.

Scl-Ab was also effective in increasing bone formation and preventing the disease-associated decrease in bone mass and strength in models of androgen ablation, inflammation, and skeletal disuse/unloading.

Since sclerostin is expresssed in chondrocytes, the effects of Scl-Ab and Scl-Ab Fab were tested in the rat medial meniscal tear model of osteoarthritis (OA). Results did not indicate a significant effect on the progression of induced osteoarthritis.

In vitro studies

Study Number	Type of Study	Methods	Findings
119940	Tissue expression profile SOST	Human tissue panel Xpressway® Profile qRT-PCR was used	Human tissue expression of SOST at ≥ 1 copy/cell (based on 30 pg RNA/cell) in pulmonary artery, left atria, and kidney (aorta and mineralized tissues not included in panel).
119937	mRNA expression SOST	The study evaluated the mRNA expression of the SOST gene, encoding for sclerostin in a broad range of tissues from normal mouse, rat, cynomolgus monkey, and human, using RNA sequencing.	SOST mRNA is most consistently expressed across species in bone (not evaluated in human) and aorta (but not in the rat). Expression in kidney was limited to human. Levels in other tissues were considered (1) not detectable, (2) found in only one species and not others, (3) found in one species, but data from other species were not available to confirm the finding.

In vivo studies

Study Number	Type of Study	Methods	Findings
R20090220	Temporal effects of r13c7 on **closed fracture healing**	Male SD rats underwent a standard closed femoral mid-diaphyseal fracture stabilized with an intramedullary pin at 12-weeks of age (closed Fx model). Animals were injected SC Q2W with vehicle or r13c7 at 25 mg/kg for 1, 2, 3, 5, 7 and 9 weeks (n = 8/grp for Wks 1-2; n = 26/grp for Wks 3-9). Treatment was initiated 1 day post fracture. Endpoints included histomorphometry, densitometry (DXA, pQCT and micro-CT) and bone strength testing over the time of healing through 9 Wks post fracture.	Scl-Ab r13c7 increased bone mass in the fractured femur by Wk 3, with increases in torsional strength by Wks 5 and 9. Tx with r13c7 induced increases in bone volume and decreases in marrow volume in the external callus. However, it did not affect the fibrous or cartilaginous portion of the callus. In the intact femur, r13c7 increased bone formation in distal metaphysis and midshaft from Wks 2 to 9, corresponding to increases in DXA BMD. Scl-Ab r13c7 caused a transient increase (Wk 3 to 7) in longitudinal growth rate of the intact distal femur. However, it returned to control levels at Wk 9 and did not impact the overall length of the femur. The results indicated that Scl-Ab improved fracture healing in this animal model mainly by increasing bone volume in the external callus.

Studies not reviewed in detail

It was show in other studies that Scl-Ab was effective in increasing bone formation and preventing disease-associated bone mass and strength decreases in models of androgen ablation, inflammation, and skeletal disuse/unloading. Effects of Scl-Ab and Scl-Ab Fab were tested in the rat medial meniscal tear model of osteoarthritis (OA), based on expression in chondrocytes. Results did not indicate a significant effect on the progression of induced osteoarthritis.

Study #	Title
R20100227	Effects of Sclerostin Antibody on Bone in Orchiectomized Rats With Established Osteopenia
R20120147	Neutralization of Sclerostin by Ratized Sclerostin Antibody in Inflammatory Bone Loss
R20100239	Use of Sclerostin Antibody to Inhibit Skeletal Deterioration Due to Reduced Mechanical Loading in Adult Female Mice
ROA/AMG-14	Effects of Rat Sclerostin Antibody (25 mg/kg, sc, 2X/Week) on 3 Week Duration Rat Meniscal Tear Induced Osteoarthritis
ROA/AMG-15	Effects of Sclerostin Fab Antibody (385 µg, IA, 2X/Week) on 3 Week Duration Rat Meniscal Tear Induced Osteoarthritis

Reference ID: 4081796

Secondary Pharmacology/Theoretical Safety Issues

Summary

The Sponsor presented an extensive discussion of theoretical/potential safety issues of romosozumab, based on gene and/or protein expression of sclerostin in various tissues (Table 1, below), and the potential activation of Wnt signaling by AMG785.

Table 1. Most Consistently Reported Tissues That Express Sclerostin, Methods of Detection, Species, and Reporting References.

Tissue	Detection method	Species	Reference
Bone (osteocytes)	RT-PCR; RNA-Seq; IHC; ISH	Human, mouse, rat monkey	(Brunkow et al, 2001; Roudier et al, 2013; van Bezooijen et al, 2009); Study 119937; Study 105783
Cartilage(chondrocytes)	RT-PCR; IHC; ISH	Human, mouse, rat sheep	(Brunkow et al, 2001; Chan et al, 2011; Roudier et al, 2013; van Bezooijen et al, 2009)
Aorta/pulmonary artery	RT-PCR;RNA-Seq; Mass Spectroscopy; IHC	Human; mouse, monkey	(Brunkow et al, 2001); Study 119940; Study 119937; Study 105783
Calcified vascular smooth muscle cells and cardiac valves	RT-PCR; Western blot; IHC	Mouse, rat, human	(Brandenburg et al, 2016; Koos et al, 2013; Kramann et al, 2013; Zhu et al, 2011)
Teeth (cementocytes)	IHC	Human; mouse	(Lehnen et al, 2012; van Bezooijen et al, 2009)
Kidney	RT-PCR	Human	(Balemans et al, 2001; Brunkow et al, 2001); Study 119940; Study 119937

IHC = immunohistochemistry; ISH = in situ hybridization; RNA-Seq = ribonucleic acid sequencing; RT-PCR = reverse transcriptase polymerase chain reaction.

The issues were considered in the context of published literature as well as Sponsor's own clinical and nonclinical studies, and included: cancer, osteoarthritis, vascular calcification, increased longitudinal bone growth, hyperostosis, hypercementosis, osteonecrosis of the jaw (ONJ), altered hematopoiesis, sarcopenia, altered glucose metabolism, exacerbation of TNFα-driven inflammatory disease, and atypical femoral fractures (AFF).

Since sclerostin is mainly produced by osteocytes, chondrocytes, cementocytes, blood vessels and vascular muscle cells, and para- and autocrine effects are probably most important, issues in mineralized and adjoining tissues (eg bone marrow), teeth, joints, and the vasculature seem most plausible. Carcinogenicity due to enhanced Wnt signaling in Scl target cells is also a potentially relevant issue.

Cancer

Carcinogenicity was considered a potential concern based on the presumed role of the Wnt signaling pathway in tumor development. Factors considered in the Sponsor's discussion included the temporal effects of sclerostin inhibition on bone cell signaling pathways and the self-regulation of bone formation, the pathophysiology of sclerosteosis and Van Buchem disease, findings in SOST-/- (Scl-deficient) mice, data from long term animal studies with AMG785,

mechanistic data on effects of Scl-Ab vs PTH, and clinical data on cancer incidences. Possible effects on tumor progression were also considered.

The Sponsor concluded that the weight of evidence supports that romosozumab would not pose a carcinogenic risk to the intended patient population. Reviewer essentially agrees with this conclusion and its underlying rationale. The absence of WBC or lymphocyte increases in the rat and monkey toxicity studies, and the lack of leukemia in the animal toxicology and human studies, in particular of acute myeloid lymphoma (AML), a cancer observed in mice with specific osteoblast B-catenin activation, alleviates the concern about hematopoietic cell tumorigenicity.

Although the finding of two osteosarcomas in the high dose male group in the rat carcinogenicity study lacked statistical significance, this Reviewer does not exclude the biological relevance of this finding. The tumor incidence was marginally outside the historical control range and the tumors occurred in the group with the largest bone mass increases. However, whether or not this was a chance finding, the low incidence combined with the 20-fold exposure multiple in the affected group renders its clinical relevance unlikely. Inclusion in the product label is not considered necessary.

Osteoarthritis

Based on the hypothetical role of disrupted Wnt sigaling in osteoarthritis (OA) and the expression of Scl in chondrocytes, there is a theoretical concern about induction or exacerbation of OA. Published literature data, however, are conflicting with regard to the potential for beneficial or adverse effects of sclerostin in OA. Data from Sponsor's nonclinical studies in the rat meniscus tear model (OA model) did not show adverse effects, and data from long term toxicity and bone pharmacology studies did not show degenerative changes in joint cartilage. Sponsor concluded that the available nonclinical and clinical data support the safety of the proposed clinical treatment regimen.

Osteonecrosis of the Jaw (ONJ)

In the pivotal Phase 3 Study 20070337 (12 month placebo or AMG785, followed by 12 months of denosumab), one case of ONJ was seen in the 12-month romosozumab treatment period and one other case was observed in the romosozumab-group after one dose of denosumab given at 12 months. Two cases of ONJ were observed in ongoing Clinical Study 20110142 in Months 22 and 28 during open-label ALN treatment (at least 10 months after AMG785 dosing).

The pathophysiology of ONJ (necrotic exposed bone in maxillofacial region) is not well understood. There appears to be a strong association with suppressed bone resorption/turnover and use of relatively high doses of antiresorptives (e.g. IV bisphosphonates, and RANKL-Ab denosumab). The event also appears to be linked to underlying infection or inflammation and is often preceded by dental surgical procedures. Accumulation of unrepaired microcracks has been put forward as one of the relevant underlying mechanisms (Kim et al, Clin Oral Invest, 20: 2251-2258, 2016).

Based on the established association with anti-resorptive treatment, the ONJ cases in Study 20070337 may be related to the suppression of alveolar bone resorption by AMG785. By

comparison, in the 2-year rat study alveolar inflammation associated with molar attrition (tooth wear) was not associated with bone necrosis. Sponsor argued that in other animal studies with Scl-Ab (intact, OVX, periodontitis, osteotomy or other models) bone resorption was still partially preserved also in the context of local injury, and fracture callus remodeling was not impaired. This is unlike the results from studies with BPs or RANKL-inhibitor denosumab, in which osteoclastogenesis and callus remodeling can be suppressed or delayed. Sponsor also used clinical bone marker and histomorphometry data, which showed suppression of cancellous bone resorption in both AMG785 and denosumab treated, to conclude that the resorption suppression by romosozumab is less generalized than by denosumab and that it is unlikely that AMG785 would pose a meaningful risk for an increased risk of ONJ in the patient population. In this Reviewer's opinion it is uncertain whether or not this conclusion is justified. This is partly because it is not clear whether the animal data that were used to support the lack of risk have adequate predictive value for pharmacologically induced ONJ in humans. Besides, the clinical histomorphometry data showed more suppression of cancellous bone formation in the romosozumab than the denosumab group. An additional study in an adequate rodent model that has shown bisphosphonate-mediated induction of ONJ, may be useful to provide more relevant information.

Atypical femoral fractures (AFF)

In the pivotal Phase 3 Study 20070337, in the first 12-month study period, there was one case of AFF following 3.5 months of romosozumab treatment, in a patient with apparent prodromal pain in the fracture area before study start. Four cases of AFF have also occurred in Study 20110142, an ongoing trial including romosozumab and alendronate (ALN) treatment periods, but only after 16-28 months of ALN exposure, with or without previous AMG785 exposure. There were no cases in Study 20060326, a multi-dose Phase 2 study, including placebo, romosozumab (various doses of 70-210 mg QM or Q3M, up to 24 months), alendronate and teriparatide arms, and denosumab extension and romosozumab (210 mg QM) retreatment phases.

The pathogenesis of AFF is unclear, but is thought to be related to sustained suppression of bone resorption. Prolonged treatment with anti-resorptives (eg bisphosphonates) increases the risk of AFF, and the background incidence of 1 in 100,000 patient-years in the normal population can increase to 50 per 100,000 patient-years in bisphosphonate-treated patients. The suppression of bone resorption may be associated with osteocyte aging and death which could adversely affect a number of microscopic bone tissue processes/properties, e.g. microcrack repair, tissue homogeneity, matrix collagen properties (e.g. due to accumulation of advanced glycation end products, AGEs) and extent of mineralization or crystallinity (Geissner et al, J Biomech, 48: 883-894, 2015). These factors are all considered important for preservation of bone quality and strength. Long term disruption of any of these processes may lead to reduced toughness of bone material, making it more brittle and susceptible to stress fractures (i.e., fracture due to repetitive loading). Animal studies in intact dogs have shown that bisphosphonates can reduce cortical rib bone toughness/material strength after relatively long treatment periods (Burr et al, Bone 71: 58-62, 2015), and this may be related to the occurrence of human AFF. However, an unequivocally predictive marker or mechanical parameter for AFF risk has not been established.

The Sponsor carried out an in-depth evaluation of the weight of evidence for a potential increased risk of AFF. It was concluded that the nonclinical data did not provide any evidence of

bone toxicity, impairments in bone quality (e.g. increased brittleness) or disruption of bone repair or remodeling upon short or long term treatment with AMG785. This Reviewer basically agrees with this assertion, based on the aggregate data from intact and OVX animal studies, several of which included bone mass and biomechanical measurements. There was one femoral/acetabular fracture each in the mid (10 mg/kg) and high dose (100 mg/kg) groups in the 6-month rat and monkey toxicity studies, respectively. However, both cases were not associated with clinical signs and the conclusion that the fractures were probably pre-existing is supported by the lack of a bone safety signal in the other long term nonclinical pharmacology and toxicology studies conducted at equivalent doses.

Intact mice may be an underused model to test effects on bone quality/strength. In mice treated for relatively short periods with alendronate (8 wks), whole bone strength of the femur was enhanced but this was accompanied by an increase in brittleness or decrease in predicted material strength (Uveges et al, JBMR 24(5): 849-859, 2009; Misof et al, Bone 36: 150-158, 2005). By contrast, Scl-Ab decreased femoral bone brittleness in mice (Sinder et al, Bone 71: 115-123, 2015). A study in a pharmacologically responsive mouse model with AMG785 and a bisphosphonate control may provide additional information on cortical bone mechanical properties.

AFF and ONJ are unexpected events with AMG785 treatment, because the product was at least initially considered an anabolic agent. Their small incidence and relatively early occurrence (3-10 months) in the Phase 3 study could support an argument that they are not treatment-related; on the other hand the incidence appears larger than the background incidence, which causes some concern that a specific type or location of Scl-Ab induced resorption suppression, possibly in combination with the enhanced formation effects, may cause unanticipated bone safety issues not signaled by the reassuring nonclinical bone quality data. Additional nonclinical evidence may be obtained from studies to: (1) address the issue of ONJ in an adequate surgical rat model, and (2) assess bone quality in AMG785- or m13c7-treated mice, to help guide future regulatory decisions.

Other theoretical safety issues

Based on nonclinical and clinical safety data, other issues including or regarding vascular calcification, longitudinal bone growth, dental effects, hematopoiesis, sarcopenia, glucose metabolism and inflammatory disease do not appear to be a significant concern. Hyperostosis is the desired effect of the product and at the selected clinical dose of 210 mg QM it does not appear to lead to bone overgrowth with adverse consequences. The animal hematology changes (eg RBC, Hct decreases) at high doses were most likely secondary to the marked bone increases, and have been observed with other products that increase bone mass. The submitted nonclinical information also suggests that issues in other organs in which sclerostin is expressed, such as kidney, heart and lung, are unlikely. Reviewer agrees with Sponsor that the proposed clinical treatment regimen (210 mg romosozumab, QM, for 12 months) is unlikely to pose a significant increase risk related to these theoretical concerns in the intended patient population.

4.4 Safety Pharmacology

Summary

A neurobehavioral study in rats and a cardiovascular/respiratory study in monkeys did not show significant adverse effects at doses of 30, 100 and 300 mg/kg (≤100x human dose, mg/kg basis). Also, in the monkey toxicity studies of 1-month and 6-month duration, there were no effects on ECG or blood pressure at doses ≤300 mg/kg SC or IV, and ≤100 mg/kg SC, respectively. All studies were GLP compliant.

AMG785, being a monoclonal antibody, is not expected to interact with the hERG channel current and a hERG test was not performed.

CNS

Study Number	Organ System	Species / Strain	Route	Doses (mg/kg)	N/s/g	Findings
106335	CNS	Rat/SD	IV	0, 30, 100, 300	5	No signs of neurobehavioral effects upon 14-day treatment

Cardiovascular/respiratory system

Study Number	Organ System	Species / Strain	Method/ Route	Doses/ Concentrations	N/s/g	Findings
105781	Cardio-vascular system	Monkey/ cynomolgus	IV	0, 30, 100, 300	4F	300 mg/kg: increased heart rate, increased systolic/ diastolic/ mean arterial pressure Changes were not continuous (only in light-on phase of study) and within control range; not considered adverse.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Summary

AMG785 was measured using ELISA-based methods, mostly validated ones, in rat, rabbit and monkey sera. In some studies, rodent versions of the humanized antibody AMG785 (rat 13c7 (r13c7) and mouse 13c7 (m13c7)) were used because AMG785 causes anti-drug antibody (ADA) formation in those species. PK of AMG785 was evaluated after SC and IV dosing in rats and monkeys. AMG785 has a high and similar affinity to sclerostin across species, and shares more than 90% sequence homology. Single dose PK was evaluated in rats for all three antibodies (humanized AMG785, r13c7 and m13c7), while only AMG785 was evaluated in monkeys. Multiple dose AMG785 TK was evaluated in rats and monkeys. The PK of two formulations of AMG785, made for first in human (FIH) and commercial administration, respectively, was compared in monkeys.

Reference ID: 4081796

A single dose of AMG785 given by SC injection yields a Tmax of 24h-48h in rats (1-35 mg/kg), and Tmax of 24h-93h in monkeys (3-30 mg/kg). SC bioavailability in rats ranged from 50-100% in the 1-35 mg/kg dose range. SC bioavailability in monkeys was approximately 100% at 100 mg/kg. Plasma $T_{1/2}$ in rats increased and clearance decreased with increasing IV doses, ranging from 6h to 28h at 0.1-10 mg/kg. Terminal T1/2 of an SC dose in monkeys was 36h-88h in the 3-10 mg/kg dose range.

AMG785 exhibits non-linear PK in rats and monkeys, with greater than dose-proportional increase in exposure at doses <10 mg/kg, and linear PK with dose-proportional exposure increases at ≥ 10 mg/kg. Upon weekly dosing in rats and monkeys (3-300 mg/kg), Tmax was 24h-96h and terminal T1/2 upon recovery was 60h-94h (rat) or 74h-116h (monkey). Accumulation was less than 2-fold with weekly dosing. There were no PK sex differences.

There were no tissue distribution studies. AMG785 was transported across the placental barrier. Volume of distribution (Vss) was 37-59 mL/kg and similar to plasma volume (30 mL/kg). No conventional metabolism studies were conducted since AMG785 is an antibody subject to catabolic peptide and amino acid degradation. Clearance may also involve typical IgG removal by the reticuloendothelial system. No specific excretion studies were conducted. Nonclinical PK interaction studies were also not conducted, since DDI risk is very small.

TK data were available from all pivotal repeat dose toxicity studies. Anti-drug antibody (ADA) formation was observed in rats and monkeys resulting in lower exposure and reduced PD response. Hence, ADA positive animals were excluded from TK analysis in studies of 6 months or longer duration. This was not an issue in single dose studies since ADA development generally requires 3 to 4 wks of dosing.

Assays

Assays to detected AMG785 antibodies (ADAs) were ECL-based homogenous bridging immunoassays based on the bivalent characteristics of the antibody binding. The testing strategy consists of a screening assay and a specificity assay. The screening assay is performed to detect the presence of binding antibodies. Samples with a signal-to-noise (S/N) value greater than the cut point are then tested to confirm response specificity. Samples that deplete in the presence of excess soluble drug are reported as positive for the presence of anti- romosozumab antibodies. Also, an ECL-based competitive target binding assay was developed to detect the presence of antibodies that are capable of disrupting the binding of romosozumab to sclerostin in serum samples. This assay also follows a tiered two-assay approach consisting of a screening assay and a confirmatory assay.

Absorption

Single dose studies

Pharmacokinetics and Pharmacodynamics of Antibodies A (m42F4) and B (m13C7) Following Single Intravenous or Subcutaneous Administrations in Sprague-Dawley Rats *(Study 105144)*

- Male rats were given IV or SC doses of m13c7 at 0.1-10 mg/kg.
- PK profile is shown in Fig. 1.

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- Exposure was non-linear, with an 800-fold increase in AUC from 0.1 to 10 mg/kg.
- Median Tmax was 24h, and Tmax range was 24-72h.
- BA was 100% based on 1 mg/kg data (Table 5).

Figure 1. Mean (SD) Concentration-Time Profiles Following Single IV or SC Administration of m13c7 to Sprague-Dawley Rats (Study 105144)

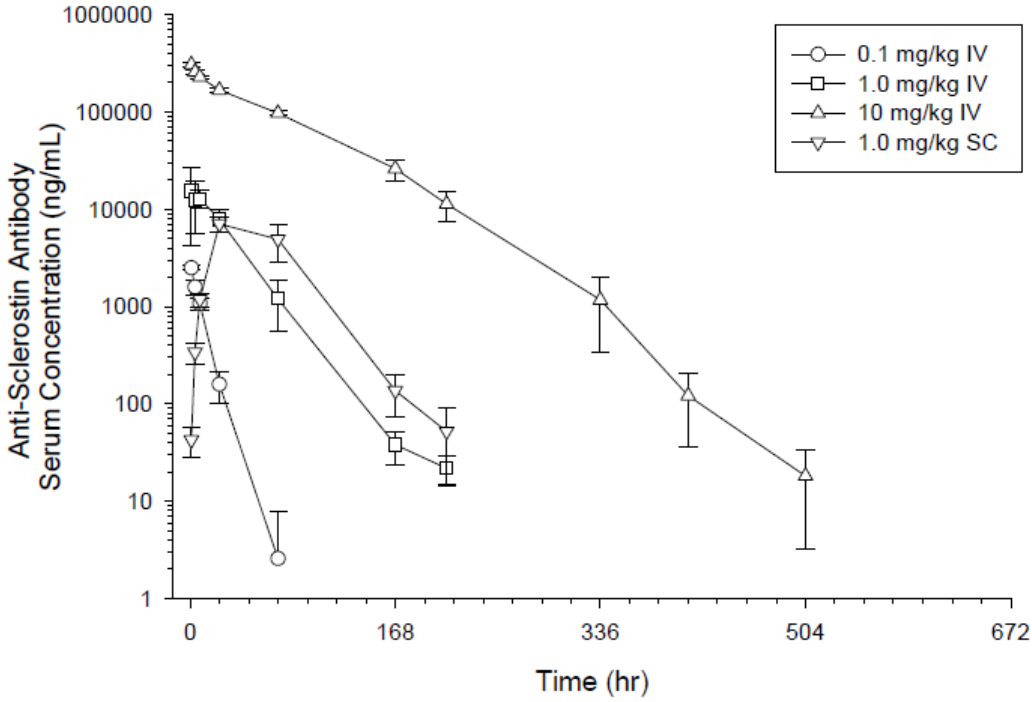


Table 5. Mean (SD) Noncompartmental Pharmacokinetic Parameters After Single Dose IV and SC Administration of m13C7 to Male Sprague-Dawley Rats (Study 105144)

Dose(mg/kg), Route (n)	t_{max} (hr)	C_0 or C_{max} (µg/mL)	AUC_{inf} (µg·hr/mL)	CL or CL/F (mL/hr/kg)	$t_{1/2,z}$ (hr)	V_{ss} (mL/kg)
0.1, IV (4)	NA	2.94 (0.28)	23.1 (3.3)	4.4 (0.6)	5.93 (0.85)	36.8 (2.6)
1, IV (4)	NA	19.9 (9.9)	472 (22)	2.12 (0.01)	18.8 (0.9)	58.7 (12.8)
10, IV (4)	NA	326 (23)	18000 (1260)	0.558 (0.037)	28.2 (2.8)	37.1 (1.9)
1, SC (4)	24 (24 – 72)	7.24 (1.11)	481 (109)	2.16 (0.50)	20.1 (1.4)	NA

AUCinf = Area under serum concentration-time curve from time 0 to infinity; C0 = Estimated initial concentration after IV administration; Cmax = maximum observed concentration after SC administration; CL = serum clearance after IV administration; CL/F = apparent serum clearance after SC administration; NA = not applicable; $t_{1/2,z}$ = terminal half-life; t_{max} = time of C_{max}; V_{ss} = Volume of distribution

An 8 Week Compound Selection Dose Range-finding and Pharmacokinetic Study in the Cynomolgus Monkey
(Study 105876)

- Female cynomolgus monkeys (N=3-4/grp) received monthly administrations of romosozumab at 0, 3, 10, and 30 mg/kg SC for two months.
- Doses were given with a 4-wk interval, so that most drug was eliminated before the 2nd dose was given.
- The PK concentration-time profiles are shown in Fig.2, below.
- Exposure increased non-linearly. The 10-fold increase in dose from 0.1-10 mg/kg yielded a 12-fold increase in Cmax and a 21-fold increase in AUCinf (Table 7, below).
- Tmax ranged from 45h to 93h
- CL/F values decreased with increasing dose with a 2.1-fold decrease from 3-30 mg/kg.
- Mean half-life values increased with increasing dose, ranging from 41h to 71h.

Figure 2. Mean (SD) Concentration-Time Profiles Following 2 Monthly SC Administration of Romosozumab at 3, 10 and 30 mg/kg to Cynomolgus Monkey)

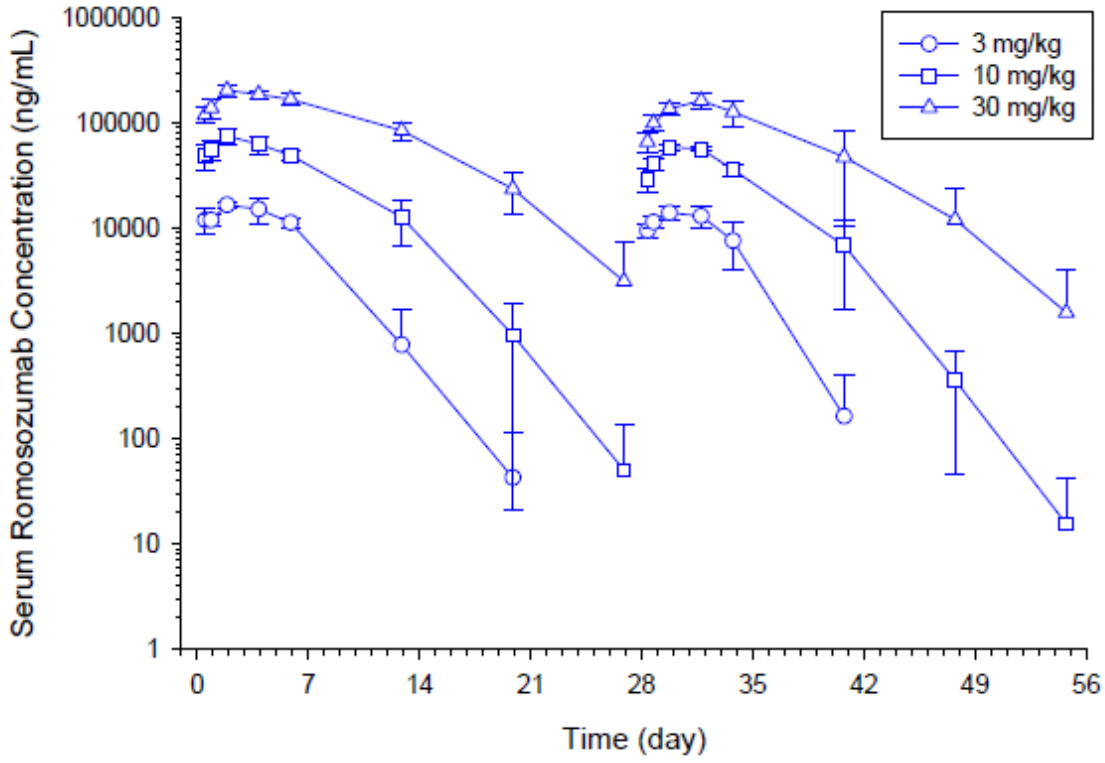


Table 7. Mean (SD) PK Parameters Following Single SC Administration of Romosozumab to Female Cynomolgus Monkey (Study 105876)

Dose, Route (n)	t_{max} (hr)	C_{max} (µg/mL)	AUC_{inf} (µg·hr/mL)	CL/F (mL/hr/kg	$t_{1/2,z}$ (hr)
3 mg/kg, SC (3)	45 (45-93)	17.7 (0.6)	2570 (440)	1.19 (0.20)	40.7 (12.6)
10 mg/kg, SC (3)	45 (45-93)	79.9 (6.3)	13600 (1400)	0.739 (0.074)	51.1 (6.6)
30 mg/kg, SC (3)	45 (45-93)	210 (18)	54300 (6600)	0.559 (0.071)	71.4 (21.0)

Pharmacokinetic Report for "A Single Subcutaneous Dose Pharmacokinetic Study of AMG 785 Manufactured by the FIH Process and CPD Process in Naïve Male Cynomolgus Monkeys"
(Study 113155, non-GLP)

NOTE: Study 113155 was reviewed by Dr. Andrea Benedict. The review was filed in DARRTS on March 2, 2017.

- This study was a non-GLP single-dose subcutaneous PK bridging study in naïve male cynomolgus monkeys.
- The data provided evidence that the AMG785 drug products manufactured using Process 1 and Process 2 are similar from a nonclinical perspective.

Distribution, metabolism, excretion
No studies were conducted.

PK Drug Interactions
Romosozumab is not expected to have direct impact on cytochrome P450 and other drug metabolizing enzymes or transporters. In addition, romosozumab is not expected to modulate cytokine levels which could exert an indirect impact on CYP450 activities. Therefore, no pharmacokinetic drug interaction studies were conducted.

Reference ID: 4081796

5.2 Toxicokinetics

Rat toxicity studies

Table 8. Romosozumab TK Parameter Summary After 14-Day, 1-Month and 6-Month Weekly Subcutaneous Dosing in Sprague-Dawley Rats

Study	Dose in mg/kg (route)	First Dose			Last Dose				
		Tmax (hr)	C_0 or Cmax (ug/mL)	$AUC_{0\text{-}168h}$ (ug.hr/mL)	Tmax (hr)	C_0 or Cmax (ug/mL)	$AUC_{0\text{-}168h}$ (ug.hr/mL)	AR	$t_{1/2,z}$ (hr)
105909 (14-day)	30 (SC)	72	204	24400	72	315	41700	1.71	NC
	100 (SC)	72	504	68400	72	855	107000	1.56	NC
	300 (SC)	48	1150	158000	48	2090	254000	1.60	NC
	300 (IV)	NA	6760	437000	NA	7990	608000	1.39	NC
105908 (1-month)	10 (SC)	72	46.4	5400	72	55.7	5960	1.10	61.6
	100 (SC)	96	519	66400	48	1190	147000	2.22	75.5
	300 (SC)	96	1160	157000	48	1540	176000	1.12	81.0
107425[a] (6-month)	3 (SC)	72	15.8	1420	72	16.5	1840	1.29	NC
	10 (SC)	72	64.9	6930	48	89.8	12900	1.86	59.5
	100 (SC)	72	684	80500	96	1030	124000	1.55	84.0

[a]TK parameter data from anti-drug antibody positive animals were excluded from analyses.
Values are presented as mean with the exception of T_{max}, which is presented as median.
C_0 = Estimated initial concentration after IV administration; C_{max} = maximum observed concentration after SC administration; $AUC_{0\text{-}168}$ = Area under serum concentration-time curve from time 0 to 168 hours; t_{max} = time of C_{max}; AR = accumulation ratio calculated as $AUC_{0\text{-}168,\ last\ dose}$ /$AUC_{0\text{-}168,\ first\ dose}$; NC = not calculated

Rat 2-year carcinogenicity study

Study Number	Species	Study Duration, Dose Frequency	Doses (mg/kg)	N/sex/group	Male Cpl (ng/mL)	Female Cpl (ng/mL)
107895	Rat/ Sprague-Dawley	12 months, weekly dosing			Wk 13	Wk 13
			3	60	9660	4910
			10	60	79500	74600
			50	54(M), 60(F)	589000	836000

Rat reproductive toxicity studies

In rat reproductive studies with different dosing schedules and durations, measurements of AMG785 plasma concentrations were made on different days in F0 and/or F1 animals. See individual study reviews for TK data.

Monkey toxicity studies

Table 9. Romosozumab TK Parameter Summary After 14-Day, 1-Month, 6-Month and 12-Month Weekly Subcutaneous Dosing in Cynomolgus Monkeys

Study	Dose in mg/kg, Route (n, sex)	First Dose			Last Dose				
		Tmax (hr)	C_0 or Cmax (ug/mL)	$AUC_{0\text{-}168h}$ (ug.hr/mL)	Tmax (hr)	C_0 or Cmax (ug/mL)	$AUC_{0\text{-}168h}$ (ug.hr/mL)	AR	$t_{1/2,z}$ (hr)
105779 (14- day)	30, SC (3F)	72	221	29600	72	353	43400	1.47	NC
	100, SC (3F)	48	979	121000	48	1270	140000	1.44	NC
	300, SC (3F)	48	2400	295000	48	3800	487000	1.65	NC
	300, IV (3F)	NA	5180	413000	NA	7290	597000	1.30	NC
105776 (1-month)	10, SC (5M/5F)	48	67.5	8270	24	205	23800	3.06	100
	30, SC (5M/5F)	48	289	37800	24	569	77200	2.05	114
	300 , SC (5M/5F)	48	2500	304000	48	5180	645000	2.17	144
	300, IV (5M/5F)	NA	5910	407000	NA	7630	588000	1.43	149
107426[a] (6-month)	3, SC (5-6M, 5-6F)	48	29.5	3060	48	30.6	3490	1.12	90.7
	10, SC (5-6M, 4-6F)	48	107	13100	48	139	17100	1.28	73.7
	100, SC (6M, 6F)	48	1590	178000	24	2280	301000	1.74	116
107903[a] (12- month)	3, SC (6F)	48	23.0	122	24	32.3	172	1.42	NC
	30, SC (15F)	48	295	1620	24	538	2950	1.85	NC

[a] TK parameter data from anti-drug antibody positive animals during the treatment phase were excluded from analysis.

Values are presented as mean with the exception of t_{max}, which is presented as median.

$AUC_{0\text{-}168}$ = Area under serum concentration-time curve from time 0 to 168 hours; AR = accumulation ratio calculated as $AUC_{0\text{-}168,\ last\ dose}$ /$AUC_{0\text{-}168,\ first\ dose}$; C_0 = estimated initial concentration after IV administration; C_{max} = maximum observed concentration after SC administration; Mon = month; NC = not calculated; t_{max} = time of C_{max}

Impact of ADA on PK/TK and PD

- Binding anti-drug antibodies (ADA) and their impact on TK were evaluated in 1-month, 6-month, 12-month, 2-year, and all reproductive toxicology or pharmacology studies in rats and monkeys.
- Neutralizing ADAs were measured in 1-month, 6-month and 12-month monkey studies, and in the 2-year lifetime pharmacology (ie carcinogenicity) study in rats (107895).
- PK in single dose or ≤1 month studies is not expected to be impacted by ADA development as 3-4 wks of dosing is generally required for an immune response.
- The presence of binding or neutralizing ADA resulted in reduced systemic exposure. Thus, TK and toxicity data from animals with ADA formation were excluded from 6-month rat and monkey toxicity studies (107425, 107426), the lifetime rat pharmacology study (107895), and from the fertility/EFD (108061) and PPND (108062) studies in rats.
- In the 12-month bone quality and carcinogenicity studies in rats, trough concentrations of AMG785 were measured only; data from the 12-mo bone quality study showed no evidence of change in exposure over time in ADA-negative animals.

Exposure Multiples

Human PK

Species	Study Nr.	Dose (mg)	Cmax (µg/mL)	Tmax (days)	AUC0-τ (µg·h/mL)	T½ (days)
Human (postmenopausal women)	119384	210	28.1*	5	12888*	13

*Data from Population PK Report 119384 (based on PK data from 11 clinical studies)

Reference ID: 4081796

Table 6. AUC Exposure Margins in Pivotal Toxicology Studies of Romosozumab in Sprague Dawley Rats and Cynomolgus Monkeys

Human Dose (mg)	Human $AUC_{0\text{-}tau}$ (µg·hr/mL)	Exposure Multiple (Based on $AUC_{0\text{-}tau}$ at NOAEL)			
		Rat 6 month	Monkey 6 month	Rat F/EFD	Rat Carcinogenicity
210 QM	12888	38	93	56	19

$AUC_{0\text{-}tau}$ = area under the romosozumab serum concentration-time curve with the dosing period of tau; F/EFD = combined fertility and embryo-fetal development; NOAEL = no adverse effect level; QM = every month.

The exposure margins were calculated by comparing toxicokinetic data at the NOAEL at week 26 from the 6-month GLP rat (Study 107425; 124000 µg·hr/mL after QW dosing) and monkey (Study 107426; 301000 µg·hr/mL after QW dosing) toxicology studies, on day 13 after gestation from the GLP rat F/EFD study (Study 108061; 179760 µg·hr/mL after QW dosing), and predicted systemic exposure at 50 mg/kg for the lifetime rat study (Study 107895; 62000 µg·hr/mL after QW dosing). Human $AUC_{0\text{-}tau}$ for romosozumab was determined following romosozumab SC 210 mg QM as monotherapy in population PK analysis (Study 119384). Exposure margin calculations were then adjusted for the difference in the dose intervals between the rat and monkey studies (week) and the human studies (4 weeks).

The exposure margins were calculated by the following equation:

$$\text{Human Exposure Margin} = \frac{\text{Animal } AUC_{0\text{-}1wk}}{\text{Human } AUC_{0\text{-}4wk}} \times \frac{\text{Human Dose Interval (4 weeks)}}{\text{Animal Dose Interval (1 week)}}$$

Table 7. C_{max} Exposure Margins in Pivotal Toxicology Studies of Romosozumab in Sprague Dawley Rats and Cynomolgus Monkeys

Human Dose (mg)	Human C_{max} (µg /mL)	Exposure Multiple (Based on C_{max} at NOAEL)			
		Rat 6 month	Monkey 6 month	Rat F/EFD	Rat Carcinogenicity
210 QM	28.1	110	325	223	55

C_{max} = maximum observed serum concentration; F/EFD = combined fertility and embryo-fetal development; NOAEL = no adverse effect level; QM = monthly.
The exposure margins were calculated by comparing toxicokinetic data at the NOAEL at week 26 from the 6-month GLP rat (Study 107425; 776 µg/mL after QW dosing) and monkey (Study 107426; 2280 µg/mL after QW dosing) toxicology studies, on day 13 after gestation from the GLP rat F/EFD study (Study 108061; 1570 µg/mL after QW dosing), and predicted systemic exposure at 50 mg/kg for the lifetime hamster study (Study 107895; 388 µg/mL after QW dosing). Human C_{max} value for romosozumab was determined following romosozumab SC 210 mg QM as monotherapy in population PK analysis (Study 119384).

The exposure margins were calculated by the following equation:

$$\text{Human Exposure Margin} = \frac{\text{Animal } C_{max}}{\text{Human } C_{max}}$$

Table 2. Romosozumab Dose Levels for 2 Year Lifetime Pharmacology Study (3, 10, and 50 mg/kg QW): Projected Dose/Exposure Multiples Relative to a 210 mg QM Clinical Regimen

Margin Expressed as Multiple of Human Dose			
Rat Dose (mg/kg)	Human Dose (mg)	Human Dose (mg/kg)	Rat/Human Dose Ratio [a]
3	210	3	1.0
10	210	3	3.3
50	210	3	16.7

Margin Expressed as Multiple of Human Exposure				
Human Dose (mg/kg)	Human AUC_{0-24} (mg·hr/mL) [b]	Exposure Multiple (based on AUC_{0-168} of rat doses) [c]		
		3 mg/kg	10 mg/kg	50 mg/kg
3.5	13.1	0.6	3.9	19.2

AUC_{0-168}, AUC_{0-24} = area under the concentration-time curve from time zero to 168 hours post dose or time zero to 24 hours post dose, F = female, M = male, Q4W = every 4 weeks, QM = once monthly, SC = subcutaneous.

[a] Dose margins are based on a 210-mg clinical dose to a 70-kg subject, calculated as (mg/kg species)/(mg/kg human).

[b] Clinical simulated steady state AUC_{τ} (τ = 1 month) is 546 µg·day/mL = 13.1 mg·h/mL. This value is generated using a population pharmacokinetic model to simulate the 210-mg QM treatment in Study 20060326.

[c] The week 25 $AUC_{0-168hr}$ values from 6-month repeat-dose rat toxicology study 107425 have been multiplied by 4 to enable direct comparison with AUC_{τ} for the clinical 210 mg QM dosing regimen. The $AUC_{0-168hr}$ values (mg·hr/mL, gender averaged) are as follows: 3 mg/kg: 1.84; 10 mg/kg: 12.9; 50 mg/kg: 59.8. The $AUC_{0-168hr}$ values for 3 and 10 mg/kg reflect exposures in anti-drug antibody negative animals. The 6-month rat toxicology study did not include a 50 mg/kg dose, and thus the steady state $AUC_{0-168hr}$ value was simulated using a population pharmacokinetics model of study 107425.

Reviewer's comment: In Table 2 above, Human AUC_{0-24} is an error and should be Human $AUC_{0-\tau}$

6 Toxicology

Toxicology Studies

Table 1. Tabular Listing of Nonclinical Toxicology Studies

Study Title	Testing Facility	GLP	Amgen Study No.
Repeat-dose Studies			
A 14-Day Subcutaneous and Intravenous Injection Toxicity Study of AMG 785 in the Sprague Dawley Rat	(b) (4)	No	105909
1-Month Subcutaneous Injection Toxicity Study of AMG 785 in the Sprague Dawley Rat With a 10-Week Recovery Period		Yes	105908
AMG 785: A 6-Week (Once Weekly) Subcutaneous Injection Toxicology Study in the Sprague Dawley Rat		Yes	121854
6-Month Subcutaneous Injection Toxicity Study if Weekly Administration of AMG 785 in the Sprague Dawley Rat With a 14-Week Treatment-free Free Period		Yes	107425
AMG 785: 29-Day Subcutaneous Injection Exploratory Toxicokinetic and Pharmacodynamic Study in the Female New Zealand White Rabbit		No	117870
14-Day Subcutaneous or Intravenous Injection Toxicity of AMG 785 in Cynomolgus Monkeys		No	105779
1-Month Subcutaneous and Intravenous Injection Toxicity Study of AMG 785 in the Cynomolgus Monkey Followed by a 10-Week Recovery Period		Yes	105776
6-Month Subcutaneous Injection Toxicity Study of Weekly Administration of AMG 785 in the Cynomolgus Monkey With a 14-Week Treatment-free Period		Yes	107426
Carcinogenicity			
AMG 785: 104 Week Subcutaneous Lifetime Pharmacology Study in the Sprague Dawley Rat		Yes	107895

Study Title	Testing Facility	GLP	Amgen Study No.
Carcinogenicity			
AMG 601 and AMG 589: Exploratory 28-day Subcutaneous Toxicology Study in the Sprague Dawley Rat With a 2-Week Recovery	Amgen Inc Thousand Oaks, CA	No	115823
IgG_2 Control Antibody (AMG 589): 104 Week Subcutaneous Carcinogenicity Study in the Sprague Dawley Rat	(b) (4)	Yes	115707
Reproductive and Developmental Toxicity			
Subcutaneous Dose-range Finding Development Study of AMG 785 in Rats		Yes	108057
Subcutaneous Developmental Toxicity Study of AMG 785 in Rats		Yes	108059
AMG 785: Fertility and Embryo-fetal Development Study in the Rat		Yes	108061
AMG 785: Pre-and Postnatal Development Study in the Sprague Dawley Rat		Yes	108062
Local Tolerance			
7-Day Subcutaneous and Intravenous Single Injection Site Reaction Study of AMG 785 in Female Sprague Dawley Rats	Amgen Inc. Thousand Oaks, CA	No	106718
Local Tolerance Test in Sprague Dawley Rats After Single Subcutaneous Administration of AMG 785	(b) (4)	Yes	112795
Single Dose Subcutaneous Local Tolerability Study of AMG 785 in Male Sprague Dawley Rats	Amgen Inc. Seattle, WA	No	113234
Mechanistic Studies			
r13C7: Exploratory Single Dose Subcutaneous Toxicology Study in the Aged Ovariectomized Female Sprague Dawley Rat	Amgen Inc. Thousand Oaks, CA	No	115877

Study Title	Testing Facility	GLP	Amgen Study No.
Other Toxicity Studies			
Mechanistic Studies			
7097r13C7:Exploratory 26-Week Subcutaneous Toxicology Study in Aged Ovariectomized Female Sprague Dawley Rat With an 18-Week Recovery	Amgen Inc. Seattle, WA	No	115777
AMG 785 and hPTH (1-34): Exploratory 26-Week Subcutaneous Toxicology Study in the Sprague Dawley Rat	Amgen Inc. Seattle, WA	No	115776
Other Studies	(b) (4)		
Cross-reactivity Study of Biotin-AMG 785 With Normal Human, Cynomolgus Monkey, New Zealand White Rabbit and Sprague Dawley Rat Tissues		Yes	105783
A 12-Month Bone Quality Study to Determine the Effects of Weekly Subcutaneous Injection of AMG 785 in the Ovariectomized Sprague-Dawley Rat		Yes	107899
AMG 785: 6 Month Subcutaneous Pharmacodynamic Study in the Aged Ovariectomized Cynomolgus Monkey		Yes	118025
A 52 week Bone Quality Study to Determine the Effects of Weekly Subcutaneous Injection of AMG 785 in the Aged Ovariectomized Cynomolgus Monkey		Yes	107903

6.1 Single-Dose Toxicity

Single dose toxicity studies were not conducted with this antibody.

6.2 Repeat-Dose Toxicity

Rat studies

Written Summary

Studies of 14-day, 1-month, 6-week and 6-month duration were conducted in rats. The studies were adequately conducted.

AMG785 was generally well tolerated and there was no treatment-related mortality in any of the rat studies.

The 14-day study with weekly doses of 30, 100, 300 mg/kg SC, or 300 mg/kg IV in the rat (Study 105909) showed increased bone formation, hyperostosis and increased spleen hematopoiesis. The NOAEL was 300 mg/kg, with AUC(0-168h) exposures of 254 and 608 mg.h/mL, for SC and IV dosing, respectively.

The 6-week study with weekly doses of 10 and 50 mg/kg SC in the rat (Study 121854) was conducted to evaluate effects in the skull. Results included increased bone formation as well. Subperiosteal bone was a mixture of woven and lamellar bone, similar but not identical to embryonic intramembranous bone.

The pivotal studies of 1- and 6-month treatment duration in rats with recovery (Studies 105908 and 107245) mainly showed effects related to the pharmacodynamic activity of AMG785, including dose-related increases in bone formation markers and increases in cancellous and cortical bone mass and thickness as evaluated by densitometry (DXA/pQCT) and histopathology. Resorption markers were not clearly affected, although some increases were observed in recovery periods. A summary of the data follows, but further details can be found in the tabular summary below.

Anti-AMG785 antibodies were detected in both 1- and 6-month studies, leading to reduced AMG785 exposure. In the 6-month study, ADA positive animals were excluded from PK analysis. AUC was generally dose-proportional and study findings were generally dose-related. AUC was similar in males and females. TK data showed slight but inconsistent accumulation between Day 1 and Week 26.

The pharmacologic effect on bone led to secondary changes in hematology and the hematopoietic system. The hematologic effects, e.g. RBC decrease and other blood cell changes (eg in platelet count or volume) were most likely an indirect effect of increased bone formation and narrowing of the hematopoietic bone marrow space, although a partially direct effect of AMG785 on marrow hematopoietic cells cannot be entirely excluded. Some non-RBC blood cell changes in female rats (e.g. WBC, lymphocyte decreases) were also observed at 100 mg/kg in the 6-month study. There were no effects on differential WBC counts.

Serum phosphorus was increased in 100-300 mg/kg males in the 1- and 6-month studies, with unclear cause. Significance of (transient) glucose increases in both studies was unclear.

Histologic effects included hyperostosis, extramedullary hematopoiesis, injection site findings (males and females), and a few muscle (necrosis), teeth (odontoma) and kidney histopathology findings in single males.

Hyperostosis consisted of increases in trabecular number and thickness (hyperostosis), firm marrow, and decreases in cortical bone marrow space due to endosteal bone apposition. The bone effects were seen at all doses in all rat studies. The increase in spleen and/or liver extramedullary hematopoiesis was an adaptive response to the anemia secondary to the pharmacologic bone effect. Injection site irritation was observed after 6 months of dosing with 100 mg/kg.

Minimal skeletal muscle necrosis, seen in 1- and 6-month studies in 1 high dose male each was of unclear relation to treatment. Biological significance of mandibular odontoma (mixed tumor of dental tissue origin) in one high dose male rat in the 6-month study was unlikely to be treatment-related. No dental cell/tissue tumors were seen in the 2-year carcinogenicity study with group sizes of N=60/s/g at doses up to 50 mg/kg.

A femoral neck fracture was observed in 1 mid-dose male (10 mg/kg) at Wk 26 (by X-ray) and was still perceptible at Week 40 (end of treatment-free phase). The fracture was chronic and resulted in a non-union and pseudoarthrosis at the left coxo-femoral joint (hip joint). Fibrosis with embedded bone debris and intact femoral head was noted in the acetabulum section and correlated with the thickening noted macroscopically. Sponsor considered the finding incidental and suggested it may have occurred before study initiation as there were no signs of lameness noted during the study and the microscopic changes showed "chronic fracture with pseudoarthrosis". Bone fractures are unusual in rats and the cause of the fracture is uncertain. Considering the lack of clinical signs, the fracture was likely incidental and present before study start. However, the similar location of another femur fracture in a high dose (100 mg/kg) female monkey in the 6-month monkey study renders the finding noteworthy.

Tabular Summary
(1-month and 6-month studies in rats)

Rat toxicity study findings and AUC/exposure multiples

Study Number	Treatment/ Recovery Group size	Route/ Frequency	Dose (mg/kg)	AUC(0-168h) (mg.hr/mL) / Exposure Multiple *	Main Effects (listed at lowest dose observed)
105908	1 month / 10-week recovery N= 10/s/g main study; N= 5/s/g recovery; N= 12/s/g for TK	SC; QW	10	5.96 / **1.9x**	Anti-AMG 785 binding antibodies detected in 4% (10 mg/kg) and 17% (300 mg/kg) of rats. Animals not excluded for analyses. Increased bone formation (markers, non-dd) Bone densitometry: Increase in tibial trabecular and cortical densitometric bone density, content and thickness (dd) (M,F). Tibia: Total and trabecular BMC metaphysis increased up to 1.4x and 1.75x, after 1 month Bone increase generally larger in M than in F.

					Decreased RBC/Hct, slight, non-dd (M); increased RDW, slight, non-dd (F); increased reticulocyte count, dd, min-to-moderate (i.e. regenerative anemia) (M,F) Decrease platelet count and volume, slight, non-dd (M) Urea increase, slight (mainly in F) Hyperostosis sternum and tibia, with dose-related incidence/severity (M,F) Increase in extramedullary hematopoiesis, dd, compensatory (M,F)
			100	147/ **46x**	Decreased platelet count, non-dd (F) Serum phosphorus increase, slight, dd (M)
			300	176/ **55x**	**NOAEL** (excluding effects secondary to PD) Decrease in deoxypyridinoline (DPD), moderate (M) Glucose increase, slight (M) Skeletal muscle necrosis, minimal (1/10 M) <u>*End of recovery*</u> *Bone formation normalized; increase in resorption markers observed in recovery; bone mass maintained/increased, platelet changes persisted*
107425	6 months / 14-week recovery Initial grp size Main: N= 10/s/g Recovery: N= 5/s/g (no separate TK animals) Final grp size (after elimination based on ADA): Main: 10,6,6,7 (M) 9,6,9,8 (F) Recovery: 5,3,4,5 (M) 5,3,5,5 (F)	SC Weekly	3	1.84 / **0.6x**	Anti-AMG 785 binding antibodies in <u>all groups</u> (60%, 25%, 18% in 3, 10, 100 mg/kg grps; 34% avg incidence). TK: Slight, variable accumulation between Day 1 and Wk26. Bone densitometry: DXA: Increase in femur and lumbar spine BMD and BMC, dd (M,F); pQCT: Increase in proximal tibia (metaphyseal (total, trabecular, and cortical) bone area, BMD and BMC. Increase at 3 mg/kg not ss (M,F). Bone increase generally larger in M>F. Spine: BMD and BMC increased up to 1.5-1.7-fold at wk26; Tibia: trabecular BMD and BMC increases up to 2.5-3.5--fold at wk26. Hyperostosis in lumbar vertebra (minimal-marked), sternum (min-moderate) and right tibia (min-severe). Increase in extramedullary hematopoiesis in spleen, dd (recovered)
			10	12.9 / **4.0x**	Bone densitometry: pQCT: Increase in proximal tibia diaphyseal thickness and periosteal circumference, and decrease in endosteal circumference, dd (M,F) Transient increase in osteocalcin (OC, bone formation marker), dd, max at Wk 4 (M,F)

					CTx elevated (Wk 12, M,F) or reduced (Wk 26, F) Slight decrease in platelet number (F) and increase in platelet volume (M) Serum glucose increase, transient, dd (F) Thickening of bone including skull cap (M,F) Bone marrow, firm Increase in extramedullary hematopoiesis in liver, dd (recovered)
			100	124 / **39x**	**NOAEL** (excluding effects secondary to PD) Increase in % reticulocytes (15-90%) (F>M) Decrease in WBC, lymphocyte, basophil, monocyte, and eosinophil counts (F only, some effects transient). No effects on WBC differential counts. ALKP increase, slight (M,F) Serum P increased (M), reversible Minimal skeletal muscle degeneration/necrosis (2/11 M); Mandibular odontoma (1/11M); Renal pelvis dilated (2M); various kidney histopath in 1-2M Injection site mononucl. infiltration (M,F) <u>End of recovery</u>: *Increase in DPD in M,F (all groups), OC normalized. Bone increases were diminished (3, 10), or increased further (100 mg/kg).* *Hyperostosis slightly diminished, skull hyperostosis newly observed.* *FEMUR (HIP) FRACTURE in 1/5 MD (10 mg/kg) male, probably incidental since no clin signs.* *ADA incidence maintained at 3 mg/kg and increased in 10 and 100 mg/kg grps (52% avg incidence).*

* Exposure Multiple = [Animal AUC(0-168h) x 4]/[Human AUC(0-τ) at the proposed clinical dose of 210 mg] (Human AUC = **12888 ug h/mL**; data from Clinical Population PK Report **119384A**). Data from ADA-positive animals with Cpl<50% than avg for ADA-negative animals were not included in the analysis.
Abbreviations: dd=dose-dependent; ss = statistically significant

Toxicokinetics of AMG 785 in Rats (6 month study, weekly dosing, SC)

(Data from both ADA$^+$ and ADA$^-$ animals) (Data from ADA-negative rats in TK section of review)

Time	Parameter	Males			Females		
		3 mg/kg	10 mg/kg	100 mg/kg	3 mg/kg	10 mg/kg	100 mg/kg
Week 1	Tmax (hr)	72	96	72	72	72	96
	Cmax (µg/ml)	15.1	57.1	500	16.6	81.5	912
	$AUC_{0\text{-}168h}$ (µg h/ml)	1,370	6,260	57,500	1,450	7,570	103,000
Week 12	Tmax (hr)	72	168	168	72	48	96
	Cmax (µg/ml)	15.0	92.3	1160	11.6	103	1540
	$AUC_{0\text{-}168h}$ (µg h/ml)	679	10,500	132,000	900	9,780	174,000
Week 26	Tmax (hr)	72	ND	ND	72	48	96
	Cmax (µg/ml)	14.6	102	687	17.3	109	1,280
	$AUC_{0\text{-}168h}$ (µg h/ml)	779	10,200	66,700	1,110	10,600	112,000
Week 27-40	Terminal $T_{1/2}$ (hr)	NC	62.6	93.2	NC	NC	107
	$AUC_{(0\text{-}\infty)}$ (µg h/mL)	173	5,840	130,000	NC	1,370	86,000

ND = No data; NC = Not calculated

Rabbit studies

A 29-day exploratory study was conducted in the rabbit with doses up to 300 mg/kg SC (Study 117870). ADAs were detected first on Day 15, and increased to up to 100% on Day 22, in parallel with up to 10-fold reductions in serum concentrations. Some ADA-positive rabbits showed immune complex disease with vascular injury and inflammation in several organs. Bone did have the expected pharmacologic response (increased formation) but this was attenuated after ADA developed. Rabbit was not considered a suitable species for embryo-fetal developmental studies.

Monkey studies

Written Summary

Studies of 14-day, 1-month, and 6-month duration were conducted in cynomolgus monkeys. The studies were adequately conducted.

AMG785 was well tolerated. There was no treatment-related mortality and there were no toxicologically relevant clinical signs or body weight effects in the monkey studies.

The 14-day study with weekly doses of 30, 100, 300 mg/kg (SC), or 300 mg/kg IV) showed increased bone formation markers, but no effect on resorption markers (Study 105779). The NOAEL was 300 mg/kg, with AUC(0-168h) exposures of 487 and 597 mg.h/mL, at 300 mg/kg SC and IV, respectively.

Reference ID: 4081796

The pivotal 1- and 6-month studies in monkeys mainly showed effects related to the pharmacodynamic activity of AMG785 in bone, including dose-related increases in bone formation (markers, histomorphometric indices) and increases in cancellous and cortical bone mass and thickness as measured by densitometry (DXA/pQCT of spine, femur, tibia, radius) (Studies 105776 and 107426). Resorption markers were not affected. Bone strength was increased concomitantly and bone quality appeared unaffected. A summary of data from these studies follows, but further details can be found in the tabular summary below.

Anti-AMG785 antibodies were detected in both 1- and 6-month studies, leading to reduced AMG785 exposure. In the 6-month study, ADA positive animals were excluded from TK analyses.

AUC was generally dose-proportional and study findings were generally dose-related. Exposure was very similar in males and females. TK data showed slight accumulation.

Slight, non-dose-related decreases in RBC parameters were observed in males in the 1-month study, and in males and females in the 6-month study. They may have been due indirectly to increases in bone mass or a direct effect of AMG785 on bone marrow cells. There were no effects on differential WBC counts.

Transient and reversible non-dose-related decreases in serum calcium (slight) were observed in females in the 1-month study. Small decreases in serum Ca and P were also seen in the 6-month study (maximal ca. 10-15% at 100 mg/kg).

Electrocardiogram parameters (wave forms and interval times) and blood pressure were not adversely affected.

Histological changes in bone included hyperostosis, i.e. increased trabecular and cortical bone thickness. No bone cell changes or woven bone formation were detected at the end of the 6-month dosing phase.

There was no increase in extramedullary hematopoiesis in any of the monkey studies.

One female (Animal No. 456) at 100 mg/kg/dose presented bone findings in the left coxofemoral joint, sampled because of macroscopically small acetabulum and small femoral head with irregular surfaces and pale discoloration. Microscopic findings consisted of chronic fracture of the acetabulum (with non-union and hemorrhage), and moderate-marked degeneration of acetabular/femoral articular cartilage, and correlated with the macroscopic observations. The changes were considered initiated by established trauma (fracture) leading to secondary osteoarthrosis. This interpretation is supported by the absence of skeletal clinical signs during the treatment period, suggesting a pre-study event; therefore, the fracture-related findings in this animal were not considered

treatment-related. Reviewer agrees with Sponsor's conclusion. However, the similar location of a femur fracture in a mid-dose (10 mg/kg) male rat in the 6-month rat study makes the finding noteworthy.

Tabular Summary

(1-month and 6-month studies in monkeys)

Monkey toxicity study findings and AUC/exposure multiples

Study number	Treatment/ Recovery Group size	Route/ Frequency	Dose (mg/kg)	AUC(0-168h) (mg.hr/mL) / Exposure Multiple *	Main Effects (Findings listed at lowest dose)
105776	1 month 10-week recovery N=3/s/g (main study) N=2/s/g (recovery)	SC, QW (high dose SC/IV)	10	23.8 / **7.4x**	Anti-AMG 785 antibodies detected in 6/40 (15%) of monkeys in 30 and 300 mg/kg grps, mainly during recovery period, with 2 of 6/40 (5%) developing neutralizing antibodies. Animals not excluded for analyses. Bone densitometry: DXA/QCT: Increase in Bone area, BMC, BMD and/or cortical thickness (lumbar spine, proximal femur and proximal tibia). Bone increase generally larger in F than in M. Increases in osteocalcin, BSAP and PINP (bone formation markers), non-dd (M,F) Increase in DPD (F only), non-dd Decrease in RBC and Hb, slight, non-dd (M) Decrease in serum calcium, transient D15, slight (F) Hyperostosis of sternum and tibia, dose-related severity (M,F)
			30	77.2 / **24x**	Decrease in Hb, minimal (M)
			300 (SC or IV)	SC: 645 / **200x** IV: 588 / **182x**	**NOAEL** (excluding effects secondary to PD) No spleen/liver extramedullary hematopoiesis Liver cellular infiltration (M,F) Skeletal muscle degeneration/necrosis in 1/3M (IV) (minimal) Injection site fibrosis or inflammation (severity?) (M) <u>End of recovery</u>: *Formation markers declined late in recovery.* *RBC/Hb and serum Ca decreases recovered.* *Bone increase maintained or further increased (spine*

					BMD and tibial cortical area still ca. 1.3x pre-TX level after 10-wk recovery). *Hyperostosis increased during recovery.*
107426	6 months 14-week recovery Initial grp size Main: N= 4/s/g Recovery: N= 2/s/g Final grp size (after elimination based on ADA): Main: 4,3,4,4 (M) 4,3,3,4 (F) Recovery: 2,1,2,2 M 2,1,2,2 F	SC, QW	3	3.49 / **1.1x**	Anti-AMG785 antibodies developed in 8/36 monkeys (22%), with 5/26 (14%) developing neutralizing antibodies (Nab). TK: Slight accumulation between Day 1 and Wk25. Bone densitometry: DXA/pQCT: Increase in DXA BMD and BMC at lumbar spine and femur, dd, at all doses (M,F). Increase in QCT BMD /BMC at proximal tibia metaphysis and diaphysis, more pronounced in metaphysis. QCT of radius showed BMD and/or BMC increase in F>M, mostly at 10-100 mg/kg. No effects on BP and EKG Decrease in RBC and Hct, minimal-slight Decrease in serum calcium and phosphorus, minimal-slight, transient, dd, possibly due to increased bone formation Hyperostosis in vertebrae, sternum and tibia at all doses, with dd incidence and severity (incr trabecular plus reduced medullary space) Histomorphometry and mechanical testing showed expected dose-related increases, mostly in early dosing phase, in bone formation on cancellous and cortical surfaces and increases in strength, similar to those in OVX animal bone quality studies. Endocortical bone formation effect was longest lived. Bone quality (correlation mass vs strength) maintained, and mineralization was normal. No adverse neurological effects by clinical observation.
			10	17.1 / **5.3x**	Transient increases in markers BSAP and osteocalcin, not at 3mg/kg. Resorption markers unaffected. Injection site inflammation in males.
			100	301 / **93x**	**NOAEL** (excluding effects secondary to PD) Transient increase in P1NP in F (Wk 4) Ectopic ossification in adrenal gland and acute inflammation of bone marrow in 1/4M (relevance uncertain). One HD female had chronic fracture in/near hip joint (see end-of-recovery findings), likely non-treatment-related. *End of recovery:* *BMD/BMC increase appeared recovered minimally after 14 weeks, but difficult to estimate due to small N/s/g.*

					Hematology and serum Ca,P decreases reversed. Hyperostosis still observed in all groups, but with lesser incidence/severity. One HD female had chronic FEMUR (HIP) FRACTURE near acetabulum, probably incidental- w/o clinical signs.

* Exposure Multiple = [Animal AUC(0-168h) x 4]/[Human AUC(0-τ) at the proposed clinical dose of 210 mg] (Human AUC = **12888 ug h/mL**; data from Clinical Population PK Report **119384A**). Data from ADA-positive animals were not included for this calculation
Abbreviations: dd=dose-dependent; ss = statistically significant

Toxicokinetics of AMG 785 in Monkeys (6 month-study, weekly dosing, SC)

(Data from both ADA$^+$ and ADA$^-$ animals) (Data from ADA-negative monkey in TK section of review)

Time	**Parameter**	**Males**			**Females**		
		3 mg/kg	**10 mg/kg**	**100 mg/kg**	**3 mg/kg**	**10 mg/kg**	**100 mg/kg**
Day 1	Tmax (hr)	48	48	48	48	48	24
	Cmax (µg/ml)	29	104	1,420	30	111	1,760
	$AUC_{0\text{-}168h}$ (µg.h/ml)	3,030	12,800	164,000	3,080	13,300	192,000
Week 25	Tmax (hr)	48	48	24	48	60	36
	Cmax (µg/ml)	28	128	2,260	33	152	2,310
	$AUC_{0\text{-}168h}$ (µg.h/ml)	3,310	17,100	302,000	3,670	17,100	300,000
ADA-negative animals only		**Males and Females Combined**					
		3 mg/kg		**10 mg/kg**		**100 mg/kg**	
Week 25	Terminal $T_{1/2}$ (hr)	90.7		73.7		116	
	Terminal $AUC_{0\text{-}\infty}$ (µg.h/mL)	4,700		32,200		511,000	

6.3 Local Tolerance

Summary

Local tolerance at the SC injection site was specifically assessed using solutions with different AMG785 concentrations (Studies 113234, 112795, 106718). AMG785 elicited a minimal local response characterized by mononuclear cell infiltrates in repeat dose studies. Single dose administrations showed transient, concentration-dependent inflammatory responses and/or edema. Local tolerance to sodium and calcium acetate formulations appeared similar (Studies 113234 and 112795).

6.4 Other Toxicity Studies

Mechanistic Studies

Mechanistic studies included Studies 115877 and 115777 in OVX SD rats, and Study 115776 in intact SD rats. These studies are described in the Pharmacology section of this review (Primary Pharmacodynamics).

Other Studies

Cross Reactivity Study of Biotin-AMG 785 with Normal Human, Cynomolgus Monkey, New Zealand White Rabbit and Sprague Dawley Rat Tissues

Study Nr. 105783

(b) (4)

Study initiation date: May 24, 2006
GLP: Yes

Key study findings:

- In this in vitro study biotinylated AMG785 (2 and 20 ug/mL) was used to label tissues with sclerostin protein expression.
- Biotinylated AMG 785 specifically stained osteocytes in bone samples from humans, monkeys and rabbits.
- Biotinylated AMG 785 failed to stain osteocytes in rat bone samples, possibly raising issues concerning the sensitivity of the immunohistochemical methodology, since clear PD effects of AMG 785 were seen in the rat.
- One of three monkeys exhibited specific staining of stromal cells of the tunica media of either the aorta or pulmonary artery. This tissue was unexpectedly present in one of the heart sections. The absence of comparable staining in the other 2 monkey donors or in any of the human, rabbit or rat donors may reflect the absence of aorta tissue in these sections

Table 17B. Other Studies - Study Type – Other
Test Article: romosozumab

Species/Strain or Test Model	Method of Administration	Concentration (μg/mL)	Sex and No. per Group	Noteworthy Findings	Study Number (GLP Status)
Tissue cross-reactivity in Sprague Dawley rat, New Zealand white rabbit, cynomolgus monkey, and human tissues	In vitro – single application to frozen tissue samples	2 and 20 Biotin-AMG 785	Tissue panels from rat, rabbit, monkey, and human	Osteocyte staining in human, monkey, and rabbit. Stromal fiber staining in the aorta or pulmonary artery present in heart section from one monkey. No unexpected tissue binding or cross-reactivity.	105783 GLP

GLP = Good Laboratory Practices

7 Genetic Toxicology

The genotoxic potential of AMG785 was not evaluated. This is in accordance with Guidance ICH S6(R1). AMG785 is a recombinant protein and contains no linkers or non-protein portions. Thus, it is highly unlikely to react with DNA or other chromosomal material.

8 Carcinogenicity

The carcinogenic potential of AMG785 was evaluated in a 2-year lifetime pharmacology (carcinogenicity) study in Sprague Dawley rats at weekly doses of 3, 10 and 50 mg/kg. The protocol was discussed with ECAC on October 11, 2011. Dose selection was based on expected multiples of human exposure and pharmacologic effect. The study was considered adequate and negative for neoplastic findings.

The study was reviewed by Dr. Miyun Tsai-Turton and discussed with ECAC on February 14, 2017. The review was filed in DARRTS for BLA 761062 on March 27, 2017.

A 2-year Subcutaneous Carcinogenicity Study
(Study 107895) (b) (4)

STUDY SUMMARY
RAT STUDY DURATION (weeks): A minimum of 91 weeks for males and 98 weeks for females
STUDY STARTING DATE: November 07, 2011 (dosing initiated)
STUDY ENDING DATE: September 30, 2013 (in-life phase completed)
RAT STRAIN: Sprague-Dawley rats
ROUTE: Subcutaneous injection
DOSING COMMENTS: Weekly

NUMBER OF RATS: 60/sex/group (intended). After exclusion of ADA-positive animals, N/group was (for males) 60, 60, 60, 54 and (for females) 60, 60, 60, 60, for control, low dose, mid dose and high dose, respectively.

RAT DOSE LEVELS (mg/kg):
- **Vehicle control** (Ctrl, Group 1): 0 mg/kg/week
- **Low Dose** (LD, Group 2): 3 mg/kg/week
- **Mid Dose** (MD, Group 3): 10 mg/kg/week
- **High Dose** (HD, Group 4): 50 mg/kg/week

BASIS FOR DOSES SELECTED: Doses for this study were based on the expected pharmacologic effect in bone, clinical exposure multiples, and the lack of significant toxicity in a completed 6 month rat toxicity study.

PRIOR FDA DOSE CONCURRENCE: Yes

RAT CARCINOGENICITY: Negative.

RAT TUMOR FINDINGS: **There were no significant AMG785-related tumor findings.**

RAT STUDY COMMENTS:

- The 104-week rat study via sc injection was conducted to assess the carcinogenic potential of AMG785. The study was terminated at Week 91 for male groups and Week 98 for female groups. The survival at the end of study was between 25-40% and comparable across all groups. Non-neoplastic changes associated with the pharmacological effect of AMG785 included effects in bones (hyperostosis), spleen and liver (secondary extramedullary hematopoiesis), and injection sites (mononuclear cells infiltrate).

- The Sponsor identified two statistically significant neoplastic findings: renal lipoma in females (N = 1, 0, 0, 3 in ctrl, LD, MD, HD; p =0.0486 by trend test; incidence in HD females slightly outside the historical control range of 0-2), and adrenal cortical adenoma in 10 mg/kg males (N = 0, 2, 6, 2 in ctrl, LD, MD, HD; p = 0.0169 by pairwise comparison, within historical control range of 0/120-6/60). Since renal lipoma in females is generally considered a rare tumor, this would be considered a statistically significant trend since the p-value (0.0486) was ≤ 0.05. However, due to low incidence and lack of pre-neoplastic precursor lesions, the increased incidence of renal lipoma in HD females was not considered to be of toxicological significance. Since adrenal cortical adenoma in males is generally considered a common tumor and a p-value of 0.0169 (> 0.01) does not indicate statistical significance, and since there was a lack of dose response (N=0, 2, 6, 2 across groups), the increased incidence in the 10 mg/kg MD males was not considered of toxicological significance. Sponsor concluded there were no significant neoplastic changes associated with AMG785 administration.

- FDA tumor analysis: Statistical review of the tumor data showed that there was an increase in incidence of adrenal cortical adenoma in 10 mg/kg males, that was statistically significant if considered a rare tumor (pairwise test FDA p=0.0184 < 0.05); and an increase in incidence of pancreatic islet cell adenoma in females (N=0, 0, 3, 3) that was statistically significant if considered a rare tumor (trend test p = 0.0323 < 0.05). However, adrenal cortical adenoma in males was considered a common tumor based on average historical control incidence of ca. 2% (20/1057). Therefore the increase in MD males was not considered statistically significant. The islet cell adenoma incidence in MD and HD females (3/60, 3/60) was within the historical

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control range provided by Sponsor (0/60-5/60) and was therefore not considered toxicologically significant. The increase in renal lipoma in 50 mg/kg females (p = 0.0429, trend test) was concluded to be not statistically significant based on the concurrent control of 1/60 (i.e. common tumor) and the p-value being >0.01. In conclusion, FDA review did not identify any statistically significant increases in tumor incidences in male or female rats given AMG785 for up to 98 weeks at doses of 3, 10, 50 mg/kg/wk (equivalent to **0.6, 4x, 19x** the human AUC at the proposed monthly dose of 210 mg).

- There were two osteosarcomas noted in the males dosed with 50 mg/kg/week. The finding was not statistically significant by trend test or pairwise comparison. One of the tumors was detected at gross necropsy as a macroscopic lesion/mass in the brain and also by radiographic skull/frontal bone production (Animal #4069, Day 587, fatal osteosarcoma, skull). The other tumor was detected in the tibia by focal radiographic bone loss followed by tibia histopathology in an animal with death caused by pituitary adenoma (Animal #4041, Day 572, incidental osteosarcoma, tibia). The incidence in the high dose male group was 3.7% (2/54), marginally exceeding the historical control range of 0-3.3%. Sponsor noted that the use of radiography in the current study was responsible for detecting one of the two tumors. Based on this study design feature, late onset and solitary occurrence of bone tumors, and lack of pre-neoplastic findings or other types of bone tumors, the Sponsor considered the osteosarcomas in the high dose males to be spontaneous occurrences. Although not statistically significant, the two osteosarcomas in the high dose male group, in which bone mass increase was largest, may have been treatment-related based on mechanism of action of AMG785, i.e., activation of the (pre)osteoblast. However, the 21-fold human exposure multiple suggests that the clinical significance of the tumor finding, even if treatment-related, is unlikely.

- Macroscopically, there were AMG785-related non-neoplastic findings in bones (miscellaneous, calvarium femur, lumbar vertebrae L5-L6, sternum and tibia) and spleen. AMG785 also caused dose-dependent bone thickening in males and females, correlating with increases in bone mineral content (BMC) by ex vivo peripheral quantitative computed tomography (pQCT) and hyperostosis microscopically. This effect was usually observed in all bones collected per protocol. An increased incidence of spleen enlargement was noted in females at ≥ 3 mg/kg and in males at 10 mg/kg, correlating with increased extramedullary hematopoiesis microscopically.

- Microscopically, there were non-neoplastic changes associated with AMG785. Bones: increased incidence of hyperostosis was noted in all dose groups. Spleen: increased incidence of secondary extramedullary hematopoiesis was noted in all dose groups (male: 13/60, 38/60, 44/60, 40/54 and female: 37/60, 49/60, 57/60, 60/60 in Groups 1, 2, 3, and 4 respectively). Liver: increased incidence of secondary extramedullary hematopoiesis was noted in all dose groups (male: 5/60, 13/60, 13/60, 12/54 and female: 22/60, 25/60, 41/60, 39/60 in Groups 1, 2, 3, and 4 respectively). Injection

sites: mononuclear cells infiltrate was noted in all dose groups. Changes in bones, spleen, and liver were dose-dependent, whereas changes in injection sites were not dose dependent.

- There were no satellite TK groups included in this study. Blood samples were collected in Week 13 for TK and ADA analysis. Animals positive for binding and neutralizing antibodies were then removed from the study. The retained number of animals was N=60/grp for all male and female groups, except it was N=54/grp for high dose males. In retained animals, anti-drug antibodies (ADAs) were still present in 18 males at 3 mg/kg, 3 males at 10 mg/kg, and 10 males at 50 mg/kg, and in 1 female at 50 mg/kg. The mean AMG785 serum concentration(s) in ADA positive animals were lower than in ADA negative animals among those retained by approx. 0.8x, 0.8x and 0.5x for the LD, MD, HD males, and 0.3x for the HD female.

Reviewer comment on rat study findings:
In rat carcinogenicity studies with daily SC dosing with PTH or PTHrP analogues, marked dose-dependent increases in osteosarcoma, osteoblastoma, osteoma, and/or osteoblast hyperplasia have been observed, also at relatively low human exposure multiples. The concomitant bone mass increases in the animals with bone tumors were similar to or smaller than those observed in the current AMG785 study. This underscores an important difference between sclerostin antibody and PTH products with regard to nonclinical bone tumorigenicity.

Key Study Findings (From Dr. Tsai-Turton's review)

- AMG785 was given to Sprague Dawley rats at 0 (vehicle), 3, 10, 50 mg/kg/week (60/sex/group) weekly via sc injection for a minimum of 91 weeks in males and 98 weeks in females. Blood samples were collected on Week 13 for TK analysis.
- There were no AMG785 treated effects on clinical observation, body weight, or food consumption.
- There was no AMG785 treatment effect on survival. Prior to the end of treatment period (Week 91 males and Week 98 females), there were between 36-43 rats/sex/group that had died or were euthanized. AMG785 had no effects on the overall survival rate or mortality.
- There were increased bone radiopacity in almost all males and females treated with AMG785 that correlated with thickening of the bone (macroscopically) and hyperostosis (microscopically). This was an expected pharmacological effect of AMG785.
- Marked dose-related increases in bone mass and geometry were noted at the femur metaphysis and diaphysis. Trabecular bone mineral density (BMD) was 4-fold and 6-fold higher in males and females, respectively, when compared to vehicle controls.
- AMG785 did not cause a statistically significant increase in neoplastic findings.
- AMG785 did cause non-neoplastic findings. However, findings were limited to pharmacological effect of AMG785, including hyperostosis, secondary extramedullary hematopoiesis in spleen/liver, and mononuclear cell infiltrate at the injection sites.

- There were no satellite TK groups included in this study. TK and ADA analysis was performed in Week 13. ADA-positive animals (up to 33% and 70% of animals in LD female and male groups) had reduced mean serum AMG785 concentration when compared to ADA-negative animals (by 41%, 69%, and 86% in females and by 10%, 43%, and 53% in males, at 3, 10, and 50 mg/kg respectively). Binding and neutralizing ADA positive animals were excluded in Week 13 so that final group size was N=54/grp for HD males and N=60/grp for all female and all other male groups. Anti-drug antibodies (ADAs) were still present in retained animals, in 1 female and 10 males at 50 mg/kg, 3 males at 10 mg/kg, and 18 males at 3 mg/kg. Serum AMG785 concentrations were lower in these animals by up to 50% and 70% (HD males and female, respectively).
- AMG785 was not carcinogenic in Sprague-Dawley rats at doses up to 50 mg/kg/week for 91 weeks in males and 98 weeks in females. Expected pharmacological effects of AMG785 (hyperostosis in bones, secondary extramedullary hematopoiesis in spleen and liver, and mononuclear cells infiltrate at injection sites) were observed in AMG-785 treated animals.

Exposure multiples in rat carcinogenicity study

TK Parameters and Multiples of Human Exposure in the Lifetime Pharmacology Study in SD rats

Study Number	Species	N/s/g	Duration, Dose Frequency	Doses (mg/kg)	N/s/g	Male Cmin (ng/mL) (Wk 13)	Female Cmin (ng/mL) (Wk 13)
107895	Rat/ Sprague-Dawley	N=60/group or N=54/group (50 mg/kg males)	24 months, weekly dosing	3	60	9660	4910
				10	60	79500	74600
				50	54(M), 60(F)	589000	836000
						$AUC_{(0\text{-}168h)}$ (µg hr/mL) (M and F, average)	**$AUC_{(0\text{-}1month)}$ (µg.hr/mL) (M and F, average) ($4xAUC_{(0\text{-}168h)}$)**
				3	N/A	1840	7360
				10	N/A	12900	51600
				50*	N/A	59800	239200
						Exposure Multiple (M and F, average)**	
				3	N/A	**0.6x**	
				10	N/A	**4.0x**	
				50	N/A	**19x**	

* AUC(0-168h) values for the 50 mg/kg dose were calculated based on population PK analysis of the data from the 6-month rat toxicity study (#107425) Data from ADA-positive animals were not included.

** Exposure Multiple = [Animal AUC(0-168h) x 4]/[Human AUC(0-τ) at the proposed clinical dose of 210 mg]; (Human AUC(0-τ) = 12888 ug.h/mL, based on Population PK Report 119384A).

N/A = Not Applicable

9 Reproductive and Developmental Toxicology

Summary

Reproductive studies were conducted in rats, since the product is strongly immunogenic in rabbits. In both the combined fertility/embryo-fetal development (FEED) study and the definitive embryo-fetal development (EFD) study in rats, romosozumab at doses of 100 and/or 300 mg/kg (**17x-56x**) the proposed monthly 210 mg clinical dose, based on AUC exposure) caused a slight increase in the incidence of reduced ventral processes on the 6th cervical vertebra, a skeletal variation, in the absence of other developmental delays or maternal toxicity. This finding is sometimes considered a developmental delay in a skeletal process that is not present in this cervical vertebra in humans. Since other delays in vertebral development/ossification were not observed, and the variation is not considered toxicologically relevant or relevant for humans, the finding may not need to be included in the product label.

External skeletal malformations, including fore- or hindpaw syndactyly (fused digits) and polydactyly (extra digits), occurred in 7/16 fetuses of 1 litter at the high dose of 300 mg/kg in the definitive embryo-fetal development study, at approximately **32x** human AUC based on TK data from dose range finding EFD study. The skeletal malformations exceeded historical control values. Other skeletal malformations and variations were also observed in 3 of the 7 affected fetuses in this litter. While these anomalies were not observed in any litters in the combined F/EFD or the PPND study, it is recommended that the findings be included in the label, because incidence exceeded historical control range, and the findings are likely treatment-related based on the known role of sclerostin in the skeleton and the presence of this type of skeletal developmental abnormality in humans and mice with genetic sclerostin deficiency.

In a pre- and post-natal study in rats, romosozumab caused transient decreases in food intake during the first two weeks of dosing at 60 and 300 mg/kg and increases in incidence of sparse hair coat at 300 mg/kg in the F0 generation females. In the F1 generation, there were slight but statistically significant decreases in bone mass in male and female pups at 60 and 300 mg/kg, and changes in cortical geometry in male pups at doses ≥10 mg/kg. The doses of 10, 60 and 300 mg/kg are equivalent to **1.5x, 19x and 56x** the proposed clinical 210 mg dose, based on GD13 AUC data from the FEED study. No skeletal abnormalities in the C6 cervical vertebrae were observed in the F1 generation pups at any dose.

Reproductive toxicity study data are included in the label, conforming to regulations, including the findings in animal EFD and PPND studies. The sought indication is the treatment of osteoporosis in postmenopausal women. (b) (4) (b) (4).

9.1 Fertility and Early Embryonic Development

AMG785: Fertility and Embryo-Fetal Development Study in the Rat
(108061) (GLP)
(b) (4)

NOTE: Study 113155 was reviewed by Dr. Laurie McLeod-Flynn. The review was filed in DARRTS for BLA 761062 (SD1) on March 29, 2017.

Key Study Findings

- Male and female Sprague Dawley rats were given once weekly SC doses of AMG 785 before cohabitation, through mating and through the period of organogenesis, at dose levels of 0, 10, 60, 300 mg/kg (N=25/s/g main study; 4/s/g TK). Dams were euthanized and fetuses examined on GD21.
- There were no effects on mortality, clinical signs, body weight, food consumption or necropsy observations.
- No effects on mating, fertility, male reproductive parameters (sperm analyses or organ weights), ovarian or uterine parameters, embryo-fetal survival or fetal body weights were observed.
- At 300 mg/kg, there were 3 fetuses from 3 litters that had reduced ventral processes (which develop into the rat carotid tubercles) on the 6th cervical vertebrae, slightly exceeding the historical range of the test facility, which was considered to represent a developmental delay (development of the ventral processes of the cervical vertebrae proceed in an anterior to posterior direction and the ventral processes on the 7th cervical vertebrae had not started to develop at gestation day 21). No other fetal morphology changes were observed at any dose level.

9.2 Embryonic Fetal Development

Subcutaneous Dose-Range Finding Development Study of AMG785 in Rats
(108057) (GLP)
(b) (4)

NOTE: Study 113155 was reviewed by Dr. Laurie McLeod-Flynn. The review was filed in DARRTS for BLA 761062 (SD1) on March 29, 2017.

Key Study Findings

- A dose range finding study was conducted in pregnant SD rats given two SC doses of 0, 30, 100, 300 mg/kg, on Gestation Days (GD) 6 and 13 (N=8/s/g main study, N=8/s/g for TK). C-sections and maternal/fetal observations were performed on GD21. Exposure was determined on Days 6 ($AUC_{0\text{-}168h}$) and GD13 ($AUC_{0\text{-}144h}$).
- AMG 785 was well-tolerated. No treatment related effects were observed on maternal or fetal parameters at any dose tested.

- There were no dose-dependent differences in litter or fetal incidences of any gross external, soft tissue or skeletal alterations.
- Fetal ossification site averages were generally comparable among the four dose groups.

Subcutaneous Developmental Toxicity Study of AMG785 in Rats
(108059) (GLP)
(b) (4)

NOTE: Study 108059 was reviewed by Dr. Eric Andreasen. The review was filed in DARRTS for AMG785-IND 103077 on June 18, 2009.

Key study findings:

- AMG 785 was administered to pregnant SD rats at doses of 0, 30, 100, 300 mg/kg, twice, subcutaneously, on Gestation Days 6 and 13 (N=25 F/grp). Dams were euthanized on GD21 and fetuses were examined.
- Toxicokinetics (serum concentrations only) and antibody assessment of each dam were determined on GD 21 after euthanization.
- No treatment related effects were observed on maternal parameters at any dose tested.
- At 0, 30, 100, and 300 mg/kg, the litter incidence of malformations or variations was 5 (21.7%), 5 (26.3%), 10 (41.7%) and 9 (40.9%), respectively.
- Seven fetuses from one litter in the 300 mg/kg dose group had **extra digits** (polydactyly) on the fore- and/or hindpaws and six of these fetuses also had **fused digits** (syndactyly).
- One to 3 fetuses from the same litter at 300 mg/kg also had incompletely ossified phalanges, misaligned metacarpals, large ulnae, misaligned metatarsals and large tibias, irregularly shaped metacarpals, broad ribs, and irregularly shaped ilia.
- Irregular shaping of the arch in the 6th cervical vertebra was also observed in 4 to 5 fetuses from 4 litters in the 100 and 300 mg/kg group. The incidence of litters and fetuses with **irregular shaped 6th vertebrae** at 100 (litters 17%; fetuses 2%) and 300 mg/kg (litters 18%; fetuses 3%) was greater than the historical control range (litters 0-12.5%; fetuses 0-1.7%) for the testing facility and should be considered AMG 785 related.
- There was a dose responsive increase in anti-AMG 785 binding antibodies with 4% of the controls expressing antibodies and 25%, 20%, and 64% of the 30, 100 and 300 mg/kg groups expressing antibodies on GD 21.
- **NOAEL for maternal toxicity was 300 mg/kg** (**56x** the proposed 210 mg clinical dose, AUC comparison).
- **NOAEL for fetal toxicity was 30 mg/kg** (**4.9x** the proposed 210 mg clinical dose, AUC comparison) based on fore- and hindlimb skeletal malformations at 300 mg/kg, and the cervical vertebral ossification delay at 100 and 300 mg/kg.

9.3 Pre- and Postnal Development

AMG785: Pre- and Postnatal Development Study in the Sprague Dawley Rat *(108062) (GLP)*

(b) (4)

NOTE: Study 108062 was reviewed by Dr. Miyun Tsai-Turton. The review was filed in DARRTS on March 27, 2017.

Key Study Findings

- AMG 785 was administered at SC doses of 0, 10, 60, and 300 mg/kg, weekly, to female Sprague Dawley rats beginning 6 weeks before cohabitation, and continuing weekly through the gestation and lactation periods.
- F0 generation:
  - Dosing of females did not result in any unscheduled deaths or macroscopic observations, and there were no effects on body weights or body weight gain at any dose level.
  - AMG 785 transiently reduced food intake during the first two weeks of dosing at ≥ 60 mg/kg and increased the incidence of sparse hair coat at 300 mg/kg, during the premating, gestation and lactation periods.
  - AMG 785 administration did not result in any effects on mating, fertility, or natural delivery parameters.
  - There were no effects on any litter parameters, including pup viability or pup body weights during the pre-weaning period.
- F1 generation pups:
  - Distal femur, metaphysis (pQCT) (Day 21 pp):
    - Slight, but mostly statistically significant decreases in total, (sub/) cortical and/or trabecular BMC and BMD, at 60 and 300 mg/kg, in males and females (NAOEL = 10 mg/kg). Effects were the same at both doses of 60 and 300 mg/kg (ca. **-8 to -9%** decrease). No effect on total bone area at any dose.
    - Slight but significant increases in total and trabecular (not cortical) BMD, at 10 mg/kg, in males and females. Effect size for trabecular BMD was **+14% in M, +9% in F**.
  - Distal femur, diaphysis (pQCT) (Day 21 pp):
    - Males only: Minimal decreases in total area, periosteal circumferences, endosteal circumference and CSMI, at all doses, significant at 10 and/or 60 and/or 300 mg/kg (NOAEL ≤10 mg/kg). Also in males, cortical thickness increased slightly (ca. **10%**) but significantly at 300 mg/kg.
  - The significance of the decreases in bone mass and/or size in rat pups exposed in utero and during lactation, which were different from the increases seen in adult animals, is unclear. Sponsor noted that the data were consistent with delayed postnatal development of high bone mass in SOST -/- mice and

sclerosteosis subjects. However, this reviewer does not agree with that assessment since the changes included increases in bone BMD and thickness.
- No skeletal abnormalities in the C6 cervical vertebrae at any dose.
- No effects on femur length or microscopic changes in bone on Day 21 postpartum.
- No AMG 785-related effects on survival, growth, sexual maturation, behavioral endpoints, mating and fertility, male reproductive organ weights or ovarian and uterine parameters.

Multiples of human exposure in rat reproductive toxicity studies

Study Number	**Dose (mg/kg)**	**$AUC_{(0-168h)}$ (ug.h/mL)**	**$AUC_{(0-1mo)}$ (ug.h/mL) ($4xAUC_{(0-168h)}$**	**Human Exposure Multiple (based on $AUC_{(0-1mo)}$ comparison)***	**Human Exposure Multiple (based on mg/kg comparison)***
108061	10	4752	19008	**1.5x**	3.3x
	60	60480	241920	**19x**	20x
	300	179760	719040	**56x**	100x
Study Number	**Dose (mg/kg)**	**$AUC_{(0-144h)}$ (ug.h/mL)**	**$AUC_{(0-1mo)}$ (ug.h/mL) ($4xAUC_{(0-144h)}$**	**Human Exposure Multiple (based on $AUC_{(0-1mo)}$ comparison)***	**Human Exposure Multiple (based on mg/kg comparison)***
108057	30	15800	63200	**4.9x**	10x
	100	53300	213200	**16.5x**	33x
	300	103000	412000	**32x**	100x

*Human $AUC_{(0-1month)}$ at 210 mg (3 mg/kg) = 12888 ug.h/mL (Clinical Population PK Report 119384A).

10 Special Toxicology Studies

Mechanistic studies to evaluate the bone cell responses to AMG785 are described in the Pharmacology section of this review.

The tissue cross reactivity study conducted with biotin-AMG785 (Study 105783) is described in the Toxicology section (6.4 Other toxicity studies) of this review.

No other special toxicology studies were conducted.

Reference ID: 4081796

11 Integrated Summary and Safety Evaluation

The Sponsor of BLA 761062, Amgen Inc, is seeking regulatory approval of their marketing application for romosozumab (210 mg once monthly, by subcutaneous (SC) injection) for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

Romosozumab (AMG785) is a humanized IgG2 sclerostin antibody. It inhibits the action of sclerostin, a negative regulator of bone formation. The consequence is an increase in bone formation, a decrease in bone resorption, and an increase in bone mass and/or size. In clinical trials with once monthly doses of 210 mg SC, this led to a statistically significant reduction in incidence of new vertebral fractures (-73%) and non-statistically significant reductions in nonvertebral (-25%) and hip fractures (-46%). BMD increases were observed in spine, total hip and femur neck, but small decreases in BMD were detected in distal radius. Bone formation markers were increased and resorption markers decreased.

The applicant completed an adequate nonclinical development program that consisted of in vitro and in vivo pharmacology studies, mechanistic studies, PK/ADME studies, and toxicology studies. The latter included general toxicity studies in rats and monkeys, local tolerance studies in rats and monkeys, a 2-year rat carcinogenicity study, and rat reproductive toxicity studies. Most studies were conducted using the SC dosing route. Dosing frequency in the animal studies was usually once weekly.

Mechanism of Action

Sclerostin-antibodies bind the osteocyte glycoprotein product sclerostin with high affinity, preventing its interaction with LRP4, LRP5 and LRP6 co-receptors of the Wnt receptor complex. This activates para- and autocrine canonical Wnt signaling in cells of the osteoblast lineage (osteocytes, osteoblasts and lining cells). The transcriptional changes that ensue lead to a rapid increase in bone formation and a decrease in bone resorption. The process involves time-dependent alterations in the expression of a multitude of Wnt targets, extracellular matrix genes and bone cell activity modulators. Upon chronic dosing, the osteoblast bone formation response appears to be subject to negative feedback or self-regulation. The effects of Scl-Ab are highly bone tissue-specific due to predominant expression of Scl protein in the osteocyte.

Primary Pharmacology

AMG785 binds with similar affinity to sclerostin from human, monkey and rat (Kd = 11, 23, and 3 pM, respectively). In vitro assays showed that AMG785 was able to prevent the sclerostin-mediated inhibition of bone mineralization.

Long term bone pharmacology ("bone quality") studies were conducted in OVX rat and monkey models of postmenopausal osteoporosis. Treatment with AMG785 was started after 2-month (rat) or 4-month (monkey) bone depletion periods. The 12-month OVX rat study was conducted at weekly doses of 3, 10 and 50 mg/kg (0.6x, 4x, 19x human AUC exposure at the

QM dose of 210 mg), and the 12-month OVX monkey study at 3 and 30 mg/kg (1.3x and 22x human AUC exposure at the QM 210 mg dose). The monkey study included a 6-month post-treatment recovery group.

The main effects in these studies consisted of dose-related increases in bone formation and cancellous and cortical bone mass (BMD/BMC) at all skeletal sites evaluated (spine, femur, tibia, radius), correlating with increases in bone strength. Bone mass increased most rapidly in the first months of treatment and continued to increase progressively albeit at a slower rate through 12 months. DXA-BMD increases were most pronounced in spine, proximal tibia, proximal femur and femoral neck, and least pronounced at distal femur and distal radius (all regions). While cortical BMD (pQCT) was minimally decreased in the first 6 months in distal radius diaphysis, cortical BMC and thickness were not affected or slightly increased. Densitometry, structural and mechanical parameters in the higher dose groups were usually increased to levels exceeding those in sham controls. Most bone effects diminisheded in the 6-month recovery group in the monkey study. The effects observed in the animals were generally consistent with the BMD effects observed in clinical studies with a romosozumab dose of 210 mg QM. Based on monkey and human data, a 12-month clinical treatment period appears to be adequate, since the BMD increases occurred mainly in the first months and strength changes are likely to parallel these effects.

Bone formation markers peaked in both species during the first 3 months of treatment, returning towards control levels at 12 months. Resorption markers, however, were increased in both rats and monkeys with maximal effects at 3 (monkey) or 6-9 months (rat). The latter was probably due to enhanced bone resorption/remodeling at intracortical and possibly other bone surfaces caused by the treatment-related increase in serum PTH, outweighing the decreases in resorption at trabecular and endocortical surfaces at a systemic level. By contrast, data from clinical studies showing that increases in formation markers were accompanied by decreases in resorption markers. Serum PTH was also increased in romosozumab treated clinical study subjects but this effect was less pronounced than in animals probably due to adequate calcium and vitamin D supplementation in the clinical studies.

Histomorphometry of cancellous and cortical bone parameters was performed at 3, 6, and 12 months in OVX monkeys, and at 12 months in rats. Treatment-related increases in cancellous bone volume were due to increases in trabecular thickness, and increases in cortical bone thickness were due to enhanced endosteal and/or periosteal bone apposition. Dynamic bone formation indices were increased at all surfaces (trabecular, endosteal, periosteal and intracortical/Haversian), particularly at earlier time points. Bone formation rates, largest at trabecular, endosteal and intracortical surfaces in control animals, were all increased by AMG785, but periosteal bone formation was usually increased to the largest extent.

In both rats and monkeys, the increases in periosteal and endosteal bone formation rates were probably accompanied by increases in resorption (not measured) based on comparatively small changes in bone thickness. This also pertained to Haversian surfaces where increased formation rates resulted merely in non-significant or transient increases in cortical porosity.

Resorption as indicated by eroded surface fraction was decreased in cancellous and cortical bone of monkey ilium and rib, respectively, and in monkey femoral cortex and rat tibia at end of study, although the effect in rat was very small. There were no significant effects on Mlt and O.Th. An increase in wall thickness in vertebral bone was the result of decreases in both resorption and reversal periods and a slight increase in formation period.

Biomechanical testing demonstrated increases in compressive, bending and shear strength parameters in vertebrae, femur shaft and femur neck, respectively. In monkeys, material strength of humerus cortical beams was not affected. Bone quality is comprised of bone material and structural properties. Statistically significant correlations between bone mass and strength parameters indicated that bone quality, when defined as slope of mass vs. strength regression lines, was maintained upon AMG785 treatment at all bone sites evaluated. Bone quality was slightly improved at the 30 mg/kg dose in rat and monkey vertebrae, probably due to improvements in architectural, not material properties. The data did not raise any concerns about potential adverse effects on extrinsic (whole bone) or intrinsic (material) bone strength.

A 6-month OVX monkey study with a dose of 3 mg/kg, equivalent to clinical exposure, was performed to further evaluate the transient decreases in cortical vBMD in radius and tibia observed in the 12-month OVX monkey study. The study showed that AMG785 caused slight decreases in pQCT-derived volumetric BMD (radius and tibia), while DXA-BMD of all radius regions was increased. The pQCT vBMD decreases were associated with increased intracortical bone turnover and cortical porosity, which was most prominent in radius but also observed in tibia. However, pQCT-BMC and cortical thickness of both radius and tibia were increased and there were no decreases in dia- and metaphyseal bone strength of the radius.

In a 10-week study in adolescent male monkeys with a Q2W dose of 30 mg/kg there were no adverse effects on bone tissue characteristics, evidenced by bSEM and FTIRM analyses. Global mineralization was not affected by AMG785, BMDD was minimally affected in trabecular bone, and matrix/mineral properties, crystallinity and collagen cross linking were not affected in any bone compartment. The small changes in some of the measured parameters were unlikely to have negative effects on bone tissue quality.

A detailed analysis of vertebral remodeling kinetics in a 28-week study in male monkeys at 30 mg/kg Q2W showed that AMG785 caused decreases in resorption depth and resorption period as well as an enhanced resorption rate. Combined with a (transient) increase in formation period this resulted in increased wall thickness and a positive bone balance in individual bone remodeling units. Data from the 12-month OVX monkey study and the 10-week study in male monkeys showed that AMG785-mediated increases in bone formation were initially modeling-based, resulting from a rapid activation of bone lining cells. The modeling-based formation attenuated with time, and remodeling-based formation continued steadily increasing bone mass as described above. The study results generally showed skeletal site- and surface-specific effects of AMG785 in rats and monkeys.

Several other studies were conducted in OVX rats with a rat surrogate Scl-Ab, r13c7, to avoid an immunogenic response. The results again showed increases in vertebral and femoral BMD, improved trabecular bone structure, and increases in vertebral and femoral strength. Suppression of resorption markers and histologic resorption indices in the r13c7-treated rat resembled the anti-resorptive effect of AMG785 in humans, in contrast to the increases in resorption parameters in the AMG785-treated OVX rats. Additional animal studies showed positive effects of AMG785 on bone mass and strength in models of other bone loss models, and positive effects on bone healing without untoward effects on bone remodeling in macroscopic fracture repair models.

Mechanistic studies confirmed the self-regulation of the osteoblastic bone formation response with initial increases in osteoblast numbers due to activation of lining cells, followed by reductions in osteoprogenitor number, upregulation of osteocyte transcription factors involved in inhibition of cell cycle progression, and upregulation of extracellular Wnt inhibitors (e.g. SOST).

In conclusion, the bone study data showed positive effects on bone mass and strength and did not reveal any obvious signals of impairments in bone quality or bone mechanical properties. The effects of AMG785 resembled those of increased mechanical loading. This is not surprising in light of the recognized role of sclerostin in the bone response to loading.

Safety pharmacology

AMG785 had no adverse effects on neurobehavioral effects in the rat at single doses up to 300 mg/kg (IV). Single IV doses up to 300 mg/kg had no effects on cardiovascular parameters and respiratory rate in monkeys. Also in monkeys, there were no ECG or blood pressure changes in 1-month and 6-month repeat dose studies at doses up to 300 mg/kg (SC or IV) or 100 mg/kg (SC), respectively.

PK/ADME

AMG785 exhibits non-linear PK in rats and monkeys, with greater than dose-proportional increases in exposure at doses <10 mg/kg, and linear PK with dose-proportional exposure increases at ≥ 10 mg/kg. This is consistent with target mediated drug disposition for IgGs. In rats, SC bioavailability in rats was 100% at 1 mg/kg, and 50% at 35 mg/kg, and in monkeys it was approximately 100% at 100 mg/kg. Plasma $T_{1/2}$ in rats increased and clearance decreased with increasing IV doses, ranging from 6h to 28h at 0.1-10 mg/kg. Terminal T1/2 of an SC dose in monkeys was 36h-88h in the 3-10 mg/kg dose range.

Upon weekly dosing in rats and monkeys (3-300 mg/kg), Tmax was 24h-96h, and terminal T1/2 upon recovery was 60h-94h (rat) or 74h-116h (monkey). Accumulation was less than 2-fold with weekly dosing. There were no sex differences in TK in repeat dose studies. Elimination occurs by catabolic peptide and amino acid degradation, or IgG removal by the reticuloendothelial system. In the embryofetal development studies, AMG785 was detected in fetal rat serum (35-90% of maternal serum concentrations), indicating transplacental transfer.

Two different drug substance formulations were manufactured and used during development. The Process 1 drug substance formulation (70 mg/mL AMG785) was used in Phase 1-2 clinical studies, in early nonclinical studies, and in 6-month rat and monkey toxicity studies. The commercial Process 2 drug substance formulation (b) (4) was used in Phase 1-3 clinical studies, and in rat reproductive toxicity and carcinogenicity studies. An SC single-dose monkey PK bridging study provided support that AMG 785 Process 1 and Process 2 drug products are similar from a nonclinical perspective.

Anti-drug antibody (ADA) formation was observed in rats and monkeys resulting in lower exposure and reduced PD response, particularly when ADAs were neutralizing. Hence, neutralizing ADA- and/or binding ADA-positive animals were either removed from longer term studies, or removed from data analysis including PK evaluations. AMG785 was highly immunogenic in rabbits and this species was not used for toxicity assessments.

A tissue cross-reactivity immunohistochemistry study showed binding of AMG785 to osteocytes in human, cynomolgus monkey, and rabbit, but not rat bone. Binding was also observed in aorta or pulmonary artery in a monkey. The cause of the lack of rat osteocyte staining is unclear. It is unlikely to be related to the lack of resorption suppression in the AMG785, but not the r13c7 treated rat, since the rat did have a clear and most likely osteocyte-mediated anabolic response to AMG785.

Toxicity

Repeat dose studies of 14-day, 1-month and 6-month duration were conducted in rats and monkeys. Pharmacological bone responses were seen at all study doses in both species, evidenced by increases in bone formation markers, bone mass and bone volume, changes in resorption markers and histomorphometric formation indices, bone thickening, hyperostosis and firm marrow. In both species, bone effects were present at the lowest doses equivalent to expected human exposure. Based on pharmacologic responsiveness, rats and monkeys were adequate test species.

Other findings included decreases in RBC in rats and monkeys, and decreases in platelet counts, reticulocyte count or % and WBC (all cell types), and increased compensatory spleen and/or liver extramedullary hematopoiesis in rats. These changes were most likely secondary to the bone effects. Serum calcium (Ca) and phosphorus (P) were decreased in monkeys, possibly due to enhanced bone mineral formation. A direct effect of AMG785 on blood forming elements in the marrow, in particular myeloid cell proliferation, was a concern based on the finding of acute myeloid leukemia (AML) in mice with constitutively activated osteoblast Wnt/β-catenin activation (Kode et al, Nature 506(7687): 240-244, 2014). However, this concern was allayed by the lack of significant changes in WBC cell or differential counts and the likely transient nature of the enhanced β-catenin signaling in the osteoblast upon treatment with Scl-Ab.

Incidental findings in a few animals in high-dose rat and monkey study groups at large human exposure multiples were of uncertain or unlikely toxicological significance. Serum glucose and phosphorus increases in rats may have been treatment-related but were of unclear significance. Compared to the 1-month studies, the 6-month studies did not show significant additional toxicities. Recovery group findings demonstrated partial reversibility of the bone findings and reversibility of the hematology and serum Ca and P changes.

In aged OVX monkeys treated for up to 12 months with doses of 3 and/or 30 mg/kg/wk, equivalent to 1 and 22 times human exposure at 210 mg QM, radiography did not show exacerbation of arthritis or spondylosis and did not result in aortic calcification. Immuno-phenotyping of peripheral blood lymphocytes did not indicate changes in absolute or relative numbers of various types of B-cells.

Rat studies: NOAEL and exposure multiples

Study Number	**Species Study type Duration**	**Doses (mg/kg/wk)**	**AUC* (mg·h/mL)**	**AUC Exposure Multiple****
105908	Rat Toxicity 1 month	10, 30, **300**	6, 147, **176**	1.8x, 46x, **55x**
107425	Rat Toxicity 6 months	3, 10, **100**	1.84, 12.9, **124**	0.6x, 4x, **38x**
107895	Rat Carcinogenicity 98 weeks	3, 10, **50**	1.84, 12.9, **59.8**	0.6x, 4x, **19x**
108057	Rat Embryofetal toxicity (dose range finding) 21 days	30, 100, 300	15.8, 53.3, **103** (A)	4.9, 16.5, **32x**
108059	Rat Embryofetal toxicity 21 days	**30**^{f1}, **100**^{f2}, 300	**15.8**^{f1}, **53.3**^{f2}, 103 (A)	**4.9**^{f1}, **16.5**^{f2}, 32x
108061	Rat Fertility and embryofetal toxicity 9 weeks	10, **60**^{f1}, 300	4.6, **60.5**^{f1}, 180 (B)	1.5x, **19x**^{f1}, 56x
108062	Rat Pre- and postnatal development 12-13 weeks	**10**^{f3}, **60**^{m}, 300	**4.6**^{f3}, **60.5**^{m}, 180 (B)	**1.5x**, **19x**, 56x

* $AUC_{(0\text{-}168h)}$ values from last sampling time in toxicology studies, except for Study 108059 ($AUC_{(0\text{-}144h)}$)
** AUC Exposure Multiple = [Rat AUC@NOAEL] x 4 / [Human AUC of 12.888 mg·h/mL] (Report 119384A)
NOAEL values are **bold; m**=maternal toxicity**; f1 =** reduction in 6th cervical vertebral process**, f2 =** syn/polydactyly**, f3 =** altered pup bone mass/structure parameters
(A) TK data from dose range finding Study 108057
(B) TK data from Study 108061

Monkey studies: NOAEL and exposure multiples

Study Number	Species Study type Duration	Doses (mg/kg/wk)	AUC* (mg·h/mL)	AUC Exposure Multiple**
105776	Monkey Toxicity 1 month	10, 30, **300**	23.8, 77, **645**	7.4x, 24x, **200x**
107426	Monkey Toxicity 6 months	3, 10, **100**	3.49, 17.1, **301**	1.1x, 5.3x, **93x**

* AUC values are from last sampling time in the toxicology studies

** AUC Exposure Multiple = [Monkey AUC @ NOAEL] x 4 / [Human AUC of 12888 ug·h/mL] (Report 119384A)

NOAEL values are **bold**

Safety monitoring in clinical trials was adequate to address potential issues identified by animal data. Clinical safety data did not show hematological or clinical chemistry effects. Changes in calcium included decreases in serum Ca at Month 1 to 12 (-2% to -1% vs pbo), decrease in urine Ca from Month 6 and 12 (-14, -8% vs pbo). Serum phosphorus was decreased at Month 12 by ca. 3% vs pbo. Serum PTH was increased in human subjects at Month 3 (+45% vs pbo) and Month 12 (+20% vs pbo). In monkeys, PTH was increased at Wk 10 (+90% to +130% vs OVX controls) and Wk 50 (+110% to +50% vs OVX controls), at 3 to 30 mg/kg, respectively, consistent with a larger stimulation of bone resorption/remodeling at intracortical and possibly periosteal surfaces. There was no imbalance in the number of leukemia cases in placebo and romosozumab groups and AML was not observed in romosozumab-treated study subjects.

Local tolerance

Local tolerance at the SC injection site was specifically assessed using solutions with different AMG785 concentrations. Single dose administrations showed transient, concentration-dependent inflammatory responses in male rats. Local tolerance to sodium and calcium acetate formulations (Process 1 and Process 2, respectively) appeared similar. Both were associated with minimal inflammatory infiltrates in repeat dose rat and monkey studies.

Genotoxicity

Genotoxicity testing was not performed. The product is a recombinant IgG2 protein of naturally occurring amino acids and is not expected to react with DNA or other chromosomal material.

Carcinogenicity

AMG785 was evaluated for carcinogenicity in a 2-year 'life-time pharmacology' study in Sprague Dawley rats. Doses used were 3, 10, and 50 mg/kg/week, equivalent to human exposure multiples of 0.6x, 4x, and 19x, based on AUC comparison. AMG785 had no effect

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on mortality or cause of death. Effects included marked bone mass increases and increased skeletal opacity, histologic hyperostosis, and extramedullary hematopoiesis. There were no statistically significant increases in tumor incidences at any dose.

Two osteosarcomas were found in the 50 mg/kg male group, one at necropsy in tibia and one by radiography in skull. The incidence (3.7%) marginally exceeded historical control range (0-3.3%). While there was a concern about osteosarcoma based on the precedence of bone tumorigenicity with PTH, and the two tumors were observed in the dose group with the highest bone mass increase, the lack of statistical significance, the potentially increased assay sensitivity based on use of radiography, and the high 20x exposure multiple, all suggest that these tumors are not of toxicological or clinical relevance. In addition, mechanistic data from OVX rat studies have suggested lack of osteoprogenitor proliferative activity of Scl-Ab. Hence, inclusion of the finding in the product label is not warranted.

The absence of bone tumors in this study, even at high human exposure multiples and marked bone mass increases, is in striking contrast with the bone tumor response observed with anabolic PTH- or PTHrP-related peptides. These compounds have caused osteosarcomas in 2-year rat studies at relatively low human exposure multiples based on unknown mechanism and of uncertain clinical relevance. The lack of tumors with AMG785 may be related to the transient self-limiting bone formation response. Lack of tumorigenicity of AMG785 is also suggested by other evidence including clinical data, offsetting potential limitations in the relevance of data from the AMG-785 treated rat.

Reproductive Toxicity

A fertility and embryo-fetal development (FEED) study was conducted in rats at doses of 10, 60 and 300 mg/kg, equivalent to **1.5x, 19x, and 56x** human exposure, based on AUC comparison. There were no effects on male or female fertility. AMG785 caused a slight increase in the incidence of reduced ventral processes on the 6th cervical vertebra at 300 mg/kg (56x human AUC), in the absence of maternal toxicity. Other adverse effects on vertebral development/ossifications were not observed. The reduction in the ventral process represents a developmental delay and was absent in pups postnatally (see PPND study). This particular anatomical structure is not present in humans. Therefore, while the finding is treatment-related, it is not considered clinically relevant and does not need to be included in the product label.

The definitive embryo-fetal development (EFD) study was conducted in rats at doses of 30, 100 and 300 mg/kg. This was equivalent to at least **5x, 17x, and 32x** human exposure, based on TK data from dose range finding Study 108057 with the same doses and human PK data at 210 mg QM. In 4/25 litters in the 100 and 300 mg/kg groups each, fetuses were found to have reduced ventral processes on the 6th cervical vertebrae, with fetal and litter incidences exceeding historical control ranges. External and skeletal malformations including syndactyly and polydactyly were observed in 7 of 16 fetuses in one of the 22 litters, at the high dose of 300 mg/kg. Some of the 7 affected fetuses also had associated skeletal malformations. Litter and fetal incidences exceeded historical control ranges in this study. The anomalies were not

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present in the other two pivotal reproductive toxicity studies. Across studies, litter incidence was 1/75, and fetal incidence was 7/1021, i.e. 0.7%. The Sponsor eventually concluded this finding was not treatment-related. However, this reviewer believes that treatment-relatedness cannot be excluded, in part based on the occurrence of syndactyly in $SOST^{-/-}$ mice and humans with sclerosteosis. NOAEL is 100 mg/kg, or **17x** human exposure. The reviewer recommends that this finding be mentioned in the product label.

In a pre- and post-natal study in rats, conducted at doses of 10, 60 and 300 mg/kg, equivalent to **1.5x, 19x, and 56x** human exposure, based on AUC comparison, minimal or slight but significant decreases in femoral bone mass (vBMD, vBMC) were observed in F1 males and females at 60 and 300 mg/kg, and altered femur cortical geometry (smaller bones) was seen in males at 10, 60 and 300 mg/kg (NOAEL <**1.5x** human exposure). Increases in bone BMD and thickness were also observed. The significance of the small bone decreases is unclear but being negative the findings constitute a slight safety concern. The changes are the opposite of those expected upon sclerostin inhibition. Lack of consistent bone mass increases might be in analogy with the delay in the postnatal development of high bone mass in SOST-/- mice until 4-8 wks of age. However, the bone decreases were not expected. Skeletal abnormalities in the 6th cervical vertebrae or digital malformations were not observed in the F1 pups. The lack of these abnormalities supports the hypothesis that the observation of reduced processes in the EFD study represented a developmental delay. There were no effects on any developmental endpoint including reproductive performance of F1 pups after lactation day 21.

Nonclinical assessment of clinical concerns

An extensive discussion of theoretical safety issues and potentially increased risks of various adverse effects was included by the Sponsor in the Secondary Pharmacology section of the BLA. Based on all submitted nonclinical and clinical information and information from published literature, the weight of evidence suggested that carcinogenicity is unlikely to be a significant concern with AMG785 treatment. The issues related to osteoarthritis, vascular calcification, increased longitudinal bone growth, hyperostosis, hypercementosis, altered hematopoiesis, sarcopenia, altered glucose metabolism, and exacerbation of TNFα-mediated inflammation are also unlikely to constitute significant safety concerns for the intended clinical treatment population.

The clinical team has expressed concern about the anti-resorptive effects of romosozumab. This is based on one case each of atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ) in Phase 3 study 20070337 in the initial 12-month romosozumab treatment period, and one additional case of ONJ after one dose of denosumab in the second 12-month treatment period. Increases in the risks of these serious adverse events are known to be associated with long term use of anti-resorptives such as bisphosphonates and denosumab, hence the clinical concern. Indeed, histomorphometry data from clinical Study 20070337 clearly showed romosozumab-related decreases in endocortical and trabecular eroded surface, the latter to a similar extent as denosumab. Animal histomorphometry data provided similar information.

An animal model for AFF does not exist. However, in long term studies in alendronate treated dogs, resorption suppression has been associated with reductions in strength parameters, particularly post-yield toughness, which indicates an increase in bone brittleness often considered an underlying cause of AFF. The bone mechanical changes may be due to lack of repair of microcracks resulting from drug-induced resorption inhibition. The Sponsor's nonclinical AMG785 studies, several of which included adequate bone strength assessments, provided strong evidence of a lack of bone quality or strength impairments. Regarding ONJ, there were no adverse effects on jaw bone in the Sponsor's chronic toxicity studies and data from a published study in a rat periodontal ligation model showed increases in alveolar bone and continued resorptive activity although clinical endpoints were not included in the study. Nevertheless, the ideal nonclinical model and the bone quality parameter(s) that are most predictive for increased risks of clinical AFF and/or ONJ are not well established.

A study to evaluate the effect of AMG785 on femoral bone strength in mice to address the concern about AFF does not seem warranted, as data from published literature suggest that Scl-Ab increases cortical bone material strength and does not cause the increase in femur brittleness observed with alendronate treatment (Sinder et al, Bone 71: 115-123, 2015; Misof et al, Bone 36: 150-158, 2005; Uveges et al, JBMR 24(5): 849-859, 2009).

If the clinical team has concerns regarding the ability of romosozumab to cause osteonecrosis of the jaw (ONJ), a nonclinical study could be conducted to examine the effects of r13c7 in a rat surgical ONJ model (refer to Kim et al., Bone 81:442-448, 2015). Adequate dose selection and inclusion of a bisphosphonate control arm would be recommended for such a study. Zoledronic acid treatment, in combination with dental extraction, has been shown to induce ONJ in this model, and the ONJ was accompanied by a shift in alveolar bone microcrack size to larger values. Such a nonclinical study would be useful if it could provide helpful information from a clinical or regulatory perspective.

Conclusions

Taken together, the submitted nonclinical information is adequate and supports the safety of the proposed treatment with once-monthly subcutaneous doses of 210 mg in the intended treatment population. AMG785 was generally well tolerated by animals at doses equivalent to large human exposure multiples, and apart from indirect effects related to the pharmacological activity, little toxicity was observed. Information available from humans with sclerostin deficiency disorders or SOST knockout mice is also generally reassuring regarding bone safety, general toxicity and carcinogenicity. The embryofetal digit anomalies observed with AMG785 treatment replicate similar observations in humans and mice with sclerostin deficiencies.

Label
Pharmacology/Toxicology Labeling Recommendations are included in the Executive Summary.

- Section 8: Edit section and language to comply with current PLLR policies
- Section 12.1: Mechanism of Action: Edit language based on above discussion
- Section 13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility: Edit language
- Section 13.2: Animal Toxicology and/or Pharmacology: Edit language to adequately describe findings in nonclinical bone pharmacology studies

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12 Appendices

APPENDIX 1

A 52 Week Bone Quality Study to Determine the Effects of Weekly Subcutaneous Injection of AMG785 in the Aged Ovariectomized Cynomolgus Monkey
(Study No. 107903)
(b) (4) *(2011-2014)*
(GLP/QA) (Dec 8, 2014)
Batch/Lot Nr: 0010085638, FDP Batch #1026275, Material #20009614AI1

METHODS
Cynomolgus monkeys (b) (4) ages 8.5-17.5 years, weight 3-5kg, were acclimatized for 6-8 weeks before an 8-week baseline period. They were then sham-operated or ovariectomized (OVX-ed) and AMG785 treatment was started after a 17-week bone depletion period. Sham-operated animals were dosed with vehicle (**0 mg/kg/wk**) once weekly for 52 weeks (Grp 1). OVX groups were treated with subcutaneous doses (1.45 mL/kg) of **0, 3, 30 mg/kg/wk** for 52 weeks (Grps 2, 3, 4), or for 26 weeks followed by vehicle for 26 weeks (**30/0 mg/kg/wk**; Grp 5). Dose levels were aimed at achieving an increase in spine BMD of ca. 10-15% at 3 mg/kg, and a higher but less than saturated response at 30 mg/kg. Monkeys were not supplemented with calcium (Ca) or Vitamin D (VitD).

Text Table 2
Experimental Design

Group Number	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Original Allocation Animal Numbers	Allocation for Interpretation Animal Numbers
1/ Sham Vehicle Control	0	0	151-161, 163-166, 172	151-161, 163-166, 172
2/ OVX Vehicle Control	0	0	251-266	251-266
3/ AMG 785 (OVX)	3	2.1	351-366	356-358, 360, 363, 365
4/ AMG 785 (OVX)	30	21	451-466	451-458, 460-466
5/AMG 785 (OVX) [a]	30	21	551-563, 565-566, 584	551-558, 560-563, 566, 584

[a] Group 5 animals were dosed for 26 weeks followed by a 26-week recovery period.
The dose volume was 1.43 ml/kg.

In-life observations/measurements in main study animals:
- Mortality (2x/day)
- Clinical observations: Menses daily, detailed observations weekly
- Detailed clinical observations (weekly)
- Body weight (weekly) and food consumption (daily)
- Clinical pathology (hematology/coagulation, clinical chemistry, urinalysis (at various time points in study)
- Toxicokinetics:

    - Samples taken at 7 time points, up to 7 days post-dosing, on Day 1, and Wks 10, 26, 52; also pre-dose samples taken in Wks -1, 5, 13, 15, 19, 26, 29, 33, 37, 41, 45, 52; Grp 5 samples taken during the week after Wk 26
    - AMG785 measured by validated ELISA
    - Parameters Cmax, Tmax (median), AUC0-t (until last time with quantifiable concentration)
- Anti-drug antibodies:
    - Samples taken in Wks -1, 13, 26, 52
    - ADA measured by validated electrochemiluminescence immune-assay
    - ADA-positive samples analyzed for Ab neutralization activity by bioassay
    - Neutralizing ADA-positive and part of ADA-positive animals excluded from analyses
- Biochemical markers of bone resorption CTx (serum) and NTx (urine), and bone formation BAP, PINP and OC (serum) at end of baseline, at end of bone depletion, Wks 9/10, 23/24, 37, 49/50, and pre-sacrifice
- Hormones (estradiol, PTH, VitDOH2) (same times as turnover markers)
- DKK1/FGF23 (similar times as turnover markers)
- Radiography in vivo (end of Tx, end of recovery)
- Immunophenotyping of lymphocytes (CD45+ Total Lymphocytes, CD45+/CD3-/CD20+ B cells) in Wk35. This evaluation was done because changes in bone marrow B cell numbers have been reported in sclerostin knock-out mice
- Labeling for histomorphometry (15 and 5 days pre-sampling) (tetracycline pre-Wk 13, alizarin complexone pre-Wk 27, calcein pre-necropsy); biopsies for interim histomorphometry at Weeks 13 and 27: Rib and ilium

Densitometry (in vivo) (same side throughout study)

- DXA of several bone sites, of all animals, taken during acclimation/baseline, at end of bone depletion, and Wks 11/12, 24/25, 51/52; parameters: Area, BMD, BMC

Text Table 15
DXA Reported Parameters

Scan site	Reporting Area (cm^2), BMC (g), BMD (g/cm^2)
Whole Body	Global
Lumbar Spine	Total L1-L4
Thoracic Spine	Total T9-T12
Right Proximal Tibial Diaphysis	1/3 site
Right Distal Femur	Distal (R1)
Right Proximal Femur	Global, neck (R1) and trochanter (R2)[a]
Right Distal Radius	Total, 1/3 and ultra distal (UD)

[a] the area of R2 was not reported as the area of this region of interest was predefined.

- PQCT of several bone sites (1x during baseline, end of bone depletion, and Wks 11/12, 24/25, 51/52), with parameters:
  - Metaphysis: Area, BMC, BMD (total, trabecular, cortical/subcortical)
  - Diaphysis: Area, BMC and BMD (Total, cortical), Ct.Th., and periosteal and endosteal circumference

Text Table 17
pQCT Reported Parameters

Scan Site	Reporting
Metaphysis Site: Right distal radius Right proximal tibia	total area (mm^2), BMC (mg/mm) and BMD (mg/cm^3) trabecular BMC (mg/mm) and BMD (mg/cm^3) cortical/subcortical BMC (mg/mm) and BMD (mg/cm^3)
Diaphysis Site: Right radial diaphysis Right tibial diaphysis	total area (mm^2), cortical area (mm^2), BMC (mg/mm) and BMD (mg/cm^3) cortical thickness (mm) periosteal circumference (mm) endosteal circumference (mm)

Terminal procedures

- Complete necropsy, organ weight (uterus), tissue collection, histology evaluation of bone (left femur, ilium-biopsy site, rib- biopsy site, L2 vertebra), lesions/masses, injection site

Histology and histomorphometry (undecalcified tissue; static and dynamic parameters)

- Interim biopsy samples (Wk 13 and 27): rib (cortical bone) and ilium (cancellous bone)
- End of study:
  - Vertebrae (L2) (cancellous bone)
  - Femur (neck - cancellous bone; and diaphysis – cortical bone)
  - Rib (cortical bone)

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Text Table 20
Cancellous bone region evaluation parameters

STRUCTURAL	DYNAMIC
Tissue area (T.Ar)[@]	Mineralizing surface (MS/BS)
Bone volume (BV/TV)	Single label surface (sLS/BS)
Mineralized volume (Md.V/TV)	Double label surface (dLS/BS)
Osteoid volume (OV/BV)	Mineral apposition rate (MAR)
Trabecular thickness (Tb.Th)	Adjusted apposition rate (Aj.AR)
Trabecular separation (Tb.Sp)	Osteoid maturation rate (Omt)
Trabecular number (Tb.N)	Mineralization lag time (Mlt)
Osteoid thickness (O.Th)	BFR*, surface referent (BFR/BS)
Osteoid surface (OS/BS)	BFR*, volume referent (BFR/BV)
Osteoblast surface (Ob.S/BS)	Activation frequency (Ac.f)
Osteoclast surface(Oc.S/BS)	Formation period (FP)
Eroded surface (ES/BS)	Formative surface (Fo.S/BS)
Wall thickness (W.Th)	Quiescent surface (QS/BS)

[@] Not reported: used to derive other variables *BFR: Bone Formation Rate

Text Table 21
Cortical Bone Evaluation Parameters

STRUCTURAL	DYNAMIC
Total tissue area (Tt.T.AR)	Periosteal single label surface (Ps.sL.Pm/Ps.Pm)[a]
Cortical area (Ct.Ar)	Periosteal double label surface (Ps.dL.Pm/Ps.Pm)[a]
Medullary area (Me.Ar)	Periosteal labelled surface (Ps.L.Pm/Ps.Pm)[a]
Cortical area, relative (%Ct.Ar)	Periosteal MAR (Ps.MAR)
Medullary area, relative (%Me.Ar)	Periosteal BFR, surface referent (Ps.BFR/BS)
Cortical width (Ct.Wi)	Endocortical single label surface (Ec.sL.Pm/Ec.Pm)[a]
Periosteal perimeter (Ps.Pm)	Endocortical double label surface (Ec.dL.Pm/Ec.Pm)[a]
Endocortical perimeter (Ec.Pm)	Endocortical labelled surface (Ec.L.Pm/Ec.Pm)[a]
Percent porosity area (%Po.Ar)	Endocortical mineral apposition rate (Ec.MAR)
Haversian wall thickness (H.W.Th)	Endocortical BFR, surface referent (Ec.BFR/BS)
Endocortical eroded surface (Ec.E.Pm/Ec.Pm)	Endocortical quiescent surface (Ec.Q.Pm/Ec.Pm)
	Endocortical formative surface (Ec.Fo.Pm/ Ec.Pm)
	Haversian single label surface (H.sL.Pm/H.Pm)
	Haversian double label surface (H.dL.Pm/H.Pm)
	Haversian labelled surface (H.L.Pm/H.Pm)
	Haversian mineral apposition rate (H.MAR)
	Haversian BFR, surface referent (H.BFR/BS)
	Haversian BFR, volume referent (H.BFR/BV)

[a] Parameters evaluated for the cortical analysis of L2 and Femoral Neck (terminal necropsy) and of Ilium (Week 13 and Week 27).

Densitometry (ex vivo)

- DXA: of each bone specimen destined for biomechanical strength testing
- Peripheral QCT: of all specimens destined for biomechanical testing

Text Table 24
Ex vivo DXA Reported Parameters

Scan site	Reporting Area (cm^2), BMC (g), BMD (g/cm^2)
Right femur	Global, proximal (R1), central (R2) and distal (R3)
L3 and L4 vertebral bodies*	Global
L5 and L6 vertebral cores*	Global

* Data obtained from the specimens were averaged.

Text Table 26
Ex vivo pQCT Reported Parameters

Scan Site	Reporting
Femur at the expected breaking point	total area (mm^2), BMC (mg/mm) and BMD (mg/cm^3) cortical area (mm^2), BMC (mg/mm) and BMD (mg/cm^3) cortical thickness (mm) periosteal circumference (mm) endosteal circumference (mm) cross-sectional moment of inertia in the plane of bending, CSMI (mm^4)
L3, L4 vertebral bodies* mid-section	Total area (mm^2), Total and trabecular BMC (mg/mm) Total and trabecular BMD (mg/cm^3)
L5, L6 vertebral cores* mid-section	Trabecular area (mm^2), BMC (mg/mm) and BMD (mg/cm^3)

* Data obtained from the specimens were averaged.

Micro CT scanning

- Micro-CT (ex vivo) of L3, Femoral Neck (FN), humeral cortical beam, L6 core
- Parameters: vBMD mgHA/cm^3, BMC mg HA or mg HA/mm, Region Area (mm^2), Bone Area (mm^2), tissue BMD mg HA/cm^3, trabecular BV/TV (%) and Tb parameters, Ct.Th (mm), porosity, SMI (structure model index, reflecting rod vs plate structure), DA (degree of anisotropy)

Biomechanical testing

- Vertebral body (L3, L4) and core (L5, L6): compression
- Femur: 3-point bending test
- Femoral neck: shear test
- Humerus (cortical beams): 3-point bending test
- Correlation analysis between densitometry and ex-vivo densitometry parameters

Bone ash testing

- Tissue mineralization (%) calculated as ratio of ash to dry weight

Statistical analysis

- The number of animals was 16F/grp, but due to Ab (ADA) formation fewer animals were available to provide reliable data. For statistical analyses and result interpretation, the following numbers of animals/group were generally used:
  - 16 (sham and OVX vehicle groups) (Grps 1 and 2)
  - 6 (3 mg/kg groups) (Grp 3)
  - 15 (30 mg/kg group dosed for 52 week) (Grp 4)
  - 14 (30 mg/kg group dosed for 26 weeks with 26 weeks of recovery) (Grp 5)

RESULTS

Anti-drug antibodies

- Several animals had (A) Binding ADAs (B) Neutralizing ADAs (**Text Tables 33 and 34)**
- This led to exclusion of several treated animals, resulting in data for statistical analysis from N=16, 16, 6, 15, 14, in Grps 1, 2, 3, 4, 5 (**Text Table 35**)

Reference ID: 4081796

Text Table 33
Anti-AMG 785 Binding Antibody Positive Animals per Dose Group [a]

Group (Dose)	Week -1	Week 13	Week 26	Week 52	All Postdose Period Combined
sham vehicle control	0% (0/16)	6% (1/16)	6% (1/16)	25% (4/16)	25% (4/16)
OVX vehicle control	0% (0/16)	6% (1/16)	6% (1/16)	6% (1/16)	13% (2/16)
3 mg/kg	19% (3/16)	63% (10/16)	75% (12/16)	75% (12/16)	75% (12/16)
30 mg/kg dosed for 52 weeks	6% (1/16)	50% (8/16)	50% (8/16)	31% (5/16)	63% (10/16)
30 mg/kg dosed for 26 weeks with 26 weeks of recovery	6% (1/16)	38% (6/16)	63% (10/16)	69% (11/16 [b])	81% (13/16)
All AMG 785-dosed animals	10%(5/48)	50% (24/48)	63% (30/48)	58% (28/48)	73% (35/48)

[a] Results are expressed as percentage and incidence. Incidence is the number positive/number evaluated

Text Table 34
Anti-AMG 785 Neutralizing Antibody Positive Animals per Dose Group [a]

Group (Dose)	Week -1	Week 13	Week 26	Week 52	All Postdose Period Combined
sham vehicle control	0% (0/16)	0% (0/16)	0% (0/16)	0% (0/16)	0% (0/16)
OVX vehicle control	0% (0/16)	0% (0/16)	0% (0/16)	0% (0/16)	0% (0/16)
3 mg/kg	0% (0/16)	0% (0/16)	56% (9/16)	63% (10/16)	63% (10/16)
30 mg/kg dosed for 52 weeks	0% (0/16)	0% (0/16)	0% (0/16)	6% (1/16)	6% (1/16)
30 mg/kg dosed for 26 weeks with 26 weeks of recovery	0% (0/16)	6% (1/16)	13% (2/16)	56% (9/16)	56% (9/16)
All AMG 785-dosed animals	0% (0/48)	2% (1/48)	23% (11/48)	42% (20/48)	42% (20/48)

[a] Results are expressed as percentage and incidence. Incidence is the number positive/number evaluated

Text Table 35
Anti-AMG 785 Antibody Positive Animals postdose (after Animal Exclusion per Study Plan Amendment 16)

Group (Dose, Operation)	Binding Antibodies [a]	Neutralizing Antibodies [a]
sham vehicle control	25% (4/16)	0% (0/16)
OVX vehicle control	13% (2/16)	0% (0/16)
3 mg/kg	33% (2/6)	0% (0/6)
30 mg/kg dosed for 52 weeks	60% (9/15)	0% (0/15)
30 mg/kg dosed for 26 weeks with 26 weeks of recovery	76% (11/14)	50% (7/14)
All AMG 785-dosed animals	63% (22/35)	20% (7/35)

[a] Results are expressed as percentage and incidence. Incidence is the number positive/number evaluated

Toxicokinetics

Animals with significant/neutralizing ADA (i.e. N=10 at 3 mg/kg, N=1 at 30 mg/kg, N=2 at 30 mg/kg recovery) were eliminated from analysis.

- AUC(0-t) at Wk 52: **172 and 2950 ug·day/mL (**3 and 30 mg/kg), or 4128 and 70800 ug.hr/mL
- Exposure increased in first weeks and reached maximum by Wk 10
- Accumulation ratios 1.4x and 1.9x (3 and 30 mg/kg), Wk 52 vs Wk 1; AUC(0-t) increased 13x, 17x, 17x, 17x (Wks 1, 10, 26, 52), for 10x dose increase (3 to 30 mg/kg)
- Concentrations below LLOQ after study Wk 33 in the recovery group

Exposure Multiples (based on Week 52 PK data)

Data (Wk 52)	**3 mg/kg/wk**	**30 mg/kg/wk**
Tmax (hrs)	24	24
Cmax (ug/mL)	33	538
AUC (0-168h) (ug.day/mL)	172	2950
Monthly AUC (ug.day/mL)*	688	11800
Monthly AUC (ug hr/mL)	16512	283200
AUC multiple (monkey vs human)	**1.3x**	**22x**
Dose (mg/kg) multiple (monkey vs human)	**1x**	**10x**

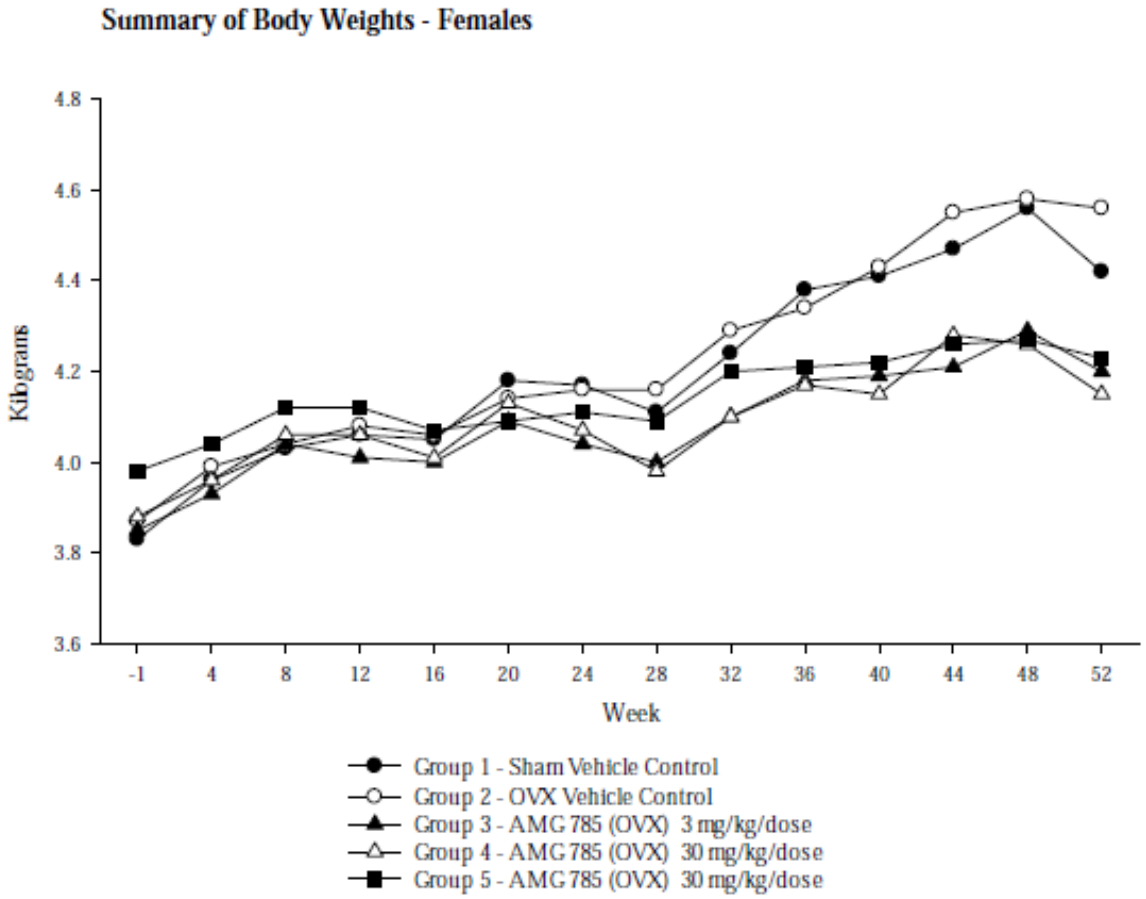
(Human AUC = 546 ug.day/mL = 12888 ug.h/mL; data from Clinical Population PK Report 119384A)
*Monthly AUC = 4 x weekly AUC

Mortality, Clinical Observations

- Unremarkable

Body Weight

- Increase in BW in all groups over time; no difference between OVX and sham
- Decrease (vs Sham and OVX) in all AMG-treated AFTER Wk 24 (approx. -8% vs ctrl at Wk 52).
- Cause of BW decrease in AMG-treated is unclear (occurred concomitant with INCREASE in bone mass/volume/weight) but may be related to an effect of AMG785 on fat mass/adipocytes



Food Consumption

- Unremarkable

Clinical pathology

- OVX: Expected changes due to OVX, e.g., increased ALP due to increased bone turnover, increases in serum Ca and P, decrease in serum estradiol; no effects on urine parameters.
- AMG785: Some changes in RBC/Hb (transient decrease in 30 mg/kg grps), neutrophils (transient increase at 30 mg/kg in Grp 5 in Wk33), serum ALKP (increases at 3 and 30 mg/kg in Wk49), serum Ca (decreases in 30 mg/kg grps through Wk 23/24), and serum Alb/Glob (increases in Grps 3 and 4 in Wk 49); no effects on urine parameters.

Immunophenotyping

- Increase in total lymphocyte count and in absolute and relative B cell counts in OVX vs sham ctrls; no effects in AMG-treated vs OVX controls
- No effects of AMG785 on total lymphocyte or B-cell counts

Organ weignts

- Reduced uterus weight in OVX vs Sham (-67%), as expected; no effect of AMG785.

Gross pathology

- Absence of ovaries in all OVX animals; uterus small in a few OVX animals; No remarkable effects of AMG785.

Histopathology

- Mononuclear cell infiltration (minimal-slight) at injection sites in 3 but not in 30 mg/kg group, possibly immunologically mediated, since there was also a larger ADA response in this group.
- Increase in amount but not incidence of woven bone in rib (absent in recovery animals), but not iliac bone biopsy defect sites at 30 mg/kg.
- No AMG 785-related microscopic changes in bone or marrow, such as a defective organization of osteoid matrix or marrow fibrosis in any samples examined at any timepoint.

Hormones (Text Fig. 6, below)

- OVX effect: slight decreases in serum PTH and VitD (not shown)
- AMG effect: Significant increases in PTH and VitD, both continuing throughout treatment period

DKK1 and FGF23

FGF23 increased in OVX vs sham, and transiently decreased at Wk 9/10 by 30 mg/kg AMG785.

Radiography

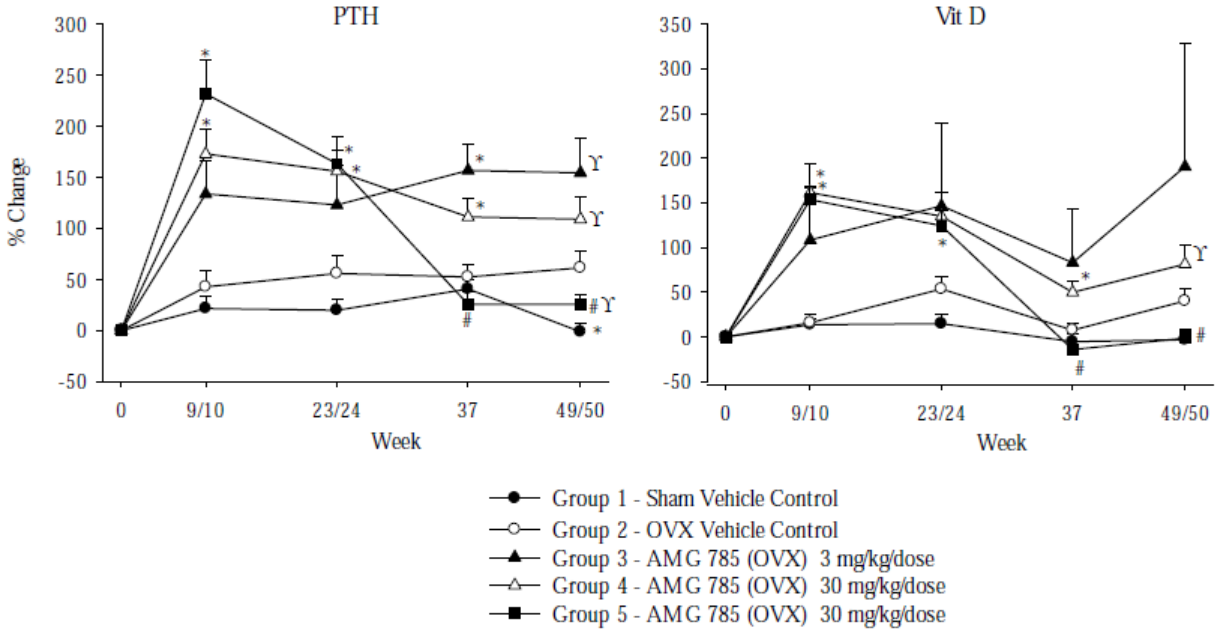
No evidence of proliferative changes or aorta mineralization.

Bone turnover markers (Text Figs. 3 and 4)

- OVX
  - Increases in formation (2-3x) and resorption markers (2x) vs sham, due to OVX-induced stimulation of turnover (data not shown).
- AMG785:
  - Increases in bone formation markers BAP, PINP and OC, as expected based on neutralization of sclerostin, at both 3 and 30 mg/kg.
  - Increases in resorption markers CTx and NTx, at both doses. Urine NTx data were probably least reliable.
  - Increases in formation and resorption were maximal at the two earlier time points (Wks 9/10-23/24) and decreased thereafter, but markers remained above OVX levels at Wk 52.

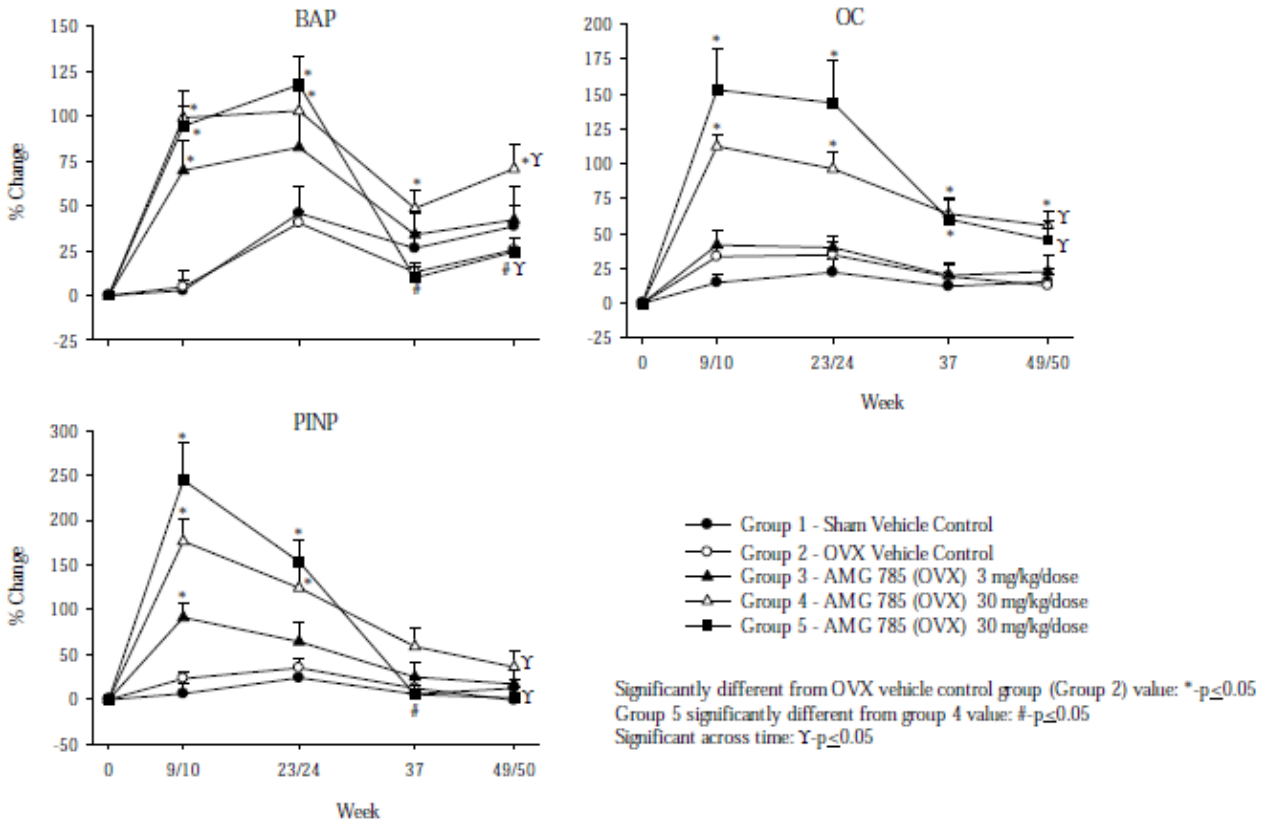
Reference ID: 4081796

Text Figure 6
Hormones - Mean (SEM)
Percentage Change from End of Bone Depletion Period



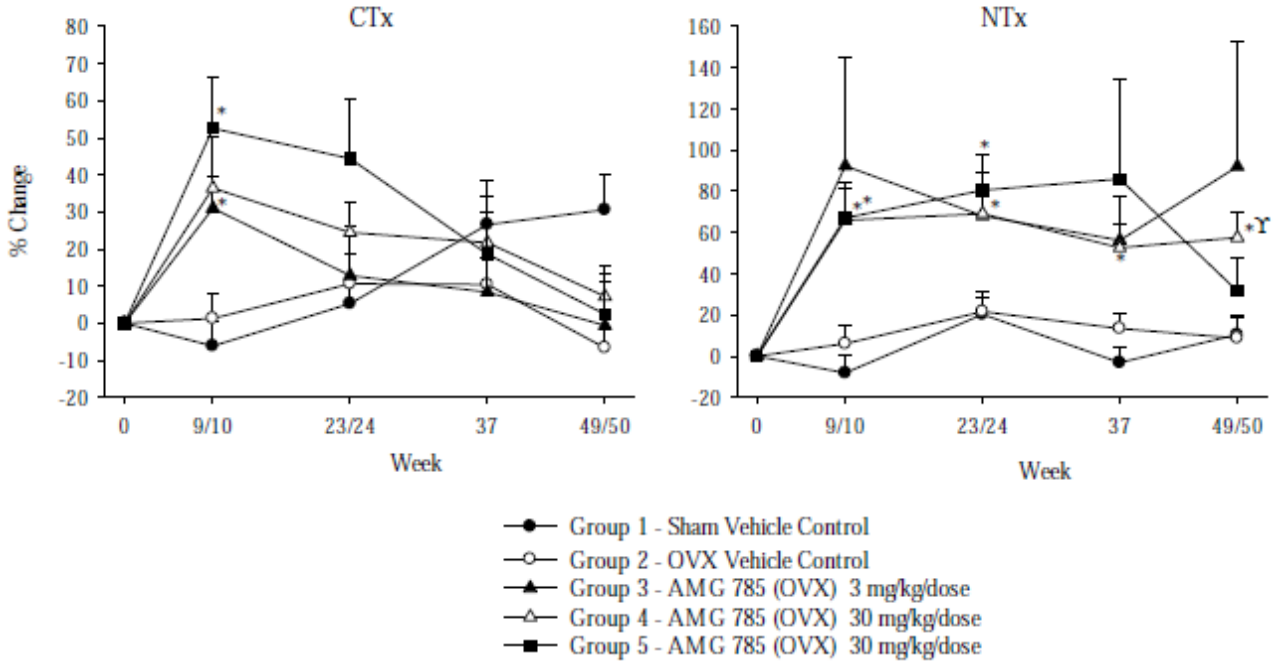
Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: ϒ-p≤0.05

Text Figure 3
Bone Formation Markers - Mean (SEM)
Percentage Change from End of Bone Depletion Period



Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: ϒ-p≤0.05

Text Figure 4
Bone Resorption Markers - Mean (SEM)
Percentage Change from End of Bone Depletion Period



Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: ϒ-p≤0.05

Reviewer comments:

- *Both formation and resorption markers were dose-dependently and transiently increased by AMG785.*
- *Maximum effect was at Wks 9/10, except NTx showed continued increase through Wk 52. NTx data are probably least reliable.*
- *The transient increase in bone resorption (and part of the increase in formation) markers by AMG785 may be related to the observed increase in PTH leading to stimulation of bone turnover (ie resorption and formation).*
- *The increase in formation markers is consistent with the increases in bone formation parameters (eg BFR) at trabecular and cortical (endosteal, intracortical and periosteal) bone surfaces.*
- *The increase in resorption markers is in apparent contrast to the decreases in histomorphometric resorption parameters in cancellous bone of ilium (ES/BS, Wk 13) and cortical bone of rib (Ec.E.Pm %, Wks 13, 27, 52) and femur (Wk 52). However it is consistent with the likely increases in intracortical and periosteal bone resorption or turnover.*

- *In OVX rats, one of two analyzed resorption markers (CTx) was also increased, but resorption marker DPD was unaffected.*
- *In humans, in the 24-month Phase 3 study 20070337 with an initial 12-month AMG785-only Tx period, formation markers were increased and resorption markers decreased. The increase in BF markers was largest in Month 1 (ca. 120% vs pbo) and no longer seen after ca. 9 months, while the decrease in BR markers was maximal in Month 1 (ca. - 50% vs pbo) but continued through Month 12.*

Densitometry (in vivo)

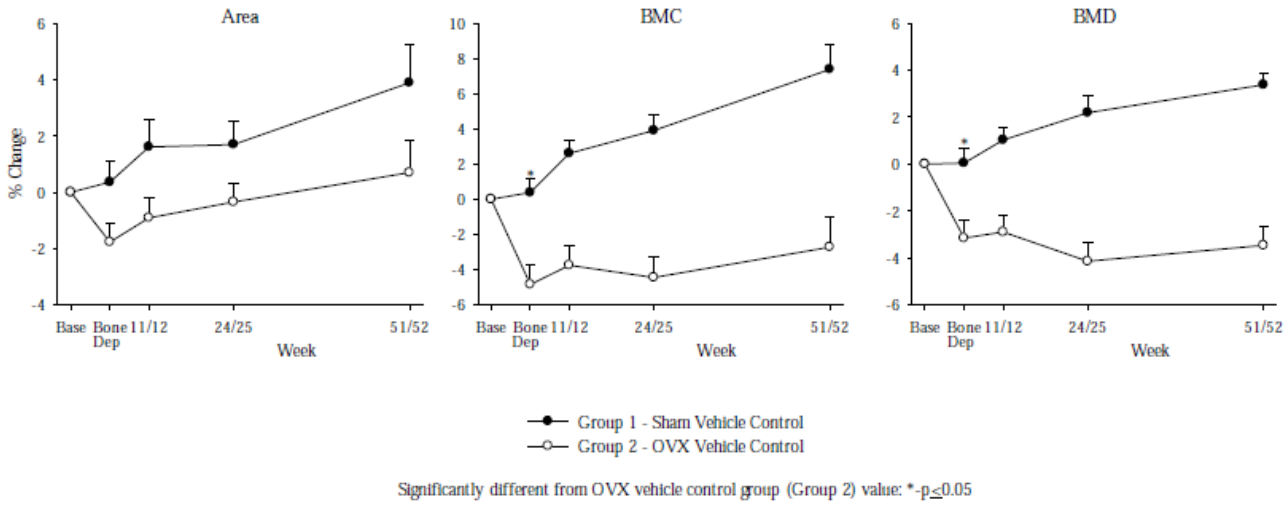
- *Data in Text Figures represented as % change from end-of-bone-depletion period*
- *Statistical analyses were of effects "collapsed across time", ie, changes in Tx vs OVX from 3 time points added together.*

DXA (in vivo)

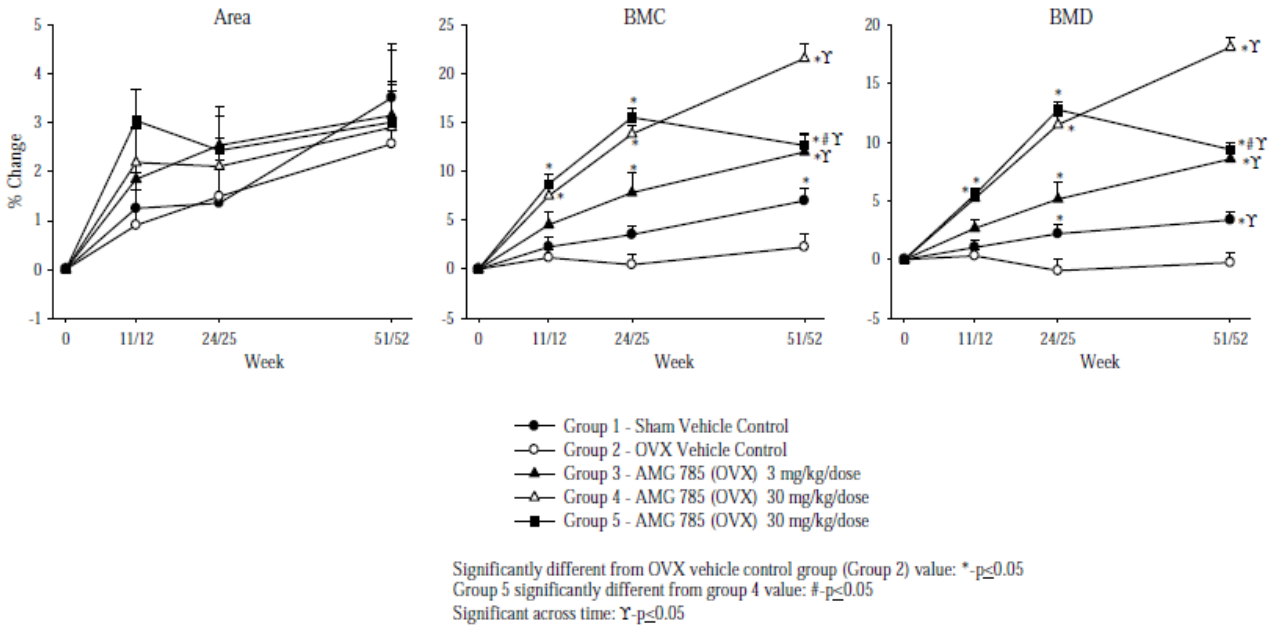
Whole Body: (**Text Figs. 7 and 8**)

- OVX:
  - Decreases in BMD (-3%), Area and BMC in OVX vs. sham. However, after the bone depletion period, Area and thus BMC increased in both sham and OVX animals due to an effect on "body composition" according to Sponsor. BMD was only slightly decreased from Wk 12-52.
- AMG treatment:
  - Dose-related increases in BMD and BMC, and small transient increases in Area.
  - BMD and BMC effects continued throughout 51/52 wks.

Text Figure 7
Bone Densitometry Values by DXA as Percent Change from Baseline Period - Whole Body - Mean (SEM)



Text Figure 8
Bone Densitometry Values by DXA as Percent Change from End of Bone Depletion Period - Whole Body - Mean (SEM)



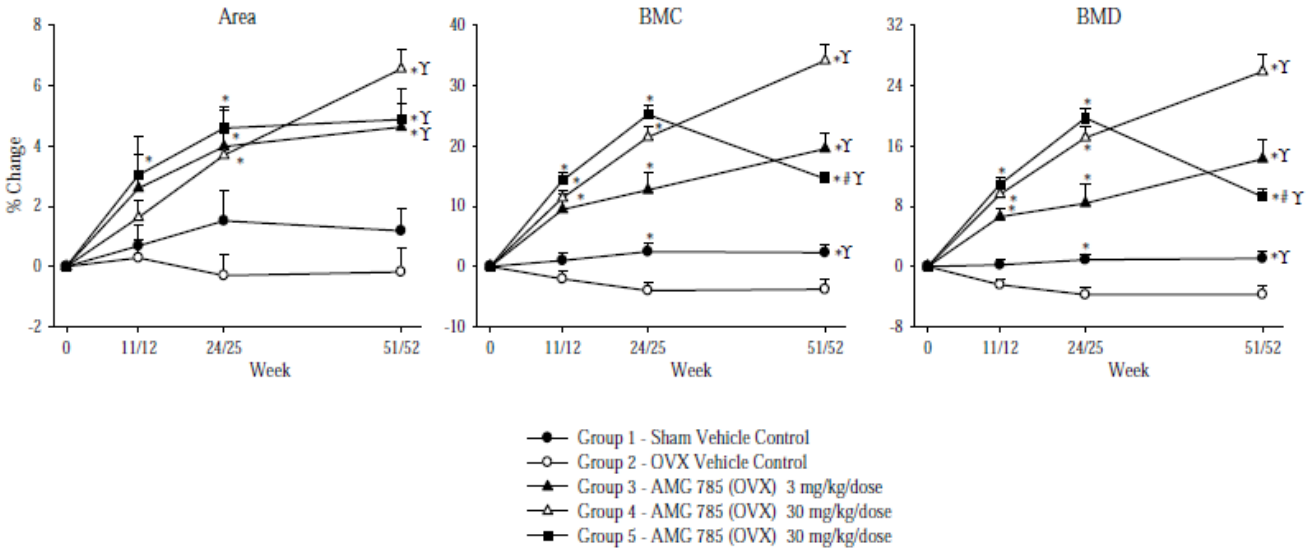
Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: ϒ-p≤0.05

DXA Lumbar Spine L1-L4 (**Text Figs 9 and 11**):

- OVX:
  - Decreases in Area, BMD and BMC during 4-month bone depletion period, continuing up to 26 weeks during the 12-month Tx period.
- AMG-treatment:
  - Dose-dependent, statistically significant increases in Area, BMC and BMD, at 3 and 30 mg/kg.
  - Increases were slightly larger (i.e., faster) in first 11/12 weeks of Tx, but continued thereafter.
  - Bone parameters in AMG-treated OVX groups exceeded sham levels in both 3 and 30 mg/kg groups by Wk 11/12.
  - Effect appeared maximal at 3 mg/kg, despite higher AUC exposure at 30 mg/kg (22x vs 1.3x human AUC).
  - In the 30 mg/kg recovery group, Tx discontinuation led to reversal of BMD (and BMC) effects after Wk 24/25; however Tx withdrawal did NOT lead to significant reversal of the AMG effect on Area.

- Results for thoracic spine (T9-T12) were very similar

Text Figure 11
Bone Densitometry Values by DXA as Percent Change from End of Bone Depletion Period – Lumbar Spine (L1-L4) - Mean (SEM)



Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: ϒ-p≤0.05

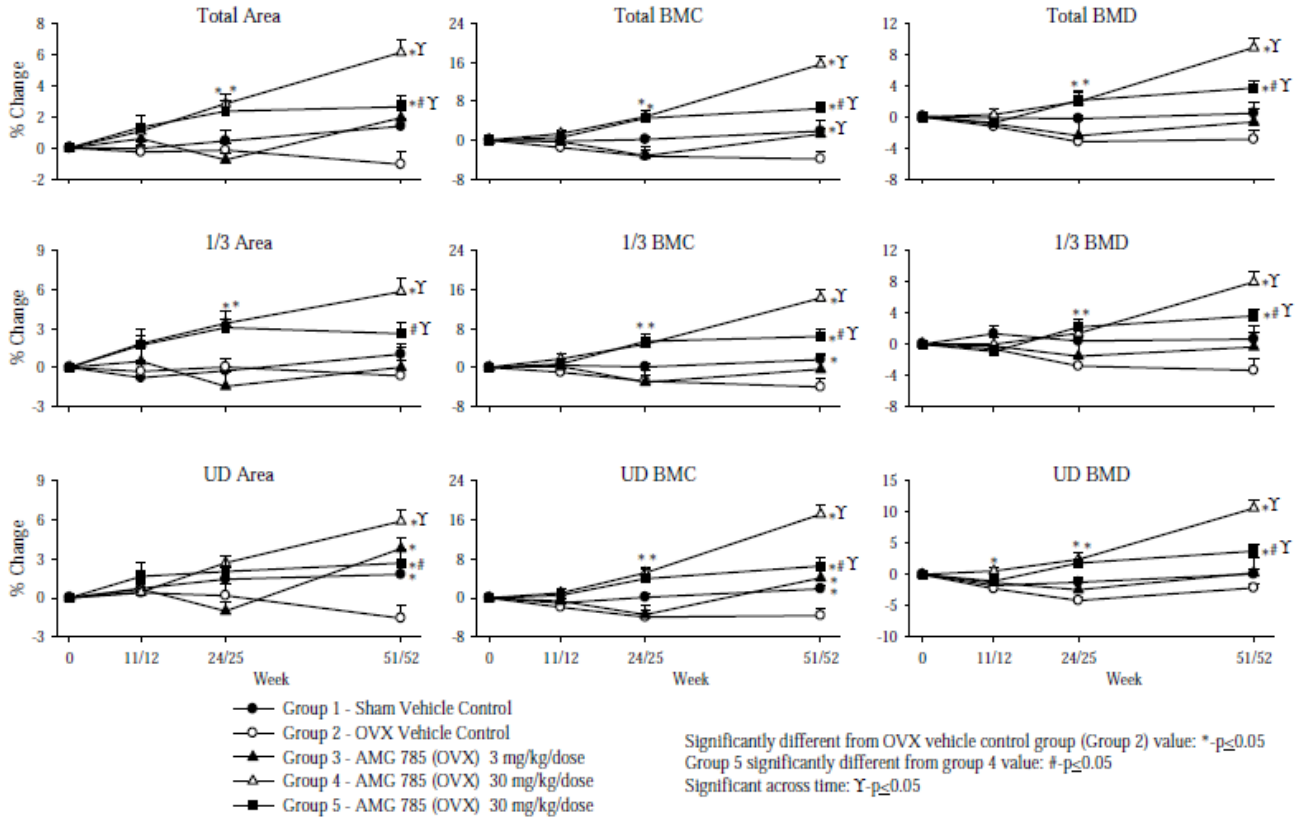
Reviewer Comment:
The increase in vertebral BMD at Wk 52 was ca. 17% at the 3 mg/kg dose, a dose equivalent to 1.4x the human 210 mg dose based on AUC. This was very similar to the spine BMD change vs placebo at the end of the 12-month AMG treatment period in Phase 3 Study 20070337 (ca. 13%), suggesting similar bone efficacy in monkeys and humans.

DXA Distal Radius (**Text Fig 14**):

- OVX:
  - Small decreases in Area (UD part), BMD and BMC during 4-month bone depletion period, and continuing mainly in first 24/25 wks of Tx period (see Text Fig 14).
- AMG treatment:
  - Significant increases in Area, BMD and BMC in total distal radius at 30 mg/kg (Text Fig 14). Increase in BMD vs. OVX control was +9%, +8% and +11 % for total, 1/3 and UD radius, respectively.
  - Increases occurred mainly after Wk 11/12 at 30 mg/kg and after 24/25 weeks at 3 mg/kg
  - Increases at 3 mg/kg were much smaller than at 30 mg/kg, and 1/3 Radius-Area was not increased at this dose.

- Parameters in 30 mg/kg grp exceeded OVX levels by Wk 24/25 and sham levels by Wk 52.
- Tx withdrawal caused a non-significant reversal of effects.

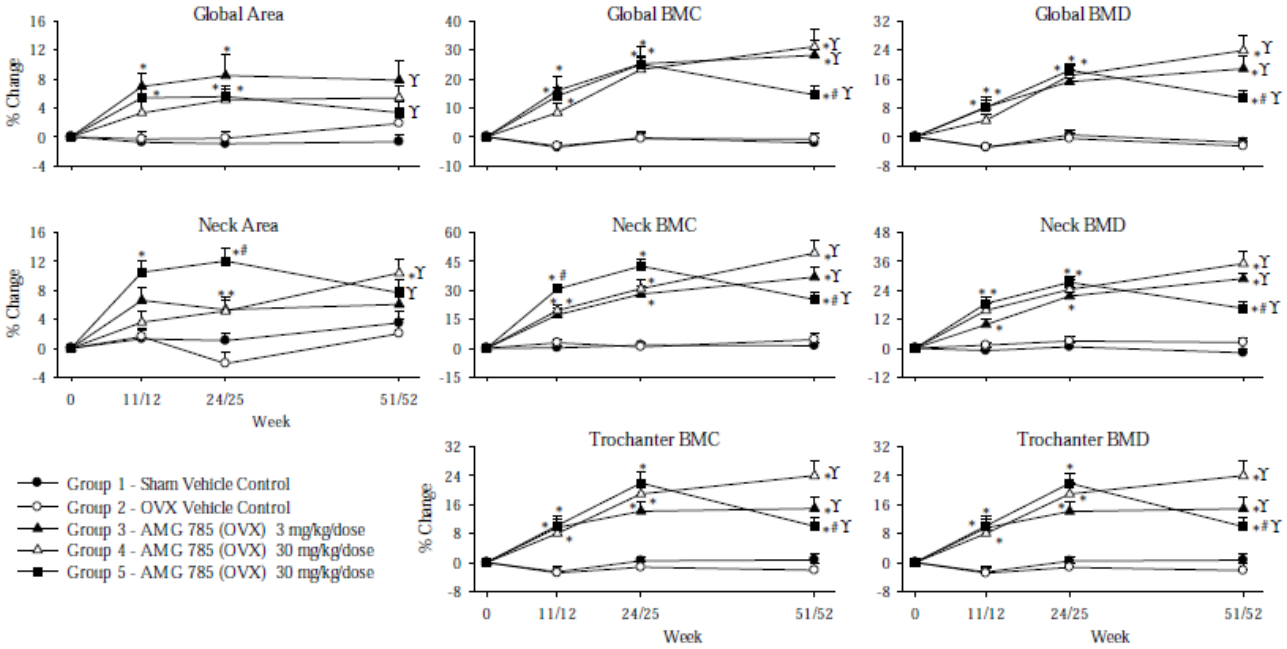
Text Figure 14
Bone Densitometry Values by DXA as Percent Change from End of Bone Depletion Period – Distal Radius – Mean (SEM)



DXA Proximal Femur (**Text Fig 16**):

- OVX:
  - Decreases in Area, BMD and BMC during 4-month bone depletion period, and continuing through first 11/12 wks of Tx period.
- AMG treatment:
  - Significant increases in Area, BMD and BMC in global Proximal Femur, trochanter, and femoral neck, of similar magnitude at both doses.
  - BMD increase +22% and +26% at 3 and 30 mg/kg, for global proximal femur; +28% and +34% for Femoral Neck at Wk 51/52) (vs. OVX control).
  - Increases in all parameters occurred mainly in first 24/25 weeks at both doses.
  - Parameters exceeded sham levels at both doses by Wk 11/12.
  - In the 30mg/kg recovery group, Tx withdrawal led to significant reversal of effects on Area BMD and BMC.

Text Figure 16
Bone Densitometry Values by DXA as Percent Change from End of Bone Depletion Period – Proximal Femur – Mean (SEM)

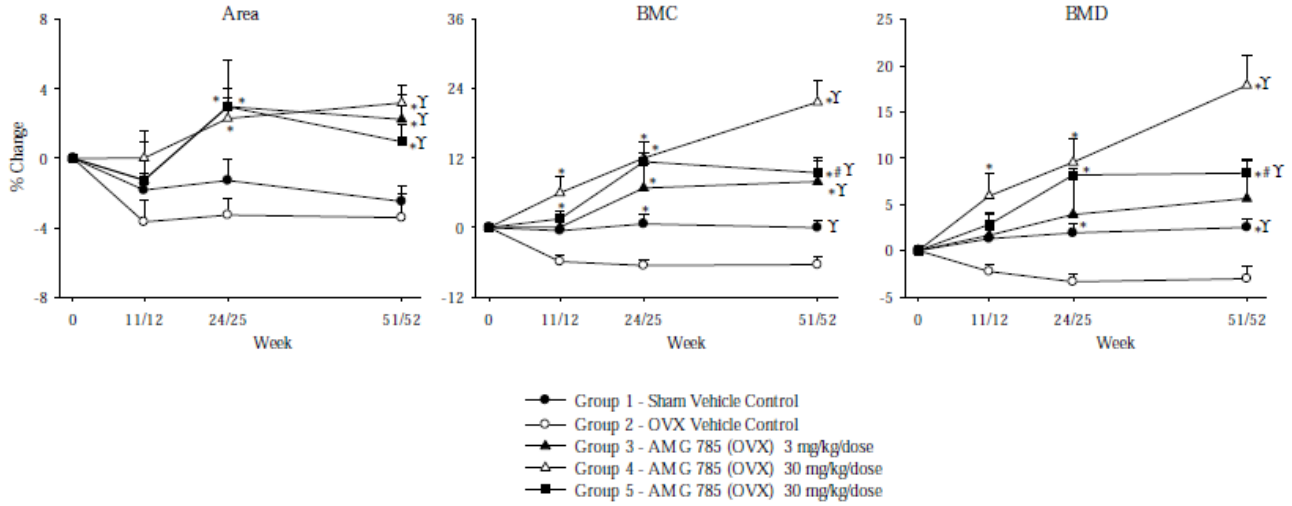


Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: ϒ-p≤0.05

DXA Distal Femur (**Text Fig 18**):

- OVX:
  - Decreases in Area, BMD and BMC during 4-month bone depletion period, continuing through first 11/12 wks of Tx period.
- AMG treatment:
  - Significant dose-related increases in Area, BMD and BMC.
  - BMD increase +6% and +18% at 3 and 30 mg/kg at Wk 51/52 (values not OVX ctrl-corrected).
  - Increases occurred mainly in first 24/25 weeks at both doses.
  - Parameters exceeded sham levels by Wk 24/25 (or earlier at 30 mg/kg) at both doses.
  - In the 30mg/kg recovery group, Tx discontinuation led to very slight reversal of effects on Area BMD and BMC

Text Figure 18
Bone Densitometry Values by DXA as Percent Change from End of Bone Depletion Period – Right Distal Femur - Mean (SEM)



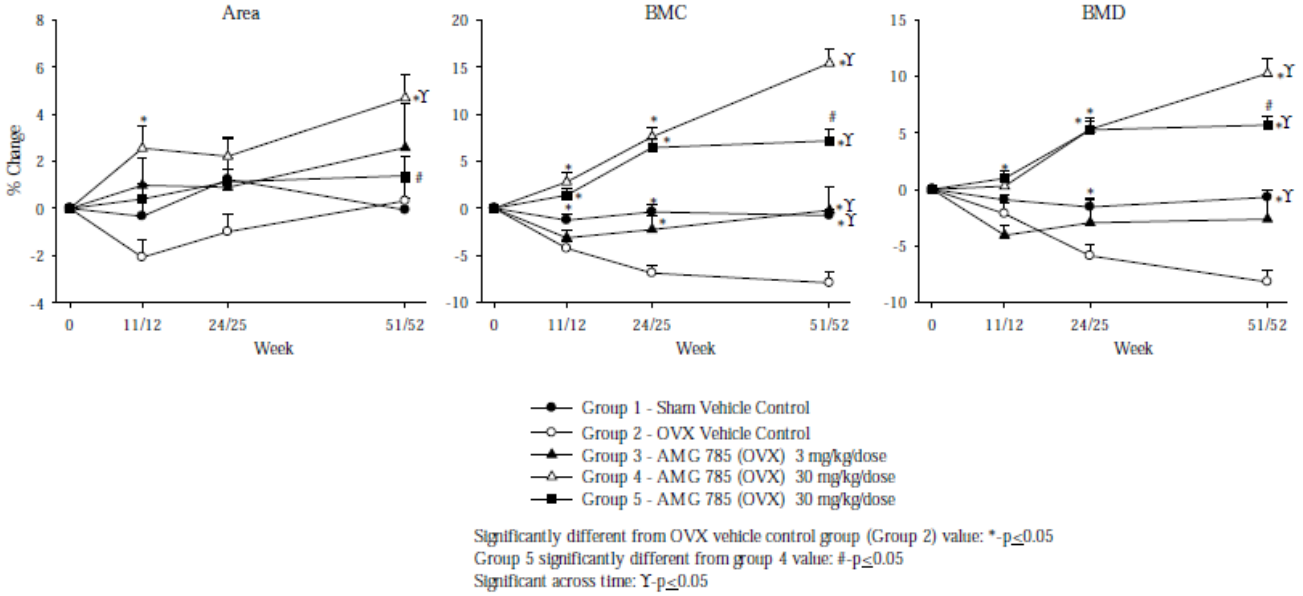
Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: ϒ-p≤0.05

Reviewer Comment (DXA femur):
Global BMD increase at 3 mg/kg at 12 months vs OVX control was approx. 20% (global proximal femur) and 25% (femoral neck). This was much larger than the change vs placebo in Phase 3 study 20070337 at 12 months (total hip 5.8% and femoral neck 5.2%).

DXA Proximal Tibia Diaphysis (**Text Fig 20**):

- OVX:
  - Decreases in BMC, BMD and Area in OVX animals relative to sham controls during 4-month bone depletion period (decrease was -2% for BMD). Decreases continued during Tx period.
- AMG treatment:
  - Dose-related increase in Area (small) and BMD at 3 and 30 mg/kg resulting in dose-related increase in BMC.
  - Change in BMD vs OVX control was +5% (at 3 mg/kg) and +18% (at 30 mg/kg) by Wk 52 (-8% in OVX controls).
  - Parameters Area, BMD and BMC exceeded sham levels at 30 mg/kg by Wk 11/12.
  - BMD and BMC increased clearly in first 6 months, but continued to increase after 6 months.

Text Figure 20
Bone Densitometry Values by DXA as Percent Change from End of Bone Depletion Period - Tibial Diaphysis - 1/3 - Mean (SEM)



Reviewer Comment:
The DXA data showed increases in all parameters and are consistent with the increases in bone formation markers. They showed the largest effects in the first 3-6 months of treatment for all bones except distal radius. In human study 0337, BMD of lumbar spine was also increased mainly in the first 6 months of the 12-mo Tx period; in total hip, BMD increased at slower rate after 6 months, and femoral neck BMD increased throughout the 12 months Tx. It is not clear which bone site and surface contributes most to the changes in markers. Trabecular bone mass is smaller than cortical mass (20% vs 80%) but total trabecular surface is probably larger.

<u>pQCT (in vivo)</u>

Metaphysis (proximal tibia and distal radius)

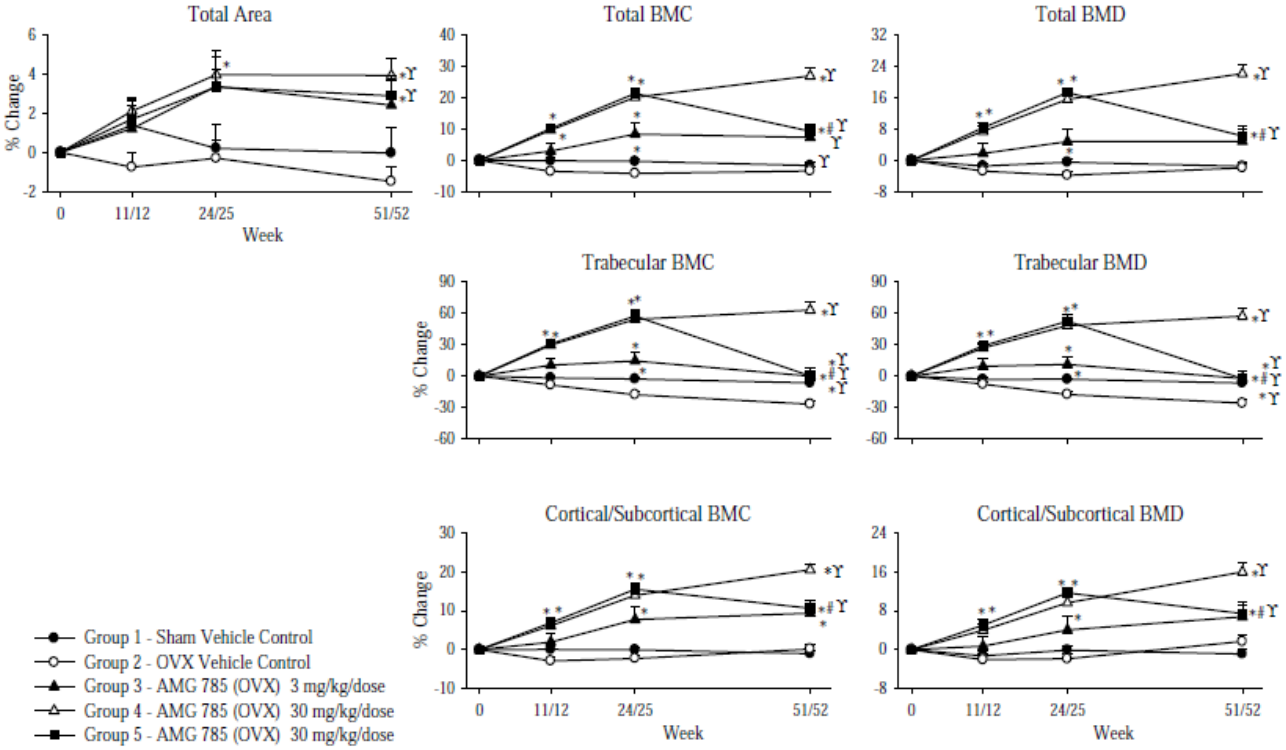
- OVX (tibia and radius) (**Text Fig. 21**):
  - Decrease in BMD, Area and BMC during bone depletion period, continuing through 11/12 weeks (cortical BMD) to 52 weeks (trabecular BMD).
  - Total slice BMD was decreased by -4% and -5% during depletion (tibia and radius, resp).
  - Clear decreases in all BMC and BMD values (total, cortical, trabecular)
- AMG785-treatment
  Proximal Tibia (**Text Fig. 23**):

- Dose-related increases in Total, Trabecular and Cortical BMC and BMD at both doses. Trabecular BMD increase at 3 and 30 mg/kg was +9% and 27%, by 52 wks.
- Increases in Total Area at both doses with same time dependence
- Metaphyseal (sub)cortical area (ie thickness) was not significantly affected, based on BMC vs BMD comparison.
- Bone parameters in AMG-treated OVX groups surpassed sham levels in both 3 and 30 mg/kg groups by end of Tx.
- In the 30mg/kg recovery group, Tx discontinuation led to decreases in BMD and BMC but not Area effects vs the 30 mg/kg group after Wk 24/25.

Distal Radius (**Text Fig. 24**):

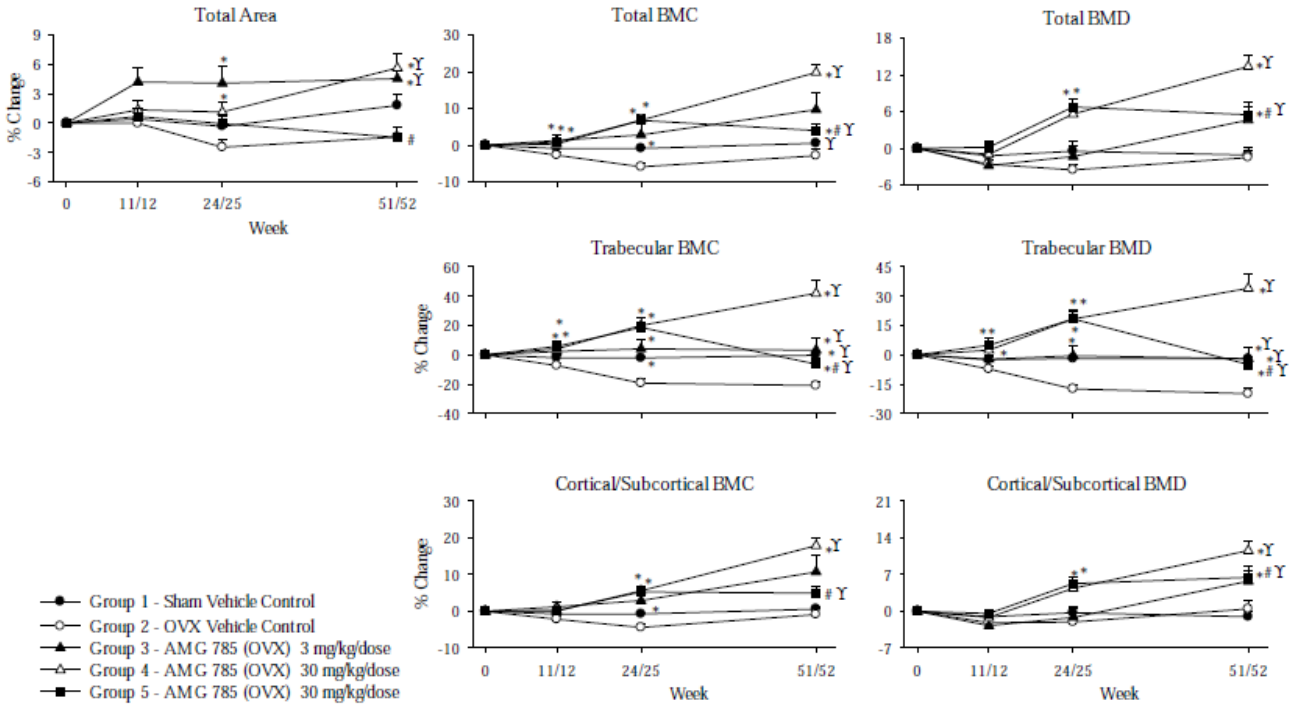
- Dose-related increases in Total, Trabecular and Cortical BMC and BMD at both doses. Effects on BMD and BMC were generally smaller than in proximal tibia.
- Slight increases in Total Area at both doses, with increase occurring earlier in 3 vs 30 mg/kg group
- Metaphyseal (sub)cortical area (ie thickness) was not significantly affected, based on BMC vs BMD comparison.
- Parameters exceeded sham levels in both 3 and 30 mg/kg AMG785 groups by end of Tx.
- In the 30 mg/kg recovery group, there were decreases in BMD, BMC and Area effects vs the 30 mg/kg groups after Wk 24/25.

Text Figure 23
Bone Densitometry Values by pQCT as Percent Change from End of Bone Depletion Period - Proximal Tibia - Metaphysis Site - Mean (SEM)



Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: ϒ-p≤0.05

Text Figure 24
Bone Densitometry Values by pQCT as Percent Change from End of Bone Depletion Period - Distal Radius - Metaphysis Site - Mean (SEM)



Significantly different from OVX vehicle control group (Group 2) value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant across time: Y-p≤0.05

Reviewer Comment (pQCT metaphyses):
AMG caused marked increases in BMD and BMC particularly in trabecular but also (sub)cortical bone compartments, along with slight increases in bone area in both tibia and radius metaphyses. Changes were more pronounced for proximal tibia than distal radius.

pQCT
Diaphysis (proximal tibia and distal radius)

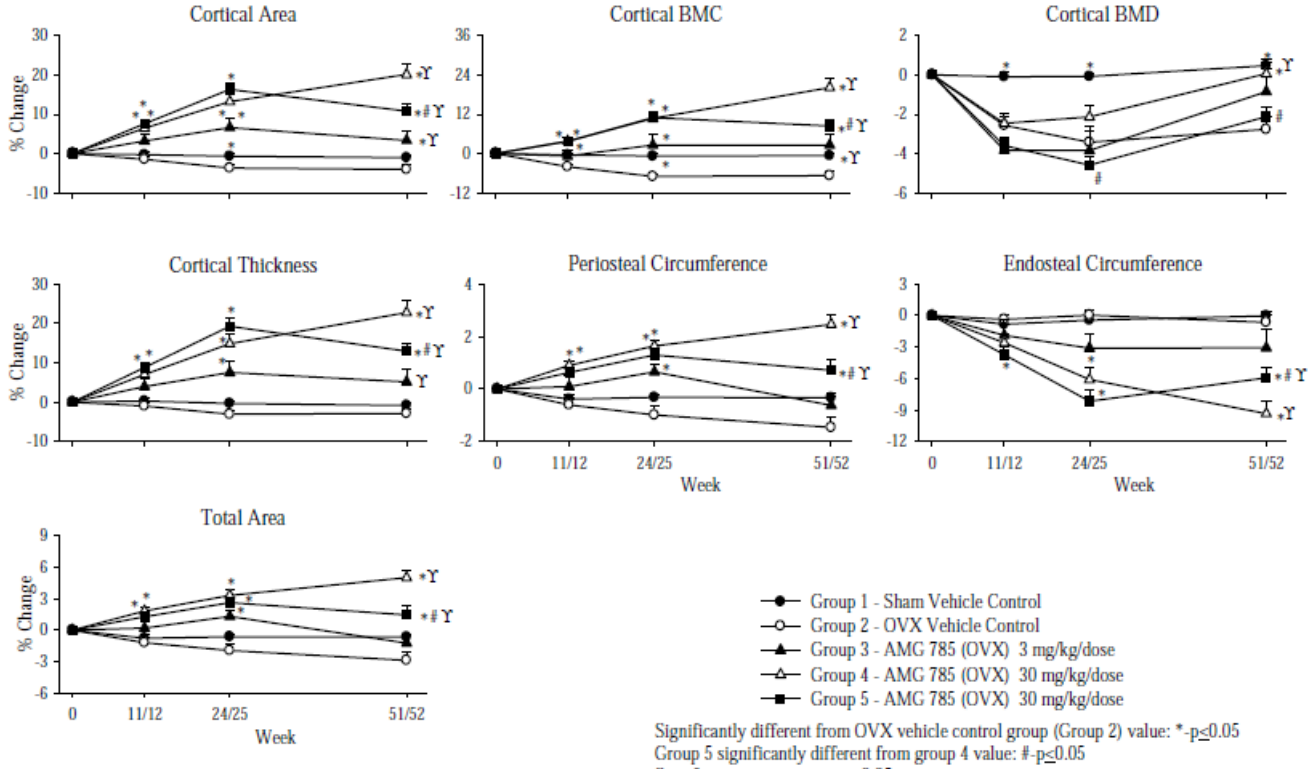
- OVX:
  - Decrease in Total Area (Bone Slice) and periosteal circumference (**Text Fig. 25**)
  - Decrease in Cortical BMD, BMC, Area and Thickness. BMC loss was -5% and -3% during bone depletion and -4% and -3% during the 52-wk Tx period (tibia and radius, respectively).
  - No clear effect on endosteal circumference
- AMG-treatment:
  Diaphysis Proximal Tibia (**Text Fig. 27**)
  - Dose-related increase in Total Area and periosteal circumference (Circ. up to 4%)

- Dose-related increase in Cortical Thickness and Cortical Area (Ct.Th up to 20%)
- Dose-related increase in Cortical BMC (+5% and +23% at 3 and 30 mg/kg, by 52 wks)
- Minimal, non-dose-related transient DECREASE in Cortical BMD, maximal at Wk 11/12
- Dose-related decrease in Endosteal Circumference (up to -9%)
- In the 30 mg/kg recovery group, all effects (except cortical BMD) were reversed towards untreated OVX levels.

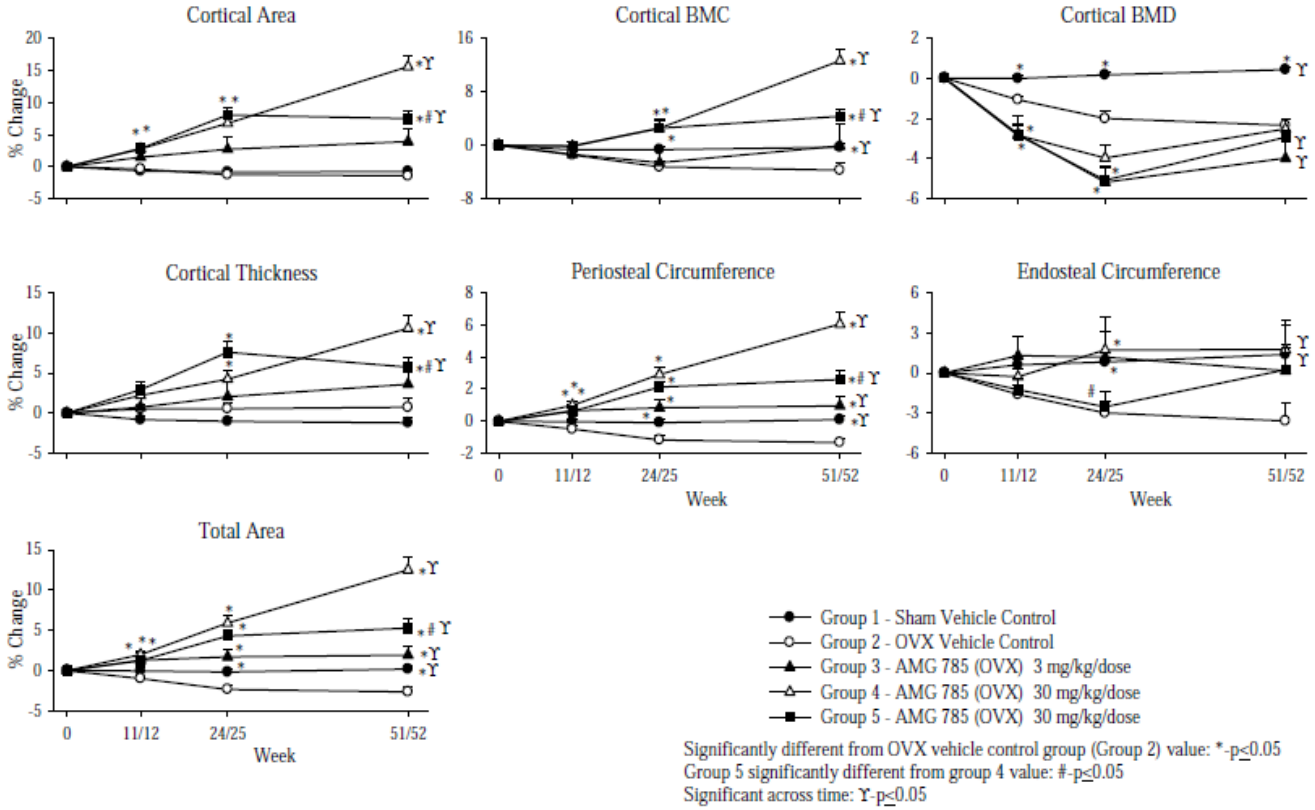
Diaphysis Distal Radius (**Text Fig. 28**)

- Dose-related increase in Total Area and periosteal circumference (Circ. up to 8%)
- Dose-related increase in Cortical Thickness and Cortical Area (Ct.Th. up to 10%)
- Dose-related increase in Cortical BMC; at 3 mg/kg, the effect did not occur until after Wk 24/25.
- Small, non-dose-related transient DECREASE in Cortical BMD, maximal at Wk 24/25
- Small, non-dose-related, INCREASE in endosteal circumference beyond OVX control significant at 30 mg/kg (increase up to +5%)
- In the 30 mg/kg recovery group, all effects were reversed towards untreated OVX levels.

Text Figure 27
Bone Densitometry Values by pQCT as Percent Change from End of Bone Depletion Period - Proximal Tibia - Diaphysis Site - Mean (SEM)



Text Figure 28
Bone Densitometry Values by pQCT as Percent Change from End of Bone Depletion Period - Distal Radius - Diaphysis Site - Mean (SEM)

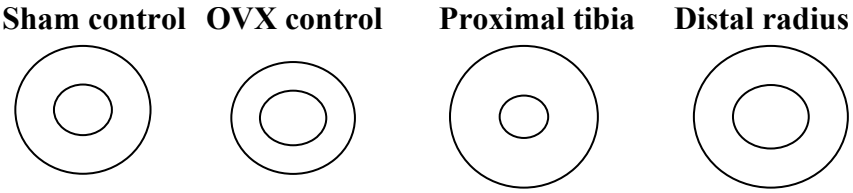


Reviewer Comment (pQCT diaphyses):
pQCT showed that AMG785 caused increases in cortical BMC, periosteal circumference, total and cortical area, and cortical thickness in both bones. These changes were more pronounced for proximal tibia than distal radius. Cortical BMD was transiently decreased in distal radius more than in proximal tibia. Endosteal circumference was DECREASED for proximal tibia, and INCREASED for distal radius.

<u>Schematic drawing of changes in cortical bone after 12 months</u>
<u>(Effects at 30 mg/kg, inflated)</u>

- *OVX caused cortical thickness (Ct.Th) decrease due to decreased periosteal circumference with no effect on endosteal circumference in both bones.*
- *In proximal tibia, AMG caused cortical thickness increase mainly through endosteal bone apposition and a little through bone widening.*

- *In distal radius, AMG caused bone thickness increase too, but that was mainly due to increased periosteal bone circumference, since endosteal circumference was increased as well.*
- *At the radius endosteal surface, resorption outperformed formation, while in tibia endosteal formation dominated resorption.*



Selected data summary:

Text Table 36
Effect of OVX and AMG 785 Treatment on Selected Bone Densitometry Parameters as Percent Change from Baseline Period

Parameters	Groups	End of Bone Depletion	Week 11/12	Week 24/25	Week 51/52
Lumbar Spine (L1-L4) BMD (DXA)	Sham	1	0	1	1
	OVX	-4	-2	-4	-4
	AMG 785 3 mg/kg	-3	7	8	14
	AMG 785 30 mg/kg	-3	10	17	26
Proximal Femur BMD (DXA)	Sham	2	-3	1	-2
	OVX	-9	-3	0	-3
	AMG 785 3 mg/kg	-9	8	15	19
	AMG 785 30 mg/kg	-4	5	17	24
Proximal Tibia Trabecular BMD (pQCT)	Sham	4	-3	-3	-7
	OVX	-14	-7	-18	-26
	AMG 785 3 mg/kg	-12	9	11	-2
	AMG 785 30 mg/kg	-9	27	48	57
Proximal Tibia Diaphysis Cortical Thickness (pQCT)	Sham	0	0	0	-1
	OVX	-2	-1	-3	-3
	AMG 785 3 mg/kg	-3	4	7	5
	AMG 785 30 mg/kg	-1	7	15	23
Distal Radial Diaphysis Cortical BMD (pQCT)	Sham	0	0	0	0
	OVX	0	-1	-2	-2
	AMG 785 3 mg/kg	-1	-3	-5	-4
	AMG 785 30 mg/kg	0	-3	-4	-3

Reviewer Comment:
The monkey finding of decreased distal radius pQCT-vBMD (Study 107903) was reproduced using HRpQCT in a 6-month OVX monkey study 118025 (0, 3 mg/kg) with extensive bone evaluations. Serum PTH was increased in humans and OVX monkeys and may be responsible for this BMD effect through stimulation of intracortical bone remodeling and increased porosity. A discussion of this effect is included in the pharmacology and integrated summaries of this BLA review.

Densitometry – ex vivo

Ex vivo measurements were done on bones to be used for biomechanical testing, including:

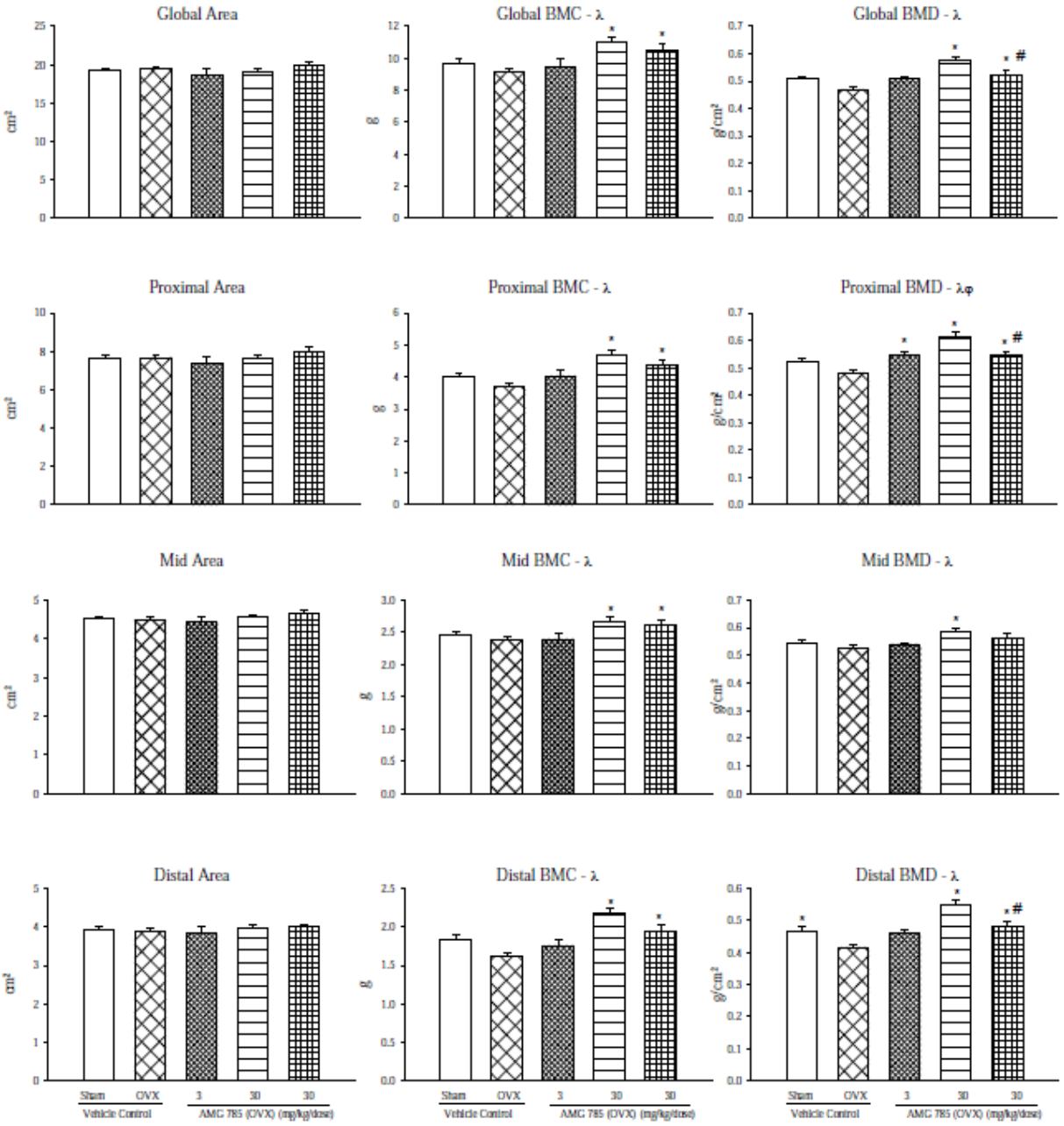
- DXA (femur: global, proximal, mid; L3+L4 vertebral bodies; L5+L6 vertebral cores)
- pQCT (femur diaphysis; L3+L4 vertebral bodies, L5+L6 vertebral cores).

DXA

Femur (entire) (**Text Fig. 29**)

- OVX effect:
  - Decreases in BMC and BMD (not area) vs sham
- AMG effect:
  - Dose-related increases in BMD and BMC at 3 and 30 mg/kg, significant at 30 mg/kg. Both BMC and BMD increased to above-sham levels at the high dose of 30 mg/kg.
  - Change in global BMD at 30 mg/kg was +22%/14% vs OVX/sham controls.
  - After recovery from 6 months of 30 mg/kg, values reversed in all bone regions relative to the continuous 30 mg/kg group, but stayed above OVX levels (near 3 mg/kg levels).

Text Figure 29
Bone Densitometry Values by DXA Parameters – Right Femur – Mean (SEM)

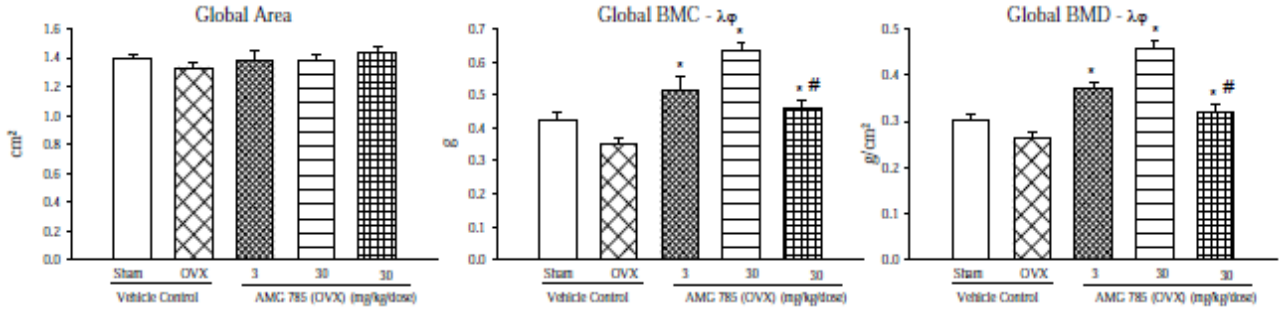


Significantly different from OVX vehicle control group value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant linear dose effect: λ-p≤0.05
Significant quadratic dose effect: φ-p≤0.05

L3+L4 vertebrae (**Text Fig. 30**)

- OVX effect:
  - Decreases in BMC and BMD (not area) vs sham controls
- AMG effect:
  - Dose-related increases in BMD and BMC at 3 and 30 mg/kg (not in area), significant at both doses, values exceeding sham
  - Change in BMD at 3 and 30 mg/kg was +41%/+22% and +75%/+51% vs OVX/sham controls
  - Recovery grp: Decrease in BMD and BMC vs 30 mg/kg treated, to levels between OVX and 3 mg/kg groups

Text Figure 30
Bone Densitometry Values by DXA Parameters – Vertebral Body L3+L4 – Mean (SEM)

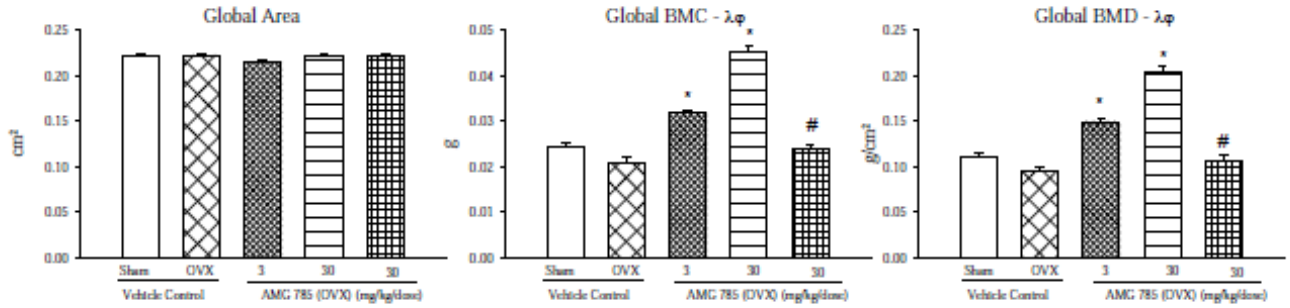


Significantly different from OVX vehicle control group value: *-$p \leq 0.05$
Group 5 significantly different from group 4 value: #-$p \leq 0.05$
Significant linear dose effect: λ-$p \leq 0.05$
Significant quadratic dose effect: φ-$p \leq 0.05$

L5+L6 cores (**Text Fig. 31**)

- OVX effect:
  - Decreases in BMC and BMD (not in area) vs sham controls. BMD decrease was -14% vs sham control.
- AMG effect:
  - Dose-related increases in BMD and BMC at 3 and 30 mg/kg, significant at both doses, with values exceeding sham controls.
  - Increase in core BMD at 3 and 30 mg/kg was +58%/36% and +117%/87% vs OVX/sham controls, respectively.
  - Recovery grp: Reversal of BMD and BMC effects to levels slightly above OVX and lower than 3 mg/kg group values.

Text Figure 31
Bone Densitometry Values by DXA Parameters – Vertebral Cores L5+L6 – Mean (SEM)



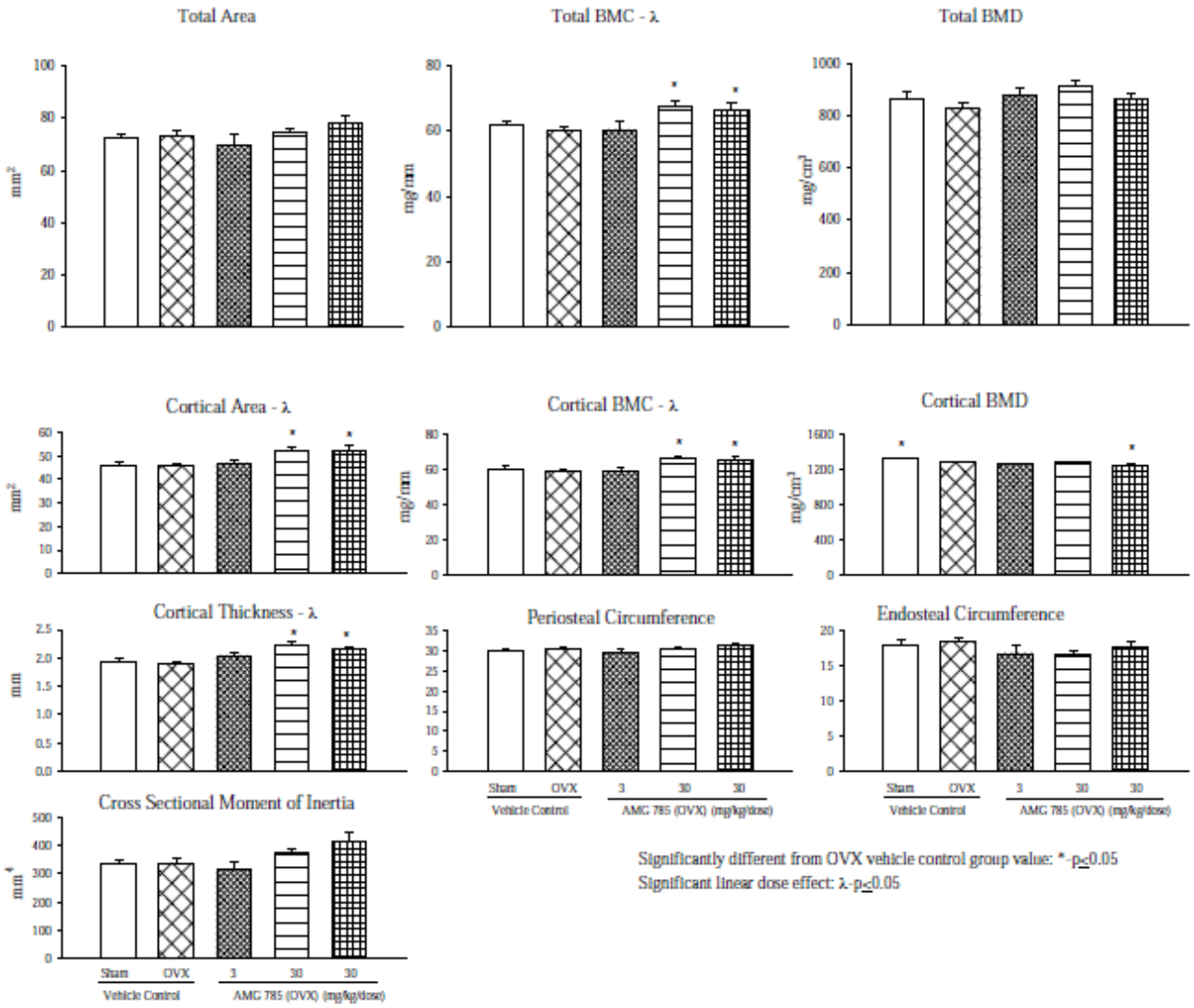
Significantly different from OVX vehicle control group value: * - $p \leq 0.05$
Group 5 significantly different from group 4 value: # - $p \leq 0.05$
Significant linear dose effect: λ - $p \leq 0.05$
Significant quadratic dose effect: φ - $p \leq 0.05$

pQCT

Femur diaphysis (**Text Fig. 32**)

- OVX effect:
  - Decreases in Total BMC and BMD, Cortical BMC and area (not BMD) vs sham controls, not significant
  - Cortical BMD decrease was -3% vs sham control.
- AMG effect:
  - Dose-related increases in Total BMD and BMC, Cortical Area, Cortical Thickness and Cortical BMC at both doses, significant at 3 and/or 30 mg/kg. Parameters increased to above-sham levels at 30 mg/kg.
  - Increase in BMC at 30 mg/kg was +12%/+10%, cortical thickness +18%/+16% and endosteal circumference -10% vs OVX/sham controls.
  - No significant effect on Total Area or periosteal circumference.
  - No effect on Cortical BMD.
  - Small decrease in endosteal circumference at 3 and 30 mg/kg.
  - Slight increase in I (moment of inertia, reflecting distribution of mass around center) at 30 mg/kg.
  - Recovery grp: Marginal reversal of AMG-induced changes (except I), with values staying above OVX and sham levels (between 3 and 30 mg/kg levels).

Text Figure 32
Bone Densitometry Values by pQCT Parameters – Right Femoral Diaphysis – Mean (SEM)

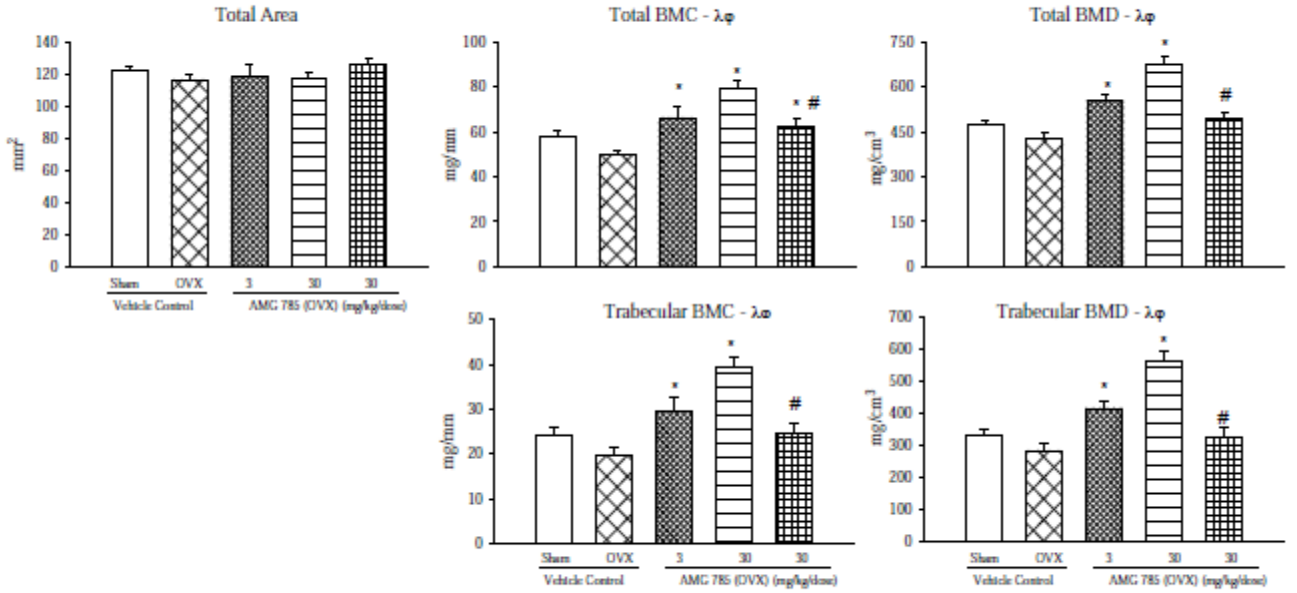


L3+L4 Vertebral Bodies (**Text Fig. 33**)

- OVX effect:
  - Decreases in Total Area, BMC and BMD, and in Trabecular BMC and BMD vs sham controls, not significant. Decrease in trabecular BMD was approx. 20% vs sham controls.
- AMG effect:
  - Dose-related increases in Total BMD and BMC, and trabecular BMD and BMC, significant at 3 and/or 30 mg/kg. Parameters increased to above-sham levels at 3 mg/kg.

- Increases in total BMD were +31%/+18% and +50%/+44% vs OVX and sham controls, respectively.
- Increases in trabecular BMD were +47%/+26% and +99%/+71% vs OVX and sham controls, respectively.
- No significant effect on Total Area.
- Recovery grp: Marked reversal of AMG-induced changes; Wk-52 values similar to sham levels.

Text Figure 33
Bone Densitometry Values by pQCT Parameters – Lumbar Vertebra L3+L4 (Averaged) – Mean (SEM)

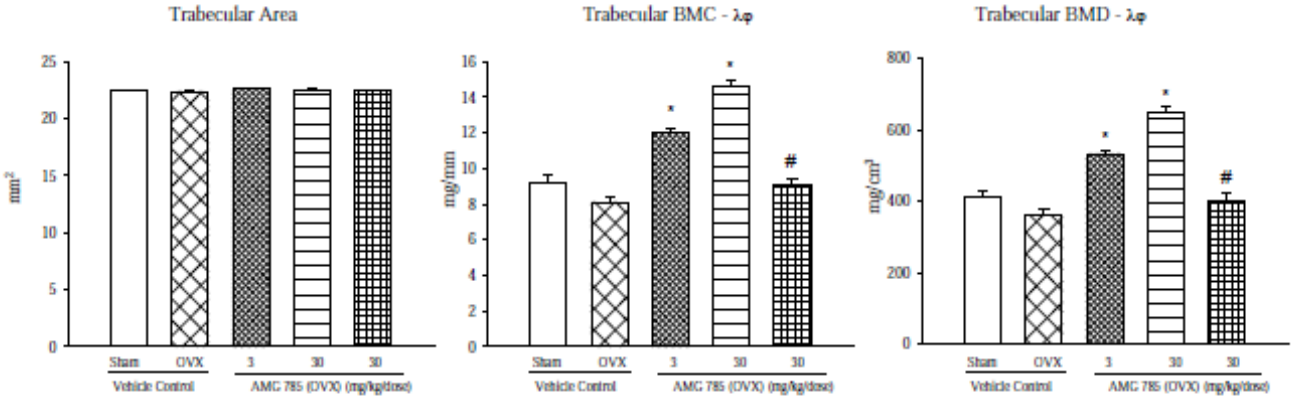


Significantly different from OVX vehicle control group value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant linear dose effect: λ-p≤0.05
Significant quadratic dose effect: φ-p≤0.05

L5+L6 Vertebral Cores (**Text Fig. 34**)

- OVX effect:
  - Decreases in Trabecular BMC and BMD
- AMG effect:
  - Dose-related increases in trabecular BMD and BMC, significant at 3 and/or 30 mg/kg. Parameters increased to above-sham levels at both 3 and 30 mg/kg.
  - Recovery grp: Reversal of AMG-induced changes (except I)
  - Effects very similar to those in L3+L4 vertebral bodies

Text Figure 34
Bone Densitometry Values by pQCT Parameters – Vertebral Cores L5+L6 – Mean (SEM)



Significantly different from OVX vehicle control group value: * - $p \leq 0.05$
Group 5 significantly different from group 4 value: # - $p \leq 0.05$
Significant linear dose effect: λ - $p \leq 0.05$
Significant quadratic dose effect: φ - $p \leq 0.05$

Reviewer Comments:

- *The ex vivo data on femur and vertebra (DXA and pQCT) generally showed similar results as in vivo DXA and pQCT of these and other bones.*
- *Femur ex vivo pQCT corresponded better to tibia than radius in vivo pQCT, showing mainly endosteal bone apposition.*

Micro-CT – ex vivo

L3 Vertebral Body (**Text Figs. 35, 36, 37**)

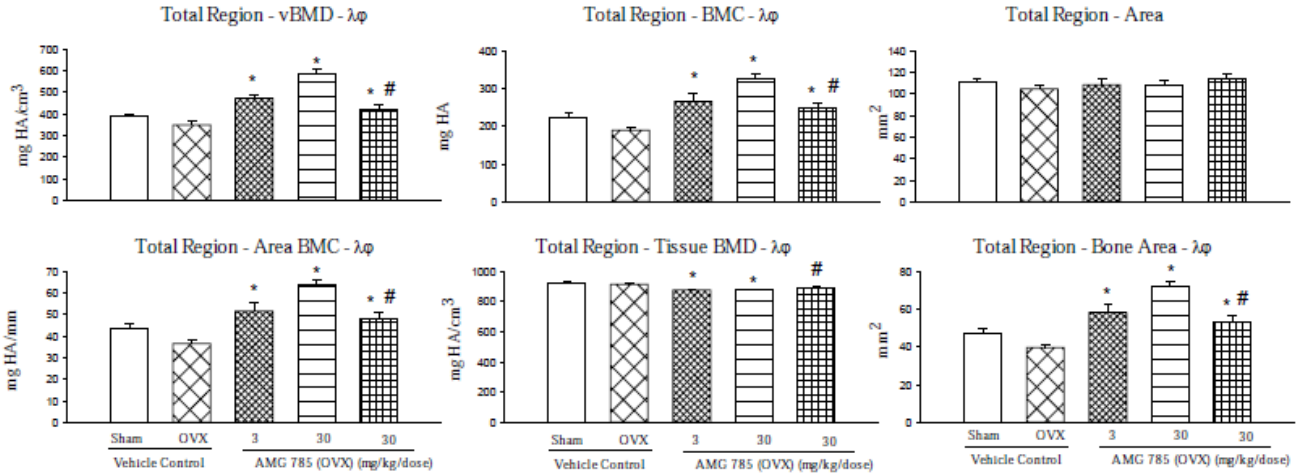
- OVX effect:
  - *Total and Trabecular Region*:
    - Decreases (non-significant) in vBMD, BMC, Area, Area BMC, Bone Area, BV/TV, and/or Tb.Th. Slight increase in trabecular SMI (ie more rod-like structure). No significant effect on tissue BMD (i.e. BMD of bone material per se). Decreases in various parameters after 52 wks were -5 to -15% (total), larger for trabecular and smaller for cortical regions.
- AMG effect:
  - *Total Region:*
    - Dose-related increases (significant) in Total vBMD, BMC, Area BMC, Bone Area (no effect on Area); vBMD increase was +35%/+22% and +68%/+52%, at 3 and 30 mg/kg, vs OVX/sham controls
  - *Trabecular Region:*
    - Dose-related increases (significant) in Trabecular vBMD, BMC, Area BMC, Bone Area, and BV/TV (+45% to +98%), and in Tb.Th (latter

increased by +55%/+37% and +96%/+73% at 3 and 30 mg/kg vs OVX/sham ctrls)
        - TbN slightly increased at 30 mg/kg only
        - Dose-related decrease in Trabecular region Area (-18%), significant at 30 mg/kg
        - Dose-related decrease in Tb.Sp (small) and SMI (indicting more plate-like trabecular structure); no effect on DA (degr of anisotropy).
    - *Cortical Region:*
        - Dose-related increases (significant) in vBMD, BMC, Area, Area BMC, Bone Area, and Cortical Thickness (latter increased by +17%/+16% and +60%/+59% at 3 and 30 mg/kg, vs OVX/sham controls)
    - *All Regions:*
        - Small, but significant, non-dose-related decreases in tissue BMD (=BMD of bone material only), at 3 and 30 mg/kg, of approx. -4% vs OVX and sham controls for the trabecular region, and -3% for the cortical region.
    - *Recovery grp:*
        - Marked reversal of all AMG-induced changes; Wk-52 values similar to sham levels.

Reviewer Comment:

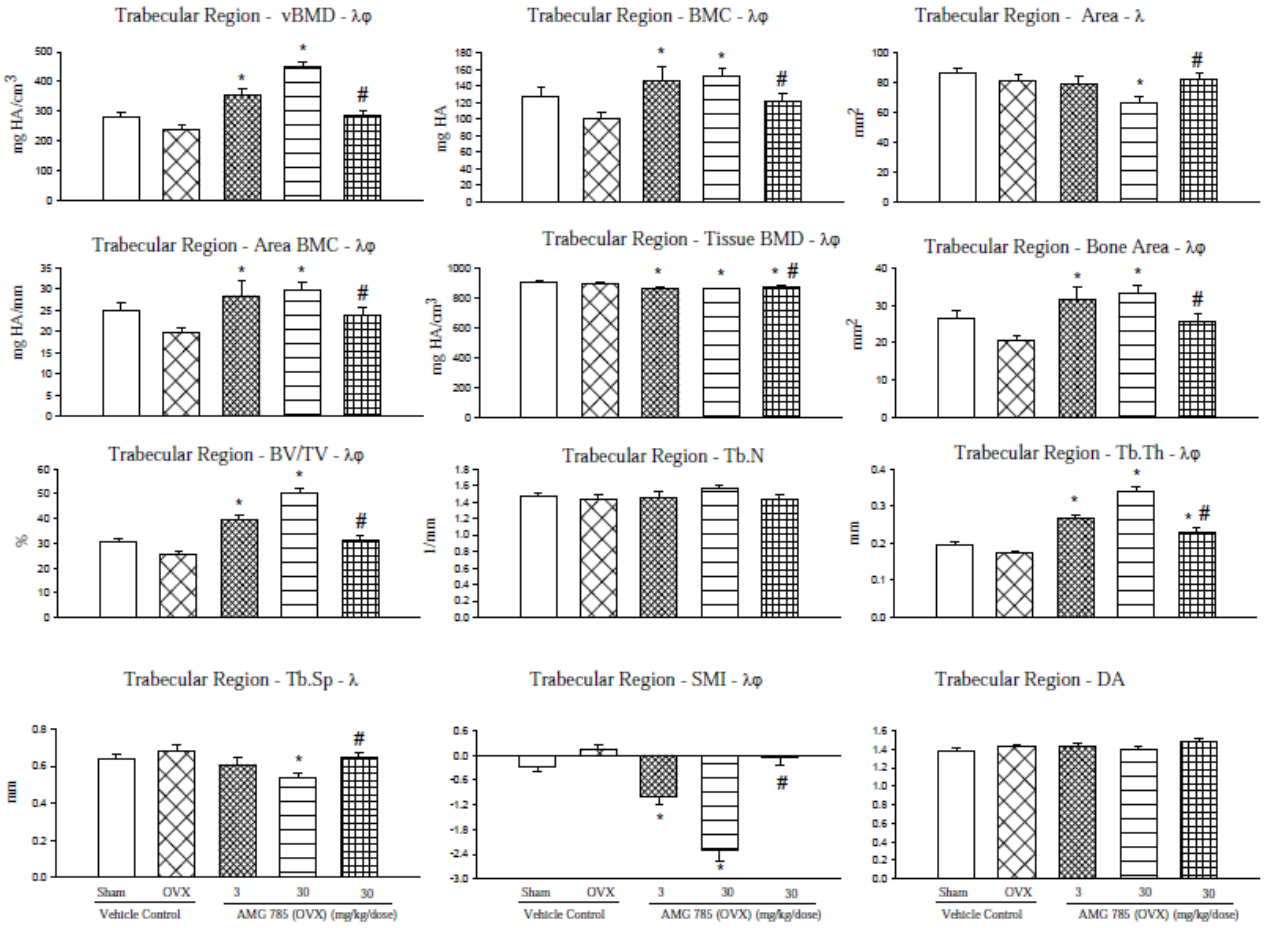
- *The decrease in tissue BMD may be an artifact due to larger sizes (BMC) of the bone specimens in which tBMD was decreased (Fajardo et al 2009); this is supported by lack of tBMD change in cortical beams (see below)*

Text Figure 35
Micro-CT Parameters – L3 Vertebral Body – Total Region – Mean (SEM)



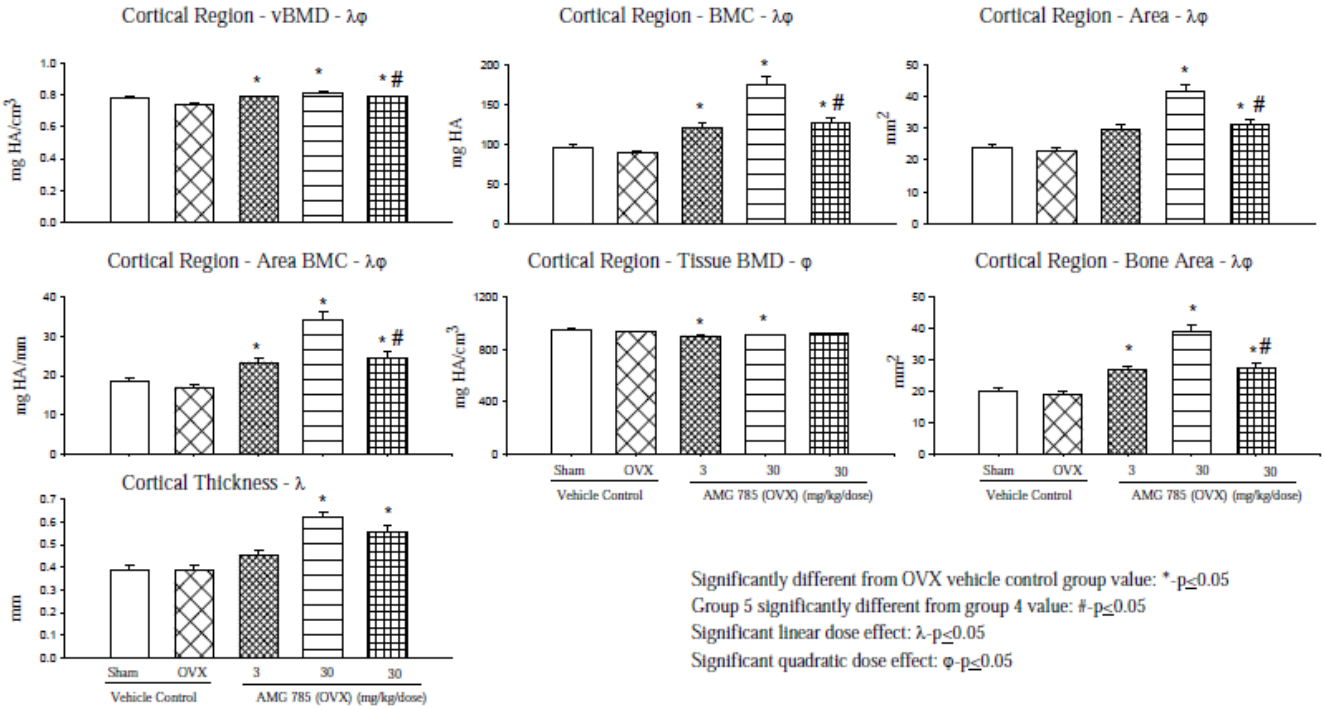
Significantly different from OVX vehicle control group value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant linear dose effect: λ-p≤0.05
Significant quadratic dose effect: φ-p≤0.05

Text Figure 36
Micro-CT Parameters – L3 Vertebral Body – Trabecular Region – Mean (SEM)



Significantly different from OVX vehicle control group value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant linear dose effect: λ-p≤0.05
Significant quadratic dose effect: φ-p≤0.05

Text Figure 37
Micro-CT Parameters – L3 Vertebral Body – Cortical Region – Mean (SEM)



L6 caudal core

- Changes upon OVX and AMG treatment were very similar to those observed in the trabecular region of the vertebral body L3.

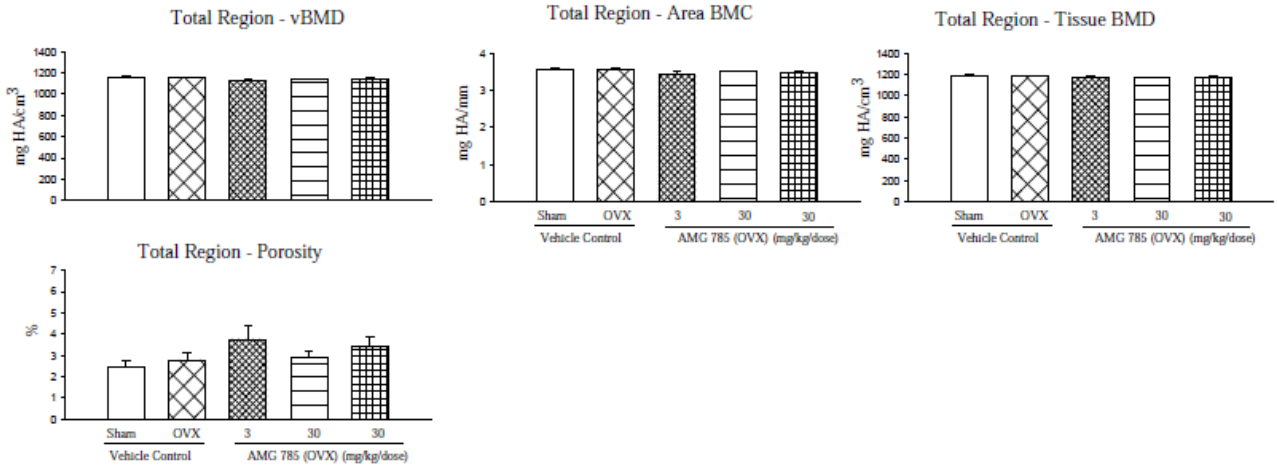
Femoral neck

- Changes upon OVX and AMG treatment were very similar to those observed in the trabecular region of the vertebral body L3.
- However, magnitude of changes was smaller and they were most often not significant for the 3 mg/kg and the 30 mg/kg-recovery groups.

Humeral cortical beam (**Text Fig. 42**)

- OVX effect:
  - None
- AMG effect:
  - Porosity increase at 3 mg/kg but not at 30 mg/kg (not significant).
  - No effect on tissue BMD.

Text Figure 42
Micro-CT Parameters – Humeral Cortical Beam – Total Region – Mean (SEM)



Reviewer Comment:

- *The micro-CT data were consistent with data from densitometry and histomorphometry evaluations.*
- *Tissue BMD means the tissue mineral density of bone without its internal or surrounding soft tissue compartments. The reliability of the vertebral tissue BMD values is uncertain, since measurement of this parameter by micro-CT is subject to possible methodological errors.*

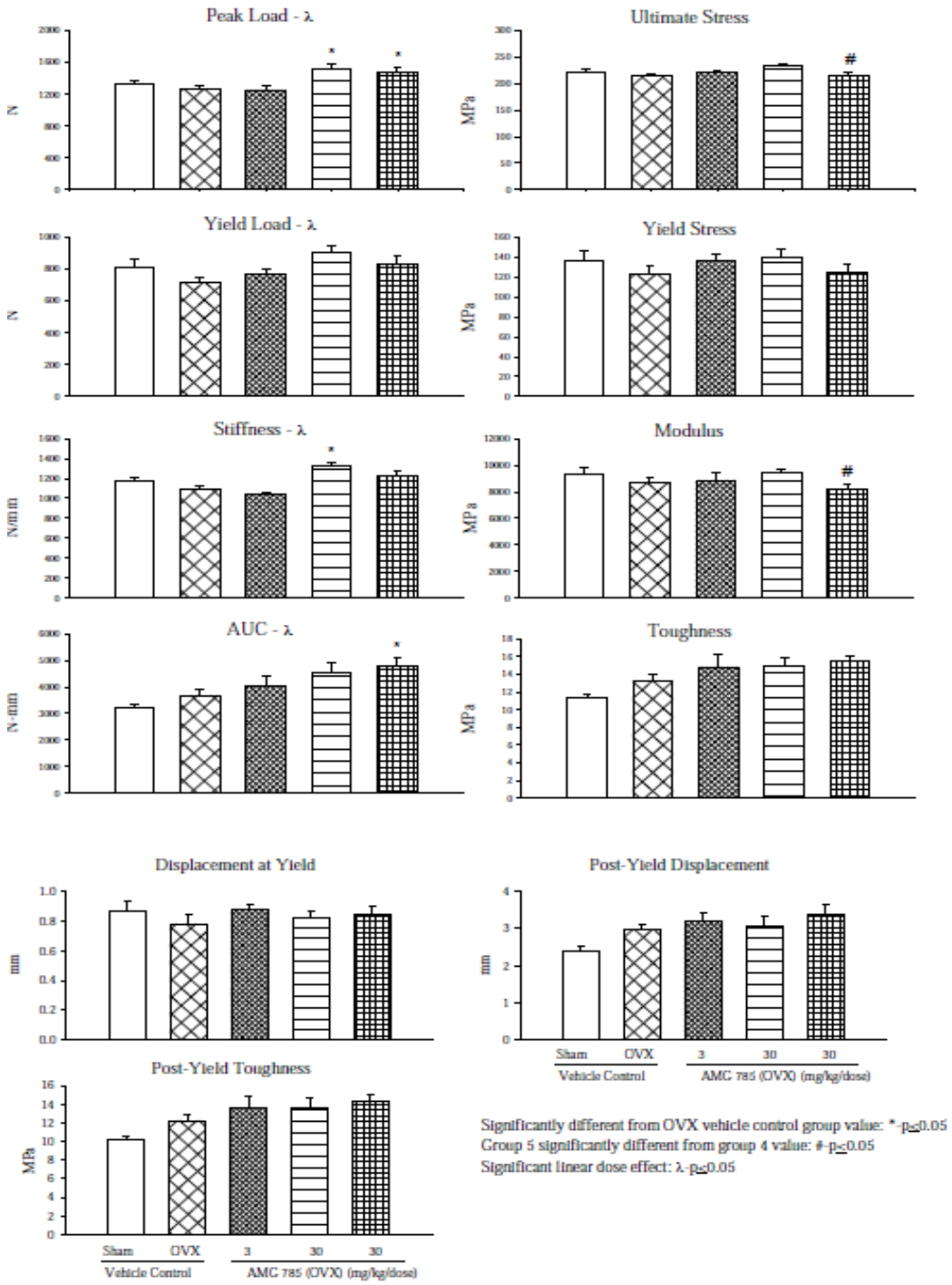
Biomechanical testing

(Femur shaft and neck, humerus beam, and lumbar vertebral bodies and cores)

Femur shaft 3-point bending (**Text Fig. 43**):

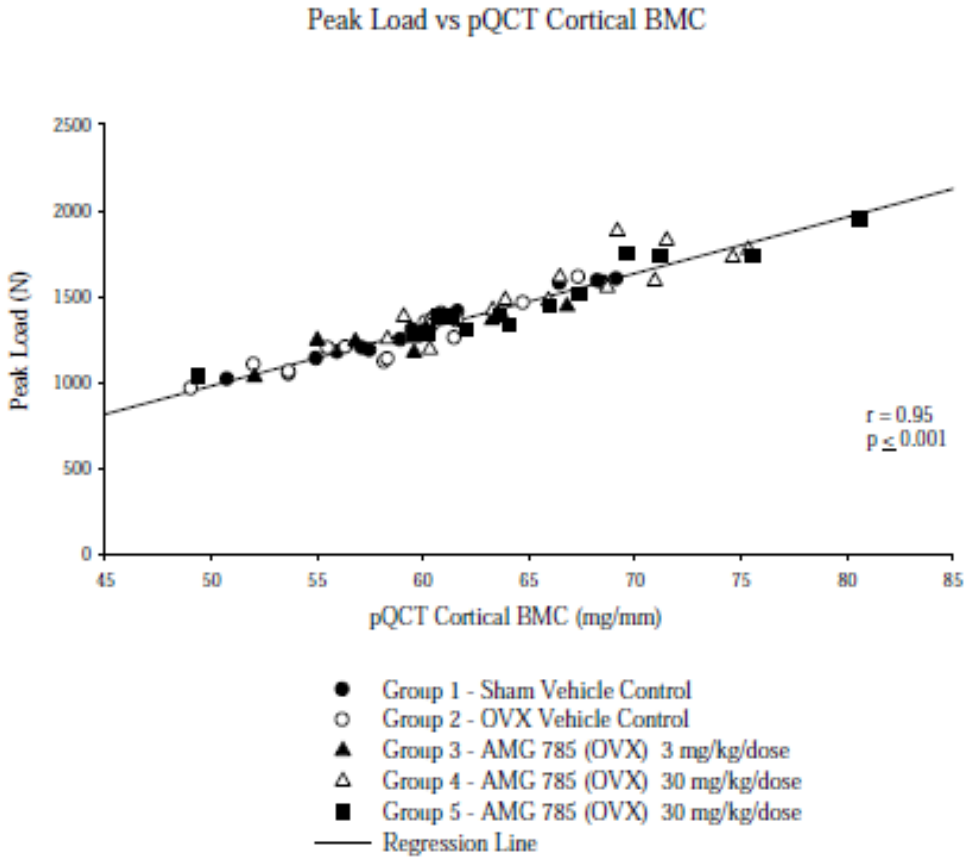
- OVX effect: Some expected changes of OVX were observed (decreases in peak load Fu, yield load, stiffness) but they were not statistically significant.
- AMG effects:
  - Dose-related increases in peak load, yield load, stiffness and AUC, some significant, of 20-25% vs OVX controls (15-40% vs sham control) at 30 mg/kg; also increases in geometry-corrected parameters
  - Increases in total toughness and post-yield toughness (and possibly also pre-yield toughness), not significant
  - Recovery group:
    - Reversal of most parameters, except (post-yield) toughness; whole-bone values remained above OVX control.
- Correlations density-strength:
  - Peak load correlated well with ex-vivo pQCT femoral diaphysis cortical BMC (**Text Fig. 44**), and also with mid-femur ex vivo DXA BMC (not shown).

Text Figure 43
Biomechanics Parameters – Femur – 3-point Bending – Mean (SEM)



Significantly different from OVX vehicle control group value: *-p≤0.05
Group 5 significantly different from group 4 value: #-p≤0.05
Significant linear dose effect: λ-p≤0.05

Text Figure 44
Regression Plot of Biomechanics - Femur 3-point Bending vs. Femur pQCT BMC



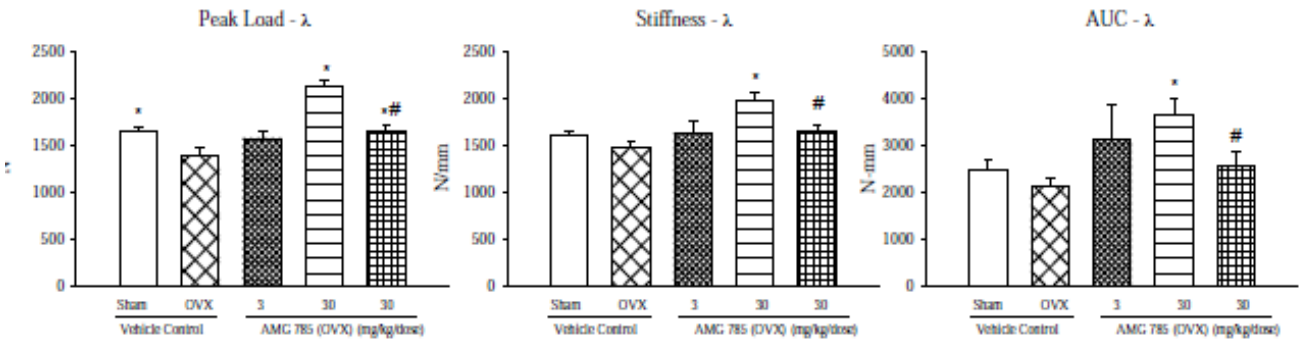
Humerus beam 3-point bending:

- OVX effect: None significant
- AMG effects:
  - None significant
  - Recovery group:
    - Small decreases in AUC and toughness vs 30 mg/kg group, but effects were not statistically significant
- No correlation analysis

Femoral neck shear (**Text Fig. 47**):

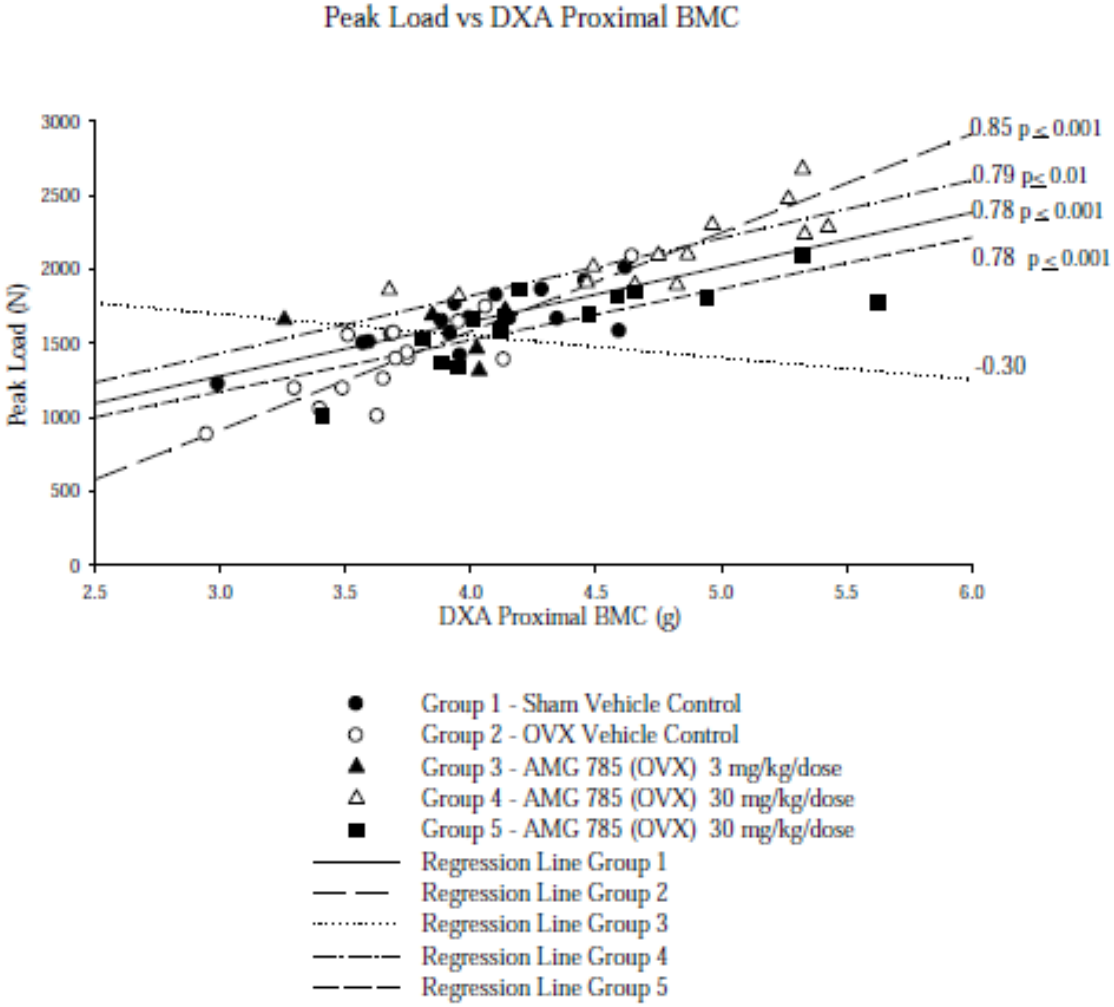
- OVX effect:
  - Decreases in peak load Fu, stiffness and AUC, but they were not statistically significant.
- AMG effects:
  - Marked increases in peak load, stiffness, AUC, significant at 30 mg/kg (35-75% vx OVX control; 25-50% vs sham)
  - Recovery group:
    - Reversal of all parameters to levels significantly lower than those in non-recovery group and similar to sham controls.
- Correlation mass-strength
  - Peak load correlated significantly with ex-vivo DXA proximal femur BMC (**Text Fig. 48)** and BMD (not shown), except in 3 mg/kg group (low N).
  - Slope of OVX control regression line slightly steeper than for other groups; slopes of sham and 30 mg/kg groups similar.

Text Figure 47
Biomechanics Parameters – Femoral Neck – Mean (SEM)



Significantly different from OVX vehicle control group value: *-$p<0.05$
Group 5 significantly different from group 4 value: #-$p<0.05$
Significant linear dose effect: λ-$p<0.05$

Text Figure 48
Regression Plot of Biomechanics - Femoral Neck Shear vs. Proximal Femur DXA BMC

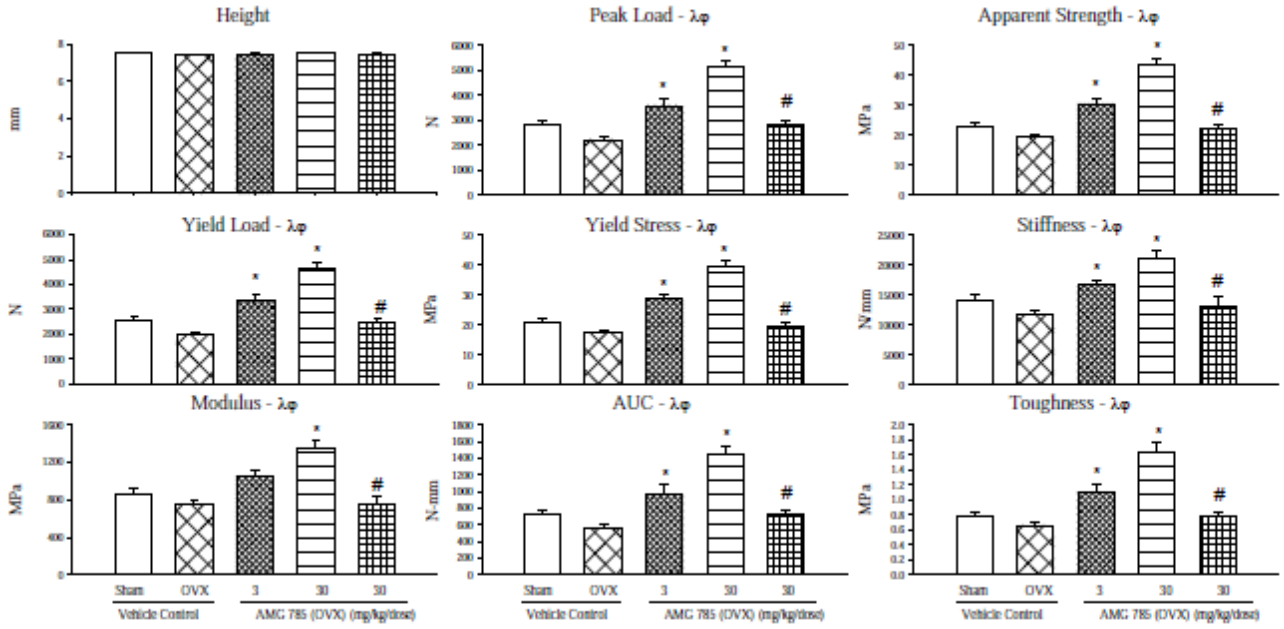


Vertebral body L3+L4 compression (**Text Fig. 50**):

- OVX effect:
  - Decreases in peak load Fu, yield load, stiffness and AUC, but they were not statistically significant (similar to femur diaphysis results). No effect on height.
- AMG effects:
  - Increases in peak load, yield load, stiffness, AUC; and increases in related normalized parameters (app strength, yield strength, modulus, toughness).
  - No effects on height
  - Recovery group:
    - Reversal of all parameters, to levels signif diff from non-recovery group.

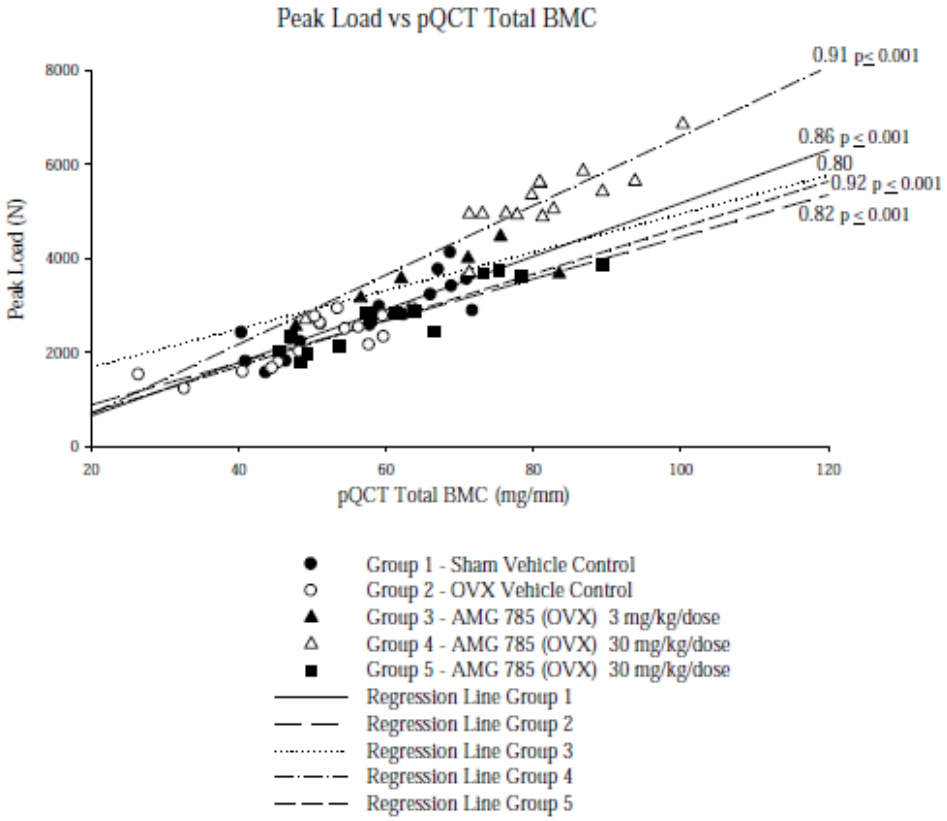
- Correlations mass-strength:
  - Peak load correlated significantly with ex-vivo pQCT BMC (**Text Fig. 51**), and apparent strength correlated with BMD (not shown), in all groups except 3 mg/kg (probably due to low N).
  - Slope of 30 mg/kg regression line steeper than for other groups, suggesting improved bone quality, when 'quality' is defined as the slope of this regression line.

Text Figure 50
Biomechanics Parameters – Lumbar Vertebra Bodies L3+L4 Averaged – Mean (SEM)



Significantly different from OVX vehicle control group value: *-$p \leq 0.05$
Group 5 significantly different from group 4 value: #-$p \leq 0.05$
Significant linear dose effect: λ-$p \leq 0.05$
Significant quadratic dose effect: φ-$p \leq 0.05$

Text Figure 51
Regression Plot of Biomechanics – L3+L4 Average Vertebral Body Compression vs. pQCT Total BMC

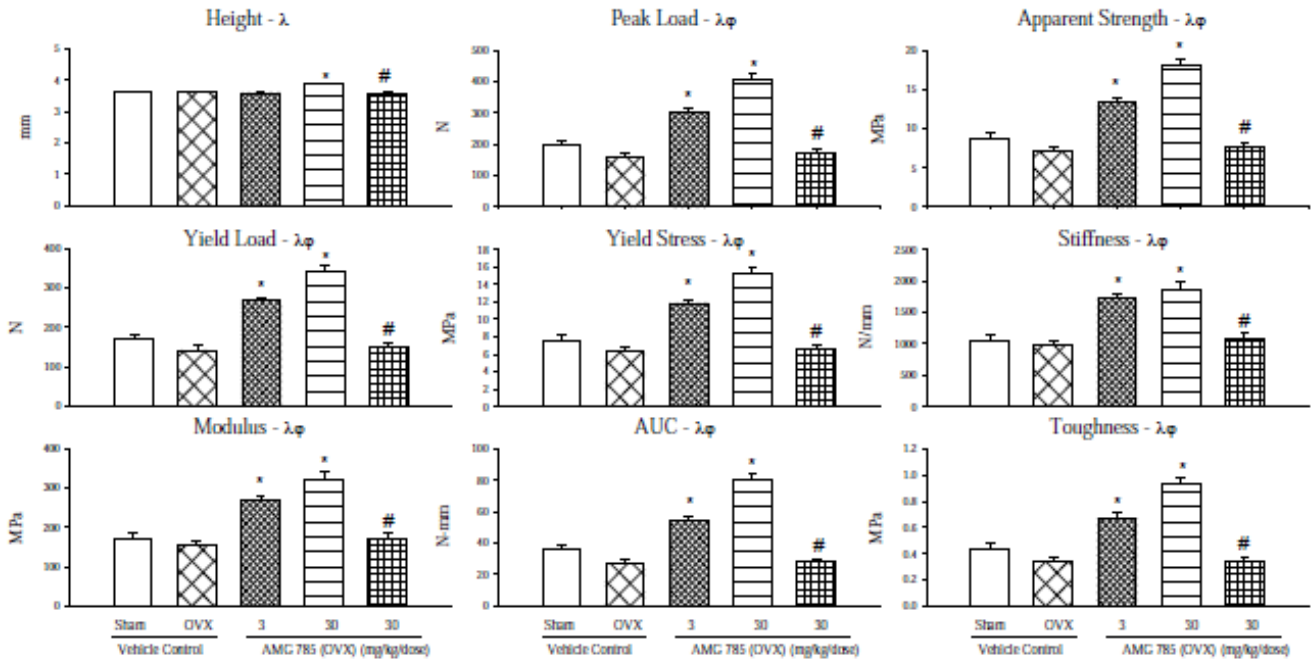


Vertebral cores L5+L6 compression (**Text Fig. 53**):

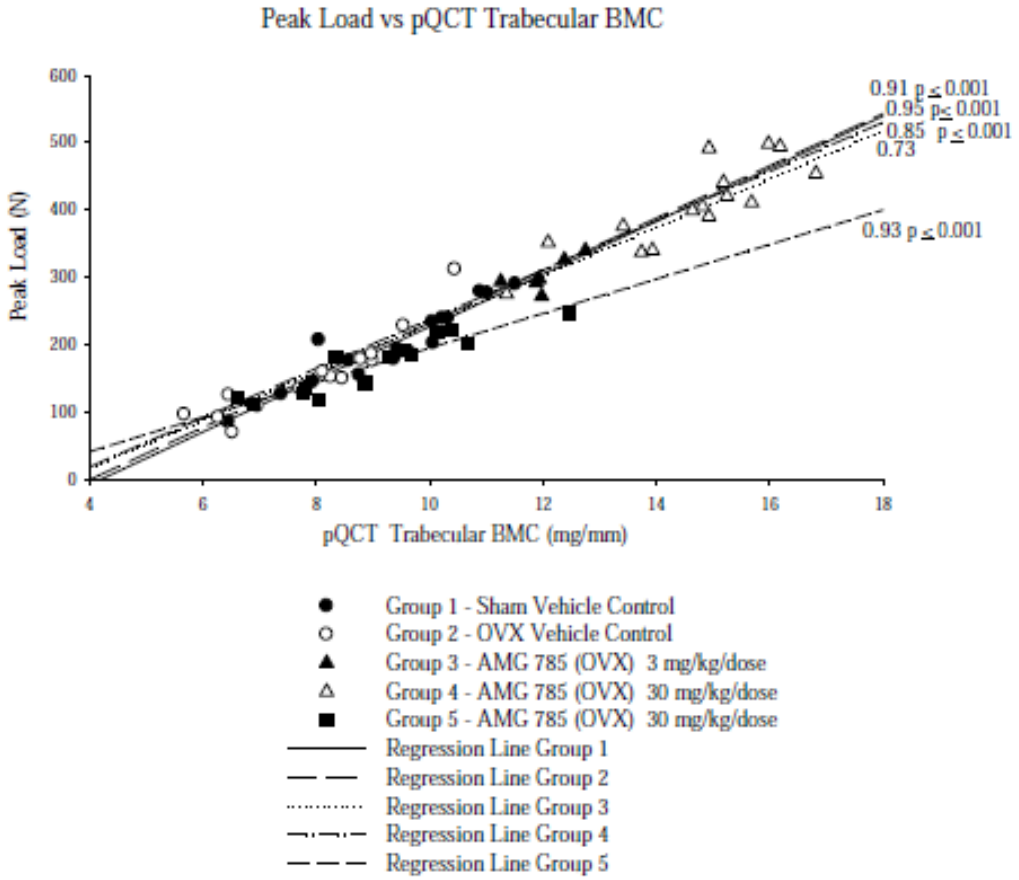
- OVX effect:
  - Decreases in peak load Fu, yield load, stiffness and AUC, but they were not statistically significant (similar to femur diaphysis results). No effect on height.
- AMG effects:
  - Increases in peak load, yield load, stiffness, AUC; and increases in related normalized parameters (app strength, yield strength, modulus, toughness).
  - No effects on height
  - Recovery group:
    - Reversal of all parameters, to levels significantly different from 30 mg/kg non-recovery group.
- Correlations density-strength:
  - Peak load correlated well with ex vivo pQCT-BMC (**Text Fig. 54**), and apparent strength correlated with BMD (not shown); correlation significant for all groups except 3 mg/kg.

- Negative shift of regression line BMC vs Fu in 30 mg/kg recovery group suggested possible impairment in bone quality in this group; however it is not clear whether this was a biologically significant finding.

Text Figure 53
Biomechanics Parameters – Lumbar Vertebra Cores L5+L6 Caudal and Cranial Averaged – Mean (SEM)



Text Figure 54
Regression Plot of Biomechanics – L5+L6 Average Vertebral Cores vs. pQCT Trabecular BMC



Reviewer Comments:

- *Strength parameters were generally positively affected at either 30 mg/kg (femur diaphysis), or at both 3 and 30 mg/kg (vertebral bone and femoral neck).*
- *Good correlations between mass and strength were observed in vertebrae and femur diaphysis, and reasonable correlations in femoral neck (typical for these studies).*
- *Bone material properties appear unaffected based on humerus beam data.*
- *There was no negative effect on post yield toughness ie brittleness of femoral diaphysis or humerus beams.*
- *Some improvement of vertebral bone quality occurred at 30 mg/kg, when quality is defined as the slope of the mass-strength regression line.*
- *The strength data confirmed that BMD is an acceptable surrogate for bone strength with AMG treatment.*
- *Histology showed no adverse effects.*

Histomorphometry

- Interim data (Ilium, rib); End of Tx data (Vertebra L2, femur, rib)
- Embedding undecalcified in MMA; evaluation with Image-Pro Plus analyzer, 2 sections of ilium, rib and femur, 1 section of L2
- Structural and dynamic parameters
  - Cancellous bone: Ilium, L2, femoral neck
  - Cortical bone: Ribs, femur midshaft
- Some cortical dynamic parameters also measured in ilium (interim biopsies), femoral neck and L2 (end of study)
- Histology of stained sections (Goldner Trichrome, Toluidine Blue) adjacent to unstained ones

Cancellous bone

Iliac biopsies (Wk 13 and 27) (**Text Tables 3 and 4**):

- OVX effects (Text Fig 1):
  - Decreases in BV/TV and trabecular parameters
  - Slight increases in ES/BS (eroded surface %)
  - Increases in various parameters reflecting osteoblastic bone formation (due to expected increase in turnover)
- AMG effects
  - Dose-related (Wk 13 and/or Wk 27) increases in BV/TV and Tb.Th (with decrease in Tb.Sp), OS/BS (osteoid surface %) and Ob.S/BS (osteoblast surface %) (**Text Figure 1,** below)
  - Increases in BFR/BS (and BFR/BV) (bone formation rate), larger in Wk 13 than in Wk27 (**Text Fig. 2**)
  - Dose-related decrease in ES/BS (eroded surface %) (indicates suppression of resorption) at Wk 13 only (**Text Fig. 1**)
  - Dose-related increase in Ac.F (activation frequency), Wk 13 > Wk 27
  - Dose-related increase in Fo.S/BS (formative bone surface %); and decrease in QS/BS (quiescent surface %)

Reviewers Comment:
Comparing the values of BFR/BS in OVX controls, for cancellous bone of ilium, femoral neck, vertebra, and rib and femur diaphysis shows the following:

- *Cancellous bone BFR/BS is larger in ilium at Wks 13 and 27 than in vertebra and femoral neck at Wk 52, and the value is similar to endocortical BFR/BS in cortical bone (rib and femur)*
- *Cortical bone BFR/BS is ca. **1-2x** larger at Haversian surfaces (rib all time points, and femur Wk52) than at endocortical surfaces (rib and femur); BFR/BS value is smallest at periosteal surfaces (rib and femur) (ca. **1/10x** BFR/BS at endocortical surface, approx.)*
- *This comparison puts the systemic bone formation and resorption indices in perspective, since they reflect formation/turnover at all surfaces with contributions proportional to the total area of the different surfaces. The total surface area is*

Reference ID: 4081796

probably largest for trabecular bone, followed by Haversian cortical, and then periosteal and endocortical bone.

Femoral Neck (End of Tx)
- OVX effects:
  - Decrease in BV/TV
  - Increases in parameters reflecting osteoblastic activity (OV/BV, OS/BS, Ob.S/BS)
  - Increases in ES/BS and W.Th
  - Increase in BFR/BS and BFR/BV
- AMG effects
  - Dose-related increases in BV/TV and Tb.Th (with decrease in Tb.Sp)
  - Increase in W.Th (wall thickness is thickness of bone deposited after resorption in individual BRU)
  - Continued increase in BFR/BS and BFR/BV (bone formation rate)
  - Slight increase in Fo.S/BS and decrease in QS/BS
  - Recovery group 30 mg/kg:
    - Reversal of trabecular bone volume and thickness increase (ie DE-crease), BFR increases (ie DE-creases), and % formative and quiescent surface changes
    - No change in W.Th vs pre-recovery (ie W.Th still increased vs OVX control)
    - Large increase in ES/BS (*ES/BS not affected in 30 mg/kg grp*)

L2 vertebra (End of Tx)
- OVX effects:
  - Decreases in BV/TV and trabecular parameters (**Text Fig. 1**)
  - Increases in parameters reflecting osteoblastic activity (OV/BV, OS/BS, Ob.S/BS)
  - Slight increase in BFR (n.s.)
- AMG effects
  - Dose-related increases in BV/TV and Tb.Th (with decrease in Tb.Sp) (**Text Fig. 1**)
  - Increase in W.Th
  - Increase in BFR/BS (bone formation rate)
  - Recovery group 30 mg/kg:
    - Reversal of trabecular bone increase
    - No change in W.Th vs pre-recovery (ie W.Th still increased vs OVX control)
    - No increase in ES/BS (unlike FN)

There were no adverse effects on bone histology at these cancellous sites.

Reviewer's comment:
- *The highlighted numbers in the Text Tables of Histomorphometric Variables indicate statistically significant effects*

Text Table 3
Summary of Histomorphometric Variables – Cancellous Bone of Ilium at Week 13

		Phase	Week 13								
		Surgery	Sham	OVX		OVX		OVX		OVX	
	AMG 785 mg/kg/dose		0	0		3		30		30[a]	
	Units		Value	Value	% vs SC	Value	% vs VC	Value	% vs VC	Value	% vs VC
BV/TV	%	Mean	25.7	19.9	-23	**36.1**	82	**34.7**	74	**32.0**	61
		SD	7.4	8.2		7.2		9.0		10.4	
Md.V/TV	%	Mean	24.7	18.8	-24	**32.4**	72	**31.4**	67	**29.2**	55
		SD	7.1	7.8		7.2		8.4		9.8	
OV/BV	%	Mean	4.01	5.65	41	10.61	88	**9.51**	68	**9.09**	61
		SD	2.64	1.93		5.81		1.95		1.56	
Tb.Th	µm	Mean	126	106	-16	**152**	43	**162**	53	**162**	53
		SD	25	27		19		28		31	
Tb.Sp	µm	Mean	381	458	20	**274**	-40	**325**	-29	385	-16
		SD	105	115		56		114		165	
Tb.N	mm^{-1}	Mean	2.04	1.83	-10	2.37	29	2.15	18	1.96	7
		SD	0.37	0.36		0.25		0.48		0.52	
OS/BS	%	Mean	30.8	41.8	36	**67.4**	61	**75.2**	80	**76.0**	82
		SD	15.5	10.9		12.7		7.8		7.5	
Ob.S/BS	%	Mean	**11.2**	19.5	74	**30.5**	56	**32.9**	68	**33.5**	72
		SD	7.8	8.4		9.0		8.9		10.5	
Oc.S/BS	%	Mean	1.89	2.36	25	2.57	9	1.51	-36	1.82	-23
		SD	1.09	0.98		1.37		0.77		1.17	
ES/BS	%	Mean	18.7	19.8	6	15.8	-20	**10.4**	-47	**10.9**	-45
		SD	7.0	5.9		6.8		3.3		6.4	
W.Th	µm	Mean	31.8	30.3	-5	32.8	8	33.7	11	**38.3**	26
		SD	4.5	2.6		4.6		4.9		7.7	
MS/BS	%	Mean	23.9	35.5	48	**59.1**	66	**71.0**	100	**73.3**	107
		SD	16.9	11.9		6.0		9.9		8.0	
MAR	µm/d	Mean	0.69	0.73	5	0.74	2	0.77	5	***0.85***	17
		SD	0.13	0.11		0.15		0.09		0.11	
Aj.Ar	µm/d	Mean	0.52	0.59	15	0.65	9	0.72	21	**0.81**	36
		SD	0.24	0.13		0.15		0.13		0.12	
Mlt	d	Mean	29.8	19.9	-33	20.3	2	17.0	-14	14.9	-25
		SD	24.2	8.2		7.5		6.5		3.6	
BFR/BS	$µm^3/µm^2/yr$	Mean	61.6	93.6	52	**157.6**	68	**198.8**	112	**227.6**	143
		SD	48.4	31.0		22.5		35.9		38.8	
BFR/BV	%/yr	Mean	**95.6**	181.2	90	211.4	17	**248.7**	37	***285.5***	58
		SD	64.8	57.9		45.7		46.5		41.6	
Ac.f	yr^{-1}	Mean	**1.85**	3.01	63	**4.65**	54	**5.95**	98	**6.12**	103
		SD	1.39	0.98		0.74		1.22		1.26	
Fo.S/BS	%	Mean	31.6	44.4	40	**71.0**	60	**80.0**	80	**81.0**	82
		SD	19.2	13.8		6.3		8.9		8.0	
QS/BS	%	Mean	49.6	35.9	-28	**13.2**	-63	**9.6**	-73	**8.1**	-77
		SD	21.9	16.4		6.0		8.4		7.0	

SC = Sham Vehicle Control; VC = OVX Vehicle Control
Values in bold are significantly different from OVX Vehicle Control
Values in italic are significantly different from AMG 785 (OVX) 30 mg/kg/dose group (Group 4)
[a] Dosed for 26 weeks followed by 26 weeks recovery period

Text Table 4
Summary of Histomorphometric Variables – Cancellous Bone of Ilium at Week 27

		Phase	Week 27								
		Surgery	Sham	OVX		OVX		OVX		OVX	
	AMG 785 mg/kg/dose		0	0		3		30		30[a]	
	Units		Value	Value	% vs SC	Value	% vs VC	Value	% vs VC	Value	% vs VC
BV/TV	%	Mean	22.4	18.1	-19	**38.7**	114	**43.0**	137	**38.6**	113
		SD	7.4	10.3		9.7		7.6		12.5	
Md.V/TV	%	Mean	21.8	17.2	-21	**36.7**	114	**40.9**	138	**37.0**	115
		SD	7.5	9.7		9.1		7.3		12.3	
OV/BV	%	Mean	**2.89**	4.88	69	4.97	2	4.75	-3	4.65	-5
		SD	2.21	2.05		2.32		1.78		1.67	
Tb.Th	µm	Mean	133	114	-14	**180**	57	**205**	79	**189**	65
		SD	28	34		21		35		39	
Tb.Sp	µm	Mean	496	662	34	**302**	-54	**282**	-57	**344**	-48
		SD	168	415		102		83		182	
Tb.N	mm^{-1}	Mean	1.68	1.49	-12	**2.14**	44	**2.13**	43	**2.01**	36
		SD	0.38	0.48		0.40		0.43		0.51	
OS/BS	%	Mean	**25.4**	38.0	49	49.8	31	**57.7**	52	**55.7**	47
		SD	15.9	11.5		11.0		15.6		9.2	
Ob.S/BS	%	Mean	11.8	16.6	41	22.5	35	19.7	19	20.8	26
		SD	8.3	5.4		4.1		8.6		7.9	
Oc.S/BS	%	Mean	1.13	1.33	18	1.78	33	1.74	30	1.83	37
		SD	0.90	0.91		0.91		0.83		1.04	
ES/BS	%	Mean	13.6	15.6	15	16.2	4	15.1	-3	14.0	-10
		SD	5.6	4.4		8.1		4.8		5.7	
W.Th	µm	Mean	29.5	31.4	7	36.9	18	35.6	13	34.2	9
		SD	2.8	5.3		3.9		5.0		5.4	
MS/BS	%	Mean	**28.5**	40.8	43	50.6	24	**62.4**	53	**58.6**	44
		SD	13.4	10.6		4.1		8.3		9.6	
MAR	µm/d	Mean	0.52	0.61	17	0.69	13	0.68	11	0.62	1
		SD	0.15	0.10		0.13		0.10		0.13	
Aj.Ar	µm/d	Mean	0.47	0.59	24	0.65	10	0.66	14	0.61	5
		SD	0.16	0.12		0.13		0.10		0.14	
Mlt	d	Mean	22.5	18.2	-19	16.1	-12	15.5	-15	15.6	-14
		SD	14.9	4.2		3.1		3.7		3.0	
BFR/BS	$µm^3/µm^2/yr$	Mean	**59.3**	91.7	55	127.1	39	**154.3**	68	**134.1**	46
		SD	39.9	30.2		22.0		31.0		38.9	
BFR/BV	%/yr	Mean	**90.8**	164.6	81	142.7	-13	153.9	-7	145.2	-12
		SD	54.3	52.4		30.6		38.1		50.7	
Ac.f	yr^{-1}	Mean	1.55	2.53	63	3.11	23	3.59	42	3.04	20
		SD	1.17	1.03		0.49		1.43		0.88	
Fo.S/BS	%	Mean	43.3	54.4	25	67.7	24	76.5	41	72.8	34
		SD	17.8	11.9		6.4		9.3		9.9	
QS/BS	%	Mean	43.0	30.0	-30	**16.1**	-46	**8.4**	-72	**13.2**	-56
		SD	19.9	13.1		6.6		7.6		10.2	

SC = Sham Vehicle Control; VC = OVX Vehicle Control
Values in bold are significantly different from OVX Vehicle Control
[a] Dosed for 26 weeks followed by 26 weeks recovery period

Text Table 5
Summary of Histomorphometric Variables – Cancellous Bone of Femoral Neck

		Phase	End of Treatment								
		Surgery	Sham	OVX		OVX		OVX		OVX	
	AMG 785 mg/kg/dose		0	0		3		30		30[a]	
	Units		Value	Value	% vs SC	Value	% vs VC	Value	% vs VC	Value	% vs VC
BV/TV	%	Mean	16.5	14.2	-14	21.1	48	**27.0**	90	**21.3**	50
		SD	7.9	6.4		13.7		11.8		6.0	
Md.V/TV	%	Mean	16.2	13.8	-15	20.4	48	**26.4**	91	**20.9**	51
		SD	7.8	6.2		13.3		11.8		5.8	
OV/BV	%	Mean	1.72	2.75	59	2.70	-2	2.45	-11	1.95	-29
		SD	1.40	1.66		1.10		1.55		0.69	
Tb.Th	µm	Mean	152	143	-6	170	19	**238**	66	*163*	14
		SD	42	48		28		63		26	
Tb.Sp	µm	Mean	1014	1004	-1	1000	0	760	-24	675	-33
		SD	734	503		783		387		289	
O.Th	µm	Mean	6.8	7.4	9	8.4	13	6.8	-8	*8.2*	11
		SD	2.5	1.8		3.0		1.3		1.7	
OS/BS	%	Mean	16.8	27.7	65	32.0	15	33.7	22	*20.7*	-25
		SD	12.7	14.6		10.1		15.1		5.8	
Ob.S/BS	%	Mean	3.2	5.3	63	3.7	-30	5.0	-5	4.7	-11
		SD	3.2	3.5		2.5		2.7		2.3	
Oc.S/BS	%	Mean	0.69	0.69	0	0.70	1	0.73	5	***1.36***	96
		SD	0.57	0.62		0.54		0.42		0.83	
ES/BS	%	Mean	4.1	5.0	20	5.3	7	4.0	-20	***8.9***	80
		SD	3.3	2.7		3.1		2.3		4.8	
W.Th	µm	Mean	**23.0**	30.7	34	35.5	15	**51.7**	68	**57.0**	85
		SD	3.3	7.0		8.2		22.4		21.5	
MS/BS	%	Mean	13.3	19.7	48	28.0	42	28.0	42	*15.9*	-20
		SD	10.5	10.6		14.4		14.4		6.5	
MAR	µm/d	Mean	0.55	0.65	18	0.73	12	0.74	13	0.76	17
		SD	0.17	0.19		0.14		0.30		0.12	
Aj.Ar	µm/d	Mean	0.44	0.46	6	0.59	27	0.62	36	0.57	23
		SD	0.15	0.18		0.22		0.26		0.17	
Mlt	d	Mean	17.5	18.4	5	14.8	-20	20.4	11	16.1	-13
		SD	8.6	8.2		4.1		36.6		6.6	
BFR/BS	$\mu m^3/\mu m^2/yr$	Mean	28.5	48.5	70	74.3	53	73.7	52	*43.8*	-10
		SD	22.4	31.7		41.1		38.2		18.5	
BFR/BV	%/yr	Mean	41.4	67.0	62	86.0	28	64.7	-4	56.0	-17
		SD	34.6	36.2		43.9		34.4		26.3	
Ac.f	yr^{-1}	Mean	1.22	1.53	25	1.91	25	1.69	10	*0.81*	-47
		SD	0.99	1.11		0.81		1.23		0.34	
Fo.S/BS	%	Mean	20.1	29.1	45	38.8	33	38.9	34	*22.4*	-23
		SD	15.8	14.9		17.5		18.5		8.9	
QS/BS	%	Mean	75.8	65.9	-13	56.0	-15	57.2	-13	68.7	4
		SD	17.0	16.0		17.5		18.7		9.6	

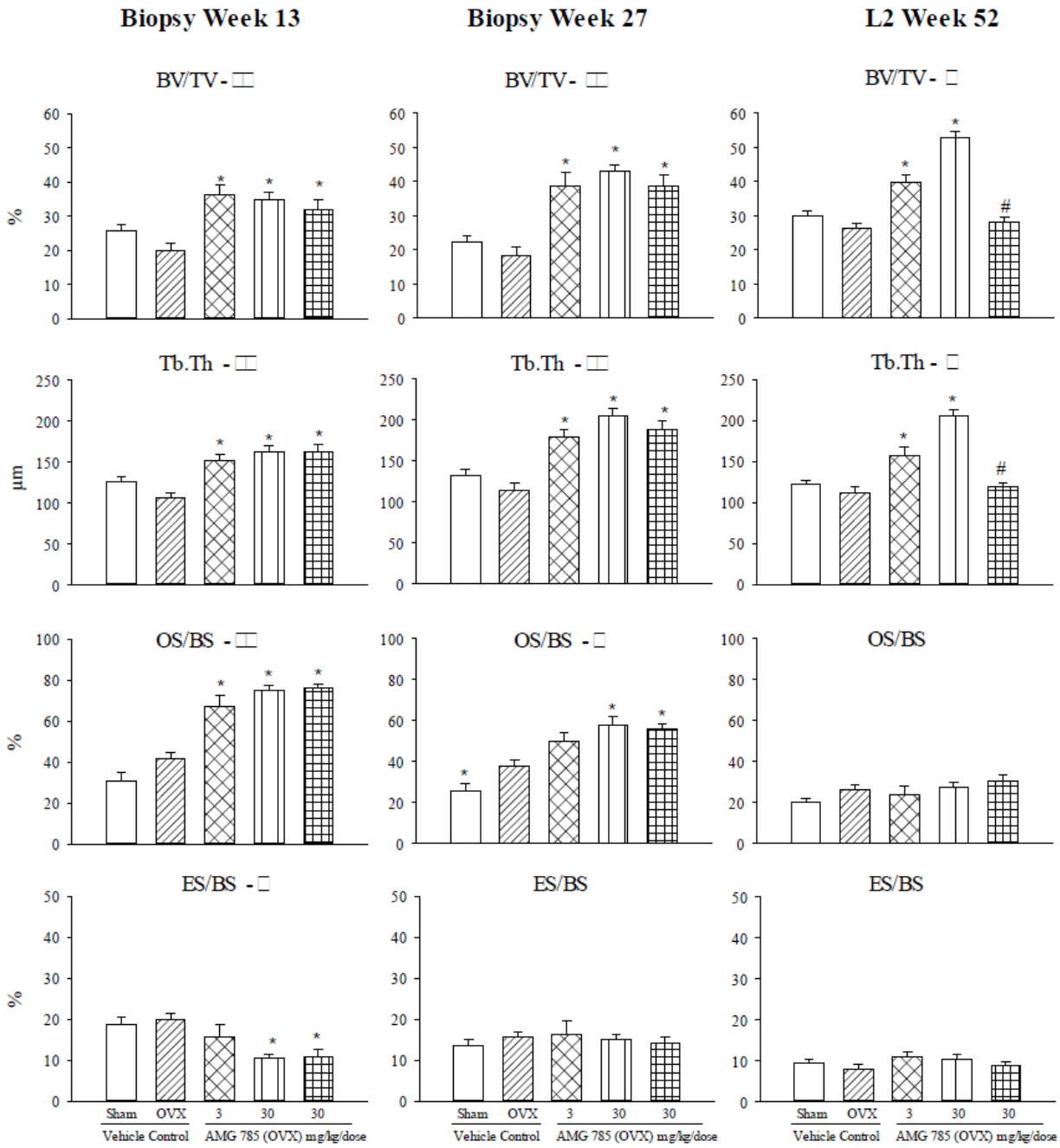
SC = Sham Vehicle Control; VC = OVX Vehicle Control
Values in bold are significantly different from OVX Vehicle Control
Values in italic are significantly different from AMG 785 (OVX) 30 mg/kg/dose group (Group 4)
[a] Dosed for 26 weeks followed by 26 weeks recovery period

Text Table 6
Summary of Histomorphometric Variables – Cancellous Bone of L2 Vertebra

		Phase	End of Treatment								
		Surgery	Sham	OVX		OVX		OVX		OVX	
	AMG 785 mg/kg/dose		0	0		3		30		30[a]	
	Units		Value	Value	% vs SC	Value	% vs VC	Value	% vs VC	Value	% vs VC
BV/TV	%	Mean	30.0	26.3	-12	**39.6**	50	**52.7**	100	*28.3*	8
		SD	5.8	5.6		5.3		8.3		5.3	
Md.V/TV	%	Mean	29.4	25.6	-13	**38.7**	51	**51.6**	102	*27.5*	7
		SD	5.7	5.4		5.3		8.0		5.1	
OV/BV	%	Mean	2.23	2.89	30	2.46	-15	2.07	-28	*2.97*	3
		SD	1.10	1.31		2.05		0.74		1.04	
Tb.Th	µm	Mean	122	111	-9	**156**	41	**206**	86	*118*	7
		SD	22	31		28		29		22	
Tb.Sp	µm	Mean	289	309	7	237	-23	**190**	-39	*303*	-2
		SD	64	46		25		58		48	
O.Th	µm	Mean	12.7	12.0	-6	13.8	15	14.3	20	13.3	11
		SD	2.3	2.4		2.6		2.2		2.4	
OS/BS	%	Mean	20.1	26.0	30	24.1	-8	27.5	6	30.4	17
		SD	7.3	10.1		10.4		9.2		12.7	
Ob.S/BS	%	Mean	10.8	16.4	53	10.9	-34	12.5	-24	*21.1*	29
		SD	5.8	9.3		5.3		7.3		11.1	
Oc.S/BS	%	Mean	1.18	1.19	1	1.96	65	1.66	39	1.38	16
		SD	0.67	0.75		0.74		1.04		0.80	
ES/BS	%	Mean	9.4	7.9	-16	10.8	37	10.2	30	8.8	11
		SD	3.7	4.0		3.2		4.8		2.9	
W.Th	µm	Mean	31.1	32.3	4	36.4	13	**38.6**	19	**38.0**	18
		SD	4.0	4.6		5.2		7.7		5.1	
MS/BS	%	Mean	16.8	18.8	12	24.1	28	23.6	26	22.6	20
		SD	5.9	9.6		8.3		10.4		9.3	
MAR	µm/d	Mean	0.70	0.75	6	0.81	9	0.80	7	0.85	14
		SD	0.14	0.12		0.10		0.18		0.10	
Aj.Ar	µm/d	Mean	0.59	0.53	-10	**0.74**	41	0.67	28	0.63	20
		SD	0.24	0.20		0.07		0.26		0.18	
Mlt	d	Mean	28.2	27.4	-3	18.8	-32	25.3	-8	23.0	-16
		SD	19.8	13.9		3.4		12.3		8.6	
BFR/BS	$\mu m^3/\mu m^2/yr$	Mean	43.0	50.8	18	71.7	41	71.6	41	68.6	35
		SD	15.2	25.1		26.6		40.7		27.1	
BFR/BV	%/yr	Mean	73.8	91.5	24	93.5	2	69.2	-24	*115.8*	27
		SD	31.7	37.8		37.2		37.3		43.0	
Ac.f	yr^{-1}	Mean	1.27	1.47	16	1.80	22	1.85	25	1.79	21
		SD	0.45	0.66		0.76		1.09		0.75	

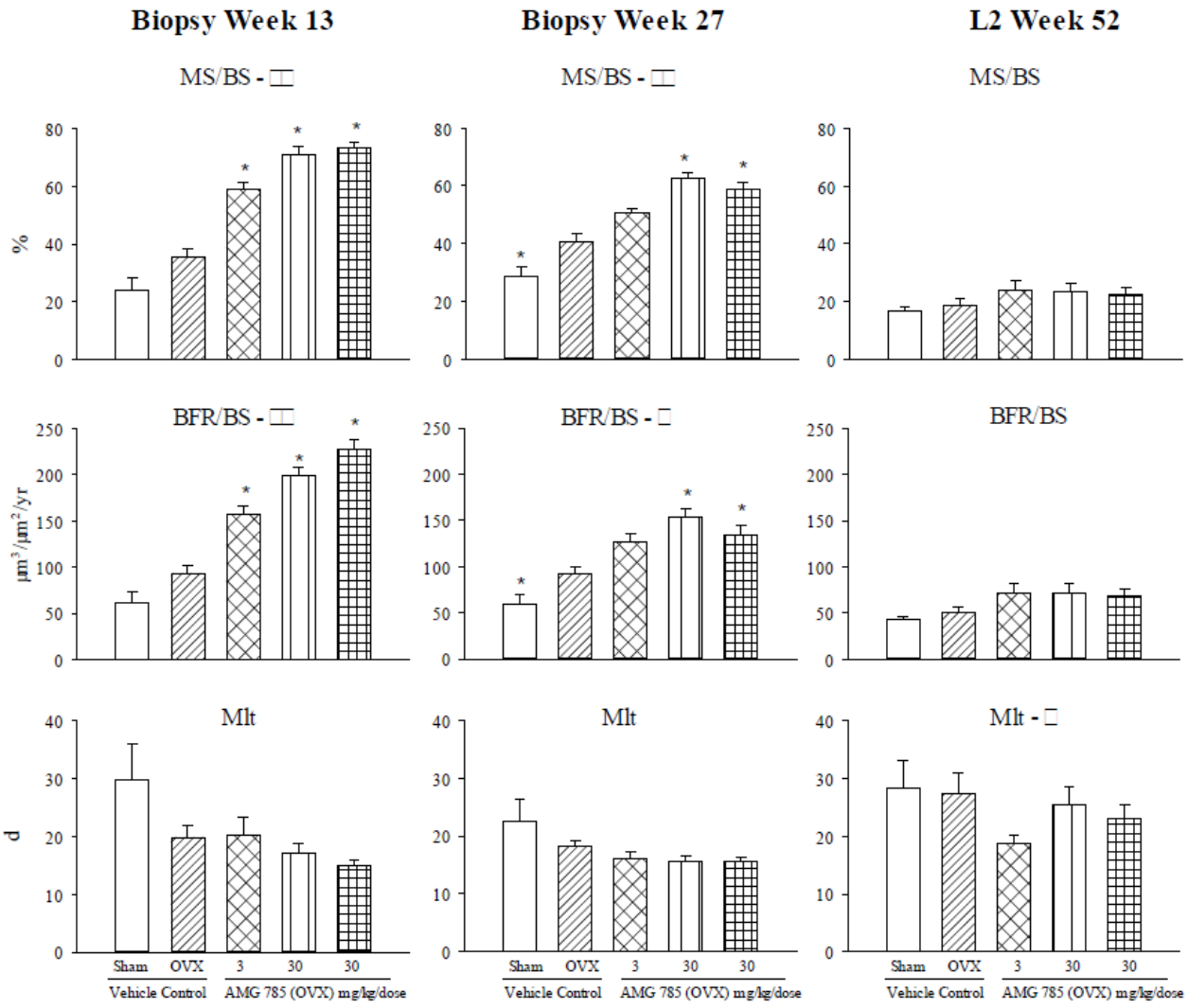
SC = Sham Vehicle Control; VC = OVX Vehicle Control
Values in bold are significantly different from OVX Vehicle Control
Values in italic are significantly different from AMG 785 (OVX) 30 mg/kg/dose group (Group 4)
[a] Dosed for 26 weeks followed by 26 weeks recovery period

Text Figure 1
Cancellous Bone Histomorphometry - Structural Parameters (Mean ± SEM)



Significantly different from OVX vehicle control group value: *-p<0.05
Significant linear dose effect: -p<0.05
Significant quadratic dose effect: -p<0.05
Group 5 significantly different from group 4 value: # -p<0.05

Text Figure 2
Cancellous Bone Histomorphometry - Dynamic Parameters (Mean ± SEM)



Significantly different from OVX vehicle control group value: *-p<0.05
Significant linear dose effect: □-p<0.05
Significant quadratic dose effect: □□-p<0.05

Cortical bone

Rib biopsies (Wk 13 and 27; and end-of-Tx Wk 52) (**Text Tables 7,8,11**):

- OVX effects:
  - Increase in cortical porosity (Po.Ar %) at Wk 13, 27 and 52, decreasing with time
  - Increase in Haversian BFR/BS (intracortical remodeling), similar at Wk 13, 27 and 52
- AMG effects:
  - Significant dose-related increase in cortical width (Ct.Wi) and cortical area (Ct.Ar), increasing over entire 52-wk Tx period (**Text Fig. 3)**
  - Slight increase in porosity (Po.Ar%) maximal at Wk 27
  - Periosteal:
    - Marked dose-rated increase in Ps.L.Pm/Ps.Pm (labeled periosteal perimeter %) and Ps.BFR/BS (periosteal BFR), most prominent at Wk 13, but also seen in Wks 27 and 52 (**Text Fig. 4**)
    - Effect on periosteal labeled and eroded perimeter, and periosteal Formative/Quiescent surface fraction was not measured
  - Endocortical:
    - Dose-related increase in Ec.L.Pm/Ec.Pm (endocortical labeled Pm %) and Ec.BFR/BS (endocortical BFR), *at Week 13* (**Text Fig 4**)
    - Marked (non)dose-related suppression of Ec.E.Pm/Ec.Pm (endocortical eroded perimeter %), most prominent at Wk 13 (*opposite of resorption marker result*) (**Text Fig 3**)
    - Dose-related increase in Ec.Fo.Pm/Ec.Pm (formative perimeter %); and decrease in Ec.Q.Pm/Ec.Pm (quiescent perimeter %) (measured at Wk 13 only)
  - Intracortical
    - Increase in H.BFR/BS (haversian formation/remodeling) at 3 mg/kg in Wk13 and at 30 mg/kg in Wk 27, but not in Wk 52 (**Text Fig 4**)
    - Increase in cortical porosity at 3 mg/kg, mainly in Wk 27
  - Recovery group 30mg/kg (Wk 52):
    - Reversal of effects on
      - Ct.Wi (ie DE-creased vs 30 mg/kg AMG785 grp)
      - Ps.L.Pm % and Ps.BFR (ie DE-creased)
      - Ps.BFR (ie IN-creased)
      - Ec.E.Pm % (ie IN-creased)

Femoral diaphysis (Wk 52, end of Tx) **(Text Table 12)**:

- OVX effects:
  - Increase in cortical porosity (Po.Ar %), as in rib
  - Marked increase in Ec.E.Pm/Ec.Pm (not seen in rib)
  - Increase in Ec.L.Pm/Ec.Pm and Ec.BFR/BS
  - Increase in Haversian BFR/BS (intracortical remodeling), as in rib

- AMG effects
  - Small non-significant increase in cortical width (Ct.Wi), as in rib
  - Periosteal:
    - Marked dose-rated increase in Ps.L.Pm/Ps.Pm and Ps.BFR/BS, as in rib
    - Effect on periosteal labeled and eroded perimeter, and periosteal Formative/Quiescent surface fraction was not measured
  - Endocortical:
    - No effects on Ec.L.Pm/Ec.Pm and Ec.BFR/BS
    - Marked non-dose-related suppression of Ec.E.Pm/Ec.Pm (-97% at both doses)
    - Dose-related increase in Ec.Fo.Pm/Ec.Pm (formative bone surface %); and decrease in Ec.Q.Pm/Ec.Pm (quiescent surface %)
  - Intracortical
    - No effect on H.BFR/BS, as in rib at Wk 52
    - No effect on cortical porosity
  - Recovery group 30mg/kg (Wk 52):
    - Reversal of effects for the following parameters:
      - Ct.Wi (ie DE-creased vs 30 mg/kg group)
      - Ps.L.Pm % and Ps.BFR (IN-creased vs 30 mg/kg group)
      - **No reversal** of suppression of Ec.E.Pm %
    - Decrease in Ec/L.Pm% and Ec.BFR vs 30 mg/kg grp (no effect on these parameters in 30 mg/kg grp)
    - Increase in Ec.Fo.Pm/Ec.Pm and decrease in Ec.Q.Pm/Ec.Pm vs 30 mg/kg grp

There were no adverse effects on bone histology at these cortical sites.

Reviewer's comment:

- *The highlighted numbers in the Text Tables of Histomorphometric Variables indicate statistically significant effects*

Text Table 7
Summary of Histomorphometric Variables –Cortical Bone of Rib at Week 13

		Phase	Week 13								
		Surgery	Sham	OVX		OVX		OVX		OVX	
	AMG 785	mg/kg/dose	0	0		3		30		30[a]	
	Units		Value	Value	% vs SC	Value	% vs VC	Value	% vs VC	Value	% vs VC
Tt.T.Ar	mm^2	Mean	7.28	7.04	-3	6.55	-7	7.53	7	7.51	7
		SD	1.13	1.32		0.84		1.47		1.26	
Ct.Ar	mm^2	Mean	4.58	4.61	1	4.93	7	**5.46**	19	**5.51**	19
		SD	0.63	0.73		0.68		0.91		0.78	
Me.Ar	mm^2	Mean	2.71	2.43	-10	1.62	-33	2.07	-15	2.01	-17
		SD	1.17	1.14		0.71		1.01		0.63	
Ct.Wi	mm	Mean	0.52	0.54	3	0.61	14	**0.64**	18	**0.65**	21
		SD	0.12	0.09		0.11		0.10		0.05	
Ec.E.Pm/Ec.Pm	%	Mean	4.0	7.9	99	**0.9**	-88	**1.9**	-75	**1.2**	-85
		SD	2.9	7.0		1.2		2.9		1.5	
% Po.Ar	%	Mean	**2.60**	5.37	106	5.59	4	4.32	-20	5.53	3
		SD	2.26	2.66		2.37		1.57		1.81	
Ps.L.Pm/Ps.Pm	%	Mean	2.0	2.3	17	17.9	663	**18.2**	679	*28.0*	1094
		SD	2.4	3.1		15.3		11.2		11.5	
Ps.MAR	µm/day	Mean	0.23	0.41	79	0.46	12	0.55	33	**0.72**	76
		SD	0.12	0.39		0.29		0.31		0.20	
Ps.BFR/BS	$µm^3/µm^2/yr$	Mean	2.3	6.9	196	39.5	469	**46.4**	569	*77.8*	1021
		SD	4.9	14.6		47.0		39.7		40.9	
Ec.L.Pm/Ec.Pm	%	Mean	13.8	22.6	64	42.0	86	**53.9**	139	**65.1**	188
		SD	15.7	17.9		16.2		22.4		13.5	
Ec.MAR	µm/day	Mean	**0.68**	0.96	42	0.82	-14	0.94	-3	0.99	3
		SD	0.26	0.21		0.14		0.14		0.15	
Ec.BFR/BS	$µm^3/µm^2/yr$	Mean	43.2	78.0	81	132.2	70	**192.6**	147	**238.1**	205
		SD	59.7	70.2		62.5		87.8		72.8	
H.L.Pm/H.Pm	%	Mean	**12.2**	29.1	140	40.2	38	29.7	2	26.7	-8
		SD	10.2	11.2		9.3		11.8		5.7	
H.MAR	µm/day	Mean	**0.82**	1.12	37	1.18	6	1.20	7	1.27	14
		SD	0.29	0.20		0.15		0.19		0.14	
H.BFR/BS	$µm^3/µm^2/yr$	Mean	**42.9**	119.0	177	**176.4**	48	134.3	13	125.3	5
		SD	46.2	46.2		54.5		54.8		35.0	
H.BFR/BV	%/yr	Mean	**9.7**	30.5	215	**48.6**	60	29.9	-2	31.4	3
		SD	14.2	14.0		22.9		14.6		13.0	
Ec.Q.Pm/Ec.Pm	%	Mean	77.9	63.9	-18	48.6	-24	**38.1**	-40	**27.2**	-57
		SD	18.7	20.4		15.7		20.3		11.1	
Ec.Fo.Pm/Ec.Pm	%	Mean	18.2	28.2	55	**50.5**	79	**60.0**	113	**71.6**	154
		SD	17.9	20.4		15.6		22.4		11.5	

SC = Sham Vehicle Control
VC = OVX Vehicle Control
Values in bold are significantly different from OVX Vehicle Control
Values in italic are significantly different from AMG 785 (OVX) 30 mg/kg/dose group (Group 4)
[a] Dosed for 26 weeks followed by 26 weeks recovery period

Text Table 8
Summary of Histomorphometric Variables – Cortical Bone of Rib at Week 27

		Phase	Week 27								
		Surgery	Sham	OVX		OVX		OVX		OVX	
	AMG 785 mg/kg/dose		0	0		3		30		30[a]	
	Units		Value	Value	% vs SC	Value	% vs VC	Value	% vs VC	Value	% vs VC
Tt.T.Ar	mm^2	Mean	7.45	6.92	-7	6.54	-6	7.36	6	**8.27**	19
		SD	1.23	1.17		1.05		1.10		1.32	
Ct.Ar	mm^2	Mean	4.53	4.42	-2	4.99	13	**5.82**	32	**6.23**	41
		SD	0.54	0.55		0.68		0.98		0.79	
Me.Ar	mm^2	Mean	2.92	2.51	-14	1.55	-38	**1.54**	-39	2.04	-19
		SD	1.12	1.18		0.98		0.75		0.73	
Ct.Wi	mm	Mean	0.50	0.52	4	0.65	25	**0.71**	36	**0.70**	35
		SD	0.08	0.10		0.13		0.16		0.07	
Ec.E.Pm/Ec.Pm	%	Mean	4.0	4.8	20	3.9	-20	**1.8**	-63	**1.3**	-73
		SD	2.6	3.5		7.3		2.0		1.5	
% Po.Ar	%	Mean	**2.48**	4.36	75	6.11	40	4.57	5	***5.90***	35
		SD	0.80	1.43		1.57		1.46		1.69	
Ps.L.Pm/Ps.Pm	%	Mean	9.0	6.9	-23	13.5	95	**25.4**	267	**26.6**	285
		SD	12.0	6.3		6.0		17.9		13.5	
Ps.MAR	µm/day	Mean	0.39	0.46	20	0.35	-24	**0.71**	55	0.61	33
		SD	0.30	0.31		0.24		0.18		0.19	
Ps.BFR/BS	$µm^3/µm^2/yr$	Mean	21.4	16.4	-23	21.0	28	**69.8**	326	**65.6**	300
		SD	49.5	21.0		21.4		53.5		36.6	
Ec.L.Pm/Ec.Pm	%	Mean	15.3	27.5	79	13.3	-52	34.2	24	40.9	49
		SD	14.3	16.9		10.3		17.1		15.5	
Ec.MAR	µm/day	Mean	0.65	0.81	25	0.77	-5	0.78	-4	0.78	-4
		SD	0.24	0.16		0.17		0.10		0.10	
Ec.BFR/BS	$µm^3/µm^2/yr$	Mean	45.3	83.5	84	38.0	-54	96.3	15	114.9	38
		SD	56.3	54.2		30.3		48.3		46.9	
H.L.Pm/H.Pm	%	Mean	**16.9**	40.2	138	40.2	0	47.9	19	**51.2**	27
		SD	9.7	11.9		8.7		14.4		10.1	
H.MAR	µm/day	Mean	**0.89**	1.07	20	1.09	2	1.16	9	1.14	7
		SD	0.18	0.13		0.09		0.12		0.10	
H.BFR/BS	$µm^3/µm^2/yr$	Mean	**56.8**	158.9	180	161.1	1	203.7	28	**213.4**	34
		SD	38.1	55.8		42.0		68.4		46.8	
H.BFR/BV	%/yr	Mean	**11.3**	37.9	235	45.4	20	45.7	21	**54.4**	44
		SD	8.0	15.8		14.1		18.3		14.9	

SC = Sham Vehicle Control
VC = OVX Vehicle Control
Values in bold are significantly different from OVX Vehicle Control
Values in italic are significantly different from AMG 785 (OVX) 30 mg/kg/dose group (Group 4)
[a] Dosed for 26 weeks followed by 26 weeks recovery period

Text Table 11
Summary of Histomorphometric Variables – Cortical Bone of Rib at Study End

		Phase	End of Treatment								
		Surgery	Sham	OVX		OVX		OVX		OVX	
	AMG 785 mg/kg/dose		0	0		3		30		30[a]	
	Units		Value	Value	% vs SC	Value	% vs VC	Value	% vs VC	Value	% vs VC
Tt.T.Ar	mm^2	Mean	6.73	6.78	1	7.07	4	**8.15**	20	7.47	10
		SD	1.46	1.34		1.54		1.38		1.40	
Ct.Ar	mm^2	Mean	4.18	4.02	-4	**5.32**	32	**6.42**	60	*5.16*	28
		SD	1.00	0.73		1.03		1.05		0.95	
Me.Ar	mm^2	Mean	2.55	2.76	8	1.75	-37	**1.73**	-37	2.31	-16
		SD	1.06	1.01		0.85		0.83		0.71	
Ct.Wi	mm	Mean	0.45	0.42	-7	**0.54**	30	**0.67**	60	*0.54*	28
		SD	0.09	0.06		0.08		0.14		0.10	
Ec.E.Pm/Ec.Pm	%	Mean	2.8	2.5	-11	2.1	-18	1.6	-35	*8.2*	225
		SD	1.6	1.9		1.4		1.5		6.1	
% Po.Ar	%	Mean	2.37	3.19	35	3.76	18	3.33	4	3.68	15
		SD	1.19	0.77		0.81		1.07		1.08	
Ps.L.Pm/Ps.Pm	%	Mean	4.5	2.9	-36	5.2	79	**10.5**	261	*0.9*	-68
		SD	5.9	3.4		6.0		7.4		1.2	
Ps.MAR	µm/day	Mean	0.36	0.32	-11	0.30	-6	0.41	28	*0.24*	-24
		SD	0.20	0.17		0.16		0.16		0.11	
Ps.BFR/BS	$µm^3/µm^2/yr$	Mean	7.7	4.7	-39	7.5	59	**17.7**	275	*1.0*	-80
		SD	12.0	7.0		10.6		15.1		1.3	
Ec.L.Pm/Ec.Pm	%	Mean	**8.2**	14.0	71	20.1	44	16.0	14	15.6	11
		SD	5.0	6.6		14.1		10.6		10.9	
Ec.MAR	µm/day	Mean	0.58	0.67	16	0.73	9	0.62	-8	*0.78*	16
		SD	0.19	0.10		0.08		0.17		0.10	
Ec.BFR/BS	$µm^3/µm^2/yr$	Mean	**18.4**	33.3	81	51.8	55	40.0	20	46.8	40
		SD	11.9	13.9		33.2		29.1		37.6	
H.L.Pm/H.Pm	%	Mean	**18.5**	35.3	91	28.6	-19	37.3	6	41.3	17
		SD	14.9	8.9		7.2		13.2		9.5	
H.MAR	µm/day	Mean	**0.78**	0.88	12	0.89	1	0.92	5	0.86	-2
		SD	0.13	0.11		0.08		0.09		0.10	
H.BFR/BS	$µm^3/µm^2/yr$	Mean	**54.7**	113.7	108	94.3	-17	128.2	13	130.6	15
		SD	45.6	32.6		30.0		52.4		36.5	
H.BFR/BV	%/yr	Mean	**11.7**	22.9	95	20.5	-11	23.7	4	28.0	22
		SD	13.0	8.4		7.3		10.3		11.0	

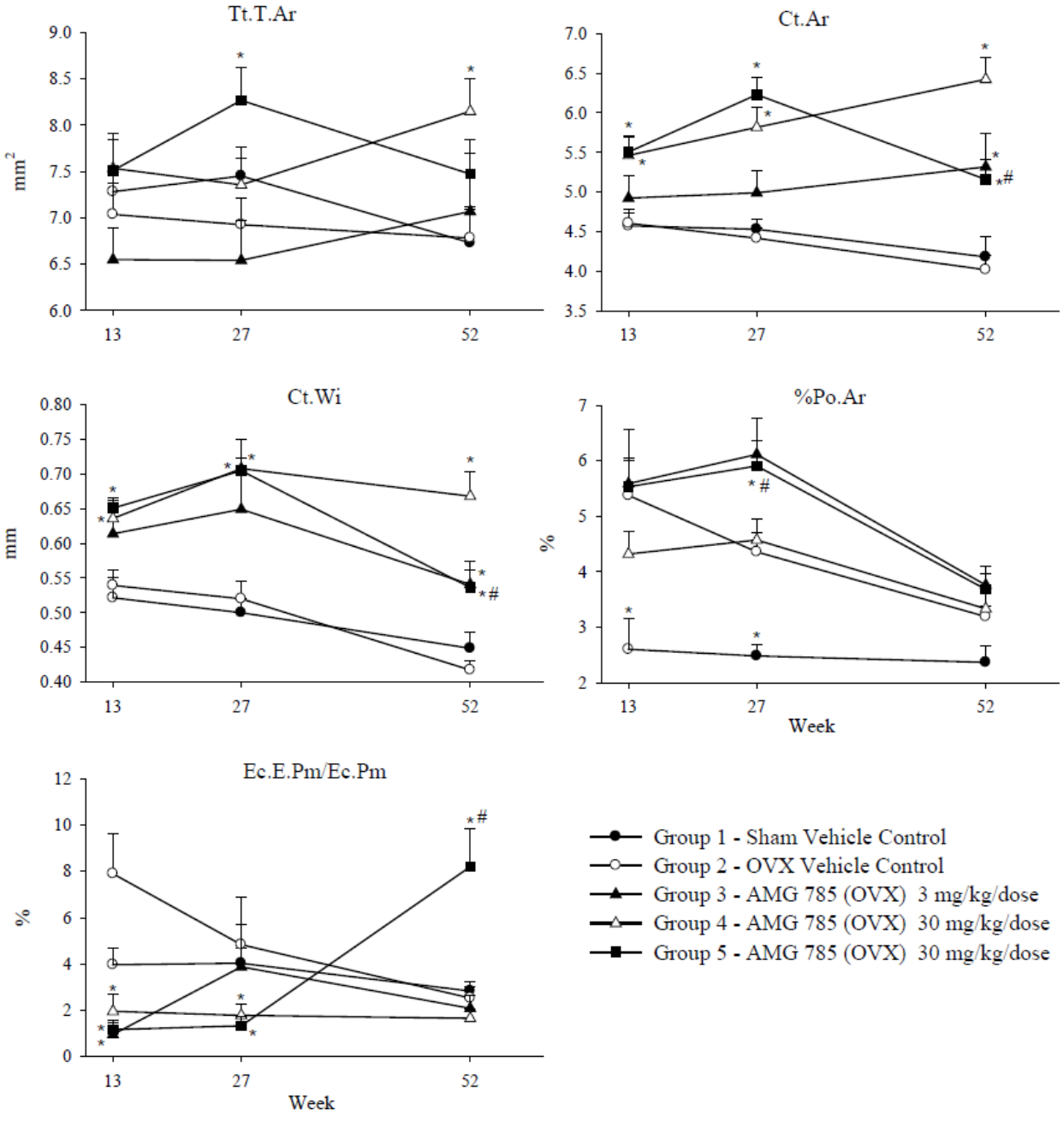
SC = Sham Vehicle Control
VC = OVX Vehicle Control
Values in bold are significantly different from OVX Vehicle Control
Values in italic are significantly different from AMG 785 (OVX) 30 mg/kg/dose group (Group 4)
[a] Dosed for 26 weeks followed by 26 weeks recovery period

Text Table 12
Summary of Histomorphometric Variables –Cortical Bone of Femoral Diaphysis

		Phase	End of Treatment								
		Surgery	Sham	OVX		OVX		OVX		OVX	
	AMG 785 mg/kg/dose		0	0		3		30		30[a]	
	Units		Value	Value	% vs SC	Value	% vs VC	Value	% vs VC	Value	% vs VC
Tt.T.Ar	mm^2	Mean	68.78	68.00	-1	65.90	-3	68.98	1	71.97	6
		SD	8.15	7.55		10.09		5.76		7.70	
Ct.Ar	mm^2	Mean	45.41	45.40	0	47.41	4	**50.93**	12	**50.04**	10
		SD	4.05	3.87		4.14		5.02		5.47	
Me.Ar	mm^2	Mean	23.37	22.60	-3	18.49	-18	18.05	-20	*21.93*	-3
		SD	6.51	5.70		7.83		4.84		4.92	
Ct.Wi	mm	Mean	1.95	1.97	1	2.17	10	**2.29**	16	2.14	8
		SD	0.20	0.16		0.19		0.27		0.20	
Ec.E.Pm/Ec.Pm	%	Mean	**0.4**	9.1	2177	**0.3**	-97	**0.2**	-97	**0.8**	-91
		SD	0.9	9.3		0.7		0.6		1.9	
% Po.Ar	%	Mean	**1.76**	2.73	55	3.00	10	2.56	-6	2.96	8
		SD	0.48	0.59		1.09		0.81		1.10	
Ps.L.Pm/Ps.Pm	%	Mean	2.4	2.9	22	9.9	240	**24.3**	737	2.3	-20
		SD	5.8	3.8		13.7		20.1		2.7	
Ps.MAR	µm/day	Mean	0.38	0.45	20	0.69	52	0.59	31	0.43	-6
		SD	0.36	0.25		0.32		0.33		0.33	
Ps.BFR/BS	$µm^3/µm^2/yr$	Mean	5.7	6.3	10	30.8	392	**70.6**	1028	5.3	-15
		SD	15.2	8.3		48.0		63.8		8.4	
Ec.L.Pm/Ec.Pm	%	Mean	**4.0**	21.6	439	22.4	4	21.9	1	*0.8*	-96
		SD	5.0	11.1		13.0		22.5		1.2	
Ec.MAR	µm/day	Mean	**0.51**	0.89	75	0.81	-9	**0.53**	-40	**0.39**	-56
		SD	0.33	0.16		0.16		0.25		0.39	
Ec.BFR/BS	$µm^3/µm^2/yr$	Mean	**9.7**	68.9	610	65.2	-5	54.5	-21	*1.8*	-97
		SD	14.5	34.4		35.9		64.6		2.8	
H.L.Pm/H.Pm	%	Mean	**3.8**	16.2	331	17.6	8	14.0	-14	14.2	-12
		SD	3.9	6.8		8.3		5.5		7.4	
H.MAR	µm/day	Mean	**0.79**	1.25	58	1.17	-7	1.20	-4	1.22	-2
		SD	0.32	0.13		0.10		0.16		0.13	
H.BFR/BS	$µm^3/µm^2/yr$	Mean	**12.8**	74.5	480	76.4	3	61.9	-17	64.6	-13
		SD	14.0	33.0		39.9		27.2		36.0	
H.BFR/BV	%/yr	Mean	**2.4**	16.3	566	17.7	9	14.0	-14	15.0	-8
		SD	3.0	7.3		10.9		8.2		10.5	
Ec.Q.Pm/Ec.Pm	%	Mean	**93.3**	59.6	-36	68.6	15	69.6	17	*98.0*	64
		SD	7.1	16.9		17.6		26.4		2.7	
Ec.Fo.Pm/Ec.Pm	%	Mean	**6.3**	31.3	396	31.1	-1	30.2	-4	*1.2*	-96
		SD	7.2	16.3		17.5		26.6		1.8	

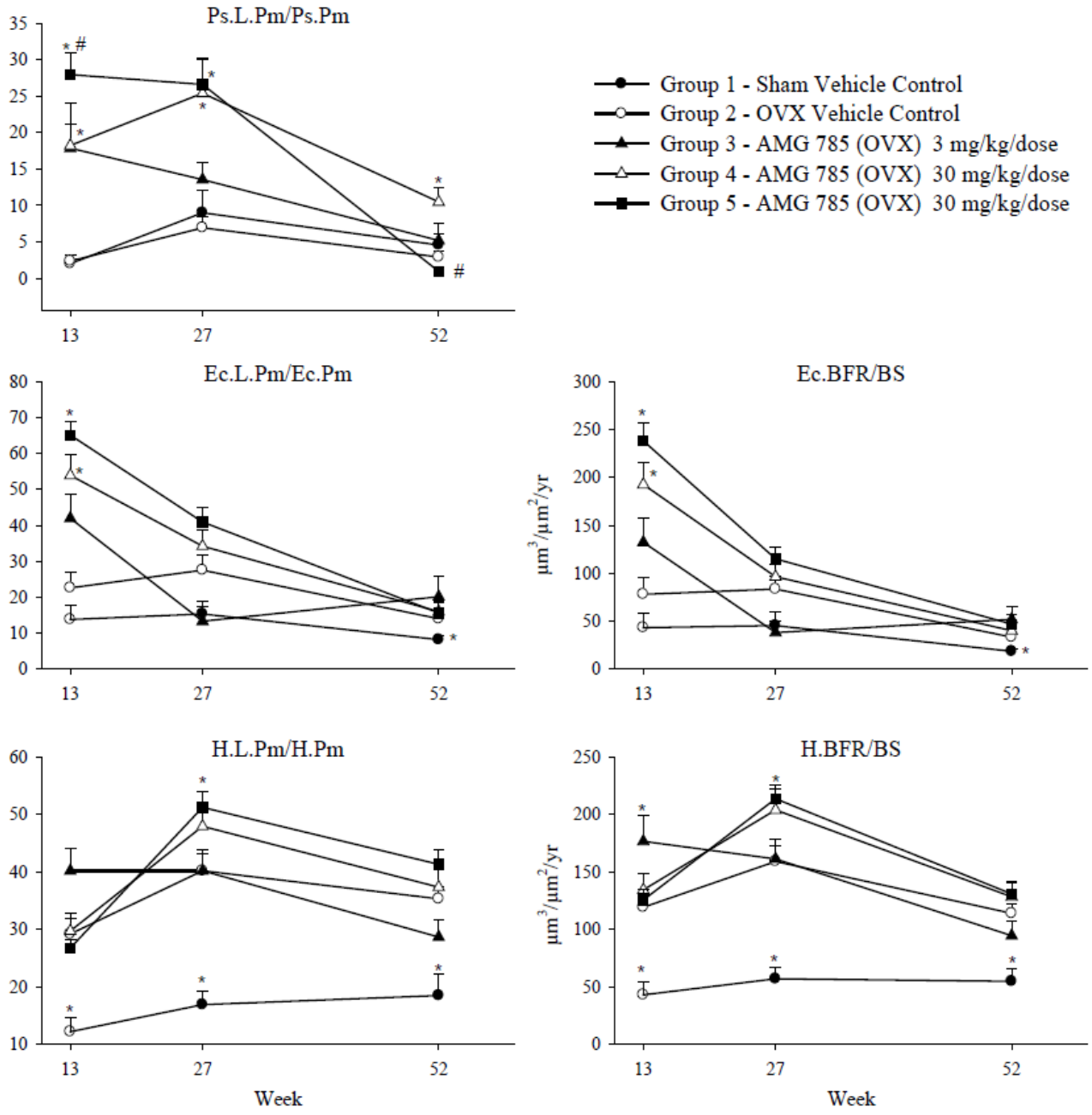
SC = Sham Vehicle Control
VC = OVX Vehicle Control
Values in bold are significantly different from OVX Vehicle Control
Values in italic are significantly different from AMG 785 (OVX) 30 mg/kg/dose group (Group 4)
[a] Dosed for 26 weeks followed by 26 weeks recovery period

Text Figure 3
Cortical Bone Histomorphometry – Rib – Structural Parameters (Mean ± SEM)



Significantly different from OVX vehicle control group value: *-p<0.05
Group 5 significantly different from group 4 value: # -p<0.05

Text Figure 4
Cortical Bone Histomorphometry - Rib - Dynamic Parameters (Mean ± SEM)



Significantly different from OVX vehicle control group value: *-p<0.05
Group 5 significantly different from group 4 value: # -p<0.05

Reviewer Comments (Cancellous HMM):

- *Decreases in ES/BS and OcS/BS in Wk 13 suggested transient suppression of resorption in cancellous bone of ilium (and also possibly of femoral neck and vertebrae at Wk 52).*

- *Lack of increases in O.Th (osteoid thickness) or Mlt (mineralization lag time) suggested there were no adverse effects on new bone matrix mineralization.*

Reviewer Comments (Cortical HMM):

- *Small-to-moderate changes in structural (i.e static) bone formation indices (TtT.AR. Ct.Ar. Ct.Th. Me.Ar and Po.Ar) were observed in cortical bone. Changes were time-dependent.*

- *The decrease in % Me.Ar was consistent with the decrease in pQCT endosteal circumference.*

- *The changes in % Me.Ar and Po.Ar were preceded or accompanied by increases in endosteal and Haversian (=intracortical) bone formation parameters (eg BFR), respectively.*

- *BFR/BS was increased at all three cortical bone surfaces, especially early in Wk 13. The increases at endosteal and Haversian surfaces were most significant due to higher control values and larger effects.*

- *The increases in BFR were consistent with the increases in systemic bone formation markers (PINP, OC, BSAP)*

- *Erosion/resorption activity at the endocortical surface (EcEPm, %) was markedly suppressed especially at the earlier time points in rib (13-27 wks), but also still at the last time point (52 wks) in femur diaphysis. Also, endocortical formative surface % was increased while quiescent surface % was decreased. This suggests that bone formation at the endocortical rib surface was modeling-based rather than remodeling-based.*

- *Overall, Haversian bone formation in rib was increased in Wk 13 and 27 at both doses. Considering the small increase in cortical porosity in Wk 27, this formation increase was probably accompanied by increased intracortical resorption.*

- *Daily dosing with teriparatide or PTH1-84 is known to have much larger effects on cortical porosity (2x-5x OVX control), particularly near the endocortical surface (Burr et al 2001, Fox et al, 2007). By comparison, AMG785 in rib caused Po.Ar to increase merely by a factor of 1.5x from 4 to 6%.*

- *Based on Ps.BFR data, resorption stimulation probably also occurred at periosteal surfaces. The increase in rib Ps.BFR/BS at 30 mg/kg was 6x, 4x and 3x in Wk 13, 27, 52. Concomitantly, Tt.T.Ar (i.e. external bone width) was increased 1.07x, 1.06x, 1.2x (Wk 13, 27, 52). Ps.BFR was also increased at 3 mg/kg (Wk 13) but TtTAr was not. This suggests that increases in Ps.BFR are accompanied by increases in periosteal resorption. However, this resorption effect probably contributed less to the overall resorption increase than resorption at the Haversian surfaces based on much smaller values and smaller % increases (Ps.BFR/BS vs H. BFR/BS).*

- *Thus the increases in Haversian and periosteal bone resorption probably related to the (transient) increase in the systemic bone resorption markers.*

- *The balance of the resorption changes at all bone surfaces led to a transient increase in resorption markers in OVX monkeys. In Phase 3 Study 20070337, however, AMG785 caused a DECREASE in resorption marker(s) during the entire first 12-month Tx period. However, data from iliac biopsies taken at 2 and 12 months showed similar dynamic changes in trabecular and cortical bone surface events in humans as in monkeys at 3 mg/kg. In humans, porosity was NOT changed in AMG785 vs pbo treated at 2 and 12 months.*

- *The intracortical and periosteal resorption increases were probably related to the observed increases in serum PTH in both monkeys and humans. PTH elevation was probably intended to maintain serum Ca at normal levels upon enhanced skeletal Ca absorption due to increased bone formation. Nevertheless, serum Ca was still slightly decreased through Wk 23/24 at 30 mg/kg.*

- *In distal radius, endosteal circumference was INCREASED (pQCT data). Thus, resorption must have dominated formation at that surface. It is not clear how the increase in inner diameter was achieved and whether it also occurred at other skeletal sites.*

CONCLUSIONS

Study design

- Monkeys were sham-operated or OVX-ed followed by a 17-wk bone depletion period. Sham-operated monkeys were dosed s.c. with **0 mg/kg/wk** for 12 months. OVX groups were given **0, 3,** or **30 mg/kg/wk** for 12 months, or **30/0 mg/kg** for 6/6 months (recovery group).

ADA

- Several animals in the 3 mg/kg weekly dosing group developed binding or neutralizing antibodies against AMG785. The result was that the initial number of 16/grp was reduced to 16, 16, 6, 15, 14 in the 0, 0, 3, 30, and 30/0 (recovery) groups, respectively.

Clinical pathology/hormones

- Serum Ca decreased in 30 mg/kg vs OVX control group.
- Serum PTH/VitD increased vs OVX controls. Effect was sustained at 3 mg/kg, but transient at 30 mg/kg.

Pharmacokinetics

- AUC(0-168h) at 3 and 30 mg/kg (172 and 2950 ug.day/mL) corresponded to monthly AUC values (4 x AUC0-168h) of 16512 and 282993 ug.hr/mL, representing multiples of 1.3x and 22x the human AUC of 12888 ug.hr/mL at the intended monthly human doses of 210 mg/kg (ca. 3 mg/kg).
- The $T_{1/2}$ of AMG785 at 3 and 30 mg/kg in intact monkeys ranged from 74 to 116 hrs (data from 6-month toxicity study 107426; from 3, 10 and 100 mg/kg dose groups). This is 2.5 to 4 times shorter than the observed half-life in humans at the 3 mg/kg dose (12.8 days; Clinical Overview, p.19).
- Cumulative monthly monkey vs monthly human AUC multiples at 3 and 30 mg/kg are 1.3x and 22x, respectively, which would be 1.3x and 2.2x larger than multiples calculated based on mg/kg comparison (1x and 10x, respectively).The difference may be due to the fact that half-life in monkeys is less than 1/4x half-life in humans while doses were given ca. 4 more frequently in monkeys vs humans.

Bone resorption and formation

- AMG785 transiently increased overall skeletal bone formation and resorption indicated by serum or urine circulating bone biomarkers. The increases were largest at 3 months (the earliest sampling time point) and decreased thereafter. However, markers were still increased as compared to OVX controls after 12 months. Effects were approx. 2.5-fold larger for formation marker P1NP vs resorption marker CTx. The formation increase was due to the primary pharmacologic effect of AMG785 to neutralize sclerostin and prevent inhibition of osteoblastic bone matrix deposition and mineralization.
- The resorption increase was probably related to the AMG-induced increase in serum PTH. The increase in resorption markers was also transient but, like the increase in

serum PTH, CTx and NTx values were still above OVX controls at 12 months. The PTH increase most likely reflected an attempt to compensate for hypocalcemia caused by osteoblastic bone mineral formation. PTH is known to stimulate Haversian (intracortical) bone remodeling and can increase cortical porosity. These events were confirmed by an early increase in H.BFR and small increases in Po.Ar in rib cortex (histomorphometry, see below).

- Serum calcium was slightly decreased.

Densitometry

DXA (spine, femur, tibia and radius)

- OVX led to expected decreases in DXA parameters BMD, Bone Area and BMC at cancellous and cortical bone sites.
- AMG increased bone mass evidenced by dose-related increases in BMC, Area and/or BMC in whole body, lumbar spine and long bones, including proximal tibia, proximal and distal femur, and distal radius. Increases occurred in both cancellous and cortical long bone regions.
- Increases were most prominent in the first 6 months, but continued thereafter.
- At 12 months, parameters usually exceeded sham levels at both 3 and 30 mg/kg doses.
- Upon recovery, the effects in the 30 mg/kg group were reversed to the levels achieved in the 3 mg/kg or sham group.
- Extent, time-dependence and dose-dependence of the AMG effects on DXA parameters were different for different bone sites and regions.
- PQCT confirmed increases in trabecular BMD in metaphyseal part of proximal tibia and distal radius.

pQCT (tibia and radius, meta- and diaphysis)

- OVX caused decreases in trabecular and cortical/subcortical BMD and BMC, and cortical thinning due to decrease in bone width with no change in medullary area.
- In proximal tibia and distal radius metaphysis, AMG increased total bone area/width, trabecular and (sub)cortical BMD and BMC. Effects were more pronounced in tibia.
- In proximal tibia and distal radius diaphysis, total area and periosteal circumference were slightly increased (effect in radius > in tibia), and cortical thickness was increased. Cortical BMD was increased in tibia. However it was transiently decreased in distal radius. In tibial diaphysis, endosteal circumference was decreased but in radius diaphysis endosteal circumference was slightly increased. PQCT of proximal or mid femur was not performed. It is not clear whether any other bones respond to AMG785 in a similar way as cortical bone of distal radius. The cause of the decrease in cortical BMD with AMG785 is not clear. It may in part be due to increased cortical remodeling and porosity, although the histomorphometry data are not entirely consistent with this interpretation. PTH receptor agonists also cause a slight decrease in BMD of the mostly cortical distal radius, possibly due to increased cortical porosity.
- AMG generally restored bone parameters to sham levels at 3 mg/kg and above sham levels at 30 mg/kg.

- The effects in the 30 mg/kg recovery group were reversed usually to the levels attained in the 3 mg/kg group.

Densitometry (ex vivo)

- Data from ex vivo DXA/pQCT of femur, vertebrae and vertebral cores to be used for mechanical testing at 52 wks showed effects very similar to those observed for vertebrae (by in vivo DXA), and proximal tibia (by in vivo pQCT). AMG effects in femur diaphysis included increased BMC and BMD, increased cortical thickness and decreased endosteal circumference. Cortical BMD was not affected.

Micro-CT (ex vivo)

- Micro-CT after 52 wks showed that AMG785 increased L3 trabecular parameters (vBMD, BMC, Tb.Th and/or Tb.N, Bone Area, BV/TV) in a dose-related manner. Changes were similar in vertebral bodies and cores. AMG785 also increased vertebral cortical bone vBMD, BMC, area, and thickness.
- Tissue BMD was decreased by AMG in vertebral trabecular and cortical regions. This may be related to increased bone porosity, or it may be a technical artefact.
- In femoral neck, AMG785 effects were similar to those in L3 trabecular bone.
- AMG785 did not significantly affect humerus cortical porosity or tissue BMD.
- The AMG785-induced decrease in L3 SMI probably indicated a change to a more plate-like trabecular structure.
- In the 30 mg/kg recovery group, the AMG785-induced changes were partially reversed to levels achieved in the 3 mg/kg group (cortical part of L3) or levels intermediate between OVX and 3 mg/kg groups (trabecular part of L3).
- Data were consistent with densitometric and histomorphometric results.

Biomechanical testing

- AMG increased bone strength parameters of the femur shaft. Effects were dose-related with some statistically significant at 30 mg/kg. Effects included increases in peak load, yield load, stiffness, AUC and (postyield)-toughness.
- The intrinsic cortical bone strength (material strength) of the humerus cortical beam was not significantly affected by AMG.
- AMG increased the strength (peak load, stiffness, AUC) of the femoral neck, consistent with significant increase in ex vivo DXA proximal femur BMD and BMC.
- AMG increased bone strength parameters in lumbar vertebrae bodies and cores, with most effects statistically significant at both 3 and 30 mg/kg. Effects included increases in peak load, yield load, stiffness, AUC and (postyield)-toughness.
- For femur shaft and vertebrae, correlations between ex vivo densitometric measures of bone mass (BMC or BMD) and bone strength (peak load or apparent strength) were very good and statistically significant. For femoral neck, there was a reasonably good significant correlation between BMC and peak load (except for the 3 mg/kg group of N=6).

- In vertebral L3+L4 bodies, bone quality appeared to be increased vs sham and OVX groups at 30 mg/kg, when bone quality was defined as the slope of the regression line between ex vivo BMC and peak load (ie as BMD increases strength increased more in 30 mg/kg vs other groups).
- There was no indication of an adverse effect of AMG treatment on bone quality or integrity. All bone strength parameters were positively affected by AMG treatment, at least after 12 months of treatment, and correlated significantly with densitometric measures. However, bone strength measurements in the current study were carried out after the 12-month treatment period only. Based on the marked decrease of endocortical resorption and the increase in cortical porosity during the initial weeks of treatment, not yet accompanied by significant endocortical and/or periosteal bone deposition, there may be a transient period of cortical bone mechanical vulnerability. However, data from the 6-month monkey Study 118025, in which meta- and diaphyseal distal radius and tibia were evaluated in more detail, allayed this concern at least to some extent. Mechanical strength may also be correlated to other aspects of bone quality that were not evaluated in the animal studies.

Histomorphometry

Cancellous bone of ilium (Wks 13 and 27), vertebrae and femoral neck (Wk 52)

- AMG caused increases in Tb.Th (with increase in Tb.Sp), BV/TV and BFR (bone formation rate), and an increase in formative and decrease in quiescent surface throughout treatment at all (2 or) 3 bone sites. Increases in osteoid and osteoblast surfaces were only apparent in Wk 13. The structural changes were due to the expected stimulatory effect of AMG on trabecular bone formation, particularly in the first few weeks/months of treatment.
- Eroded surface in AMG treated animals decreased from 20% to 16-10% (3-30 mg/kg), in Wk 13 (ilium) only. This decrease was not seen at 6 months or later. At 52 weeks, there was a slight increase in ES/BS in vertebral bone.
- AMG increased Wall Thickness in Wk 13 and 27 (Ilium) and Wk 52 (FN, vert) indicating positive bone balance at the BRU level.
- AcF was increased (ie stimulation of remodeling), significantly in Wk 13.
- At the human equivalent dose of 3 mg/kg, significant effects included changes in trabecular parameters (e.g. Tb.Th), BV/TV, BFR and formative/quiescent surface ratio.

Cortical bone of rib and femur diaphysis

- AMG markedly increased BFR rates at endosteal surfaces, Haversian and periosteal surfaces, particularly in Wk 13 (rib). Also, endocortical formative perimeter was increased and quiescent perimeter decreased at Wk 13 (rib).
- AMG markedly suppressed % endocortical eroded surface in rib (Wk 13>27>52) and in femoral diaphysis (Wk 52) to below OVX control as well as sham levels (from 9 to <0.3% in femur). Rib data suggested that the effect subsided with time, but it was still pronounced in femur at study end. The data suggest a large suppression of the osteoclasts at that surface. The concomitant increase in Ec.BFR and the changes in

formative/quiescent perimeter fractions indicated modeling rather than remodeling at the endocortical surface.

- AMG increased total and cortical area%, and cortical width of rib and femoral diaphysis, mainly at 30 mg/kg at Wk 52. Medullary area% was decreased in both bones, especially at later time points, consistent with pQCT data.
- At the Haversian surface, H.BFR was also enhanced at Wk 13 and 27 (rib) and Po.Ar % (porosity) was slightly increased in Wk 27 and 52 (rib and femur). Rib and femur medullary areas were both decreased by AMG treatment at 3 and 30 mg/kg, similar to that in the tibia according to pQCT.
- The slight AMG-induced increase in endosteal circumference in distal radius (pQCT data) suggests that resorption outperformed formation at this bone surface. There were no morphometric data for the distal radius to provide information.
- Bone width (TtTAr) at 3 mg/kg was only slightly affected at Wk 52, while periosteal BFR was markedly increased particularly early in treatment. This suggested a parallel increase in resorption at the periosteal surface. However, based on the actual BFR numbers and the relatively small total periosteal skeletal surface this resorption probably did not contribute much to the increase in average skeletal resorption.
- The histomorphometry data showed that the increases in resorption markers (NTx, CTx) were probably due, for the most part, to an early enhancement of Haversian/intracortical bone resorption, possibly with some contribution of periosteal resorption, and of trabecular resorption at later time points. The increase in resorption was likely to be PTH-dependent.
- The increases in formation markers were due to enhanced bone formation at trabecular (mostly) and cortical bone surfaces. The latter probably included mostly Haversian and endocortical surfaces but also periosteal surfaces. This is based on control BFR/BS values at different cortical surfaces (endocortical > Haversian > periosteal) and probable relative sizes of these surfaces (Haversian > endocortical and periosteal). The dynamics of the bone (re)modeling changes upon treatment with AMG785 are further discussed in the Pharmacology section and the Integrated Summary and Evaluation of this BLA review.

Comparison of bone effects in human and OVX monkey

- The following table summarizes the changes in BMD and Fx incidence in postmenopausal women (Study 20060337), and changes in BMD and strength in OVX monkeys at 3 mg/kg (Study 107903 and 118025).

	Human			OVX monkey	
	Change in BMD from baseline (Treated vs placebo)	**Change in Fx incidence**		**Effect on BMD (Treated vs OVX control)**	**Effect on strength (parameter AUC) (Treated vs OVX control**
Lumbar Spine	+12.7%	-73%		+18% (DXA, Wk52)	1.8x
Total Hip	+5.8%	-46%		+22% (DXA, Wk52) (PF)	NE
Femoral Neck	+5.2%	NE		+26% (DXA, Wk52)	1.5x
Radius	-	-		-2% (pQCT, Wk12)* -1% (pQCT, Wk 13)**	NE
	-1.2% (DXA, Mo 6)	NE		-3% (pQCT, Wk 25)* -1% (pQCT, Wk 26)**	1.05x**
	-0.5% (DXA, Mo 12)	NE		-2% (pQCT, Wk 52)*	NE
Femur (diaphysis)	NE	NE		+6% (pQCT, Wk52)*	1.1x
Nonvertebral sites	NE	-25%		-	-

PF= proximal femur
NE = not evaluated
*Study 107903
**Study 118025

APPENDIX 2

ECAC Minutes

Executive CAC
Date of Meeting: February 14, 2017

Committee: Karen Davis Bruno, PhD, OND IO Chair
Abigail Jacobs, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Jane Sohn, PhD, DNDP, Alternate Member
Kimberly Hatfield, PhD, DBRUP, Pharm Tox Team Leader
Miyun Tsai-Turton, PhD, MS, DBRUP, Presenting Reviewer

Author of Draft: Miyun Tsai-Turton

The following information reflects a brief summary of the Committee discussion and its recommendations.

BLA #: 761062
Drug Name: Romosozumab (AMG785)
Sponsor: Amgen

Background: Romosozumab (AMG785) is a humanized murine monoclonal IgG2 antibody against sclerostin, a glycoprotein that blocks bone formation by inhibiting the Wnt/ß-catenin pathway in the osteoblast. Romosozumab is expected to increase bone formation and bone mass. The sought indication for the BLA is the treatment of postmenopausal osteoporosis. Romosozumab was evaluated in Phase III studies in postmenopausal women at a dose of 210 mg by subcutaneous injection every month (QM). The intended treatment duration is 1 year. The sponsor submitted the data from a 2-year lifetime carcinogenicity study in rats to their BLA application.

Rat Carcinogenicity Study: Romosozumab was given to Sprague Dawley rats at doses of 0 (b) (4) (b) (4), 3, 10, 50 mg/kg/week (60/sex/group) weekly via sc injection for a minimum of 91 weeks in males and 98 weeks in females. Dose selection was based on the expected pharmacologic effect in bone, clinical exposure multiples, and the lack of significant toxicity in a completed 6-month rat toxicity study. ECAC concurred with the study design (October 11, 2011).

Findings: The survival at the end of study was between 25-40% and comparable across all groups. There were non-neoplastic changes associated with the

pharmacologic effect of romosozumab administration: hyperostosis, spleen and liver (secondary extramedullary hematopoiesis), and injection site mononuclear cells infiltrate. However, there were no neoplastic changes associated with romosozumab administration. FDA statistical review showed adrenal cortical adenoma in the 10 mg/kg group; pairwise comparison p = 0.0184, i.e. < 0.05) however the incidence was within the historical control range provided by the sponsor.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee agreed that there were no drug-related neoplasms in the 2-year rat carcinogenicity study results in either males or females.

Karen Davis Bruno, PhD
Chair, Executive CAC

cc:\
/Division File, DBRUP
/Kimberly Hatfield, PhD., Pharm/Tox Team Leader, DBRUP
/Miyun Tsai-Turton, Ph.D., M.P.H., Reviewer, DBRUP
/Samantha, Bell, Project Manager, DBRUP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEMMA KUIJPERS
04/07/2017

KIMBERLY P HATFIELD
04/07/2017
I have reviewed Dr. Kuijpers' evaluation of this product and concur with her conclusions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761062
Supporting document/s:	0001
Applicant's letter date:	19 July 2016
CDER stamp date:	19 July 2016
Product:	Romosozumab (AMG 785)
Indication:	Osteoporosis
Applicant:	Amgen
Review Division:	DBRUP
Reviewer:	Laurie McLeod-Flynn, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Samantha Bell

Reference ID: 4076742

1 Executive Summary

1.1 Introduction

AMG785 (romosozumab) is an anti-sclerostin antibody that neutralizes sclerostin, a bone formation inhibitor.

1.2 Brief Discussion of Nonclinical Findings

In fertility and embryo-fetal studies in rats, romosozumab (300 mg/kg; 56-fold the proposed clinical dose) caused a slight increase in the incidence of reduced ventral processes on the sixth cervical vertebra, in the absence of other developmental delays or maternal toxicity. (This finding is sometimes considered a developmental delay in a skeletal process not found in humans.) In addition, skeletal abnormalities (including syndactyly and polydactyly), occurred in 1 litter at the high dose in one embryo-fetal study (300 mg/kg; approximately 32-fold the proposed clinical dose).

1.3 Recommendations

1.3.2 Non Clinical Recommendations

Both the incidence of reduce ventral processes and the skeletal abnormalities of syndactyly and polydactyly should be included in the label.

1.3.3 Labeling

Risk summary:

(b) (4)

Animal Data:

(b) (4)

Reference ID: 4076742

(b) (4)

2 Drug Information

2.1 Drug

Code Name: AMG 785

Pharmacologic Class: Anti-sclerostin monoclonal antibody

3 Studies Submitted

3.1 Studies Reviewed

Subcutaneous dose-range finding development study of AMG 785 in rats (Study No. 108057)

AMG: Fertility and embryo-fetal development study in the rat (Study No. 108061)

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: AMG: Fertility and embryo-fetal development study in the rat

Study no.:	108061 ((b) (4) Study No. 20005072)
Study report location:	(b) (4)
Conducting laboratory and location:	
Date of study initiation:	15 June 2012
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	AMG 785 FDP, DP Batch (Lot) Number: 0010122916, FDP Batch Number: 1033427

Key Study Findings

Once weekly subcutaneous administration of AMG 785 to male and female Sprague Dawley rats before cohabitation, through mating and implantation at dose levels of 0, 10, 60, 300 mg/kg had no effect on mortality, clinical signs, body weight, food consumption or necropsy. No effects on mating, fertility, male reproductive parameters (sperm analyses or organ weights), ovarian or uterine parameters, embryo-fetal survival or fetal body weights were observed.

At 300 mg/kg, there were 3 fetuses from 3 litters that had reduced ventral processes (which develop into the carotid tubercles) on the 6th cervical vertebrae, slightly exceeding the historical range of the test facility, which was considered to represent a developmental delay (development of the ventral processes of the cervical vertebrae proceed in an anterior to posterior direction and the ventral processes on the 7th cervical vertebrae had not started to develop at gestation day 21). No other fetal effects were observed at any dose level.

Reference ID: 4076742

Methods

Doses:	0, 10, 60, and 300 mg/kg
Frequency of dosing:	Weekly
Dose volume:	4.3 ml/kg
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	(b) (4)
Species/Strain:	Rat, Crl:CD(SD)
Number/Sex/Group:	60/sex/group (31 controls/sex/group)
Study design:	Subcutaneous injection once weekly on Study Days 1, 8, 15, 22, 29 and 36 during precohabitation, (Study Weeks 1 through 6). Weekly administration continued for males through Day 78 (Days 43, 50, 57, 64 and 71 and/or 78). For females, weekly administration continued until scheduled euthanasia on GD 21 (main study animals), GD 20 (satellite TK animals) or, if mating was not detected during the cohabitation period, 13 or 14 days after the end of the cohabitation period. During Week 4 (DS 22), blood samples were collected from all animals for determination of AMG 785 serum concentrations and anti-AMG 785 antibodies (ADA). These data were used to select animals that were suitable for further evaluation based on whether they were ADA negative or if ADA positive, had lowest signal-to-noise ratio (used to assess strength of ADA response) and/or highest AMG 785 serum concentration values. At DS 22, 37% of the females and 53% of the males had measurable anti-AMG 785 antibodies (and were eliminated), with signal-to-noise (S/N) ratio ranging from less than 10 to more than 1000. Mating was initiated at Day 41/42

Observations and Results

Mortality/ Clinical Signs

No treatment related effects were observed.

Body Weight/ Feed Consumption

No treatment related effects on body weight or food consumption were observed.

Toxicokinetics

Summary of Toxicokinetic Parameters in Pregnant Rats

Dose (mg/kg)	Gestation Day 6		Gestation Day 13		AR
	Cmax (µg/mL)	AUC0-t (day*µg/mL)	Cmax (µg/mL)	AUC0-t (day*µg/mL)	
10	69.2 (11.2)	365 (66.7)	49.1 (13.0)	198 (52.1)	0.54
60	851 (89.7)	5110 (627)	616 (82.3)	2520 (270)	0.49
300	2050 (285)	12600 (1460)	1570 (101)	7490 (682)	0.59

Note: All values presented as mean (SD).
AR: Accumulation ratio
C_{max}: Maximal concentration observed after SC administration
AUC_{0-t}: Area under the concentration time curve from 0 to 168 hours postdose
GD: Gestation Day

Summary of AMG 785 Fetal-to-Maternal Serum Concentration Ratio Following Subcutaneous Administration of 10, 60, or 300 mg/kg on Gestation Day 20

Dose (mg/kg)	Mean Fetal Concentration (ng/mL)	Mean Maternal Concentration (ng/mL)	% Ratio
10	3390	3800	89%
60	54200	68900	79%
300	114000	277000	41%

Dosing Solution Analysis

All study samples analyzed had mean concentrations within or equal to the acceptance criteria of ± 10% of their theoretical concentrations.

Necropsy

No treatment related effects were observed.

Fertility Parameters:

No treatment related effects were observed on mating, fertility, male reproductive parameters (sperm analyses or organ weights), ovarian or uterine parameters, embryo-fetal survival or fetal body weights.

Fetal alterations

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
DOSE LEVEL (MG/KG)a		0	10	60	300
LITTERS EVALUATED	N	20	18b	24c	22
LITTERS WITH LIVE FETUS(ES)	N	20	18	24	22
FETUSES EVALUATED	N	278	242	344	291
LIVE	N	278	242	343	291
DEAD	N	0	0	1d	0
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	5(25.0)	6(33.3)	9(37.5)	5(22.7)
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	7(2.5)	8(3.3)	10(2.9)	7(2.4)
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	2.6 ± 4.9	3.4 ± 6.3	3.0 ± 4.0	2.5 ± 5.0

a. Dose administration occurred once weekly from Day 1 of study through the week of euthanasia.
b. Excludes values for rats that had positive ADA results, high signal-to-noise ratio, low AMG 785 exposure and/or were arbitrarily euthanized and not assigned to the main or toxicokinetic portion of the study.
c. Excludes values for rat 6410; ADA results could not be confirmed for cohort male 6115.
d. Dead fetus was excluded from summarization and statistical analyses. This conceptus appeared normal for its developmental age.

Fetal skeletal alterations

At 300 mg/kg, there were 3 fetuses from 3 litters that had reduced ventral processes (which develop into the carotid tubercles) on the 6th cervical vertebrae, slightly exceeding the historical range of the test facility, which was considered to represent a developmental delay (development of the ventral processes of the cervical vertebrae proceed in an anterior to posterior direction and the ventral processes on the 7th cervical vertebrae had not started to develop at gestation day 21). No other fetal effects were observed at any dose level.

Fetal skeletal alterations

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
DOSE LEVEL (MG/KG)a		0	10	60	300
LITTERS EVALUATED	N	20	18b	24c	22
LITTERS WITH LIVE FETUS(ES)	N	20	18	24	22
FETUSES EVALUATED	N	145	125	177	151
LIVE	N	145	125	176	151
DEAD	N	0	0	1d	0
SKULL: MANDIBLES, FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)i	0(0.0)
SKULL: MANDIBLE, SHORT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)i	0(0.0)
SKULL: TYMPANIC RINGS, FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)i	0(0.0)
SKULL: FRONTALS, CONTAIN AN INTERFRONTAL					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)	0(0.0)	0(0.0)
SKULL: PALATE, INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)	0(0.0)	0(0.0)	0(0.0)
CERVICAL VERTEBRAE: REDUCED VENTRAL PROCESSES					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	1(4.2)	3(13.6)
FETAL INCIDENCE	N(%)	1(0.7)	0(0.0)	1(0.6)	3(2.0)
CERVICAL VERTEBRAE: CERVICAL RIB PRESENT AT 7TH CERVICAL VERTEBRA					
LITTER INCIDENCE	N(%)	1(5.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	1(0.7)	0(0.0)	1(0.6)	0(0.0)
THORACIC VERTEBRAE: CENTRUM, BIFID					
LITTER INCIDENCE	N(%)	1(5.0)	2(11.1)	2(8.3)	3(13.6)
FETAL INCIDENCE	N(%)	1(0.7)	3(2.4)g	2(1.1)	3(2.0)
CAUDAL VERTEBRAE: MISALIGNED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
RIBS: THICKENED					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)f	1(0.6)h	0(0.0)
RIBS: WAVY					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	2(8.3)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)f	2(1.1)h	0(0.0)
RIBS: SHORT					
LITTER INCIDENCE	N(%)	1(5.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	2(1.4)	1(0.8)	0(0.0)	0(0.0)
RIBS: INCOMPLETELY OSSIFIED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(4.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(0.5)	0(0.0)
RIBS: FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)g	0(0.0)	0(0.0)

STERNAL CENTRA: SUMMARIZATION					
(SUMMARIZATION OF FUSED AND ASYMMETRIC)					
LITTER INCIDENCE	N(%)	0(0.0)	2(11.1)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.6)	1(0.6)	0(0.0)
STERNAL CENTRA: FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	1(0.8)e	0(0.0)	0(0.0)
STERNAL CENTRA: ASYMMETRIC					
LITTER INCIDENCE	N(%)	0(0.0)	2(11.1)	1(4.2)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	2(1.6)e,g	1(0.6)i	0(0.0)

a. Dose administration occurred once weekly from Day 1 of study through the week of euthanasia.
b. Excludes values for rats that had positive ADA results, high signal-to-noise ratio, low AMG 785 exposure and/or were arbitrarily euthanized and not assigned to the main or toxicokinetic portion of the study.
c. Excludes values for one rat; ADA results could not be confirmed for cohort male.
d. Dead fetus was excluded from summarization and statistical analyses. Conceptus appeared normal for its developmental age.
e. Fetus had other skeletal alterations.
f. Fetus had other skeletal alterations.
g. Fetus had other skeletal alterations.
h. Fetus had other skeletal alterations.
i. Fetus had other skeletal alterations.

Fetal ossification sites

No treatment related effects were observed.

9.2 Embryonic Fetal Development

Study title: Subcutaneous dose-range finding development study of AMG 785 in rats

Study no.:	108057 ((b) (4))
Study report location:	(b) (4)
Conducting laboratory and location:	
Date of study initiation:	11 August 2008
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	AMG 785, Lot number 00089336

Key Study Findings

AMG 785 was well-tolerated in pregnant rats at doses up to 300 mg/kg, administered twice during the gestation period (GDs 6 and 13). No treatment related effects were observed on maternal or fetal parameters at any dose tested. There were no dose-dependent differences in the litter or fetal incidences of any gross external, soft tissue or skeletal alterations. Fetal ossification site averages were generally comparable among the four dose groups.

Methods

Doses:	0, 30, 100, and 300 mg/kg/day
Frequency of dosing:	Weekly, on gestation days 6 and 13
Dose volume:	4.3 ml/kg
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	(b) (4) (b) (4)
Species/Strain:	Rat, Crl:CD(SD)
Number/Sex/Group:	8
Satellite groups:	8 for toxicokinetics
Study design:	All main study rats were euthanized on GD 21, and blood samples were collected for toxicokinetic and antibody analyses. All rats assigned to toxicokinetic evaluation were euthanized on GD 19, and maternal and fetal blood samples were collected for toxicokinetic, placental transfer and antibody analyses.
Deviation from study protocol:	None significant.

Observations and Results

Mortality

All rats survived until scheduled sacrifice.

Clinical Signs

No treatment related effects were observed.

Body Weight/ Feed Consumption

No treatment related effects were observed.

Toxicokinetics

Mean toxicokinetic parameters
(provided by the sponsor in a Study Report Amendment from October 27, 2015)

Dose (mg/kg)	DG 6		DG 13	
	C_{max} (mcg/mL)	AUC_{0-168} (mg hr/mL)	C_{max} (mcg/mL)	AUC_{0-144} (mg hr/mL)
30	145	17.0	184	15.8
100	418	52.0	492	53.3
300	914	115	944	103

All toxicokinetic parameters were reported to 3 significant figures
C_{max}: maximum concentration observed after SC administration
AUC_{0-168}: area under the concentration-time curve from 0 to 168 hours postdose
AUC_{0-144}: area under the concentration-time curve from 0 to 144 hours postdose

Dosing Solution Analysis

Mean measured AMG 785 concentrations for all dose formulations were within the acceptable limits (±10% of nominal concentration), and homogeneity was acceptable (≤5% RSD) for all dose formulations.

Necropsy

No treatment related effects were observed.

Cesarean Section Data

No treatment related effects were observed on corpora lutea, implantations, litter sizes, live fetuses, sex ratio, fetal body weights, resorptions or on placentae.

Offspring

There were no dose-dependent differences in the litter or fetal incidences of any gross external, soft tissue or skeletal alterations. Fetal ossification site averages were generally comparable among the four dose groups.

One fetus in the 100 mg/kg/dose group had a thin area of skin surrounding the umbilicus. At skeletal examination, this fetus had fused arches in the 5th through 7th thoracic vertebrae, a small arch in the 8th thoracic vertebra, a bifid centrum in the 9th thoracic vertebra, unilateral ossification of the centra in the 6th and 8th thoracic vertebrae and fused ribs (right 6th and 7th, proximal to distal; 10th and 11th, medial to distal). In addition to malformations, the fetus had alterations including unilateral ossification of the centrum in several thoracic vertebrae.

There was a minor reduction in the average number of ossified caudal vertebrae in the 300 mg/kg/dose group in comparison to the vehicle control group value. The average value for ossified caudal vertebrae (6.81) was below the historical range of the Testing Facility. Despite the reduction in the average number of ossified caudal vertebrae per fetus per litter that occurred in the 300 mg/kg/dose group, this minor delay in skeletal ossification was considered unrelated to maternal treatment with AMG 785 because: 1) there was no grossly observed shortening of the length of the tail; 2) there were no associated reductions in fetal body weights; and 3) average value was within the historical range of the Testing Facility (49 studies) conducted between June 2006 and June 2008 (1062 control group litters; 7853 fetuses; litter averages were 7.58 per fetus (range 6.75 to 8.01 per study) for caudal vertebrae).

Soft tissue alterations occurred in one fetus in the 300 mg/kg/dose group, and included transposed major vessels, abnormal descent of the aorta (to the right rather than the left), a persistent truncus arteriosus, extra lung lobes (one extra on the right lobe and two extra on the left lobe), an interventricular septal defect (proximal to the semilunar valves), thickening of the heart septum and small ventricles.

Reference ID: 4076742

Summary of Fetal Alterations

DOSE GROUP		I	II	III	IV
DOSE (MG/KG/DAY)a		0 (CONTROL ARTICLE)	30	100	300
LITTERS EVALUATED	N	5	8	8	8
FETUSES EVALUATED	N	69	122	107	114
LIVE	N	69	122	107	114
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	1(20.0)	1(12.5)	2(25.0)	2(25.0)
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	1(1.4)	1(0.8)	2(1.9)	2(1.8)
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	0.2 ± 0.4	0.1 ± 0.4	0.2 ± 0.5	0.2 ± 0.5

Fetal Skeletal Alterations

DOSE GROUP		I	II	III	IV
DOSE (MG/KG/DAY)a		0 (CONTROL ARTICLE)	30	100	300
LITTERS EVALUATED	N	5	8	8	8
FETUSES EVALUATED	N	36	63	55	58
LIVE	N	36	63	55	58
THORACIC VERTEBRAE: ARCHES, FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(12.5)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(1.8)b	0(0.0)
THORACIC VERTEBRAE: ARCH, SMALL					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(12.5)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(1.8)b	0(0.0)
THORACIC VERTEBRAE: CENTRUM, BIFID					
LITTER INCIDENCE	N(%)	1(20.0)	1(12.5)	2(25.0)	1(12.5)
FETAL INCIDENCE	N(%)	1(2.8)	1(1.6)	2(3.6)b	1(1.7)
THORACIC VERTEBRAE: CENTRUM, UNILATERAL OSSIFICATION					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(12.5)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(1.8)b	0(0.0)
RIBS: FUSED					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	1(12.5)	0(0.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	1(1.8)b	0(0.0)

a. Dose administration occurred on days 6 and 13 of gestation.
b. Fetus 7823-14 had other skeletal alterations.

Fetal Ossification Sites

No treatment related effects were observed.

11 Integrated Summary and Safety Evaluation

Fertility study:

Once weekly subcutaneous administration of AMG 785 to male and female Sprague Dawley rats before cohabitation, through mating and implantation (fertility study) at dose levels of 0, 10, 60, 300 mg/kg had no effect on mortality, clinical signs, body weight, food consumption or necropsy. No effects on mating, fertility, male reproductive parameters (sperm analyses or organ weights), ovarian or uterine parameters, embryo-fetal survival or fetal body weights were observed.

At 300 mg/kg, there were 3 fetuses from 3 litters that had reduced ventral processes (which develop into the carotid tubercles) on the 6th cervical vertebrae, slightly exceeding the historical range of the test facility, which was considered to represent a

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developmental delay (development of the ventral processes of the cervical vertebrae proceed in an anterior to posterior direction and the ventral processes on the 7th cervical vertebrae had not started to develop at gestation day 21). No other fetal effects were observed at any dose level.

The doses examined in this study (10, 60, 300 mg/kg) represent exposure multiples of 1.5X, 19X and 56X the proposed clinical dose of 210 mg (Human AUC = 12888 µg*h/mL; Report 119384A).

Dose ranging study:

AMG 785 was well-tolerated in pregnant rats at doses up to 300 mg/kg, administered twice during the gestation period (GDs 6 and 13). No treatment related effects were observed on maternal or fetal parameters at any dose tested. There were no dose-dependent differences in the litter or fetal incidences of any gross external, soft tissue or skeletal alterations. Fetal ossification site averages were generally comparable among the four dose groups.

One fetus in the 100 mg/kg/dose group had a thin area of skin surrounding the umbilicus. At skeletal examination, this fetus had fused arches in the 5th through 7th thoracic vertebrae, a small arch in the 8th thoracic vertebra, a bifid centrum in the 9th thoracic vertebra, unilateral ossification of the centra in the 6th and 8th thoracic vertebrae and fused ribs (right 6th and 7th, proximal to distal; 10th and 11th, medial to distal). In addition to malformations, the fetus had alterations including unilateral ossification of the centrum in several thoracic vertebrae.

The doses examined in this study (30, 100, 300 mg/kg) represent exposure multiples of 4.9X, 16.5X and 32X the proposed clinical dose of 210 mg (Human AUC = 12888 µg*h/mL; Report 119384A).

Definitive embryo-fetal study: (Study 108059; previously reviewed by Dr. Eric Andreasen – see final BLA review)

AMG 785 was well-tolerated in pregnant rats at doses up to 300 mg/kg, administered twice, subcutaneously, during the gestation period (GDs 6 and 13). No treatment related effects were observed on maternal parameters at any dose tested. At 0, 30, 100, and 300 mg/kg, the litter incidence of malformations or variations was 5 (21.7%), 5 (26.3%), 10 (41.7%) and 9 (40.9%), respectively.

Seven fetuses from one litter in the 300 mg/kg dose group had **extra digits** (polydactyly) on the fore- and/or hindpaws and six of these fetuses also had **fused digits** (syndactyly).

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One to 3 fetuses from the same litter at 300 mg/kg also had incompletely ossified phalanges, misaligned metacarpals, large ulnae, misaligned metatarsals and large tibias, irregularly shaped metacarpals, broad ribs, and irregularly shaped ilia.

Irregular shaping of the arch in the 6th cervical vertebra was also observed in 4 to 5 fetuses from 4 litters in the 100 and 300 mg/kg group. The incidence of litters and fetuses with **irregular shaped 6th vertebrae** at 100 (litters 17%; fetuses 2%) and 300 mg/kg (litters 18%; fetuses 3%) was greater than the historical control range (litters 0-12.5%; fetuses 0-1.7%) for the testing facility and should be considered AMG 785 related.

The doses examined in this study (30, 100, 300 mg/kg) represent exposure multiples of 4.9X, 16.5X and 32X the proposed clinical dose of 210 mg (Human AUC = 12888 µg*h/mL; Report 119384A), based on animal PK from dose range finding Study 108057.

Integrated analysis:

In the definitive embryo-fetal study, at 300 mg/kg (32-fold higher than the proposed clinical dose based on AUC), **extra digits** on the fore- and/or hindpaws (polydactyly; 7 fetuses in one litter) and **fused digits** (syndactyly; six fetuses in one litter) were observed. Also observed in 1-3 fetuses of this same litter were incompletely ossified phalanges, misaligned metacarpals, large ulnae, misaligned metatarsals and large tibias, irregularly shaped metacarpals, broad ribs, and irregularly shaped ilia. No related digital alterations were observed in the dose ranging study or in the fertility study.

Adverse vertebral findings were observed across the multiple studies. In the definitive embryo-fetal study, **irregularly shaped 6th vertebrae** were observed in 4 to 5 fetuses from 4 litters in the 100 and 300 mg/kg groups (16.5 and 32-fold higher than the proposed clinical dose). The incidence of litters and fetuses with **irregular shaped 6th vertebrae** at 100 (litters 17%; fetuses 2%) and 300 mg/kg (litters 18%; fetuses 3%) was greater than the historical control range (litters 0-12.5%; fetuses 0-1.7%) for the testing facility. Variations of vertebrae were also observed at 100 mg/kg in one fetus in the dose ranging study; the fetus had fused arches in the 5th through 7th thoracic vertebrae, a small arch in the 8th thoracic vertebra, a bifid centrum in the 9th thoracic vertebra, unilateral ossification of the centra in the 6th and 8th thoracic vertebrae and fused ribs (right 6th and 7th, proximal to distal; 10th and 11th, medial to distal) and unilateral ossification of the centrum in several thoracic vertebrae. In the fertility study at 300 mg/kg (56-fold higher than the proposed clinical dose), 3 fetuses from 3 litters had reduced ventral processes (which develop into the carotid tubercles) on the 6th cervical vertebrae, slightly exceeding the historical range of the test facility. Although this variation is often considered to represent a developmental delay (development of the ventral processes of the cervical vertebrae proceed in an anterior to posterior direction and the ventral processes on the 7th cervical vertebrae have not started to develop at gestation day 21), this interpretation should be made with caution in the absence of any generalized developmental delay and in the absence of toxicity. These effects are

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estimated to occur at approximately ≥16.5-fold the proposed clinical exposure, with a no adverse effect level at approximately 1.5-5-fold the proposed dose.

It is recommended that both types of effect be described in the animal data section of the pregnancy label, as follows:

Risk summary:

(b) (4)



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/s/

LAURIE L MCLEOD FLYNN
03/29/2017

KIMBERLY P HATFIELD
03/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	BLA 761062
Supporting document/s:	SD1
Applicant's letter date:	07/19/2016
CDER stamp date:	07/19/2016
Product:	Romosozumab (AMG785)
Indication:	Osteoporosis
Applicant:	Amgen
Review Division:	DBRUP
Reviewer:	Miyun Tsai-Turton, PhD, MS
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Samantha Bell

Reference ID: 4075261

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1 Executive Summary

1.1 Introduction

Romosozumab (AMG785) is a humanized murine monoclonal IgG2 antibody against sclerostin, a glycoprotein that blocks bone formation by inhibiting the Wnt/ß-catenin pathway in the osteoblast. Romosozumab is expected to increase bone formation and bone mass. The sought indication for the BLA is the treatment of postmenopausal osteoporosis. Romosozumab was evaluated in Phase III studies in postmenopausal women at a dose of 210 mg by subcutaneous injection every month (QM). The intended treatment duration is 1 year.

1.2 Brief Discussion of Nonclinical Findings

In a pre- and post-natal study in rats, romosozumab caused transient decreases in food intake during the first two weeks of dosing at ≥ 60 mg/kg, increases in incidence of sparse hair coat at 300 mg/kg in F0 generation females, and slight but significant changes in bone mass or cortical geometry in F1 generation male and/or female pups at ≥ 10 mg/kg. No skeletal abnormalities in the C6 cervical vertebrae were observed in the F1 generation pups at any dose, such as those observed in the fertility and embryofetal development study.

2 Drug Information

2.1 Drug

Code Name: AMG 785
Pharmacologic Class: Anti-sclerostin monoclonal antibody

3 Studies Submitted

3.1 Studies Reviewed

Study No 108062 – PPND Study
AMG 785: Pre- and Postnatal development study in the Sprague-Dawley rat

9 Reproductive and Developmental Toxicology

9.3 Prenatal and Postnatal Development

Study title: AMG785: Pre- and Postnatal Development Study in the Sprague Dawley Rat

Study no.:	108062
Study report location:	Amgen Inc (Thousand Oaks, CA)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	06/27/2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AMG785, Lot 0010191791, 100%

Key Study Findings

- Subcutaneous administration of AMG 785 at doses of 0, 10, 60, and 300 mg/kg/week was given to female Sprague Dawley rats beginning 6 weeks before cohabitation and continuing weekly through the gestation and lactation periods.
- In the F0 generation females, there were no unscheduled deaths or macroscopic observations, and there were no effects on body weights or body weight gain at any dose level. AMG 785

transiently reduced food intake during the first two weeks of dosing at ≥ 60 mg/kg and increased the incidence of sparse hair coat at 300 mg/kg, during the premating, gestation and lactation periods. AMG 785 administration did not result in any effects on mating, fertility, or natural delivery parameters. There were no effects on any litter parameters, including pup viability or pup body weights during the pre-weaning period.

- In the F1 generation pups, there were no effects on femur length or microscopic changes in bone on Day 21 postpartum. Slight, but significant changes were noted in bone mass or cortical geometry in males and/or females at ≥10 mg/kg. There were no skeletal abnormalities in the C6 cervical vertebrae at any dose. There were also no AMG 785-related effects on survival, growth, sexual maturation, behavioral endpoints, mating and fertility, male reproductive organ weights or ovarian and uterine parameters.

Methods

Doses: 0, 10, 60, 300 mg/kg
Frequency of dosing: Once weekly
Dose volume: 4.3 ml/kg
Route of administration: Subcutaneous route
Formulation/Vehicle: A52SuT Placebo (b) (4) (b) (4)
Species/Strain: CD Sprague Dawley
Number/Sex/Group: 25/sex/group
Satellite groups: n/a
Study design: Females were treated with AMG785 or control article by subcutaneous injection once weekly on Study Days (DS) 1, 8, 15, 22, 29, and 36 during pre-cohabitation, cohabitation, gestation, and/or lactation periods. At Week 6 (Study Day 36), blood samples were collected to determine AMG785 serum concentration and anti-drug antibodies. The number of females retained on study after exclusion based on ADA data and were pregnant was 23, 24, 25, and 24 in the 0, 10, 60, and 300 mg/kg/day groups, respectively. Various endpoints were examined from F0 generation females to F1 generation pups.
Deviation from study protocol: Yes but they did not interfere with the study findings.

Table 1 Study No 108062: PPND Study Design.

Experimental Design

Group No.	Test Material	Dose Level (mg/kg)	Concentration (mg/mL)	Dose Volume (mL/kg)	No. Rats Assigned to Study (Group Size from Premating to Late Gestation)	Maximum No. of Rats Culled Prior to Expected Delivery	Target Group Size (Delivery to Scheduled Euthanasia)
1	Control Article	0	0	4.3	25	NA	25
2	AMG 785	10	2.3	4.3	50	25	25
3	AMG 785	60	14.0	4.3	50	25	25
4	AMG 785	300	70.0	4.3	50	25	25

NA = not applicable

Observations and Results

F_0 Dams

Survival: All F0 generation rats survived to scheduled euthanasia.

Clinical signs:

- At 300 mg/kg, AMG 785-related clinical signs of an increase in sparse hair coat (total and/or on the limbs) was

observed during the premating, gestation, and lactation periods (2 of 23 litters). At 10 and 60 mg/kg, there were no AMG 785-related clinical signs.

Body weight:

- There were no AMG 785-related effects on maternal body weights or maternal body weight gain in the F0 generation females **(Figure 1)**.

Feed consumption:

- At ≥ 60 mg/kg, AMG 785 transiently decreased mean absolute food consumption during the premating period for the intervals of DS 1 to 8 (91% and 90% of controls, respectively) and DS 8 to 15 (93% of controls) compared to controls. Thereafter, mean food consumption at ≥60 mg/kg was similar to controls. At 10 mg/kg, there were no AMG 785-related effects on mean food intake **(Figure 2)**.

Mating and fertility:

- There were no AMG 785-related effects on days needed for mating (2.2 to 2.7 days), mating index (100%) or fertility index (92.0% to 100.0%) in the F0 generation rats at any dose **(Table 2)**.

Delivery and litter observation:

- Pregnancy was confirmed in 23, 24, 25, and 24 rats in the 0, 10, 60, and 300 mg/kg dose groups, respectively. All pregnant rats delivered their litters, with the exception of one female in the 300 mg/kg dose group. There were no AMG 785-related effects on estrous cycling, natural delivery parameter in the F0 generation females **(Table 3)**.
- There were no AMG785-related effects on any litter parameter at any dose **(Tables 4 and 5)**.

Necropsy observation:

- There were no AMG 785-related macroscopic observations in the F0 generation females.

Toxicokinetics:

Maternal Rats **(Table 6)**

- On Study Day 36, overall mean AMG 785 serum concentrations in maternal rats were 30400, 685000, and 1780000 ng/mL at 10, 60, and 300 mg/kg, respectively.
- Plasma concentrations of AMG 785 for F0 generations females on Lactation Day (LD) 21 were separated into two groups: 1) for animals for which the last dose was administered between LD 14 and LD 16 (those animals received 12 doses) and 2) those that received the last dose between LD 18 and LD 20 (those animals received 13 doses).
  - For animals receiving 12 doses, mean AMG 785 serum concentrations collected at 5 to 7 days post the 12th dose were 9510, 120000, and 539000 ng/mL at 10, 60, and 300 mg/kg, respectively.
  - For animal receiving 13 doses, mean AMG 785 serum concentrations collected at 1 or 2 days post the 13th dose were 61500, 396000, and 1610000 ng/mL at 10, 60, and 300 mg/kg, respectively.

F1 Generation Pups **(Table 6)**

- On Day 21 postpartum, mean AMG 785 serum concentrations increased with increasing maternal dose

	from 10 to 300 mg/kg. ▪ There was no difference in mean AMG 785 serum concentrations between male and female pups. ▪ For mothers receiving 12 doses, F1 generation pups had mean AMG 785 serum concentrations, collected at 5 to 7 days post the 12th maternal dose, of 1610, 266000, and 963000 ng/mL at 10, 60, and 300 mg/kg, respectively. ▪ For mothers receiving 13 doses, F1 generation pups had mean AMG 785 serum concentrations, collected at 1 or 2 days post the 13th maternal dose, of 449, 171000, and 680000 ng/mL at 10, 60, and 300 mg/kg, respectively.
Dosing Solution Analysis	▪ All study samples that were analyzed had mean concentrations that were within or equal to the acceptance criteria of ± 10% (individual values within or equal to ± 10%) of their theoretical concentrations.
Other: ADAs	▪ On DS 36, after 6 weekly doses of AMG 785, the percentage of ADA positive females was 18% at 10 mg/kg, 30% at 60 mg/kg, and 56% at 300 mg/kg. In all dose groups, the signal to noise ratio (S/N) ranged from less than 2 to more than 1000. ▪ Of the animals retained on study following culling prior to the estimated day of natural delivery, all animals at 10 and 60 mg/kg were negative for anti-AMG 785 antibodies and 12% (3/25) of the animals at 300 mg/kg were positive for anti-AMG 785 antibodies with low S/N ratios (less than 2.0) indicating a weak ADA response **(Table 7)**. ▪ Weekly AMG 785 administration of each female continued until euthanasia on Lactation Day (LD) 21. On LD 21, 1 animal at 10 mg/kg, 1 at 60 mg/kg, and 5 at 300 mg/kg were positive for anti-AMG 785 antibodies. All these animals showed a weak antibody response with S/N values less than 5 **(Table 7)**. ▪ In 60 and 300 mg/kg dose groups, circulating AMG 785 exceeded assay limits and therefore may have interfered in the assay and prevented the detection of binding anti-AMG 785 antibodies.

Reference ID: 4075261

Figure 1 Study No 108062: F0 Generation Female Rat Body Weight

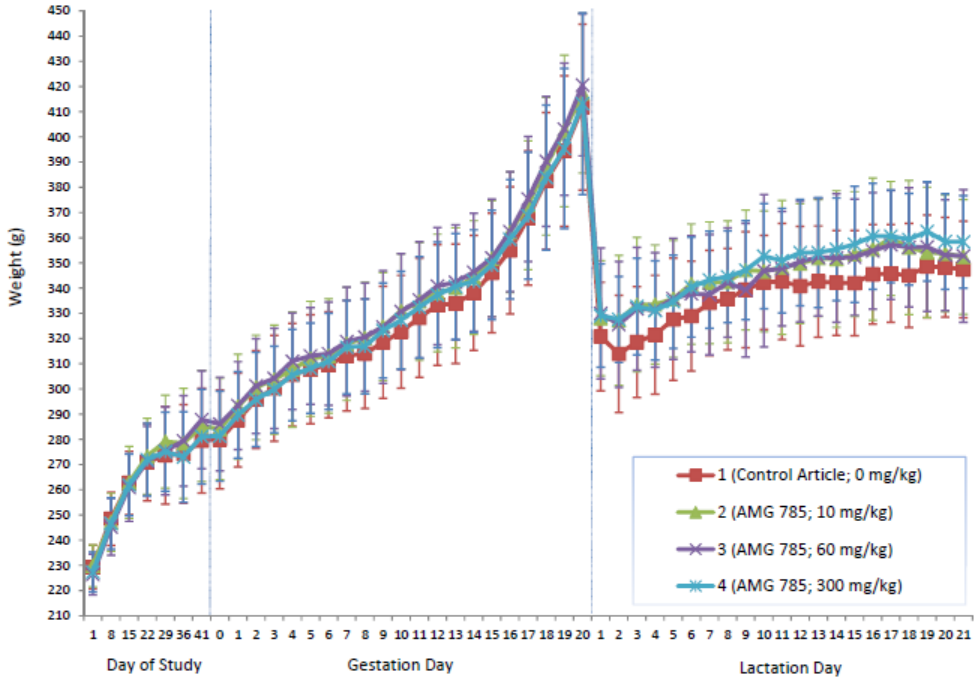


Figure 2 Study No 108062: F0 Generation Female Rat Food Consumption

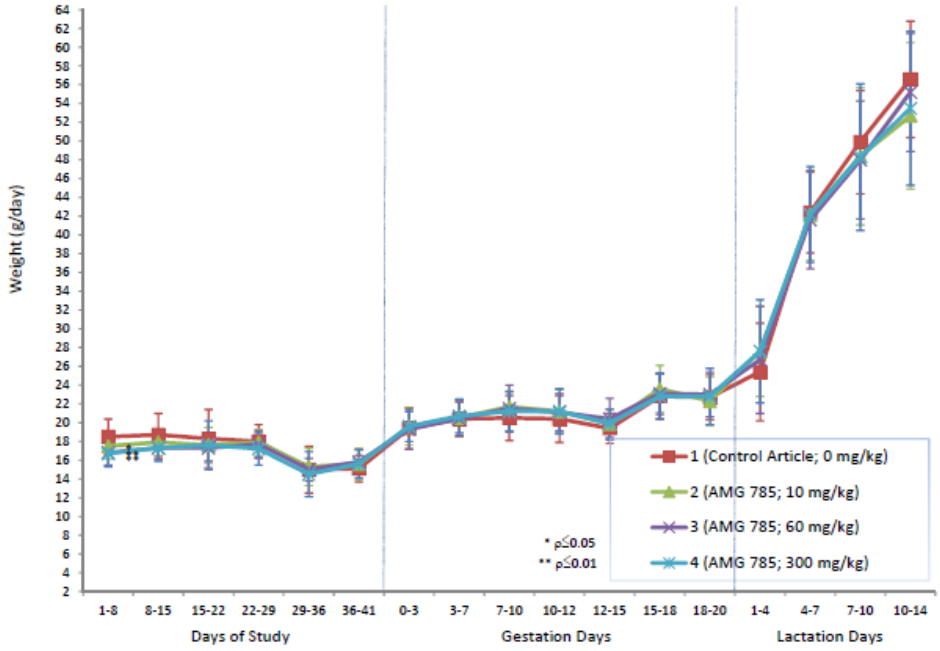


Table 2 Study No 108062: F0 generation Female Rats Mating & Fertility.

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
DOSE LEVEL (MG/KG)b		0	10	60	300
RATS IN COHABITATION	N	25	25	25	25
DAYS IN COHABITATION c	MEAN±S.D.	2.3 ± 1.3	2.7 ± 1.2	2.2 ± 1.2	2.7 ± 1.3
RATS THAT MATED	N(%)	25(100.0)	25(100.0)	25(100.0)	25(100.0)
FERTILITY INDEX d	N/N	23/ 25	24/ 25	25/ 25	24/ 25
	(%)	(92.0)	(96.0)	(100.0)	(96.0)
RATS WITH CONFIRMED MATING DATES	N	25	25	25	25
MATED BY MALE e					
DAYS 1-7	N(%)	25(100.0)	25(100.0)	25(100.0)	25(100.0)
RATS PREGNANT/RATS IN COHABITATION	N/N	23/ 25	24/ 25	25/ 25	24/ 25
	(%)	(92.0)	(96.0)	(100.0)	(96.0)

a. Includes only rats that were selected for delivery assessments.
b. Dose administration occurred once weekly from Day 1 of study through euthanasia.
c. Restricted to rats with a confirmed mating date and rats that did not mate.
d. Number of pregnancies/number of rats that mated.
e. Restricted to rats with a confirmed mating date.

Table 3 Study No 108062: F0 generation Female Rats Natural Delivery Observations.

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
DOSE LEVEL (MG/KG)b		0	10	60	300
RATS TESTED	N	25	25	25	25
PREGNANT	N(%)	23(92.0)	24(96.0)	25(100.0)	24(96.0)
DELIVERED A LITTER	N(%)	23(100.0)	24(100.0)	25(100.0)	23(95.8)
DURATION OF GESTATION c	MEAN±S.D.	22.4 ± 0.6	22.6 ± 0.5	22.3 ± 0.5	22.5 ± 0.5
IMPLANTATION SITES	N	331	344	357	314
PER DELIVERED LITTER	MEAN±S.D.	14.4 ± 3.3	14.3 ± 3.2	14.3 ± 1.8	13.6 ± 2.9
DAMS WITH STILLBORN PUPS	N(%)	2(8.7)	2(8.3)	2(8.0)	2(8.7)
DAMS WITH NO LIVEBORN PUPS	N	0(0.0)	0(0.0)	0(0.0)	0(0.0)
GESTATION INDEX d	%	100.0	100.0	100.0	95.8
	N/N	23/ 23	24/ 24	25/ 25	23/ 24
DAMS WITH ALL PUPS DYING DAYS 1-4 POSTPARTUM	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH ALL PUPS DYING DAYS 5-21 POSTPARTUM	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

a. Includes only rats that were selected for delivery assessments.
b. Dose administration occurred once weekly from Day 1 of study through euthanasia.
c. Calculated (in days) as the time elapsed between confirmed mating (arbitrarily defined as Gestation Day 0) and the day the first pup was delivered.
d. Number of rats with live offspring/number of pregnant rats.

Table 4 Study No 108062: F1 generation Litter Observations.

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
DOSE LEVEL (MG/KG)b		0	10	60	300
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	23	24	25	23
PUPS DELIVERED (TOTAL)	N	314	321	337	292
	MEAN±S.D.	13.6 ± 3.3	13.4 ± 3.3	13.5 ± 2.0	12.7 ± 3.3
LIVEBORN	MEAN±S.D.	13.5 ± 3.3	13.3 ± 3.3	13.4 ± 2.0	12.6 ± 3.3
	N(%)	311(99.0)	319(99.4)	335(99.4)	290(99.3)
STILLBORN	MEAN±S.D.	0.1 ± 0.4	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3
	N(%)	3(1.0)	2(0.6)	2(0.6)	2(0.7)
CULLED	N	88	83	82	68
INADVERTENTLY EUTHANIZED	N	0	0	0	1
FOSTERED	N	9	0	0	8
PUPS FOUND DEAD OR PRESUMED CANNIBALIZED					
DAY 1	N/N(%)	1/311(0.3)	2/319(0.6)	2/335(0.6)	1/290(0.3)
DAYS 2- 4	N/N(%)	1/310(0.3)	2/317(0.6)	1/333(0.3)	3/289(1.0)
DAYS 5- 7	N/N(%)	0/230(0.0)	0/232(0.0)	1/250(0.4)	0/225(0.0)
DAYS 8-14	N/N(%)	1/230(0.4)	2/232(0.9)	1/249(0.4)	0/225(0.0)
DAYS 15-18	N/N(%)	0/229(0.0)	0/230(0.0)	0/248(0.0)	0/225(0.0)
DAYS 19-21	N/N(%)	0/229(0.0)	0/230(0.0)	0/248(0.0)	0/225(0.0)
VIABILITY INDEX c	%	99.4	98.7	99.1	98.6
	N/N	309/311	315/319	332/335	286/290
LACTATION INDEX d	%	99.6	99.1	99.2	100.0
	N/N	229/230	230/232	248/250	225/225

DAY(S) = DAY(S) POSTPARTUM
a. Includes only rats that were selected for delivery assessments.
b. Dose administration occurred once weekly from Day 1 of study through euthanasia.
c. Number of live pups on Day 4 (preculling) postpartum/number of liveborn pups on Day 1 postpartum.
d. Number of live pups on Day 21 (weaning) postpartum/number of live pups on Day 4 (postculling) postpartum.

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
DOSE LEVEL (MG/KG)b		0	10	60	300
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	23	24	25	23
SURVIVING PUPS/LITTER c					
DAY 1 d	MEAN±S.D.	13.5 ± 3.3	13.3 ± 3.3	13.4 ± 2.0	12.6 ± 3.3
DAY 4 PRECULLING	MEAN±S.D.	13.4 ± 3.3	13.1 ± 3.3	13.3 ± 1.9	12.4 ± 3.3
DAY 4 POSTCULLING	MEAN±S.D.	10.0 ± 0.0	9.7 ± 1.6	10.0 ± 0.0	9.8 ± 0.8
DAY 7	MEAN±S.D.	10.0 ± 0.0	9.7 ± 1.6	10.0 ± 0.2	9.8 ± 0.8
DAY 14	MEAN±S.D.	10.0 ± 0.2	9.6 ± 1.6	9.9 ± 0.3	9.8 ± 0.8
DAY 18	MEAN±S.D.	10.0 ± 0.2	9.6 ± 1.6	9.9 ± 0.3	9.8 ± 0.8
DAY 21	MEAN±S.D.	10.0 ± 0.2	9.6 ± 1.6	9.9 ± 0.3	9.8 ± 0.8
PERCENT MALE PUPS PER NUMBER OF PUPS SEXED					
DAY 1 d	MEAN±S.D.	51.4 ± 17.3	49.0 ± 15.3	47.8 ± 12.0	47.2 ± 16.1
DAY 4 PRECULLING	MEAN±S.D.	51.5 ± 17.3	49.0 ± 15.3	47.6 ± 11.8	46.7 ± 16.1
DAY 4 POSTCULLING	MEAN±S.D.	49.1 ± 7.3	48.8 ± 11.5	49.6 ± 5.4	50.0 ± 7.2
DAY 7	MEAN±S.D.	49.1 ± 7.3	48.8 ± 11.5	49.8 ± 5.5	50.0 ± 7.2
DAY 14	MEAN±S.D.	48.9 ± 7.4	48.2 ± 11.9	50.0 ± 5.6	50.0 ± 7.2
DAY 18	MEAN±S.D.	48.9 ± 7.4	48.2 ± 11.9	50.0 ± 5.6	50.0 ± 7.2
DAY 21	MEAN±S.D.	48.9 ± 7.4	48.2 ± 11.9	50.0 ± 5.6	50.0 ± 7.2
LIVE LITTER SIZE AT WEIGHING					
DAY 1	MEAN±S.D.	13.5 ± 3.3	13.2 ± 3.2	13.3 ± 2.0	12.6 ± 3.3
DAY 4 PRECULLING	MEAN±S.D.	13.4 ± 3.3	13.1 ± 3.3	13.3 ± 1.9	12.4 ± 3.3
DAY 4 POSTCULLING	MEAN±S.D.	10.0 ± 0.0	9.7 ± 1.6	10.0 ± 0.0	9.8 ± 0.8
DAY 7	MEAN±S.D.	10.0 ± 0.0	9.7 ± 1.6	10.0 ± 0.2	9.8 ± 0.8
DAY 14	MEAN±S.D.	10.0 ± 0.2	9.6 ± 1.6	9.9 ± 0.3	9.8 ± 0.8
DAY 18	MEAN±S.D.	10.0 ± 0.2	9.6 ± 1.6	9.9 ± 0.3	9.8 ± 0.8
DAY 21	MEAN±S.D.	10.0 ± 0.2	9.6 ± 1.6	9.9 ± 0.3	9.8 ± 0.8

DAY = DAY POSTPARTUM
a. Includes only rats that were selected for delivery assessments.
b. Dose administration occurred once weekly from Day 1 of study through euthanasia.
c. Average number of live pups per litter, including litters with no surviving pups.
d. Includes liveborn pups.

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
DOSE LEVEL (MG/KG)b		0	10	60	300
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	23	24	25	23
PUP WEIGHT/LITTER (GRAMS)					
DAY 1	MEAN±S.D.	6.5 ± 0.8	6.7 ± 0.7	6.5 ± 0.5	6.7 ± 0.5
DAY 4 PRECULLING	MEAN±S.D.	9.0 ± 1.2	9.2 ± 1.4	9.1 ± 0.8	9.4 ± 0.9
DAY 4 POSTCULLING	MEAN±S.D.	9.0 ± 0.9	9.3 ± 1.4	9.2 ± 0.8	9.5 ± 0.8
DAY 7	MEAN±S.D.	14.5 ± 1.8	15.1 ± 2.0	14.9 ± 1.3	14.9 ± 1.6
DAY 14	MEAN±S.D.	29.3 ± 3.4	29.4 ± 3.3	28.4 ± 2.3	28.1 ± 3.3
DAY 18	MEAN±S.D.	36.0 ± 4.3	36.6 ± 3.8	35.5 ± 2.6	34.9 ± 3.8
DAY 21	MEAN±S.D.	41.8 ± 5.0	43.9 ± 4.6	41.9 ± 3.7	42.1 ± 4.8

DAY = DAY POSTPARTUM
a. Includes only rats that were selected for delivery assessments.
b. Dose administration occurred once weekly from Day 1 of study through euthanasia.

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
DOSE LEVEL (MG/KG)b		0	10	60	300
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	23	24	25	23
MALE PUP WEIGHT/LITTER (GRAMS)					
DAY 1	MEAN±S.D.	6.5 ± 0.5 [22]c	6.8 ± 0.6 [23]d	6.7 ± 0.5	6.9 ± 0.5 [22]e
DAY 4 PRECULLING	MEAN±S.D.	9.1 ± 1.0 [22]c	9.3 ± 0.9 [23]d	9.4 ± 0.8	9.7 ± 1.0 [22]e
DAY 4 POSTCULLING	MEAN±S.D.	9.2 ± 0.9	9.4 ± 0.9 [23]d	9.4 ± 0.8	9.7 ± 0.9
DAY 7	MEAN±S.D.	14.8 ± 1.8	15.1 ± 1.3 [23]d	15.3 ± 1.3	15.3 ± 1.6
DAY 14	MEAN±S.D.	29.9 ± 3.4	29.6 ± 1.8 [23]d	28.8 ± 2.3	28.7 ± 3.4
DAY 18	MEAN±S.D.	36.7 ± 4.4	36.9 ± 2.4 [23]d	36.2 ± 2.6	35.7 ± 4.0
DAY 21	MEAN±S.D.	42.5 ± 4.9	44.1 ± 3.5 [23]d	42.6 ± 3.7	43.0 ± 5.0
FEMALE PUP WEIGHT/LITTER (GRAMS)					
DAY 1	MEAN±S.D.	6.3 ± 0.9	6.5 ± 0.7	6.3 ± 0.5	6.5 ± 0.5
DAY 4 PRECULLING	MEAN±S.D.	8.8 ± 1.4	9.0 ± 1.4	8.9 ± 0.8	9.1 ± 0.9
DAY 4 POSTCULLING	MEAN±S.D.	8.9 ± 1.2	9.1 ± 1.4	9.0 ± 0.8	9.2 ± 0.9
DAY 7	MEAN±S.D.	14.1 ± 1.9	14.7 ± 2.1	14.5 ± 1.3	14.5 ± 1.5
DAY 14	MEAN±S.D.	28.7 ± 3.5	28.8 ± 3.4	27.8 ± 2.4	27.5 ± 3.2
DAY 18	MEAN±S.D.	35.3 ± 4.3	35.8 ± 4.0	34.8 ± 2.6	34.0 ± 3.5
DAY 21	MEAN±S.D.	41.1 ± 5.2	43.0 ± 4.8	41.1 ± 3.8	41.2 ± 4.6

DAY = DAY POSTPARTUM
[ ] = NUMBER OF VALUES AVERAGED
a. Includes only rats that were selected for delivery assessments.
b. Dose administration occurred once weekly from Day 1 of study through euthanasia.
c. Litter 204 had no male pups present in the litter on this day.
d. Litter 250 had no male pups present in the litter on this day.
e. Litter 344 had no male pups present in the litter on this day.

Table 5 Study No 108062: F1 Generation Pups (Birth to LD21)

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
LITTERS EXAMINED a	N	23	24	25	23
PURPLE OR BLACK DISCOLORATION b	N/N	48/15	61/12	94/17	67/11
COLD TO TOUCH	N/N	8/4	12/3	0/0	2/2
NECK OR BACK, SPARSE HAIR COAT	N/N	0/0	0/0	0/0	93/2
SCAB c	N/N	14/5	3/2	1/1	1/1
LIMB/PAW/DIGIT, SWOLLEN	N/N	1/1	9/1	7/1	1/1
DRY/FLAKING/WRINKLED/PEELING SKIN d	N/N	5/1	24/1	0/0	3/1
NOT NESTING	N/N	4/1	1/1	0/0	1/1
UNGROOMED COAT	N/N	0/0	2/1	0/0	10/1
RIGHT FORELIMB, RIGHT AXILLA AND CHEST, MISSING SKIN	N/N	0/0	0/0	0/0	1/1
RIGHT/LEFT INGUINAL AREA(S) OR NOSE, LACERATION	N/N	3/1	1/1	1/1	0/0
PORTION OF TAIL, MISSING	N/N	0/0	0/0	6/1	0/0
RIGHT HINDLIMB, LOWER MIDLINE OR RIGHT INGUINAL AREA, ULCERATION	N/N	4/2	1/1	0/0	0/0
WHOLE BODY, PALE	N/N	0/0	4/1	0/0	0/0
DEHYDRATION, MILD	N/N	126/1	0/0	0/0	0/0

N/N = TOTAL FREQUENCY (DAYS X PUPS)/LITTER WITH OBSERVATIONS
a. Tabulation restricted to adverse observations; all other pups appeared normal.
b. Includes nose, mouth, head, ears, neck, chest, right axilla, lower midline, back, limb(s)/paw(s) and/or tail.
c. Includes mouth, neck, lower midline, limb(s)/paw(s), back and/or right/left inguinal area(s).
d. Includes neck, chest, right/left axilla, lower midline, limb(s)/paw(s), back and/or tail.

Table 6 Study No 108062: TK Parameters F0 Generation & F1 Generation Pups.

Mean (SD) Serum Concentrations and Pup:Maternal Ratio Estimate of AMG 785 After Weekly Subcutaneous Administration of 10, 60, or 300 mg/kg for Animals Retained on Study

Dose (mg/kg)	Number of Doses	Days Post-dose[a]	F_0 Females			Male Pups			Female Pups		
			N	mean (SD) (ng/mL) Day 36	mean (SD) (ng/mL) LD 21	N	mean (SD) (ng/mL) LD 21	Pup/Maternal LD 21	N	mean (SD) (ng/mL) LD 21	Pup/Maternal LD 21
10	12	5-7	10	33,600 (8480)	9510 (4900)	10	1610 (1580)	0.194 (0.213)	10	1610 (1050)	0.209 (0.178)
	13	1-2	14	28,100 (11800)	61,500 (16,800)	13	484 (471)	0.00876 (0.00864)	14	416 (331)	0.00653 (0.00493)
60	12	5-7	16	707,000 (144000)	120,000 (44,900)	16	251,000 (105,000)	2.28 (1.33)	16	280,000 (139,000)	2.41 (1.12)
	13	1-2	9	647,000 (173000)	396,000 (117,000)	9	157000 (44,500)	0.462 (0.261)	9	185,000 (68,500)	0.557 (0.440)
300	12	5-7	8	1,530,000 (526,000)	539,000 (111,000)	7	915,000 (286,000)	1.84 (0.861)	7	1,010,000 (345,000)	2.01 (1.00)
	13	1-2	15	1,910,000 (596,000)	1,610,000 (252,000)	15	639,000 (290,000)	0.398 (0.171)	15	721,000 (260,000)	0.451 (0.166)

[a] Days between last dose and blood collection on LD 21.

Table 7 Study No 108062: ADA Positive F0 Generation.

Summary of Anti-AMG 785 Antibody Positive F0 Generation Animals

Dose (mg/kg)	Time Point	
	Week 6 (Study Day 36)	Euthanasia (Lactation Day 21)
0	NA	NA
10	0% (0/25)	4% (1/24)*
60	0% (0/25)	4% (1/25)
300	12% (3/25)	22% (5/23)*
All AMG 785-dosed animals	4% (3/75)	10% (7/72)

Note: This table reflects only animals retained on study prior to delivery. Results are expressed as incidence and percentage. Incidence is the number positive/number evaluated.
*Serum samples were not available for animals that were not pregnant or did not deliver.
% (number of animals ADA+/number of animals evaluated)

F_1 Generation

Survival:
- No AMG785-related death during the Postweaning period.
  - All F1 generation female rats survived to scheduled euthanasia.
  - There were two unscheduled necropsies (1 male at 10 mg/kg due to injury and 1 male at 300 mg/kg found dead with no macroscopic findings).

Clinical signs:
- There were no AMG 785-related clinical signs or macroscopic observations in the F1 generation pups during the preweaning **(Table 8)** or postweaning period at any dose.

Body weight:
- There were no effects on body weight.

Feed consumption:
- There were no effects on food consumption.

Physical development:
- There were no AMG785-related effects on sexual maturation (the age of balano-preputal separation in males or the age of vaginal patency in females) at any dose level **(Table 9)**.

Neurological assessment:
- There were no AMG 785-related behavioral endpoints including learning and memory **(Table 10)** and motor activity in the F1 generation rats.

Reproduction:
- There were no AMG 785-related effects on days needed for mating (2.4 to 2.9 days), mating index (100%) or fertility index (84.0% to 96.0%) in the F1 generation rats at any dose **(Tables 11 and 12)**.
- There were no statistically significant difference between control and any AMG 785-treated group for terminal body weight and paired absolute weights for testes or epididymides. **(Table 13)**.
- There were no AMG 785-related effects on any ovarian or uterine parameter in the F1 generation rats. Pregnancy was confirmed in 21 (84.0%), 22 (88.0%), 23 (92.0%), and 24 (96.0%) F1 generation females in the 0, 10, 60, and 300 mg/kg/day dose groups, respectively. **(Table 14)**.

Other: bone
- Pre-weaning (at Day 21 postpartum)

- There were no AMG785-related effects on the femur length **(Table 15)**.
- There were minimally decreased total and cortical/subcortical BMC and BMD (-8 to -9%) at 60 and 300 mg/kg, generally attaining statistical significance **(Table 16)**.
- There were also minimally decreased total area (-4 to -8%), periosteal circumference (-2 to -4%), endosteal circumference (-5 to -6%) and CSMI (-2 to -10%) at all doses in males that were associated with trends for increases in cortical thickness (+3 to +7%) **(Table 17)**. No changes were noted in females.
- No AMG785-related microscopic changes in the femur of F1 generation pups at any dose.
- There were no skeletal abnormalities in the C6 cervical vertebrae in the F1 generation pups at any dose **(Table 18). Note:** This finding was observed in the fertility and embryo-fetal development study.

Table 8 Study No 108062: F1 Generation Pups Mortality & Necropsy

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
LITTERS EVALUATED	N	23	24	25	23
UNSCHEDULED DEATHS (DAYS 1 TO 21 POSTPARTUM)					
PUPS STILLBORN	N	3	2	2	2
PUPS FOUND DEAD	N	2	5	4	4
TOTAL UNSCHEDULED DEATHS NECROPSIED a	N	5	3	5	1
STILLBORN	N	3	1	2	1
FOUND DEAD	N	2	2	3	0
APPEARED NORMAL	N(%)	2(40.0)	2(66.7)	4(80.0)	1(100.0)
NO MILK IN STOMACH b	N(%)	2(100.0)	1(50.0)	0(0.0)	0(0.0)
BOTTOM JAW: ABSENT	N(%)	1(20.0)	0(0.0)	0(0.0)	0(0.0)
HEAD OR MOUTH: PURPLE DISCOLORATION	N(%)	0(0.0)	1(33.3)	1(20.0)	0(0.0)

a. Restricted to pups in which complete necropsies were performed. Complete necropsies were not performed on pups in which autolysis or cannibalization precluded full evaluation.
b. Analysis restricted to pups found dead and necropsied.

Table 9 Study No 108062: F1 Generation Pups Sexual Maturation

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
MALE RATS	N	25	25	25	25
INCLUDED IN ANALYSES	N	24a	24a	25	24a
PREPUTIAL SEPARATION b	MEAN±S.D.	45.2 ± 1.5	45.3 ± 1.8	46.0 ± 1.4	45.6 ± 2.0
BODY WEIGHT AT SEPARATION (G)c	MEAN±S.D.	232.6 ± 19.4	236.8 ± 20.1	243.7 ± 19.1	239.4 ± 20.8
FEMALE RATS	N	25	25	25	25
VAGINAL PATENCY d	MEAN±S.D.	33.3 ± 1.6	33.8 ± 3.0	32.9 ± 1.8	32.8 ± 2.1
BODY WEIGHT AT VAGINAL PATENCY (G)e	MEAN±S.D.	107.3 ± 9.1	108.5 ± 12.5	107.0 ± 12.8	105.7 ± 12.0

a. Excludes values for rats that the exact day of maturity could not be determined.
b. Average day postpartum that the prepuce was observed to be separated.
c. Average body weight on day prepuce was first observed to be separated.
d. Average day postpartum that the vagina was observed to be patent.
e. Average body weight on day vagina was first observed to be patent.

Table 10 Study No 108062: F1 Generation Pups Passive Avoidance

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
MALE RATS					
SESSION 1a	N	22	23	25	22
TRIALS TO CRITERION	MEAN±S.D.	4.6 ± 1.2	4.6 ± 1.4	4.7 ± 2.2	5.0 ± 2.6
LATENCY TRIAL 1b	MEAN±S.D.	8.4 ± 4.6	10.0 ± 9.2	10.3 ± 7.4	7.5 ± 4.1
LATENCY TRIAL 2b	MEAN±S.D.	34.6 ± 16.2	30.7 ± 19.2	36.9 ± 21.6	33.4 ± 24.0
FAILED TO LEARN c	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.5)
SESSION 2a	N	22	22d	25	20d
TRIALS TO CRITERION	MEAN±S.D.	2.6 ± 0.7	3.6 ± 2.6*	3.5 ± 2.9	3.0 ± 0.8
LATENCY TRIAL 1b	MEAN±S.D.	38.8 ± 25.3	22.5 ± 23.3	37.5 ± 23.3	26.4 ± 22.6
FEMALE RATS					
SESSION 1a	N	23	24	25	23
TRIALS TO CRITERION	MEAN±S.D.	4.5 ± 1.4	4.7 ± 1.8	4.9 ± 1.4	4.6 ± 1.4
LATENCY TRIAL 1b	MEAN±S.D.	11.1 ± 12.3	8.7 ± 6.2	7.5 ± 6.4	7.9 ± 5.6
LATENCY TRIAL 2b	MEAN±S.D.	33.7 ± 19.3	36.1 ± 19.2	27.0 ± 18.6	37.6 ± 19.9
FAILED TO LEARN c	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SESSION 2a	N	23	24	25	23
TRIALS TO CRITERION	MEAN±S.D.	3.6 ± 1.5	3.8 ± 2.7	2.9 ± 0.9	2.8 ± 0.8
LATENCY TRIAL 1b	MEAN±S.D.	25.3 ± 21.5	22.4 ± 18.6	26.7 ± 23.5	35.7 ± 22.3

a. Sessions 1 (Learning Phase) and 2 (Retention Phase) of testing were separated by a one-week interval.
b. The latency was recorded in seconds.
c. Number of rats that did not meet the criterion in Session 1 (Learning Phase); Session 2 (Retention Phase) values for these rats were excluded from summarization and statistical analyses.
d. Excludes values for rats that were found dead or euthanized due to adverse clinical observations.
* Significantly different from the control group value ($p \leq 0.05$).

Table 11 Study No 108062: F1 Generation Pups Mating & Fertility (Males)

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
RATS IN COHABITATION	N	25	24a	25	24a
DAYS IN COHABITATION b	MEAN±S.D.	2.4 ± 0.9	2.9 ± 1.4	2.8 ± 1.1	2.9 ± 2.0
RATS THAT MATED	N(%)	25(100.0)	24(100.0)	25(100.0)	24(100.0)
FERTILITY INDEX c	N/N	21/ 25	21/ 24	23/ 25	23/ 24
	(%)	(84.0)	(87.5)	(92.0)	(95.8)
RATS WITH CONFIRMED MATING DATES	N	25	24	25	24
MATED WITH FEMALE d					
DAYS 1-7	N(%)	25(100.0)	24(100.0)	25(100.0)	22(91.7)
DAYS 8-14	N(%)	0(0.0)	0(0.0)	0(0.0)	2(8.3)
RATS PREGNANT/RATS IN COHABITATION	N/N	21/ 25	21/ 24	23/ 25	23/ 24
	(%)	(84.0)	(87.5)	(92.0)	(95.8)

a. Excludes values for rats that were found dead or euthanized due to adverse clinical observations.
b. Restricted to females with a confirmed mating date and females that did not mate.
c. Number of pregnancies/number of females that mated.
d. Restricted to females with a confirmed mating date.

Table 12 Study No 108062: F1 Generation Pups Mating & Fertility (Females)

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
RATS EVALUATED	N	25	25	25	25
STAGES IN INTERVAL	MEAN±S.D	3.1 ± 0.6	3.2 ± 0.8	3.1 ± 0.8	3.2 ± 0.9
RATS EXHIBITING PERSISTENT ESTRUS	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
RATS EXHIBITING PERSISTENT DIESTRUS	N(%)	1(4.0)	0(0.0)	1(4.0)	1(4.0)

PERSISTENT ESTRUS IS DEFINED AS 6 OR MORE DAYS OF ESTRUS.
PERSISTENT DIESTRUS IS DEFINED AS 6 OR MORE DAYS OF DIESTRUS.

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
FEMALES IN COHABITATION	N	25	25	25	25
DAYS IN COHABITATION a	MEAN±S.D.	2.4 ± 0.9	2.9 ± 1.4	2.8 ± 1.1	2.9 ± 2.0
FEMALES THAT MATED	N(%)	25(100.0)	25(100.0)	25(100.0)	25(100.0)
FERTILITY INDEX b	N/N	21/ 25	22/ 25	23/ 25	24/ 25
	(%)	(84.0)	(88.0)	(92.0)	(96.0)
FEMALES WITH CONFIRMED MATING DATES	N	25	25	25	25
MATED BY FIRST MALE c					
DAYS 1-7	N(%)	25(100.0)	25(100.0)	25(100.0)	23(92.0)
DAYS 8-14	N(%)	0(0.0)	0(0.0)	0(0.0)	2(8.0)
MATED BY SECOND MALE c	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
FEMALES PREGNANT/FEMALES IN COHABITATION	N/N	21/ 25	22/ 25	23/ 25	24/ 25
	(%)	(84.0)	(88.0)	(92.0)	(96.0)

a. Restricted to females with a confirmed mating date and females that did not mate.
b. Number of pregnancies/number of females that mated.
c. Restricted to females with a confirmed mating date.

Table 13 Study No 108062: F1 Generation Pups Reproductive Organ Weights (Males)

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
RATS TESTED	N	25	24	25	24
TERMINAL BODY WEIGHT	MEAN±S.D.	566.4 ± 37.8	578.0 ± 48.8	584.4 ± 46.9	592.1 ± 46.3
EPIDIDYMIDES PAIRED	MEAN±S.D.	1.60 ± 0.14	1.54 ± 0.14	1.54 ± 0.16	1.52 ± 0.15
EPIDIDYMIDES PAIRED (%)	MEAN±S.D.	0.282 ± 0.023	0.268 ± 0.030	0.265 ± 0.034*	0.257 ± 0.025**
TESTES PAIRED	MEAN±S.D.	3.75 ± 0.42	3.71 ± 0.27	3.78 ± 0.24	3.68 ± 0.33
TESTES PAIRED (%)	MEAN±S.D.	0.663 ± 0.078	0.643 ± 0.051	0.650 ± 0.066	0.623 ± 0.064

ALL WEIGHTS WERE RECORDED IN GRAMS (G). RATIOS (%) = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.
* Significantly different from the control group value (p≤0.05).
** Significantly different from the control group value (p≤0.01).

Table 14 Study No 108062: F1 Generation Pups Ovarian and Uterine Contents (Females)

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
RATS TESTED	N	25	25	25	25
PREGNANT	N(%)	21(84.0)	22(88.0)	23(92.0)	24(96.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 13 OF GESTATION	N	21	22	23	24
CORPORA LUTEA	MEAN±S.D.	16.5 ± 2.1	15.9 ± 1.6	16.4 ± 1.8	16.5 ± 1.6
IMPLANTATIONS	MEAN±S.D.	16.1 ± 1.8	15.4 ± 1.9	15.8 ± 2.2	16.2 ± 1.5
% PREIMPLANTATION LOSS	MEAN±S.D.	2.1 ± 4.0	2.9 ± 6.6	3.5 ± 8.0	1.6 ± 4.2
LITTER SIZES	MEAN±S.D.	15.2 ± 2.2	14.7 ± 2.1	15.4 ± 2.3	15.2 ± 2.2
VIABLE EMBRYOS	N	320	323	354	365
	MEAN±S.D.	15.2 ± 2.2	14.7 ± 2.1	15.4 ± 2.3	15.2 ± 2.2
NONVIABLE EMBRYOS	N	19	17	10	25
	MEAN±S.D.	0.9 ± 1.4	0.8 ± 1.0	0.4 ± 0.7	1.0 ± 1.3
% POSTIMPLANTATION LOSS	MEAN±S.D.	5.6 ± 8.8	5.1 ± 6.8	2.8 ± 4.2	6.6 ± 8.3
DAMS WITH NONVIABLE EMBRYOS	N(%)	10(47.6)	12(54.5)	8(34.8)	13(54.2)
DAMS WITH ALL NONVIABLE EMBRYOS	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE FETUSES	N(%)	21(100.0)	22(100.0)	23(100.0)	24(100.0)
PLACENTAE APPEARED NORMAL	N(%)	21(100.0)	22(100.0)	23(100.0)	24(100.0)

% PREIMPLANTATION LOSS = [(NUMBER OF CORPORA LUTEA - NUMBER OF IMPLANTATIONS) / NUMBER OF CORPORA LUTEA] x 100
% POSTIMPLANTATION LOSS = [(NUMBER OF IMPLANTATIONS - NUMBER OF LIVE FETUSES) / NUMBER OF IMPLANTATIONS] x 100

Table 15 Study No 108062: F1 Generation Pups Right Femur Length

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
RIGHT FEMUR LENGTH (MM)					
ALL PUPS	MEAN±S.D.	16.53 ± 0.79 [44]	16.64 ± 0.56 [47]	16.41 ± 0.74 [50]	16.62 ± 0.72 [44]
MALE PUPS	MEAN±S.D.	16.53 ± 0.84 [22]	16.64 ± 0.68 [23]a	16.55 ± 0.76 [25]	16.76 ± 0.66 [22]
FEMALE PUPS	MEAN±S.D.	16.53 ± 0.75 [22]	16.64 ± 0.44 [24]	16.27 ± 0.71 [25]	16.48 ± 0.76 [22]

[ ] = NUMBER OF VALUES AVERAGED
a. No male pups were present in litter 250.

Table 16 Study No 108062: F1 Generation Right Femur Metaphysis

Males

			Group	Control	AMG 785 10 mg/kg		AMG 785 60 mg/kg		AMG 785 300 mg/kg	
		Units		Value	Value	% vs. C	Value	% vs. C	Value	% vs. C
Total	Area	mm^2	Mean	9.81	9.38	-4.3	9.30	-5.1	9.53	-2.8
			SD	1.17	0.77		1.02		0.86	
	BMC	mg/mm	Mean	2.66	2.72	2.1	**2.35**	-11.6	2.45	-8.1
			SD	0.48	0.34		0.38		0.35	
	BMD	mg/cm^3	Mean	270.51	**289.81**	7.1	**252.31**	-6.7	255.94	-5.4
			SD	25.83	27.17		21.83		18.66	
Trabecular	BMC	mg/mm	Mean	0.97	1.04	7.7	0.89	-7.7	0.93	-4.3
			SD	0.28	0.18		0.20		0.17	
	BMD	mg/cm^3	Mean	177.59	**201.67**	13.6	172.55	-2.8	175.60	-1.1
			SD	37.72	30.29		23.46		20.64	
Cortical/ Subcortical	BMC	mg/mm	Mean	1.70	1.68	-1.1	**1.46**	-13.9	**1.52**	-10.3
			SD	0.22	0.17		0.19		0.19	
	BMD	mg/cm^3	Mean	384.27	397.75	3.5	**350.56**	-8.8	**354.45**	-7.8
			SD	19.65	29.69		26.55		19.44	

C = Control.
Values in bold are significantly different from Control.

Females

			Group	Control	AMG 785 10 mg/kg		AMG 785 60 mg/kg		AMG 785 300 mg/kg	
		Units		Value	Value	% vs C	Value	% vs C	Value	% vs C
Total	Area	mm^2	Mean	9.28	9.01	-2.9	8.86	-4.5	9.06	-2.3
			SD	0.85	0.86		1.10		0.96	
	BMC	mg/mm	Mean	2.61	2.66	2.1	**2.25**	-13.7	2.36	-9.6
			SD	0.31	0.35		0.40		0.32	
	BMD	mg/cm^3	Mean	281.06	295.57	5.2	**253.90**	-9.7	**259.76**	-7.6
			SD	19.09	24.69		31.40		15.16	
Trabecular	BMC	mg/mm	Mean	0.98	1.03	5.4	**0.82**	-15.9	0.90	-7.7
			SD	0.17	0.19		0.25		0.18	
	BMD	mg/cm^3	Mean	190.35	207.34	8.9	**167.77**	-11.9	179.46	-5.7
			SD	24.07	29.48		41.47		20.60	
Cortical/ Subcortical	BMC	mg/mm	Mean	1.63	1.63	0.2	**1.43**	-12.4	**1.46**	-10.7
			SD	0.15	0.18		0.18		0.15	
	BMD	mg/cm^3	Mean	392.34	403.53	2.9	**359.32**	-8.4	**358.00**	-8.8
			SD	19.92	25.66		28.52		20.70	

C = Control.
Values in bold are significantly different from Control.

Table 17 Study No 108062: F1 Generation Right Femur Diaphysis

Males

		Units	Group	Control	AMG 785 10 mg/kg		AMG 785 60 mg/kg		AMG 785 300 mg/kg	
				Value	Value	% vs. C	Value	% vs. C	Value	% vs. C
Total Area		mm^2	Mean	4.16	3.83	-8.0	3.88	-6.7	3.98	-4.3
			SD	0.43	0.31		0.24		0.34	
Cortical	Area	mm^2	Mean	1.59	1.58	-1.1	1.58	-1.1	1.65	3.7
			SD	0.13	0.13		0.12		0.15	
	BMC	mg/mm	Mean	0.99	0.98	-1.6	0.98	-0.7	1.06	6.7
			SD	0.09	0.11		0.10		0.14	
	BMD	mg/cm^3	Mean	621.97	618.32	-0.6	622.88	0.1	637.06	2.4
			SD	19.52	26.64		27.82		30.88	
	Thickness	mm	Mean	0.25	0.26	4.2	0.26	3.3	**0.27**	7.4
			SD	0.01	0.02		0.02		0.02	
Periosteal Circumference		mm	Mean	7.22	**6.93**	-4.0	**6.98**	-3.3	7.06	-2.1
			SD	0.36	0.27		0.21		0.30	
Endosteal Circumference		mm	Mean	5.67	**5.31**	-6.3	**5.37**	-5.2	**5.40**	-4.7
			SD	0.37	0.32		0.27		0.34	
CSMI		mm^4	Mean	0.77	**0.70**	-10.1	0.71	-8.7	0.76	-2.1
			SD	0.14	0.09		0.07		0.12	

C = Control
Values in bold are significantly different from Control

Females

		Units	Group	Control	AMG 785 10 mg/kg		AMG 785 60 mg/kg		AMG 785 300 mg/kg	
				Value	Value	% vs. C	Value	% vs. C	Value	% vs. C
Total Area		mm^2	Mean	3.91	3.84	-1.7	3.88	-0.6	3.84	-1.8
			SD	0.32	0.37		0.37		0.33	
Cortical	Area	mm^2	Mean	1.56	1.56	-0.2	1.57	0.8	1.63	4.4
			SD	0.11	0.15		0.13		0.14	
	BMC	mg/mm	Mean	0.98	0.97	-1.4	0.99	0.4	1.04	5.9
			SD	0.09	0.12		0.11		0.11	
	BMD	mg/cm^3	Mean	628.11	618.85	-1.5	625.03	-0.5	636.90	1.4
			SD	21.64	27.87		29.83		22.35	
	Thickness	mm	Mean	0.25	0.25	0.9	0.26	1.7	0.27	6.2
			SD	0.02	0.02		0.02		0.02	
Periosteal Circumference		mm	Mean	7.00	6.94	-0.9	6.98	-0.3	6.94	-0.9
			SD	0.28	0.33		0.33		0.30	
Endosteal Circumference		mm	Mean	5.42	5.34	-1.4	5.37	-0.9	5.26	-3.0
			SD	0.33	0.35		0.41		0.31	
CSMI		mm^4	Mean	0.72	0.69	-4.2	0.71	-0.4	0.73	1.5
			SD	0.10	0.12		0.11		0.11	

C = Control

Table 18 Study No 108062: F1 Generation Skeletal Evaluation

MATERNAL GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	AMG 785	AMG 785	AMG 785
MATERNAL DOSE LEVEL (MG/KG)		0	10	60	300
LITTERS EVALUATED	N	23	23	25	23
PUPS EVALUATED	N	133	133	148	130
APPEARED NORMAL					
LITTER INCIDENCE	N(%)	21(91.3)	22(95.6)	24(96.0)	22(95.6)
PUP INCIDENCE	N(%)	131(98.5)	132(99.2)	147(99.3)	129(99.2)
CERVICAL VERTEBRA, ARCH, CAROTID TUBERCLE, ELONGATED PROCESS, 6TH, LEFT					
LITTER INCIDENCE	N(%)	1(4.3)	0(0.0)	0(0.0)	0(0.0)
PUP INCIDENCE	N(%)	1(0.8)	0(0.0)	0(0.0)	0(0.0)
CERVICAL VERTEBRA, ARCH, CAROTID TUBERCLE, REDUCED, 6TH, LEFT OR RIGHT					
LITTER INCIDENCE	N(%)	1(4.3)	0(0.0)	1(4.0)	0(0.0)
PUP INCIDENCE	N(%)	1(0.8)	0(0.0)	1(0.7)	0(0.0)
CERVICAL VERTEBRA, ARCH, CAROTID TUBERCLE, MISSHAPEN, 6TH, LEFT					
LITTER INCIDENCE	N(%)	0(0.0)	1(4.3)	0(0.0)	0(0.0)
PUP INCIDENCE	N(%)	0(0.0)	1(0.8)	0(0.0)	0(0.0)
CERVICAL VERTEBRA, ARCH, CAROTID TUBERCLE, UNOSSIFIED, 6TH, RIGHT					
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(4.3)
PUP INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.8)

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/s/

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03/27/2017

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CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT

FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

P/T REVIEWER(s): Miyun M Tsai-Turton, Ph.D., M.S.
DATE: January 30, 2017

BLA: 761062
DRUG CODE#: AMG785
CAS#: 909395-70-6
DIVISION(s): Division of Bone, Reproductive, and Urologic Products (DBRUP)
DRUG NAME(s): Romosozumab

SPONSOR: Amgen
LABORATORY: (b) (4)
CARCINOGENICITY STUDY REPORT DATE: April 17, 2015

THERAPEUTIC CATEGORY: Osteoporosis in postmenopausal women

PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: Monoclonal antibody

MUTAGENIC/GENOTOXIC: In vitro and in vivo genotoxicity studies have not been conducted for romosozumab.

Reference ID: 4075258

RAT CARCINOGENICITY STUDY

STUDY SUMMARY

RAT STUDY DURATION (weeks): A minimum of 91 weeks for males and 98 weeks for females
STUDY STARTING DATE: November 07, 2011 (dosing initiated)
STUDY ENDING DATE: September 30, 2013 (in-life phase completed)
RAT STRAIN: Sprague-Dawley rats
ROUTE: Subcutaneous injection
DOSING COMMENTS: Weekly

NUMBER OF RATS: 60/sex/group

RAT DOSE LEVELS (mg/kg):

- **Vehicle control** (Group 1): 0 mg/kg/week
- **Low Dose** (Group 2): 3 mg/kg/week
- **Mid Dose** (Group 3): 10 mg/kg/week
- **High Dose** (Group 4): 50 mg/kg/week

BASIS FOR DOSES SELECTED: Doses for this study were based on the expected pharmacologic effect in bone, clinical exposure multiples, and the lack of significant toxicity in a completed 6 month rat toxicity study.

PRIOR FDA DOSE CONCURRENCE: Yes

RAT CARCINOGENICITY: Negative.

RAT TUMOR FINDINGS: **There were no AMG785-related tumor findings.**

- Macroscopically, there were AMG785-related macroscopic findings in bones (miscellaneous, calvarium femur, lumbar vertebrae L5-L6, sternum and tibia) and spleen. There was also AMG785-related thickening of the bone in males and females, in a dose dependent manner, correlating with the increase in bone mineral content (BMC) by ex vivo peripheral quantitative computed tomography (pQCT) and hyperostosis, microscopically. This effect was systemic, usually affecting all routinely collected bones. An increased incidence of spleen enlargement was noted in females at ≥ 3 mg/kg and in males at 10 mg/kg/dose, correlating with increased extramedullary hematopoiesis microscopically.

- Microscopically, there were no neoplastic changes associated with AMG785 administration. The sponsor identified two significant findings. Renal lipoma in 3/60 females at 50 mg/kg (p =0.0486 by trend test, when compared to 1/60 in concurrent control; marginally above historical control data range). Adrenal cortical adenoma in 6/60 males at 10 mg/kg (p = 0.0169 by pairwise comparisons, when compared to 0/60 in concurrent control; within historical control data

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range). Since renal lipoma was a rare tumor, it would be considered significant when the p value was ≤ 0.05. However, due to absence of pre-neoplastic lesion findings, the increased incidence in the female HD group had no toxicological significance. On the other hand, adrenal cortical adenoma was not a rare tumor, it would be considered significant when the p value was ≤ 0.01. Therefore, the increased incidence in the male MD group had no toxicological significance.

- Microscopically, there were two osteosarcomas noted in the males at 50 mg/kg, which were not statistically significant by trend test and pairwise comparison, but the incidence was 3.7%, marginally higher than the historical range of 3.33%. Long term use of PTH has been known to result in osteosarcomas, osteoma, and osteoblast hyperplasia. Due to lack of pre-neoplastic findings and other bone tumors, the sponsor considered these as spontaneous.

- FDA statistical review: tumor analysis did not show any statistically significant dose-response relationship in tumor incidence in tumor types tested in male rats. The pairwise comparison did show a statistically significant increase in incidence of adenoma cortical in MD groups compared to the control in male rats ($p=0.0184<0.05$) and a statistically significant positive dose response relationship in adenoma islet cell for pancreas in female rats ($p=0.0323<0.05$), if these tumor were considered as a rare tumor. No other statistically significant findings were noted for female rats.

- Microscopically, there were non-neoplastic changes associated with AMG785. Bones: increased incidence of hyperostosis was noted in all dose groups. Spleen: increased incidence of secondary extramedullary hematopoiesis was noted in all dose groups (male: 13/60, 38/60, 44/60, 40/54 and female: 37/60, 49/60, 57/60, 60/60 in Groups 1, 2, 3, and 4 respectively). Liver: increased incidence of secondary extramedullary hematopoiesis was noted in all dose groups (male: 5/60, 13/60, 13/60, 12/54 and female: 22/60, 25/60, 41/60, 39/60 in Groups 1, 2, 3, and 4 respectively). Injection sites: mononuclear cells infiltrate was noted in all dose groups. However, changes in bones, spleen, and liver were dose dependent, whereas changes in injection sites were not dose dependent.

RAT STUDY COMMENTS: The 104 week rat study via sc injection was conducted to assess the carcinogenic potential of AMG785. The study was terminated at Week 91 for male groups and Week 98 for female groups. The survival at the end of study was between 25-40% and comparable across all groups. There were non-neoplastic changes associated with AMG785 administration in bones (hyperostosis), spleen and liver (secondary extramedullary hematopoiesis), and injection sites (mononuclear cells infiltrate), which were all expected pharmacological effect of AMG785. However, there were no neoplastic changes associated with AMG785 administration. The sponsor identified two tumor findings that were significant (i.e. renal lipoma in 50 mg/kg females; $p = 0.0486$ by trend test, adrenal cortical adenoma in 10 mg/kg males; $p = 0.0169$ by pairwise comparison). Since renal lipoma (rare tumor) and adrenal cortical adenoma (common tumor) had no pre-neoplastic lesion findings, and there was a lack of dose

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response, they were considered of no toxicological significance. FDA statistical review showed that there was no statistically significant in tumor incidence in tumor types tested in male rats (except adenoma cortical in MD groups $p = 0.0184 < 0.05$) and female rats (except pancreatic islet cell adenoma, $p = 0.0323 < 0.05$, within the historical control provided by the sponsor). As a result, AMG785 had no carcinogenic potential in rats.

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STUDY REPORT

Study Title: AMG785: 104 week subcutaneous lifetime pharmacology study in the Sprague Dawley rat

Study no.:	107895
Study report location:	eCTD Module 4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 21, 2011 (protocol signed)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	DP Batch # 0010085638 and 0010122916, FDP Batch # 1026275 and 1033427, FDP Material # 2000961 and 2002240, purity assumed to be 100%
CAC concurrence:	Yes

Key Study Findings

- AMG785 was given to Sprague Dawley rats at 0 (vehicle), 3, 10, 50 mg/kg/week (60/sex/group) weekly via sc injection for a minimum of 91 weeks in males and 98 weeks in females. Blood samples were collected on Week 13 for TK analysis.
- There were no AMG785 treated effects on clinical observation, body weight, or food consumption.
- There was no AMG785 treated effect on survival. Prior to the end of treatment period (Week 91 males and Week 98 females), there were between 36-43 rats/sex/group died or euthanized. AMG785 had no effects on the overall survival rate or mortality.
- There were increased bone radiopacity in almost all males and females treated with AMG785 that correlated with thickening of the bone (macroscopically) and hyperostosis (microscopically). This was an expected pharmacological effect of AMG785.
- Marked dose-related increases in bone mass and geometry were noted at the femur metaphysis and diaphysis. Trabecular bone mineral density (BMD) was 4-fold and 6-fold higher in males and females, respectively, when compared to vehicle controls.
- **There were no AMG785-related neoplastic findings.**
- There were AMG785-related non-neoplastic findings. However, findings were limited to pharmacological effect of AMG785, including hyperostosis, secondary extramedullary hematopoiesis in spleen/liver, and mononuclear cell infiltrate at the injection sites.
- There were no satellite TK groups included in this study. However, at Week 13, there were minimal or no differences in mean AMG785 serum concentration among animals.
- Anti-drug antibodies (ADAs) were found in 1 female and 10 males at 50 mg/kg, 3 males at 10 mg/kg, and 18 males at 3 mg/kg. These ADA-positive animals had reduced mean serum AMG785 concentration when compared to ADA-negative

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animals (by 41%, 69%, and 86% in females and by 10%, 43%, and 53% in males at 3, 10, 50 mg/kg, respectively).

- All in all, AMG785 was not carcinogenic in Sprague-Dawley rats at doses up to 50 mg/kg/week for 91 weeks in males and 98 weeks in females. Expected pharmacological effects of AMG785 (hyperostosis in bones, secondary extramedullary hematopoiesis in spleen and liver, and mononuclear cells infiltrate at injection sites) were observed in AMG-785 treated animals.

Adequacy of Carcinogenicity Study and Appropriateness of Test Models:
Adequate (Pending ECAC concurrence)

Evaluation of Tumor Findings:
Adequate (Pending ECAC concurrence)

Methods

Doses:	0, 3, 10, and 50 mg/kg/week
Frequency of dosing:	Weekly
Dose volume:	1.43 ml/kg
Route of administration:	SC injection
Formulation/Vehicle:	AMG 785 Placebo: (b) (4) (b) (4)
Basis of dose selection:	Doses for this study were based on the expected pharmacologic effect in bone, clinical exposure multiples, and the lack of significant toxicity in a completed 6 month rat toxicity study.
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	60/sex/group
Age:	8 weeks
Animal housing:	Socially housed up to 3 animals of the same sex and same dosing group per cage
Paradigm for dietary restriction:	No
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	No
Deviation from study protocol:	Minor deviations (i.e. targeted temperature, delayed detailed examinations, size of mass) were noted but these had no impact on the outcome of the study

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Experimental Design

Group No.	No. of Animals				Test Material	Dose Level (mg/kg)	Dose Concentration (mg/mL)
	Initial allocation[b]		Final allocation				
	Male	Female	Male	Female			
1	60	60	60	60	Vehicle Control	0	0
2	150	150	60	60	AMG 785	3	2.1
3	80	80	60	60	AMG 785	10	7.0
4	80	80	54	60	AMG 785	50	35.0
5	10	10	-	-	Healthscreen[a]	-	-

The dose volume was 1.43 mL/kg.

[a] Aside from activities to assess health status, no other study data were collected on health screen animals.

[b] Following at least 12 weeks of treatment, animals with positive results for anti-drug antibodies (ADA) were removed from Groups 2, 3, and 4 without further evaluation, to reduce the group size to a target 60 animals/sex/group. When ADA positive incidence resulted in < 60/sex/group, ADA positive but non-neutralizing animals were re-instated to the study to ensure a minimum group size of 60/sex/group. Despite this addition, there were too many Group 4 males harboring neutralizing ADAs to achieve a group size of 60, consequently, this group was reduced to 54 animals. When after exclusion any group had > 60 animals/sex/group, further animals were removed by descending animal number order to reduce the group size to 60/sex/group. All animals assigned to the study were either negative for anti-AMG 785 or, if found positive, they were negative for neutralizing antibody.

Observations and Results

Survival/Mortality: *twice daily*

There were 36-43 rats per sex per group died or were euthanized prior to the end of the treatment period (Week 91 males; Week 98 females). Among these unscheduled deaths, in both control and treated animals, common findings were noted (neoplastic findings: pituitary gland adenoma, mammary gland fibroadenoma/adenocarcinoma; non-neoplastic findings: kidney nephropathy and heart cardiomyopathy).

With regards to neoplastic findings, pituitary gland adenoma (pars distalis) was the most common cause of death in both genders. AMG 785 treatment had no effect on the incidence of fatal pituitary adenoma compared to the vehicle control group. A higher incidence of fatal mammary gland adenocarcinoma was noted in females of the 10 mg/kg/dose (13.88%) and 50 mg/kg/dose (18.6%) dose group compared to the vehicle control females (5%). However, such increased incidence was not statistically significant by trend or pairwise comparison tests. Mammary gland neoplasms, including adenocarcinoma, are frequently encountered in Sprague-Dawley rats and the lack of relationship to AMG 785 treatment was further supported by the lack of a continuum of pre-neoplastic to neoplastic changes. The incidence of fibroadenoma and adenocarcinoma observed in this study are within the range reported for these two tumors in the in-house historical data.

With regards to non-neoplastic findings, common age-related renal (nephropathy) and cardiac (cardiomyopathy) degenerative changes were the most frequent non-neoplastic cause of death in this study and incidence was similar across control and AMG 785 treatment groups.

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Summary Mortality/Survival Data

Group	Males		Females	
	Mortality	Survival	Mortality	Survival
1	41/60	31.7%	40/60	33.3%
2	41/60	31.7%	40/60	33.3%
3	42/60	30%	36/60	40%
4	40/54	25.9%	43/60	28.3%

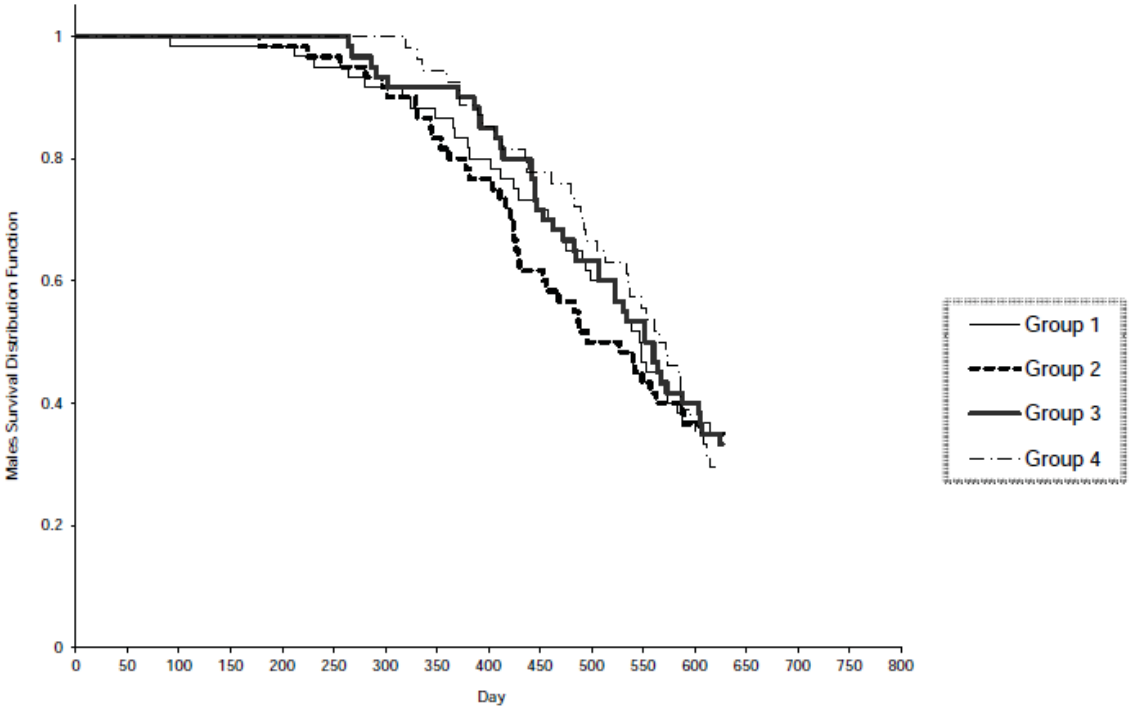
These numbers included animals that were found dead after the 91 (males) or 98 (females) week treatment period.

Summary Common Causes of Death or Morbidity

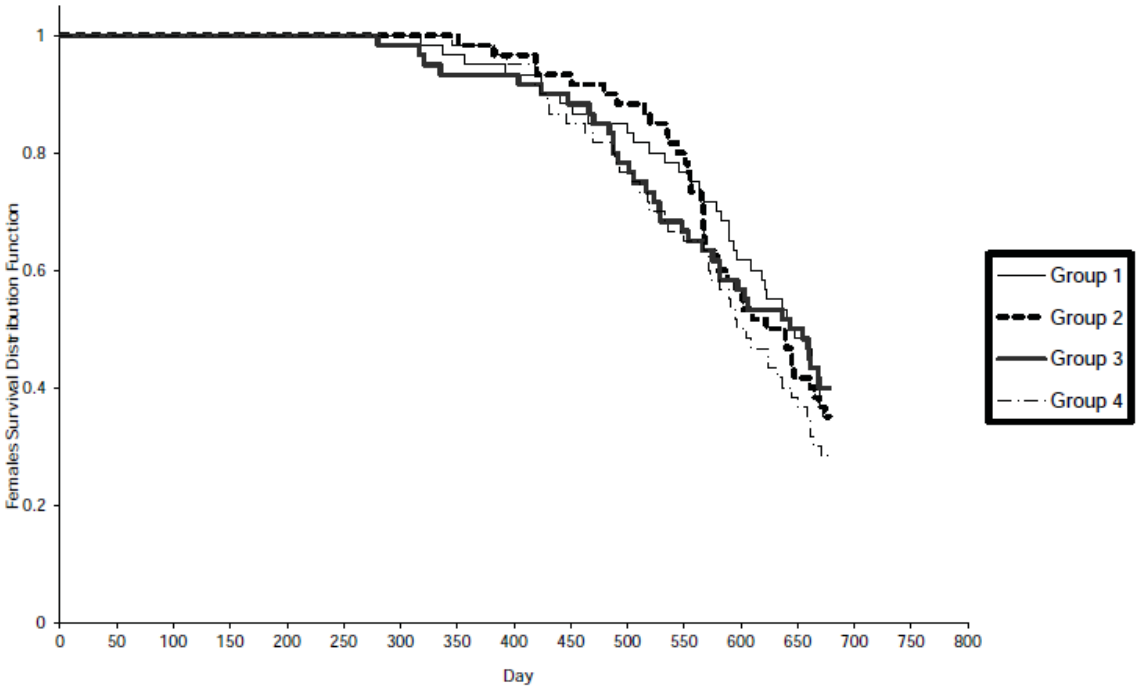
	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/dose)	0	3	10	50	0	3	10	50
Number of animals	41	41	42	40	40	40	36	43
Cause of Death								
Undetermined	13	15	16	11	2	2	0	1
Pituitary Pars Distalis Adenoma	8	7	8	10	16	20	12	19
Mammary Gland Fibroadenoma	0	0	0	1	9	7	9	7
Mammary Gland Adenocarcinoma	0	0	0	0	2	1	5	8
Kidney Nephropathy	6	2	4	3	0	0	1	2
Heart Cardiomyopathy	5	4	5	4	1	1	0	0

As shown with Kaplan-Meier estimates, weekly subcutaneous administration of AMG785 had no effects on the overall survival rates and mortality. The Log Rank test showed that there was no significance for both male and female datasets, with p-value of 0.9751 and p value of 0.5922, respectively.

Survival Curve for Each Male Group Based on Kaplan-Meier Estimates



Survival Curve for Each Female Group Based on Kaplan-Meier Estimates



Mortality Data: Statistical Results from the Overall Group Comparisons (Logrank Rest)

SURVIVAL ANALYSIS

OVERALL GROUP COMPARISONS (LOGRANK TEST)

---------- Sex=Male ----------

Considered Groups	Chi-Square	DF	Pr > Chi-Square	Significant Group Differences[1]
1, 2, 3, 4	0.2152	3	0.9751	No

---------- Sex=Female ----------

Considered Groups	Chi-Square	DF	Pr > Chi-Square	Significant Group Differences[1]
1, 2, 3, 4	1.9057	3	0.5922	No

Clinical Signs: *weekly (detailed exam)*

There were no AMG785 related clinical observations or masses. Clinical signs were generally associated with deteriorating condition of rats that died prior to scheduled sacrifice. These included abdominal distension, abnormal respiration, increased activity, cold to touch, dehydration, head tilt, generalized skin pallor, etc.

In addition, observed masses were seen in both control and treated animals (in males, 30%, 30%, 35%, and 22%, and in females, 78%, 82%, 73%, and 77% at 0, 3, 10, and 50 mg/kg/week, respectively).

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Summary of Palpable Masses

Males

Group 1 - Vehicle Control
Group 2 - AMG 785 3 mg/kg/dose
Group 3 - AMG 785 10 mg/kg/dose
Group 4 - AMG 785 50 mg/kg/dose

	Group			
Site	1	2	3	4
Number of animals per group	60	60	60	55
Number of animals with masses	18	18	21	12
Abdominal	1	3	2	3
Axillary	2	3	2	-
Cranium	1	2	3	-
Dorsal Aspect Generalized	-	1	-	-
Dorsal Cervical	1	1	-	1
Dorsal Thoracic	5	7	7	4
Hindlimb	-	1	-	1
Inguinal	-	-	3	-
Interscapular	-	-	1	-
Lower Jaw	1	-	-	-
Lumbar	-	2	3	-
Mouth	-	1	-	-
Scapular	1	1	1	1
Tail	-	2	1	-
Thoracic	-	-	-	-
Treatment Site No.01	2	-	1	-

	Group			
Site	1	2	3	4
Urogenital	4	1	2	-
Ventral Cervical	1	-	-	-
Ventral Thoracic	3	-	2	4

Summary of Palpable Masses

Females

Group 1 - Vehicle Control
Group 2 - AMG 785 3 mg/kg/dose
Group 3 - AMG 785 10 mg/kg/dose
Group 4 - AMG 785 50 mg/kg/dose

	Group			
Site	1	2	3	4
Number of animals per group	60	60	60	60
Number of animals with masses	47	49	44	46
Abdominal	15	18	13	19
Axillary	15	17	12	12
Cranium	2	-	-	1
Dorsal Cervical	3	-	-	-
Dorsal Thoracic	13	6	8	4
Hindpaw	-	-	1	-
Inguinal	15	12	14	15
Interscapular	-	-	1	-
Lumbar	2	3	-	2
Muzzle	-	1	-	-
Scapular	1	2	1	-
Tail	-	-	-	1
Urogenital	24	28	24	15
Ventral Cervical	4	5	7	6
Ventral Thoracic	26	14	14	14

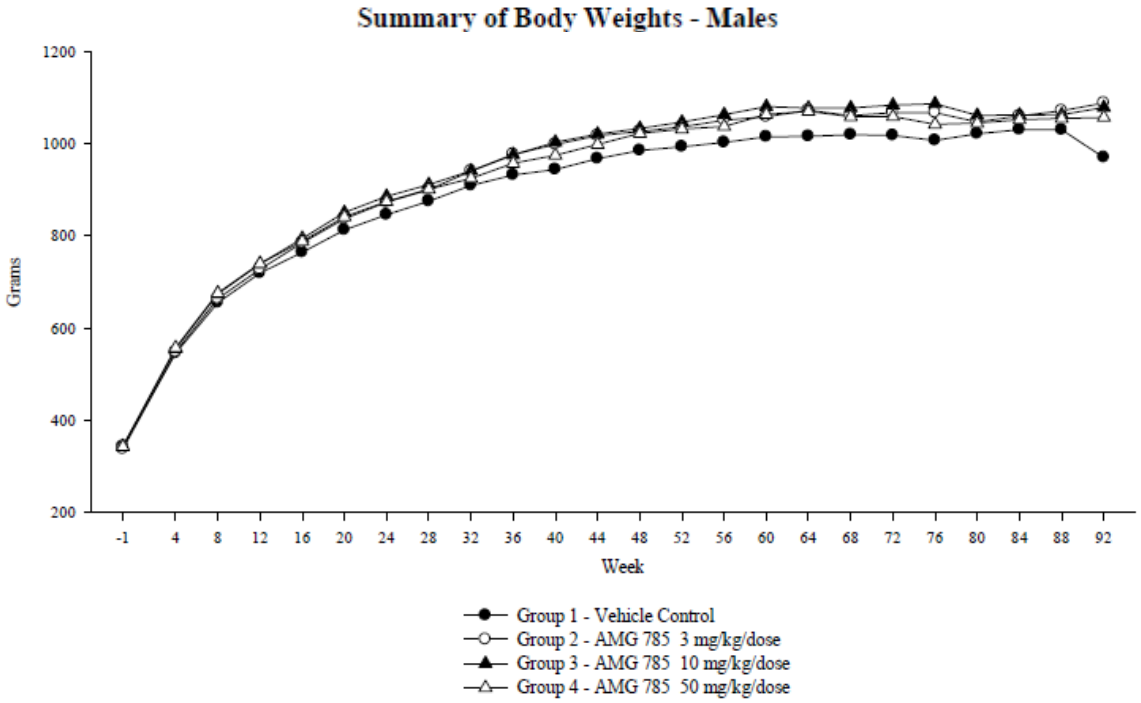
Body Weights/Food Consumption: *weekly*

There were no AMG785 related effects on mean body weight and mean food consumption during the course of the study.

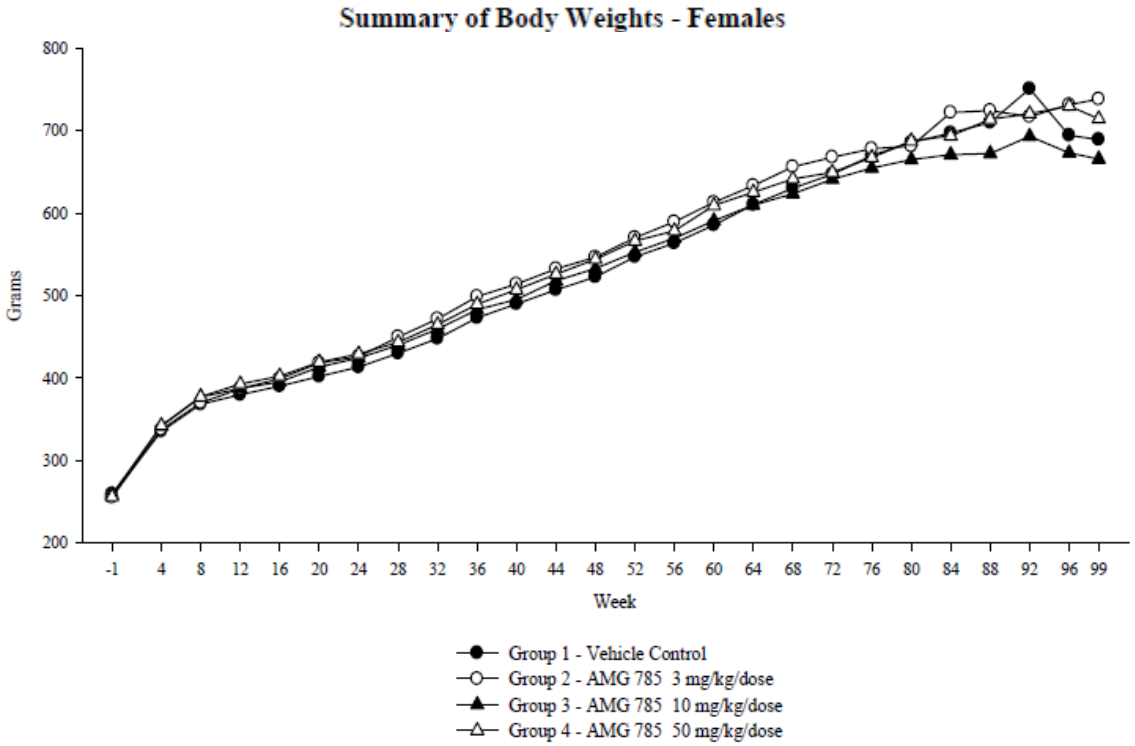
% Body Weight Gain

	MALE			FEMALE		
Group	Pre	Week 92	Gain%	Pre	Week 99	Gain%
Vehicle	343.8	970.1	182	259.1	689.1	166
AMG785 (3 mg/kg)	338.3	1088.3	222	255.3	738.1	189
AMG785 (10 mg/kg)	344.1	1078.7	213	258.5	665.6	157
AMG785 (50 mg/kg)	343.4	1057.0	208	256.1	714.4	179

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ADA and TK Parameters: *Week 13*

At week 13, 33%, 19%, and 25% of female rats developed anti-drug antibody (ADA), and 70%, 28% and 42% of male rats developed ADA at 3, 10, and 50 mg/kg, respectively.

Summary of Anti-AMG 785 Antibody Positive Animals at Week 13 (all animals)

	Females		Males	
Group (Dose)	Binding Antibodies	Neutralizing Antibodies	Binding Antibodies	Neutralizing Antibodies
1 (0 mg/kg)	N/A	N/A	N/A	N/A
2 (3 mg/k)	49/150 (33%)	N/A	105/149 (70%)	50/149 (34%)
3 (10 mg/kg)	15/80 (19%)	N/A	22/79 (28%)	10/79 (13%)
4 (50 mg/kg)	20/79 (25%)	12/79 (15%)	34/80 (42%)	24/80 (30%)

N/A = not applicable

The ADA positive samples determined by immunoassay from Groups 2 through 4 were then analyzed in the bioassay to detect the presence of neutralizing ADA (Nab). Rats in the 3, 10, and 50 mg/kg AMG 785 dosed groups with ADA positive and Nab positive were then removed from the study per the protocol amendments 7 and 8. This removal reduced the group size to: 60, 60, and 60 in females and 60, 60, and 54 in males at 3, 10, and 50 mg/kg dosed groups. Among remaining animals, all rats were negative for Nab. However, there was a total of 32 ADA positive rats retained (1 female and 31 males).

Summary of Anti-AMG 785 Antibody Positive Animals at Week 13 (retained animals per protocol amendments 7 and 8)

	Females		Males	
Group (Dose)	Binding Antibodies	Neutralizing Antibodies	Binding Antibodies	Neutralizing Antibodies
1 (0 mg/kg)	N/A	N/A	N/A	N/A
2 (3 mg/k)	0/60 (0%)	N/A	18/60 (30%)	0/60 (0%)
3 (10 mg/kg)	0/60 (0%)	N/A	3/60 (5%)	0/60 (0%)
4 (50 mg/kg)	1/60 (2%)	0/60 (0%)	10/54 (19%)	0/54 (0%)

N/A = not applicable

The TK analysis of retained animals showed that the mean serum AMG785 at 3, 10, and 50 mg/kg were 4.91, 74.6, and 836 µg/mL in retained females and 9.66, 79.5, and 589 µg/mL in retained males, respectively. There were no gender differences (≤ 2-fold) in mean AMG785 serum concentrations at Week 13.

Mean Serum AMG 785 Concentrations (ng/mL) in Retained Sprague Dawley® Rats on Week 13 Following weekly SC Administration of 3, 10, and 50 mg/kg AMG 785 in Amgen Study 107895 by Dose and Gender

		Sex	
Group/Dose		Female (Retained)	Male (Retained)
2/3 mg/kg	N	60	60
	Mean (ng/mL)	4910	9660
	SD (ng/mL)	1790	2860
	CV%	36.5	29.6
3/10 mg/kg	N	60	60
	Mean (ng/mL)	74600	79500
	SD (ng/mL)	23800	18700
	CV%	32.0	23.5
4/50 mg/kg	N	60	54
	Mean (ng/mL)	836000	589000
	SD (ng/mL)	215000	234000
	CV%	25.7	39.7

N-Number; SD- Standard deviation;

Among ADA-positive retained animals, 1 female at 50 mg/kg had serum AMG 785 concentration of 282 µg/mL (3.0 fold lower than mean serum AMG 785 concentration of ADA negative female rats) and 31 male rats had serum AMG785 concentrations of 8.31, 63, and 310 µg/mL, at 3, 10, and 50 mg/kg respectively, which were lower than the mean serum AMG785 concentration of ADA negative males; 10.2, 80.4, and 653 µg/mL at 3, 10, and 50 mg/kg, respectively). At 50 mg/kg, ADA positive males had 2.1-fold lower mean AMG785 serum concentration when compared to ADA negative males, indicating the minimal difference.

Mean Serum AMG 785 Concentrations (ng/mL) in Retained Sprague Dawley® Rats on Week 13 Following weekly SC Administration of 3, 10, and 50 mg/kg AMG 785 in Amgen Study 107895 by Dose, Gender, ADA, and Nab Results

		Sex			
		Female (Retained)		Male (Retained)	
		Anti-drug_Antibody_Result			
		Negative	Positive	Negative	Positive
		Nab_Result			
Group/Dose		NA	Negative	NA	Negative
2/3 mg/kg	N	60	NA[1]	42	18
	Mean (ng/mL)	4910	NA[1]	10200	8340
	SD (ng/mL)	1790	NA[1]	2920	2270
	CV%	36.5	NA[1]	28.6	27.3
3/10 mg/kg	N	60	NA[1]	57	3
	Mean (ng/mL)	74600	NA[1]	80400	63000
	SD (ng/mL)	23800	NA[1]	18100	25200
	CV%	32.0	NA[1]	22.6	40.1
4/50 mg/kg	N	59	1	44	10
	Mean (ng/mL)	845000	282000	653000	310000
	SD (ng/mL)	204000	NA	167000	289000
	CV%	24.1	NA	25.6	93.2

N-Number; SD Standard deviation;
NA[1] ADA positive but the samples were not tested in Nab assay

In summary, Nab-positive rats were not retained in the study and there were minimal or no difference in mean AMG 785 serum concentrations among retained animals.

In Vivo and Ex Vivo Bone Measurements: *At necropsy*

An increased bone radiopacity was noted in almost all AMG785 treated males and females (73%, 88%, and 85% in males and 97%, 93%, and 92% in females at 3, 10, and 50 mg/kg, respectively). This was systemic affecting all bones and was considered an expected pharmacological effect of AMG 785, correlating with hyperostosis of bones observed microscopically. No other AMG 785-related effects were noted based on the distribution of radiological changes among all groups. Radiographic bone production, bone loss or mixed reaction was noted in a few rats at miscellaneous bone sites or in the femur and tibia, generally correlated with macroscopic and microscopic histological changes.

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Noteworthy Radiographic Findings

	Male				Female			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/dose)	**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Animal examined	**60**	**60**	**60**	**54**	**60**	**60**	**60**	**60**
Carcass								
Increased bone radiopacity	0	44	53	46	2	58	56	55
Bone Miscellaneous								
Bone loss	1	1	3	4	1	3	2	7
Bone production	7	1	2	6	16	21	21	20
Mixed Reaction	6	2	6	2	3	3	0	0
Bone Femur								
Bone loss	1	0	2	0	0	0	0	0
Bone production	1	2	1	0	0	0	0	0
Mixed Reaction	1	0	0	0	0	1	0	0
Bone Tibia								
Bone loss	0	1	0	1	0	0	0	0
Bone production	4	4	8	2	1	2	3	2
Mixed Reaction	0	0	1	0	0	0	0	0

With regard to femur metaphysis, there was a significant increase in femural bone mineral density (BMD) in all AMG785 treated animals, in a dose dependent manner (30%, 60%, and 79% in males and 33%, 79%, and 116% in females at 3, 10, and 50 mg/kg). There was also a significant increase in femural bone mineral content (BMC) in all AMG785 treated animals, in a dose dependent manner (2x, 3x, and 4x in males and 2x, 4x, and 6x in females at 3, 10, and 50 mg/kg).

With regard to femur diaphysis, there was a significant increase in femur diaphyseal parameters in both males and females at all doses. Cortical BMD was increased in animals by 3-4% at 50 mg/kg in both sexes. Cortical thickness increased at 3, 10, or 50 mg/kg by 43%, 80% and 113% in males and by 25%, 58% and 106% in females, respectively, attributed to increases in periosteal circumference at 10 and 50 mg/kg, and marked decreases in endosteal circumference at all dose levels. These geometric changes resulted in increases in cross-sectional moment of inertia (CSMI) of 61% and 116% in males and 38% and 83% in females at 10 and 50 mg/kg, respectively.

Right Distal Femur - Metaphysis Site
Ex Vivo
Males

Group 1 - Vehicle Control Group 2 - AMG 785 3 mg/kg/dose

Group	Summary Information	Area mm²	Total BMC mg/mm	Total BMD mg/cm³	Trabecular BMC mg/mm	Trabecular BMD mg/cm³	Cortical/Subcortical BMC mg/mm	Cortical/Subcortical BMD mg/cm³
1	Mean	33.587	17.732	529.39	2.470	148.52	15.264	910.83
	SD	3.169	1.975	51.69	0.599	40.03	1.761	78.01
	N	17	17	17	17	17	17	17
2	Mean	34.025	23.139 D	685.89 D	6.125 E	365.66 E	17.015 A	1005.93 B
	SD	3.367	2.746	100.96	1.858	121.25	1.253	90.60
	N	19	19	19	19	19	19	19

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Right Distal Femur - Metaphysis Site
Ex Vivo
Males

Group 3 - AMG 785 10 mg/kg/dose Group 4 - AMG 785 50 mg/kg/dose

Group	Summary Information	Area mm²	Total BMC mg/mm	Total BMD mg/cm³	Trabecular BMC mg/mm	Trabecular BMD mg/cm³	Cortical/Subcortical BMC mg/mm	Cortical/Subcortical BMD mg/cm³
3	Mean	37.360 B	31.371 F	845.79 F	10.062 F	547.04 F	21.310 C	1144.56 C
	SD	4.296	4.037	118.97	2.652	166.14	2.219	79.52
	N	16	16	16	16	16	16	16
4	Mean	37.341 A	35.388 F	947.11 F	12.963 F	692.84 F	22.424 C	1201.33 C
	SD	2.873	6.519	154.29	4.105	207.07	2.616	110.13
	N	14	14	14	14	14	14	14

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Right Distal Femur - Metaphysis Site
Ex Vivo
Females

Group 1 - Vehicle Control Group 2 - AMG 785 3 mg/kg/dose

Group	Summary Information	Area mm²	Total BMC mg/mm	Total BMD mg/cm³	Trabecular BMC mg/mm	Trabecular BMD mg/cm³	Cortical/Subcortical BMC mg/mm	Cortical/Subcortical BMD mg/cm³
1	Mean	21.457	11.952	561.35	1.781	168.33	10.169	954.49
	SD	2.425	1.075	61.02	0.708	69.91	0.825	84.02
	N	20	20	20	20	20	20	20
2	Mean	22.062	16.332 D	744.01 C	4.478 D	409.36 D	11.853	1079.04
	SD	1.738	2.221	113.23	1.571	153.57	0.937	91.43
	N	19	19	19	19	19	19	19

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Right Distal Femur - Metaphysis Site
Ex Vivo
Females

Group 3 - AMG 785 10 mg/kg/dose Group 4 - AMG 785 50 mg/kg/dose

Group	Summary Information	Area mm²	Total BMC mg/mm	Total BMD mg/cm³	Trabecular BMC mg/mm	Trabecular BMD mg/cm³	Cortical/Subcortical BMC mg/mm	Cortical/Subcortical BMD mg/cm³
3	Mean	23.715 B	22.739 F	956.11 C	8.278 F	693.63 F	14.461 F	1218.58 F
	SD	2.064	3.919	110.21	2.624	180.13	1.573	67.50
	N	24	24	24	24	24	24	24
4	Mean	25.166 C	30.531 F	1210.49 C	13.694 F	1087.96 F	16.838 F	1332.61 F
	SD	2.149	4.313	99.87	3.002	190.18	1.628	17.73
	N	17	17	17	17	17	17	17

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Right Distal Femur - Diaphysis Site
Ex Vivo
Males

Group 1 - Vehicle Control Group 2 - AMG 785 3 mg/kg/dose

Group	Summary Information	Total Area mm²	Cortical Area mm²	BMC mg/mm	BMD mg/cm³	THICK_C mm	PERI_C mm	ENDO_C mm	CSMI mm⁴
1	Mean	23.126	13.254	17.831	1345.86	0.9442	17.0366	11.1043	27.5032
	SD	1.666	1.638	2.175	32.67	0.1273	0.6186	0.8842	4.2056
	N	18	18	18	18	18	18	18	18
2	Mean	23.341	17.187 D	23.025 D	1340.71	1.3463 C	17.1077	8.6497 C	31.4114
	SD	2.174	1.824	2.364	38.37	0.2012	0.8157	1.6262	5.6758
	N	19	19	19	19	19	19	19	19

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Right Distal Femur - Diaphysis Site
Ex Vivo
Males

Group 3 - AMG 785 10 mg/kg/dose Group 4 - AMG 785 50 mg/kg/dose

Group	Summary Information	Total Area mm²	Cortical Area mm²	BMC mg/mm	BMD mg/cm³	THICK_C mm	PERI_C mm	ENDO_C mm	CSMI mm⁴
3	Mean	27.373 C	22.281 F	30.218 F	1355.38	1.7031 C	18.5331 C	7.8325 C	44.2314 F
	SD	2.196	2.586	3.788	43.57	0.2609	0.7260	1.6783	8.1264
	N	16	16	16	16	16	16	16	16
4	Mean	30.979 C	26.731 F	37.351 F	1393.71 B	2.0104 C	19.7001 C	7.0696 C	59.5066 F
	SD	3.577	5.106	7.734	55.21	0.4082	1.1304	1.9142	15.2223
	N	14	14	14	14	14	14	14	14

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Right Distal Femur - Diaphysis Site
Ex Vivo
Females

Group 1 - Vehicle Control Group 2 - AMG 785 3 mg/kg/dose

Group	Summary Information	Total Area mm²	Cortical Area mm²	BMC mg/mm	BMD mg/cm³	THICK_C mm	PERI_C mm	ENDO_C mm	CSMI mm⁴
1	Mean	13.899	9.216	12.808	1389.15	0.8841	13.2012	7.6462	11.1090
	SD	1.356	1.046	1.507	23.57	0.0869	0.6402	0.6365	2.0936
	N	20	20	20	20	20	20	20	20
2	Mean	14.633	11.077	15.098	1364.08 A	1.1028 D	13.5542	6.6261 C	12.4969
	SD	0.923	1.240	1.598	31.59	0.1601	0.4253	0.9088	1.7655
	N	19	19	19	19	19	19	19	19

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Right Distal Femur - Diaphysis Site
Ex Vivo
Females

Group 3 - AMG 785 10 mg/kg/dose Group 4 - AMG 785 50 mg/kg/dose

Group	Summary Information	Total Area mm²	Cortical Area mm²	BMC mg/mm	BMD mg/cm³	THICK_C mm	PERI_C mm	ENDO_C mm	CSMI mm⁴
3	Mean	15.752 E	13.473 F	18.795 F	1394.73	1.3970 F	14.0560 E	5.2786 C	15.2764 F
	SD	1.402	1.693	2.462	37.85	0.1913	0.6226	0.8977	2.5528
	N	24	24	24	24	24	24	24	24
4	Mean	17.804 F	16.769 F	24.269 F	1447.16 C	1.8187 F	14.9285 F	3.5014 C	20.2870 F
	SD	2.315	2.384	3.500	28.58	0.2154	0.9632	0.8931	5.2790
	N	17	17	17	17	17	17	17	17

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

In summary, the weekly subcutaneous administration of AMG 785 at 3, 10 or 50 mg/kg for a minimum of 91 weeks for males and 98 weeks for females resulted in expected pharmacological effects on bones (increased skeletal radiopacity (whole body), and increased bone mass and geometry at the femur metaphysis and diaphysis at all dose levels).

Gross Pathology: *At necropsy*

There were AMG785-related macroscopic findings in bones (miscellaneous, calvarium femur, lumbar vertebrae L5-L6, sternum and tibia) and spleen. There was also AMG785-related thickening of the bone in males and females, in a dose dependent manner, correlating with the increase in bone mineral content (BMC by ex vivo pQCT) and hyperostosis microscopically. This effect was systemic, usually affecting all routinely collected bones.

An increased incidence of spleen enlargement was noted in females at ≥ 3 mg/kg and in males at 10 mg/kg/dose, correlating with increased extramedullary hematopoiesis microscopically.

AMG 785-related Macroscopic Changes

	Male				Female			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg)	0	3	10	50	0	3	10	50
Animal Examined	60	60	60	54	60	60	60	60
Bone Miscellaneous								
Thickening	0	19	48	48	0	4	33	52
Bone Calvarium								
Thickening	0	22	54	51	1	6	36	56
Bone Femur								
Thickening	0	25	55	50	0	9	42	57
Bone L5-L6								
Thickening	0	19	48	46	0	4	33	52
Bone Sternum								
Thickening	0	20	49	48	0	7	37	53
Bone Tibia								
Thickening	0	23	53	49	0	7	38	57
Spleen								
Enlargement	10	11	21	13	18	24	34	28

Histopathology: *At necropsy [Peer Review: Yes]*

Neoplastic

There were two tumors, renal lipoma in females and adrenal cortical adenoma in males, where incidence reached statistical significance.

With renal lipoma, a rare tumor, there was a statistically significant increase in females only, by trend test (p =0.0486). The incidence of renal lipoma was marginally increased in females at 50 mg/kg/dose when compared to concurrent control, and marginally above the historical data range for the testing facility. However, this finding was not considered AMG-785 related due low incidence, lack of pre-neoplastic precursors lesions and comparable nature and morphology to the renal lipoma in the concurrent control female.

Reference ID: 4075258

With adrenal cortical adenoma, a common tumor, there was a slight increase in males only, by pairwise comparisons test (0 vs. 10 mg/kg; $p = 0.0169$). However, this finding was not considered AMG 785-related due to the incidence being within historical control data range, the absence of a dose-related trend, and the absence of a precursor pre-neoplastic change.

Peto' s Survival Adjusted One-tailed Trend Test Results (FEMALES)

Organ	Tumor Name	*P*-Value
Kidney	Lipoma	0.0486

Pairwise Groups Comparisons Results (MALES)

Organ	Tumor Name	Comparison	*P*-Value
Adrenal	Adenoma: cortical	1 vs 3	0.0169

In addition, other common tumors with numerical imbalances were benign pheochromocytoma and thyroid c-cell adenoma in females at 3 mg/kg/dose and keratoacanthoma in the skin of the males at 10 mg/kg. However, the presence of these tumors showed lack of statistical significance (for common tumors, by pairwise comparisons), lack of relationship of these imbalances to AMG 785 treatment, absence of a dose-response relationship, and absence of precursor pre-neoplastic change. These incidences of the tumors were also within historical control data range. In addition, the incidences of pancreatic tumors seemed to be increased at 10 and 50 mg/kg/dose. However, they were within historical control for both males and females.

Reference ID: 4075258

Incidence and Historical Control Range of Selected Tumors

Sex		Male				Female			
Dose (mg/kg/dose)		0	3	10	50	0	3	10	50
Kidney	No. Examined	60	60	60	54	60	60	60	60
Lipoma									
incidence		0	0	0	1	1	0	0	3
% incidence		0	0	0	1.85	1.67	0	0	5.00
HC[a] range %									
Male 0-0.83									
Females 0-4.00									
Adrenal	No. examined	60	60	60	54	60	60	60	60
Adenoma: cortical									
incidence		0	2	6	2	6	3	1	7
% incidence		0.00	3.33	10.00	3.70	10.00	5.00	1.67	11.67
HC range %									
Male 0-10.00									
Female 0-10.00									
Benign pheochromocytoma:									
incidence		4	3	6	3	2	8	2	0
% incidence		6.67	5.00	10.00	5.56	3.33	13.30	3.33	0.00
HC range %									
Male 1.67-24.11									
Female 0-10.00									
Pancreas	No. examined	60	60	60	54	60	60	60	60
Adenoma Islet cell									
incidence		1	1	3	4	0	0	3	3
% incidence		1.67	1.67	5.00	7.40	0.00	0.00	5.00	5.00
HC range %									
Male 0-13.33									
Female 0-8.33									
Carcinoma Islet cell									
incidence		0	0	3	2	1	0	1	0
% incidence		0.00	0.00	5.00	3.70	1.67	0.00	1.67	0.00
HC range %									
Male 0-11.67									
Female 0-6.67									
Adenoma+ Carcinoma Islet cell									
incidence		1	1	6	6	1	0	4	3
% incidence		1.67	1.67	10.00	11.11	1.67	0.00	6.67	5.00
HC range %									
Male 1.79-19.00									
Female 0-13.33									

Sex		Male				Female			
Dose (mg/kg/dose)		0	3	10	50	0	3	10	50
Thyroid	No. examined	60	60	60	54	60	60	60	60
c-cell adenoma									
incidence		8	10	4	6	5	11	8	8
% incidence		13.33	16.67	6.67	11.11	8.33	18.33	13.33	13.33
HC range %									
Male 3.33-16.96									
Female 2.67-20.54									
Skin	No. examined	60	60	60	54	60	60	60	60
Keratoacanthoma									
incidence		2	1	7	0	0	1	0	1
% incidence		3.33	1.67	11.67	0.00	0.00	1.67	0.00	1.67
HC range %									
Male 0-13.39									
Female 0-1.67									

[a] Historical Control (HC)

Lastly, two osteosarcomas were noted in the males at 50 mg/kg, which were not statistically significant by trend test and pairwise comparison. One osteosarcoma (with no metastases) was noted in the left proximal tibia of Male No 4041 at Day 572, correlating with the focal radiographic bone loss (microscopically). The cause of death of this animal, determined by the sponsor, was attributed to a pituitary adenoma. The other osteosarcoma (with no metastases) was noted on the frontal bone/skull of Male No 4069 at Day 587, correlating with the gross and radiographic findings and attributing to

its cause of death (a local extension in the brain). Bone neoplasms and osteosarcomas (OSA) are rare in Sprague-Dawley rats. The incidence of spontaneous OSA in male and females Sprague-Dawley rats in two years studies conducted at the test facility ranged from 0 to 3.33%. **The incidence of OSA in males at 50 mg/kg was 3.7%, marginally higher than the historical range.** However, the sponsor argues that this historical data is based on studies where whole body radiography was not conducted and detection of OSA was limited to microscopic evaluation of sternum and macroscopic abnormalities. *Historical data from studies where whole body radiographs have been employed to detect bone neoplasms and other bone changes are not currently available.* There were no other bone tumors in this study contrasting with results of long term administration of PTH in F344 and Sprague-Dawley rats that resulted in OSA, osteoblastoma, osteoma, and osteoblast hyperplasia. In the end, the sponsor considered the OSA observed in males at 50 mg/kg as spontaneous based on the low incidence that falls within the range of reported OSA in the historical data of the test facility, late onset and solitary nature and lack of a continuum that includes proliferative precursor osteoblastic changes and benign bone tumors.

Note 1: Detailed summary of neoplastic findings and historical data provided by the sponsor are included in Appendix.

Note 2: Osteosarcomas have been seen in all rodent carcinogenicity studies with PTH and its related peptides. PTH-induced bone tumors can be mediated by sclerostin inhibition. AMG785 is an anti-sclerostin (IgG2) humanized antibody.

Non-neoplastic

Microscopic non-neoplastic changes were limited to hyperostosis of bones, secondary extramedullary hematopoiesis in spleen and liver, and mononuclear cells infiltrate at the injection sites.

Hyperostosis (an increased thickness of the trabeculae in the epiphysis and metaphysis as well as cortical thickening) occurred in a dose-dependent manner, resulting in reduction of the marrow space. There was no woven bone or other morphological changes, indicating altered bone quality. The hyperostosis was of comparable severity between bone sites (femur, tibia, L5-L6, calvarium) of the same animal, except for the sternum which was generally affected to a lesser degree. In addition, at comparable doses, it was generally more pronounced in females when compared to males. Higher femoral metaphyseal BMD was observed in females when compared to males.

Splenic extramedullary hematopoiesis was noted in both sexes with increased incidence/severity at ≥ 3 mg/kg, correlating with the macroscopic observation of spleen enlargement. Hepatic extramedullary hematopoiesis was observed in males at ≥ 3 mg/kg and in females at ≥ 10 mg/kg. The splenic and hepatic extramedullary hematopoiesis was considered compensatory and secondary to the reduced bone marrow space as a consequence of the generalized bone hyperostosis.

Reference ID: 4075258

AMG785-related mononuclear cell infiltration (focal to multifocal perivascular aggregates of lymphocytes and/or plasma cells; minimal to slight in severity) was observed at injection sites with increased incidence in males at ≥ 3 mg/kg and in females at ≥ 10 mg/kg.

A variety of spontaneous non-neoplastic (non-AMG785 related) skeletal changes were noted in the examined bones (miscellaneous, calvarium, femur, lumbar vertebrae L5-L6, sternum and tibia) and other tissues. These changes included osteophyte, bone proliferation, ectopic ossification, fibrous osteodystrophy and degenerative joint disease. However, AMG785 treatment did not modify the incidence and/or severity of these bone, periarticular or soft tissues changes.

Incidence and Severity of AMG 785-related Non-neoplastic Changes

	Sex	Male				Female			
	Dose (mg/kg/dose)	0	3	10	50	0	3	10	50
Calvarium	No. examined	60	60	59	54	60	60	60	60
Hyperostosis									
	Total Number affected	0	41	59	50	0	35	59	60
	Minimal	-	25	2	3	-	29	7	-
	Slight	-	13	32	11	-	5	34	3
	Moderate	-	3	25	26	-	1	17	37
	Marked	-	-	-	10	-	-	1	20
Femur	No. examined	60	60	60	54	60	60	60	60
Hyperostosis									
	Total Number affected	0	43	60	52	0	45	60	60
	Minimal	-	26	3	4	-	31	3	-
	Slight	-	11	20	3	-	12	21	-
	Moderate	-	4	36	29	-	2	25	6
	Marked	-	2	1	16	-	-	10	49
	Severe	-	-	-	-	-	-	1	5
Lumbar vertebrae L5-L6									
	No. examined	60	59	59	54	60	60	60	60
Hyperostosis									
	Total Number affected	0	42	59	50	0	36	59	60
	Minimal	-	27	5	4	-	28	5	-
	Slight	-	12	38	12	-	8	17	-
	Moderate	-	3	16	25	-	-	25	7
	Marked	-	-	-	9	-	-	12	43
	Severe	-	-	-	-	-	-	-	10
Sternum	No. examined	60	60	60	54	60	60	60	60
Hyperostosis									
	Total Number affected	0	32	57	50	0	23	56	60
	Minimal	-	21	16	2	-	18	15	-
	Slight	-	7	34	23	-	4	26	12
	Moderate	-	3	7	18	-	-	8	25
	Marked	-	1	-	7	-	1	7	20
	Severe	-	-	-	-	-	-	-	3

Sex	Male				Female			
Dose (mg/kg/dose)	**0**	**3**	**10**	**50**	**0**	**3**	**10**	**50**
Tibia No. examined	60	60	59	54	60	60	60	60
Hyperostosis								
Total Number affected	0	41	59	51	0	46	60	60
Minimal	-	33	4	4	-	31	3	-
Slight	-	2	25	11	-	12	17	-
Moderate	-	4	28	26	-	2	27	6
Marked	-	2	2	10	-	1	13	45
Severe	-	-	-	-	-	-	-	9
Liver No. examined	60	60	60	54	60	60	60	60
Extramedullary hematopoiesis								
Total Number affected	5	13	13	12	22	25	41	39
Minimal	5	12	11	10	17	23	36	34
Slight	-	1	2	2	5	2	5	5
Spleen No. examined	60	60	60	54	60	60	60	60
Extramedullary hematopoiesis								
Total Number affected	13	38	44	40	37	49	57	60
Minimal	6	24	33	24	13	13	8	12
Slight	3	8	8	9	10	13	19	21
Moderate	3	4	3	5	9	21	23	16
Marked	1	2	-	2	5	2	7	9
Severe	-	-	-	-	-	-	-	2
Injection site interscapular								
No. examined	60	60	60	54	60	60	60	60
Infiltration mononuclear cells								
Total Number affected	5	11	7	16	1	1	4	7
Minimal	4	11	6	15	1	1	4	7
Slight	1	-	1	1	-	-	-	-
Injection site scapular left								
No. examined	60	60	60	54	60	60	60	60
Infiltration mononuclear cells								
Total Number affected	4	14	9	11	3	2	9	11
Minimal	4	12	7	9	3	2	9	8
Slight	-	2	2	2	-	-	-	3
Injection site scapular right								
No. examined	60	60	60	54	60	60	60	60
Infiltration mononuclear cells								
Total Number affected	5	6	11	8	4	2	4	8
Minimal	5	6	8	7	4	2	4	8
Slight	-	-	3	1	-	-	-	-

Appendix

Neoplastic histopath data: all animals

MALE

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
ABDOMEN	NO.EXAM.:	-	1	-	-
ADRENAL	NO.EXAM.:	60	60	60	54
- Adenoma: cortical		-	2	6	2
- Benign pheochromocytoma		4	3	6	3
- Malignant pheochromocytoma		1	2	1	-
AORTA	NO.EXAM.:	60	60	60	53
BILE DUCT	NO.EXAM.:	1	2	-	-
BLOOD VESSEL	NO.EXAM.:	1	-	-	-
BONE-CALVARIUM	NO.EXAM.:	60	60	59	54

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
BONE-FEMUR	NO.EXAM.:	60	60	60	54
BONE-LUMB.SEC.L5-L6	NO.EXAM.:	60	59	59	54
- Metastasis		1	-	-	-
BONE MARROW	NO.EXAM.:	60	60	60	54
BONE MISCELLANEOUS	NO.EXAM.:	12	3	9	10
- Osteosarcoma		-	-	-	1
- Metastasis		1	-	-	-
BONE-STERNUM	NO.EXAM.:	60	60	60	54

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
BONE-TIBIA	NO.EXAM.:	60	60	59	54
- Osteosarcoma		-	-	-	1
- Sarcoma: metastasis		-	1	-	-
BRAIN	NO.EXAM.:	60	60	60	54
- Metastasis		-	-	-	2
- Malignant granular cell tumor		1	-	-	-
- Malignant astrocytoma		1	-	1	-
- Malignant reticulosis		1	-	-	-
- Malignant oligodendroglioma		-	1	-	-

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
CAVITY NASAL/SINUSES	NO.EXAM.:	60	60	60	54
- Carcinoma: metastasis		-	-	1	-
CAVITY ORAL	NO.EXAM.:	1	1	1	1
- Carcinoma: squamous cell		1	-	1	1
CECUM	NO.EXAM.:	60	60	60	54
COLON	NO.EXAM.:	60	60	60	54
DUODENUM	NO.EXAM.:	60	60	60	54
EPIDIDYMIS	NO.EXAM.:	60	60	60	53
- Sarcoma: metastasis		-	1	-	-

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
ESOPHAGUS	NO.EXAM.:	60	60	60	54
EYE	NO.EXAM.:	59	60	59	54
FAT	NO.EXAM.:	2	-	2	-
GALT	NO.EXAM.:	55	59	56	49
HARDERIAN GLAND	NO.EXAM.:	60	60	60	54
HEART	NO.EXAM.:	60	60	60	54
HEMOLYM. TISSUE	NO.EXAM.:	60	60	60	54
- Malignant lymphoma		3	1	5	-
- Histiocytic sarcoma		-	1	-	-

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
ILEUM	NO.EXAM.:	60	60	60	54
I.S. INTERSCAPULAR	NO.EXAM.:	60	60	60	54
- Fibroma		-	-	1	-
I.S. SCAPULAR, LEFT	NO.EXAM.:	60	60	60	54
- Fibrosarcoma		1	-	-	-
- Trichoepithelioma		-	-	1	-
- Fibroma		1	-	1	-
- Lipoma		-	-	1	-
I.S. SCAPULAR, RIGHT	NO.EXAM.:	60	60	60	54

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
JEJUNUM	NO.EXAM.:	60	60	60	54
JOINT	NO.EXAM.:	9	4	9	6
KIDNEY	NO.EXAM.:	60	60	60	54
- Lipoma		-	-	-	1
- Adenoma: tubular cell		-	1	-	-
- Carcinoma: tubular cell		1	-	-	-
- Carcinoma: transitional cell		-	1	-	-
LACRIMAL GLAND	NO.EXAM.:	3	3	3	1
LARYNX	NO.EXAM.:	60	60	60	54

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
LIVER	NO.EXAM.:	60	60	60	54
- Adenoma: hepatocellular		-	3	1	-
- Carcinoma: hepatocellular		2	2	1	-
LUNG	NO.EXAM.:	60	60	60	54
- Carcinoma: metastasis		-	1	-	-
- Sarcoma: metastasis		1	-	-	-
- Metastasis		-	-	1	-
LYMPH NODE	NO.EXAM.:	17	15	9	11
L. NODE MANDIBULAR	NO.EXAM.:	60	60	59	52
- Hemangioma		-	-	-	1

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
L.NODE MESENTERIC	NO.EXAM.:	60	60	60	54
- Hemangioma		-	2	-	1
- Hemangiosarcoma		-	2	1	-
- Lipoma		-	1	-	-
MAMMARY GLAND	NO.EXAM.:	49	55	51	47
- Fibroadenoma		1	-	-	2
- Adenocarcinoma		1	-	-	-
MENINGES	NO.EXAM.:	2	-	-	-
MUSCLE SKELETAL	NO.EXAM.:	59	59	60	53

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
MUSCLE SKELETAL MISC	NO.EXAM.:	-	-	-	1
NERVES OPTIC	NO.EXAM.:	55	57	56	53
- Metastasis		-	-	-	1
NERVE SCIATIC	NO.EXAM.:	60	60	60	54
PANCREAS	NO.EXAM.:	60	60	60	54
- Adenoma: islet cell		1	1	3	4
- Carcinoma: islet cell		-	-	3	2
- Adenoma: acinar cell		-	-	3	2
PARATHYROID GLAND	NO.EXAM.:	56	54	58	51
- Adenoma		-	-	-	1

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
PITUITARY	NO.EXAM.:	60	60	60	54
- Adenoma: pars distalis		27	16	25	23
- Carcinoma: pars distalis		-	-	-	1
- Adenoma: pars intermedia		2	-	-	-
PREPUTIAL GLAND	NO.EXAM.:	1	1	-	-
PROSTATE	NO.EXAM.:	60	60	60	54
RECTUM	NO.EXAM.:	60	60	60	54
SALIV.GL. MANDIBULAR	NO.EXAM.:	60	60	59	54
SEMINAL VESICLE	NO.EXAM.:	60	60	60	54

		MALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	54
SKIN	NO.EXAM.:	60	60	60	54
SKIN MISCELLANEOUS	NO.EXAM.:	19	21	22	19
- Carcinoma: squamous cell		2	2	3	-
- Papilloma: squamous cell		-	2	1	1
- Keratoacanthoma		2	1	7	-
- Adenoma: sebaceous		-	1	1	-
- Adenoma: basal cell		1	-	-	-
SPINAL CORD CERVICAL	NO.EXAM.:	60	60	60	54
- Metastasis		1	-	-	-

		MALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	54
SPINAL CORD LUMBAR	NO.EXAM.:	60	60	60	53
- Metastasis		1	-	-	-
SPINAL CORD THORACIC	NO.EXAM.:	60	59	58	53
- Metastasis		1	-	-	-
SPLEEN	NO.EXAM.:	60	60	60	54
- Hemangiosarcoma		1	1	1	-
STOMACH	NO.EXAM.:	60	60	60	54

		MALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	54
SUBCUTANEOUS TISSUE	NO.EXAM.:	6	8	5	6
- Fibrosarcoma		-	2	1	3
- Malignant schwannoma		2	-	-	-
- Fibroma		3	1	2	1
- Lipoma		-	2	-	1
- Malignant fibrous histiocytoma		-	1	-	-
TAIL	NO.EXAM.:	2	1	2	6
TESTIS	NO.EXAM.:	60	60	60	53
- Adenoma: interstitial cell		-	-	-	1
- Mesothelioma(M)		-	1	-	-

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
THYMUS	NO.EXAM.:	59	57	59	53
- Benign thymoma		-	-	-	1
- Malignant schwannoma		-	-	-	1
THYROID	NO.EXAM.:	60	60	60	54
- Adenoma: C-cell		8	10	4	6
- Adenoma: follicular cell		6	4	-	-
- Carcinoma: C-cell		-	-	2	-
TONGUE	NO.EXAM.:	60	60	60	54
TOOTH	NO.EXAM.:	60	60	60	54

		MALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 54
TRACHEA	NO.EXAM.:	60	60	60	54
URETER	NO.EXAM.:	56	54	58	50
URINARY BLADDER	NO.EXAM.:	60	59	60	53

FEMALE

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
ABDOMEN	NO.EXAM.:	-	-	1	1
- Sarcoma: metastasis		-	-	1	-
- Mesothelioma(M)		-	-	-	1
ADRENAL	NO.EXAM.:	60	60	60	60
- Carcinoma: cortical		1	-	-	-
- Adenoma: cortical		6	3	1	7
- Benign pheochromocytoma		2	8	2	-
- Malignant pheochromocytoma		-	2	-	-
- Sarcoma: metastasis		-	1	-	1

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
AORTA	NO.EXAM.:	60	60	60	60
BILE DUCT	NO.EXAM.:	1	-	-	-
BONE-CALVARIUM	NO.EXAM.:	60	60	60	60
BONE-FEMUR	NO.EXAM.:	60	60	60	60
BONE-LUMB.SEG.L5-L6	NO.EXAM.:	60	60	60	60
BONE MARROW	NO.EXAM.:	60	60	60	60
BONE MISCELLANEOUS	NO.EXAM.:	18	22	20	25
BONE-STERNUM	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	1	-	-

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
BONE-TIBIA	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	1	-	-
BRAIN	NO.EXAM.:	60	60	60	60
- Metastasis		1	4	-	1
- Benign granular cell tumor		1	-	-	-
- Malignant astrocytoma		1	-	-	-
- Malignant oligodendroglioma		-	-	1	-
CAVITY NASAL/SINUSES	NO.EXAM.:	60	60	60	60
- Carcinoma: metastasis		-	1	1	-

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
CAVITY ORAL	NO.EXAM.:	-	-	1	-
- Carcinoma: squamous cell		-	-	1	-
CECUM	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	-	-	1
- Leiomyoma		1	-	-	-
CERVIX	NO.EXAM.:	60	60	60	60
- Malignant schwannoma		-	-	-	1
- Benign schwannoma		-	1	-	-
- Leiomyoma		1	1	-	-
- Hemangioma		1	-	-	-

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
COLON	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	1	1	1
DIAPHRAGM	NO.EXAM.:	-	-	2	-
- Sarcoma: metastasis		-	-	1	-
DUODENUM	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	-	1	1
ESOPHAGUS	NO.EXAM.:	59	60	60	60
EYE	NO.EXAM.:	59	60	60	60

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
FAT	NO.EXAM.:	3	3	2	3
- Mesothelioma(M)		-	-	1	-
- Sarcoma: metastasis		1	-	-	1
GALT	NO.EXAM.:	60	58	57	59
HARDERIAN GLAND	NO.EXAM.:	60	60	60	60
- Carcinoma: metastasis		-	1	-	-
HEAD	NO.EXAM.:	-	1	-	-
- Carcinoma: squamous cell		-	1	-	-
HEART	NO.EXAM.:	60	60	60	60
- Malignant schwannoma		-	1	-	-

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
HEMOLYM. TISSUE	NO.EXAM.:	60	60	60	60
- Malignant lymphoma		2	-	-	-
- Histiocytic sarcoma		1	1	2	1
ILEUM	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	-	1	1
I.S. INTERSCAPULAR	NO.EXAM.:	60	60	60	60
- Fibroma		1	-	1	-
I.S. SCAPULAR, LEFT	NO.EXAM.:	60	59	60	60
I.S. SCAPULAR, RIGHT	NO.EXAM.:	60	60	60	60

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
JEJUNUM	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	-	1	-
JOINT	NO.EXAM.:	7	12	13	9
KIDNEY	NO.EXAM.:	60	60	60	60
- Lipoma		1	-	-	3
- Sarcoma: metastasis		-	1	-	-
LARYNX	NO.EXAM.:	60	60	60	60

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
LIVER	NO.EXAM.:	60	60	60	60
- Carcinoma: metastasis		-	1	-	-
- Sarcoma: metastasis		-	-	1	1
- Adenoma: hepatocellular		1	1	-	1
- Carcinoma: hepatocellular		1	-	-	-
LUNG	NO.EXAM.:	60	60	60	60
- Carcinoma: squamous cell		-	1	-	-
- Carcinoma: metastasis		2	2	-	1
- Sarcoma: metastasis		-	1	1	-
- Metastasis		1	-	-	-

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
LYMPH NODE	NO.EXAM.:	26	25	25	21
- Sarcoma (not otherwise specified)		-	-	1	-
- Metastasis		1	1	-	-
- Sarcoma: metastasis		-	1	1	-
L. NODE MANDIBULAR	NO.EXAM.:	58	59	59	60
- Carcinoma: metastasis		1	-	-	-
L.NODE MESENTERIC	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	-	-	1

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
MAMMARY GLAND	NO.EXAM.:	60	60	59	60
- Fibroadenoma		41	44	36	35
- Adenocarcinoma		15	15	16	18
- Carcinoma: squamous cell		-	-	1	-
- Adenoma		2	1	1	-
- Fibrosarcoma		-	-	1	-
MUSCLE SKELETAL	NO.EXAM.:	60	59	60	60
MUSCLE SKELETAL MISC	NO.EXAM.:	1	-	1	-
NERVES OPTIC	NO.EXAM.:	54	59	54	58

		FEMALE			
DOSE GROUP NUMBER OF ANIMALS EXAMINED		1 60	2 60	3 60	4 60
NERVE SCIATIC	NO.EXAM.:	60	60	60	60
OVARY	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	-	1	1
- Adenoma: sertoliform tubular		-	-	1	-
- Carcinoma: tubulostromal		1	-	-	-
OVIDUCT	NO.EXAM.:	59	60	60	60
PANCREAS	NO.EXAM.:	60	60	60	60
- Adenoma: islet cell		-	-	3	3
- Carcinoma: islet cell		1	-	1	-
- Adenoma: acinar cell		-	-	1	-

		FEMALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	60
PANCREAS	CONT'D.	60	60	60	60
- Sarcoma: metastasis		-	1	1	1
PARATHYROID GLAND	NO.EXAM.:	57	55	59	58
- Adenoma		-	-	1	1
PERICARDIUM	NO.EXAM.:	-	1	-	-
PITUITARY	NO.EXAM.:	60	60	60	59
- Adenoma: pars distalis		36	32	40	39
- Carcinoma: pars distalis		1	3	-	1
- Sarcoma (not otherwise specified)		-	1	-	-
- Carcinoma: metastasis		-	1	-	-

		FEMALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	60
RECTUM	NO.EXAM.:	60	60	60	60
SALIV.GL. MANDIBULAR	NO.EXAM.:	58	60	60	60
SKIN	NO.EXAM.:	60	60	60	60
SKIN MISCELLANEOUS	NO.EXAM.:	29	33	30	34
- Carcinoma: squamous cell		2	2	1	1
- Keratoacanthoma		-	1	-	1
SPINAL CORD CERVICAL	NO.EXAM.:	60	60	60	60
SPINAL CORD LUMBAR	NO.EXAM.:	60	60	60	60
SPINAL CORD THORACIC	NO.EXAM.:	60	60	60	58

		FEMALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	60
SPLEEN	NO.EXAM.:	59	60	60	60
- Sarcoma: metastasis		-	1	1	1
- Hemangioma		-	-	1	-
STOMACH	NO.EXAM.:	60	60	60	60
- Leiomyosarcoma		1	-	-	-
- Sarcoma: metastasis		-	-	1	1
SUBCUTANEOUS TISSUE	NO.EXAM.:	11	5	2	2
- Fibrosarcoma		1	2	-	1
- Sarcoma (not otherwise specified)		-	-	-	1
- Malignant schwannoma		2	-	-	-

		FEMALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	60
SUBCUTANEOUS TISSUE	CONT'D.	11	5	2	2
- Lipoma		2	-	-	-
- Malignant fibrous histiocytoma		-	1	-	-
TAIL	NO.EXAM.:	2	3	-	2
THYMUS	NO.EXAM.:	58	57	59	60
- Benign thymoma		1	2	-	-
- Malignant thymoma		-	1	-	-

		FEMALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	60
THYROID	NO.EXAM.:	60	60	60	60
- Adenoma: C-cell		5	11	8	8
- Neuroendocrine tumor		-	-	-	1
- Adenoma: follicular cell		-	2	1	2
- Carcinoma: C-cell		1	1	1	-
- Carcinoma: follicular cell		-	-	1	-
TONGUE	NO.EXAM.:	60	60	60	60
- Sarcoma: metastasis		-	1	-	-
TOOTH	NO.EXAM.:	60	60	60	60
- Odontoma		4	6	6	3

		FEMALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	60
TRACHEA	NO.EXAM.:	60	60	60	60
URETER	NO.EXAM.:	56	59	59	59
- Sarcoma: metastasis		-	-	2	-
URETHRA	NO.EXAM.:	-	1	-	-
URINARY BLADDER	NO.EXAM.:	59	60	60	60
- Sarcoma: metastasis		-	-	1	1
UTERUS	NO.EXAM.:	60	60	60	60
- Sarcoma: endometrial stromal		1	-	1	-
- Sarcoma: metastasis		-	-	-	1
- Polyp: endometrial stromal		3	4	4	5

		FEMALE			
DOSE GROUP		1	2	3	4
NUMBER OF ANIMALS EXAMINED		60	60	60	60
UTERUS	CONT'D.	60	60	60	60
- Adenocarcinoma: endometrial		1	-	1	-
- Hemangioma		1	-	-	-
VAGINA	NO.EXAM.:	60	60	60	60
- Malignant schwannoma		-	-	-	1
- Benign schwannoma		-	1	-	-

Historical control

PATHOLOGY
MICROSCOPIC FINDING HISTORICAL DATA (Male)

Species / Strain: Rat / Sprague Dawley
Route of Admin.: All routes
Age at Necropsy: From approximately 104 to 112 weeks old
Treatment Duration: 98 to 104 weeks

	Total No. of animals	Study ID:	A	B	C	D	E	F	G	H	I	J	K	L
		Study start:	1998	2000	2001	2002	1998	2002	2004	2005	2005	2007	2007	2009
	1057	Total No. of Animals Examined:	112	120	120	100	50	120	60	75	60	60	60	120
Organ **Lesion**	**Total No. of Lesions**	**%**	**%Min**	**%Max**												
ABDOMEN																
Osteosarcoma	2	0.19	0.00	2.00	0	0	0	2	0	0	0	0	0	0	0	0
ADRENAL																
Adenoma: cortical	20	1.89	0.00	10.00	1	0	1	4	0	0	0	5	6	0	2	1
Benign pheochromocytoma	123	11.64	1.67	24.11	27	12	4	17	3	7	1	10	10	4	9	19
BONE MISCELLANEOUS																
Osteosarcoma	4	0.38	0.00	3.33	0	0	0	0	0	1	0	1	0	0	2	0
KIDNEY																
Lipoma	2	0.19	0.00	0.83	0	1	0	0	0	0	0	0	0	0	0	1
PANCREAS																
Adenoma: islet cell	67	6.34	0.00	13.33	0	11	7	9	2	5	8	3	6	7	2	7
Carcinoma: islet cell	59	5.58	0.00	11.67	2	11	6	10	2	3	0	8	2	0	7	8
SKIN MISCELLANEOUS																
Keratoacanthoma	49	4.64	0.00	13.39	15	6	1	2	0	0	1	3	4	3	8	6
SUBCUTANEOUS TISSUE																
Osteosarcoma	1	0.09	0.00	1.00	0	0	0	1	0	0	0	0	0	0	0	0
THYROID																
Adenoma: C-cell	86	8.14	3.33	16.96	19	5	4	10	2	7	6	4	8	5	5	11

PATHOLOGY
MICROSCOPIC FINDING HISTORICAL DATA (Female)

Species / Strain: Rat / Sprague Dawley
Route of Admin.: All routes
Age at Necropsy: From approximately 104 to 114 weeks old
Treatment Duration: 98 to 104 weeks

	Total No. of animals			Study ID:	A	B	C	D	E	F	G	H	I	J	K	L
				Study start:	1998	2000	2001	2002	1998	2002	2004	2005	2005	2007	2007	2009
	1057			Total No. of Animals Examined:	112	120	120	100	50	120	60	75	60	60	60	120
Organ	**Lesion**	**Total No. of Lesions**	**%**	**%Min**	**%Max**												
ADRENAL																	
	Adenoma: cortical	47	4.45	0.00	10.00	3	3	5	10	2	2	1	5	6	0	3	7
	Benign pheochromocytoma	35	3.31	0.00	10.00	4	2	4	1	0	2	2	7	0	1	6	6
BONE MISCELLANEOUS																	
	Osteosarcoma	1	0.09	0.00	0.83	0	0	0	0	0	0	0	0	0	0	0	1
KIDNEY																	
	Lipoma	4	0.38	0.00	4.00	0	0	0	0	2	0	0	0	0	0	0	2
PANCREAS																	
	Adenoma: islet cell	31	2.93	0.00	8.33	1	7	3	4	1	2	0	3	5	3	0	2
	Carcinoma: islet cell	28	2.65	0.00	6.67	0	8	2	4	0	1	1	5	3	0	0	4
SKIN MISCELLANEOUS																	
	Keratoacanthoma	4	0.38	0.00	1.67	0	1	0	0	0	0	1	1	1	0	0	0
STOMACH																	
	Osteosarcoma	1	0.09	0.00	0.83	0	0	0	0	0	0	0	0	0	0	0	1
THYROID																	
	Adenoma: C-cell	91	8.61	2.67	20.54	23	11	12	7	2	6	5	2	5	3	5	10

PATHOLOGY
MICROSCOPIC FINDING HISTORICAL DATA (Male)

Species/Strain: Rat/Sprague Dawley
Route of Admin: All routes
Age at Necropsy: From approximately 110 to 112 weeks old
Treatment Duration: 104 weeks

	Total No. of animals			Study ID	A	B	C	D	E	F	G	H	I	J	K	L
				Study Start:	2000	1999	1998	2000	2001	2002	1998	2002	2004	2005	2005	2007
	1002			Total no. of animal examined:	60	65	112	120	120	100	50	120	60	75	60	60
Organ	**Lesion**	**Total No of Lesions**	**%**	**% Min**	**% Max**												
MAMMARY GLAND																	
	Adenocarcinoma	7	0.70	0.00	5.00	0	0	0	0	0	0	1	0	0	1	3	2
	Adenoma	3	0.30	0.00	2.00	0	0	0	0	0	1	1	0	0	0	0	1
	Fibroadenoma	13	1.30	0.00	4.00	1	0	2	3	1	0	1	0	1	3	0	1

PATHOLOGY
MICROSCOPIC FINDING HISTORICAL DATA (Female)

Species/Strain: Rat/Sprague Dawley
Route of Admin: All routes
Age at Necropsy: From approximately 110 to 114 weeks old
Treatment Duration: 98 to 104 weeks

	Total No. of animals	Study ID	A	B	C	D	E	F	G	H	I	J	K	L
		Study Start:	2000	1999	1998	2000	2001	2002	1998	2002	2004	2005	2005	2007
	1002	Total no. of animal examined:	60	65	112	120	120	100	50	120	60	75	60	60
Organ Lesion	Total No of Lesions	%	% Min	% Max										
MAMMARY GLAND														
Adenocarcinoma	205	20.46	5.36	33.33	14	13	6	13	40	24	11	26	15	22	13	8
Adenoma	82	8.18	0.00	18.00	3	1	3	15	6	6	9	20	5	8	0	6
Carcinosarcoma	1	0.10	0.00	0.83	0	0	0	0	0	0	0	1	0	0	0	0
Fibroadenoma	379	37.82	20.00	64.29	23	13	72	29	50	44	23	24	15	26	30	30
Fibroma	1	0.10	0.00	0.83	0	0	0	0	0	0	0	1	0	0	0	0
Fibrosarcoma	1	0.10	0.00	0.89	0	0	1	0	0	0	0	0	0	0	0	0

2 year rat study protocol: concurrence

Executive CAC
October 11, 2011

Committee:	David Jacobson-Kram, Ph.D., OND IO, Chair Paul Brown, Ph.D., OND IO, Member Aisar Atrakchi, Ph.D., DPP, Alternate Member Gemma Kuijpers, Ph.D., Presenting Reviewer
Also attending:	Eric Andreasen, Ph.D, DRUP
Author of Draft:	Gemma Kuijpers, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND #:	**100,391**
Drug Name:	AMG785
Sponsor:	Amgen Inc.

Background
AMG785 is a humanized murine monoclonal IgG2 antibody against sclerostin, a glycoprotein that blocks bone formation by inhibiting the Wnt/ß-catenin pathway in the osteoblast. AMG785 is expected to increase bone formation and bone mass. The indication for the IND is postmenopausal osteoporosis. The Phase 3 dose selected is 210 mg every month (QM). The intended treatment duration is 12 months.

Rat Carcinogenicity Study Protocol and Dose Selection
The Sponsor proposes to conduct a 2-year study in SD rats with weekly SC injections of 0, 3, 10, 50 mg/kg (70 mg/mL, 1.43 mL/kg). The vehicle is composed of (b) (4) (b) (4).

Dose selection was based on the expected pharmacologic effect in bone, clinical exposure multiples, and the lack of significant toxicity in a completed 6-month rat toxicity study. The pharmacologic effect in the rats is expected to be a multiple of 0.7x, 2x and 3x the clinical effect. Anticipated exposure multiples are 0.3x, 3.2x, and 18x.

The Sponsor plans to start the study with N= 60, 150, 80, 80/sex/grp, vehicle, low dose, mid dose and high dose, respectively, based on expected immunogenicity. Animals that develop antibodies against AMG785 at Week 13 will then be removed from the study. If the number of rats in any

Reference ID: 4075258

group becomes less than 60/sex/grp, animals with non-neutralizing Ab's will be re-introduced to render N=60/sex/grp. This approach is likely to ensure a group size of N=60/sex/grp rats testing anti-AMG785 antibody-negative.

Executive CAC Recommendations and Conclusions

Rat study:

- The Committee concurred with the Sponsor's proposed doses of 3, 10 and 50 mg/kg/week, by SC injection, based on exposure multiples and expected pharmacologic effect.
- The Committee recognized that blood sampling will be needed to determine anti-AMG785 antibodies in Week 13.
- The Committee recommended that the Sponsor include both saline and vehicle control groups in the study, if historical data on the use of the vehicle by this administration route are not available.
- The Committee noted that rats are usually 6-8 weeks rather than 10 weeks of age at the start of a 2-year study; the Committee recommended that the Sponsor consider using animals of a younger age, or justify the use of animals of an older age at start of study.

Note: If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

(a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
(b) for statistically significant or otherwise remarkable findings in the high dose group, the sponsor will need to look at the affected tissues in all of the dose groups.
(c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
(d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DRUP
/LReid, DRUP
/GKuijpers, DRUP
/MKaufman, DRUP
/ASeifried, OND IO

Reference ID: 4075258

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/s/

MIYUN M TSAI-TURTON
03/27/2017

KIMBERLY P HATFIELD
03/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761062
Supporting document/s:	SDN 1 (eCTD 0001)
Applicant's letter date:	7/19/2016
CDER stamp date:	7/19/2016
Product:	Romosozumab, AMG 785
Indication:	Osteoporosis in postmenopausal women at increased risk of fracture
Applicant:	Amgen, Inc.
Review Division:	Division of Bone, Reproductive, and Urologic Products
Reviewer:	Andrea L. Benedict, Ph.D.
Team Leader:	Kimberly P. Hatfield, Ph.D.
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Samantha S. Bell

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 761062 are owned by Amgen, Inc. or are data for which Amgen, Inc. has obtained a written right of reference.
Any information or data necessary for approval of BLA 761062 that Amgen, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 761062.

Reference ID: 4063752

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1 Executive Summary

1.1 Introduction

Amgen has submitted BLA 761062 for romosozumab (AMG 785). The product is a humanized anti-sclerostin IgG2 antibody that neutralizes sclerostin, the product of the SOST gene and an inhibitory factor in the bone formation process. Romosozumab is proposed to be indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. The recommended human dosage is 210 mg administered subcutaneously once every month for 12 doses. Romosozumab is supplied in a single-use prefilled syringe (90 mg/mL).

The sponsor submitted a nonclinical pharmacokinetic (PK) bridging study of subcutaneously administered AMG 785 Process 1 and Process 2 material in the male cynomolgus monkey to the BLA for the purposes of establishing a bridge to the chronic toxicity studies in the rat and cynomolgus monkey. This PK bridging study is reviewed herein.

1.2 Brief Discussion of Nonclinical Findings

The evidence from the non-GLP single-dose subcutaneous PK bridging study in the naïve male cynomolgus monkey (Study 113155) provides support that AMG 785 Process 1 and Process 2 drug products are similar from the nonclinical perspective.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)
909395-70-6

Generic Name
Romosozumab

Code Name
AMG785

Chemical Name
Anti-sclerostin monoclonal antibody

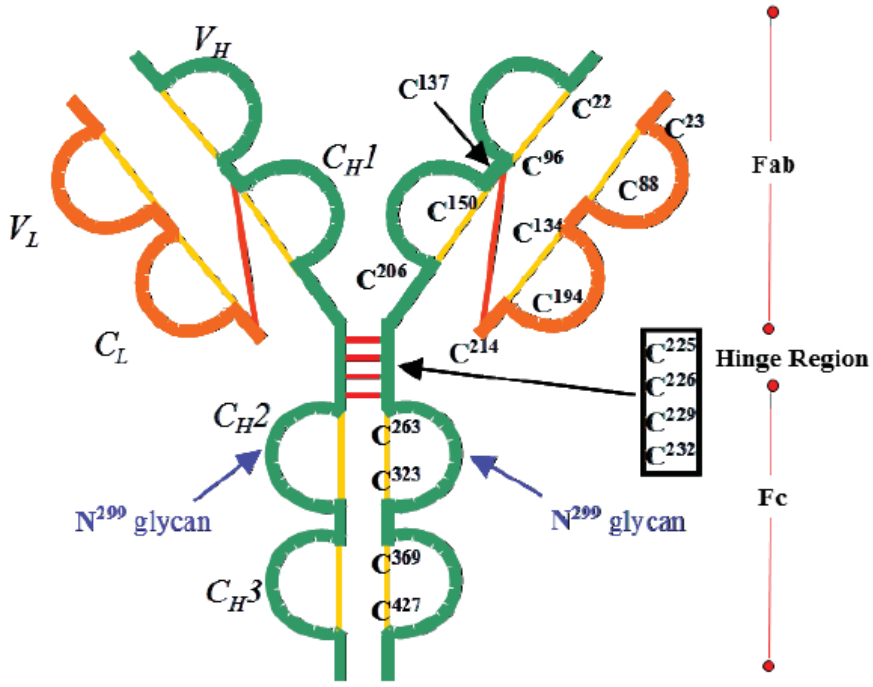
Molecular Formula/Molecular Weight
The molecular formula for the predominant romosozumab (AMG 785) heavy chain isoform (C-terminal glycine) is $C_{2189}H_{3364}N_{580}O_{682}S_{21}$, not including N-linked glycans. The molecular formula for romosozumab light chain is $C_{1031}H_{1605}N_{275}O_{337}S_{6}$. The theoretical mass of fully assembled, disulfide-bonded romosozumab antibody with heavy chain C-terminal glycine and without the addition of the N-linked glycans is 145,622 Da. The predominant glycan moiety, A2G0F, has an empirical formula of $C_{56}H_{92}N_{4}O_{39}$ and has an empirical mass of 1,445 Da. Thus, the theoretical mass of

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glycosylated romosozumab containing 2 N-linked glycans (1 per heavy chain) is 148,511 Da.

Structure or Biochemical Description
Romosozumab (AMG 785) is a humanized anti-sclerostin monoclonal antibody expressed in a Chinese hamster ovary (CHO) cell line. Romosozumab consists of 2 heavy chains of the IgG2 subclass and 2 light chains of the human kappa subclass. Each heavy chain contains 449 amino acids with 4 intrachain disulfides. Each light chain contains 214 amino acids with 2 intrachain disulfides. The schematic structure with one of the known disulfide bonding patterns (IgG2-A) is shown in Figure 1 (excerpted from the sponsor's submission).

Figure 1: Romosozumab (AMG 785) Structure



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

V_H is the variable domain of the heavy chain

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

V_L is the variable domain of the light chain

C_L is the constant domain of the light chain

Pharmacologic Class
Humanized anti-sclerostin monoclonal antibody

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 100391
IND 103077

2.3 Drug Formulation

Table 1 provides a summary of the AMG 785 drug product process materials and formulations used during drug development. The Process 1 drug substance formulation was (b) (4) (b) (4). The Process 2 drug substance formulation, which is the commercial process and formulation, is (b) (4) (b) (4)

The Process 1 drug substance formulation was used in phase 1 and phase 2 clinical studies, as well as in early nonclinical studies and in the 6-month chronic toxicity studies in the rat and cynomolgus monkey. The commercial Process 2 drug substance formulation was used in clinical studies during phase 1 through 3 of development, as well as in the nonclinical developmental and reproductive toxicity and carcinogenicity studies in the rat. The sponsor has provided a PK bridging study in the male cynomolgus monkey, to bridge between the nonclinical studies utilizing the two different process materials and formulations, which is reviewed herein.

Under the IND (IND 100391), the changes in the manufacturing process and comparability between the Process 1 and Process 2 drug substance and drug product were evaluated by the Product Quality Team. The product quality information submitted by the sponsor under the IND amendment (SDN 120 [eCTD 0118], dated October 11, 2011) was considered adequate to support the changes in the manufacturing process and to establish comparability between the Process 1 and Process 2 drug substance and drug product, and the Process 2 drug product was allowed to proceed for use in clinical studies under the IND. See the Product Quality Review of Dr. Dougherty, dated December 5, 2012, for further information. Internal discussion with the NDA's Product Quality Team on February 9, 2017, confirmed that the comparability of AMG 785 Process 1 and Process 2 materials has been adequately demonstrated from the Product Quality perspective for the NDA.

Table 1: Comparison of AMG 785 drug product process material and formulation used in nonclinical and clinical studies

Parameter	Phase 1/Phase 2	Phase 1/Phase 2/Phase 3/ Commercial
Drug Substance	Process 1	Process 2, Commercial Process
Delivery Method	IV, SC	SC
Product Presentation	70 mg/mL in vial	70 mg/mL or 120 mg/mL both in glass prefilled syringe, or 90 mg/mL in CZ syringe
(b) (4)		

2.4 Comments on Novel Excipients

There are no novel excipients for the subcutaneous route of administration. Comments on acceptability of levels of excipients in the to-be-marketed formulation will be addressed in a subsequent review.

2.5 Comments on Impurities/Degradants of Concern

Comments on impurities and degradants of concern in the to-be-marketed formulation will be addressed in a subsequent review.

2.6 Proposed Clinical Population and Dosing Regimen

Romosozumab is being proposed for the treatment of osteoporosis in postmenopausal women at an increased risk of fracture. The proposed dosing regimen is 210 mg romosozumab administered subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm.

2.7 Regulatory Background

The sponsor, Amgen, submitted the original IND (IND 100391) on October 27, 2006. There was no pre-IND meeting or communications prior to the original IND submission. Amgen submitted a new BLA submission on July 19, 2016, under BLA 761062.

3 Studies Submitted

3.1 Studies Reviewed

Study 113155: Pharmacokinetic Report for “A Single Subcutaneous Dose Pharmacokinetic Study of AMG 785 Manufactured by the FIH Process and CPD Process in Naïve Male Cynomolgus Monkeys”

3.3 Previous Reviews Referenced

- Product Quality Review of Dr. Michele K. Dougherty, IND 100391, dated December 5, 2012
- Nonclinical review of Dr. Eric A. Andreasen, IND 103077, dated June 18, 2009

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: Pharmacokinetic Report for "A Single Subcutaneous Dose Pharmacokinetic Study of AMG 785 Manufactured by the FIH Process and CPD Process in Naïve Male Cynomolgus Monkeys"

Study no.:	113155
Study report location:	Electronic Document (eCTD 0001)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not given; Report signed May 10, 2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	AMG 785 FIH (Process 1): Lot # 00089336 (used in 6-month rat and monkey studies) AMG 785 CPD (Process 2): Lot # 0010039243

Reviewer comment: This is a non-GLP study submitted as a summary report, lacking certain specifics on methodology and did not contain information about drug formulation, certificates of analysis, or dosing solution analysis.

Methods

Doses:	Target: 3 mg/kg AMG 785 FIH or 3 mg/kg AMG 785 CPD Actual: 3 mg/kg AMG 785 FIH or 2.75 mg/kg AMG 785 CPD*
Frequency of dosing:	Single-dose
Route of administration:	Subcutaneous injection
Dose concentration:	Target: 70 mg/mL AMG 785 FIH or 129 mg/mL AMG 785 CPD Actual: 70 mg/mL AMG 785 FIH or 118 mg/mL AMG 785 CPD*
Dose volume:	Target: 42.9 µL/kg AMG 785 FIH or 23.3 µL/kg AMG 785 CPD
Formulation/Vehicle:	Not given in study report
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	10 males/group
Age:	Not given
Weight:	Not given
Satellite groups:	N/A
Unique study design:	N/A
Deviation from study protocol:	1) *Due to an error in the certificate of analysis for the AMG 785 CPD material, animals in the CPD treatment group received 2.75 mg/kg instead of the targeted 3 mg/kg AMG 785 (~91.5% of the nominal dose). The certificates of analysis were not provided in the report. Also study report notes an actual concentration AMG785 CPD as 118 mg/mL but the COA was not available for confirmation. Additionally, no formulation information was provided. 2) One animal from FIH treatment group (C38468) had no measurable drug exposure and was excluded entirely from all analyses and summary statistics. ***Reviewer Comment:*** These deviations were determined to not significantly impact the outcome of the study. See further discussion below.

Objective
This non-GLP study was conducted to determine the relative bioavailability of two AMG 785 treatments (i.e., FIH and CPD) when administered as a single subcutaneous injection to naïve male cynomolgus monkeys. The FIH and CPD treatments differ in formulation and are made using different AMG 785 manufacturing processes (i.e., Process 1 and Process 2 materials, respectively).

Methods
The study report states that serum samples for PK analysis were collected from each animal at pre-dose and at 1, 4, 8, 12, 24, 48, 72, 96, 144, 192, 240, 312, 408, and 504 hours post-dose. Serum AMG 785 concentrations were determined using a validated ELISA (MET-000018 v 4.0) with a lower limit of quantitation (LLOQ) of 22.9 or 50.0 ng/mL. Serum samples for antibody analysis were collected and analyzed for the presence of binding and neutralizing antibodies using a validated immunoassay.

The study report did not provide information on the drug product formulation, certificates of analysis, or dosing solution analysis.

> ***Reviewer Comments:*** The validated ELISA method (MET-000018 v 5.0 and Study 108574) indicates that the LLOQ for this method is 50 ng/mL and the upper limit of quantitation (ULOQ) is 2500 ng/mL. It is unclear from the study report what the "LLOQ of 22.9 or 50.0 ng/mL" is referring to as described. Additionally, the study report methods section states that serum samples were analyzed for binding and neutralizing antibodies; however, no method was given or results discussed or presented in the report. One monkey in the FIH group (Animal No. C38468) did not have measureable AMG 785 exposure at any time point; however, as the other 9 monkeys in this group had measurable AMG 785 serum exposure that was relatively similar over the 504-hour observation period, it is unlikely that neutralizing antibodies greatly influenced the study outcome. Therefore, the absence of data on binding and neutralizing antibody formation from the study report does not preclude the review of this study.
>
> The study report provided lot numbers for the FIH and CPD treatments of 00089336 and 0010039243, respectively. The lot numbers given for FIH and CPD were determined to be nonclinical drug product batches representing the Process 1 drug substance formulation and the Process 2 drug substance formulation, respectively, based on information obtained from Section 3.2.P.2.3: Lot History - Manufacturing Details [Process 1 Vial] and [Process 2 Vial]. The drug product lot indicated for FIH (i.e., 00089336) was also used in the 6-month rat and monkey subcutaneous toxicity studies. The drug product lot indicated for CPD (i.e., 0010039243) appears to only have been used to represent the Process 2 drug substance formulation for this PK bridging study.
>
> Based on the Quality Overall Summary: Drug Product: Formulation Development (Section 3.2.P.2.2), Process 1 and Process 2 differ in both the manufacturing process utilized as well as product formulation.
>
> The drug products formulations are stated as follows:

- Process 1 drug product formulation: (b) (4) (b) (4)
- Process 2 (commercial process) drug product formulation: (b) (4) (b) (4)

Certificates of analysis and dosing solution analysis for FIH or CPD drug product were not provided in the report. The study report notes the following deviation: "*After an in-life portion of the study, it was discovered the certificate of analysis for the CPD material contained an error. The AMG 785 concentration was actually 118 mg/mL instead of the indicated 129 mg/mL. As a result, animals in the CPD treatment group received 2.75 mg/kg AMG 785 instead of the targeted 3 mg/kg (approximately 91.5% of the nominal dose).*" The lack of both certificates of analysis and dosing solution analysis preclude the ability to confirm the stated AMG 785 concentrations for the FIH and CPD treatments. Upon review, it has been determined that this deviation did not adversely affect the results of this study.

Observations and Results

Figure 2 and Figure 3 present the AMG 785 Concentration-Time profile on a semi-log and linear scale, respectively (excerpted from sponsor's submission). The pharmacokinetic (PK) parameters are presented in Table 2 as both absolute values and as dose normalized values.

Due to the error in dosing concentrations, a slightly higher dose of 3.0 mg/kg AMG 785 FIH (Process 1) was administered as compared to AMG 785 CPD (Process 2) at 2.75 mg/kg. Therefore, the absolute difference between the FIH and CPD doses was approximately 8% or approximately 91.5% of the target nominal dose for CPD.

The systemic exposure of a single-dose of FIH given at 3 mg/kg was found to be slightly greater than the systemic exposure of a single-dose of CPD given at 2.75 mg/kg. The absolute values for mean C_{max} and AUC indicate a difference of -11% and -17%, respectively, between the FIH- and CPD-treated animals. When corrected for the difference in dose, the mean C_{max} and AUC indicate a difference of -2.5% and approximately -10%, respectively, between the FIH- and CPD-treated animals.

Additionally, the mean T_{max} value for the CPD-treated animals was earlier, at approximately 24 hours post-dose, as compared to the FIH-treated animals that occurred at 48 hours post-dose.

Figure 2: Mean (±SD) AMG 785 Concentration-Time profiles following a single 3 mg/kg SC dose of AMG 785 given as 3 mg/kg FIH or 2.75 mg/kg CPD (semi-log scale)

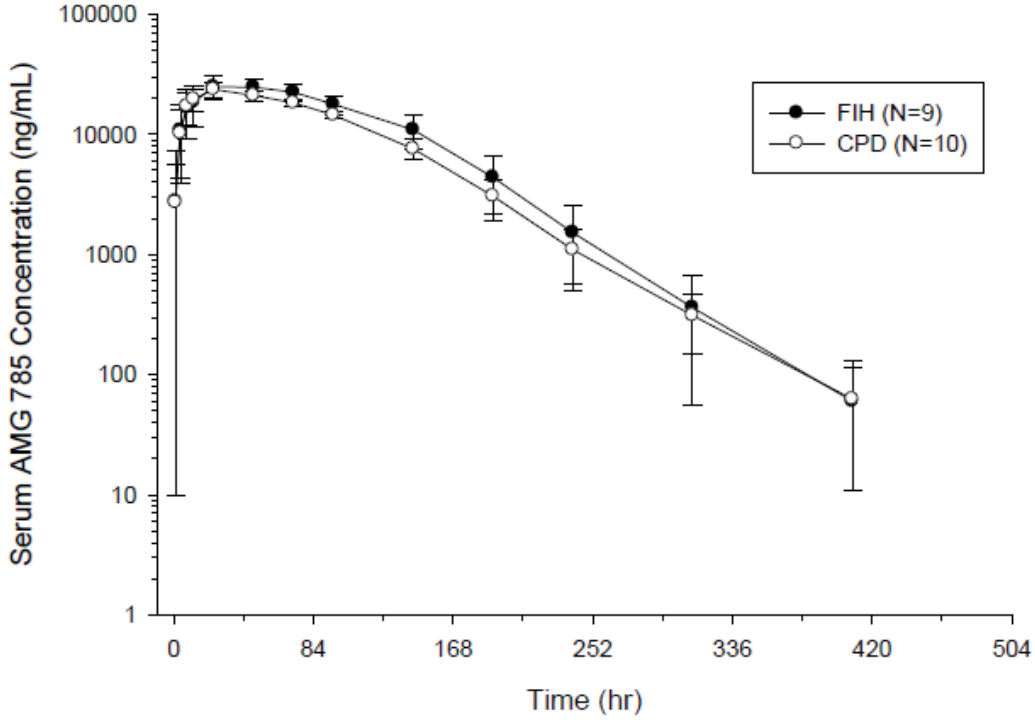


Figure 3: Mean (±SD) AMG 785 Concentration-Time profiles following a single 3 mg/kg SC dose of AMG 785 given as 3 mg/kg FIH or 2.75 mg/kg CPD (linear scale)

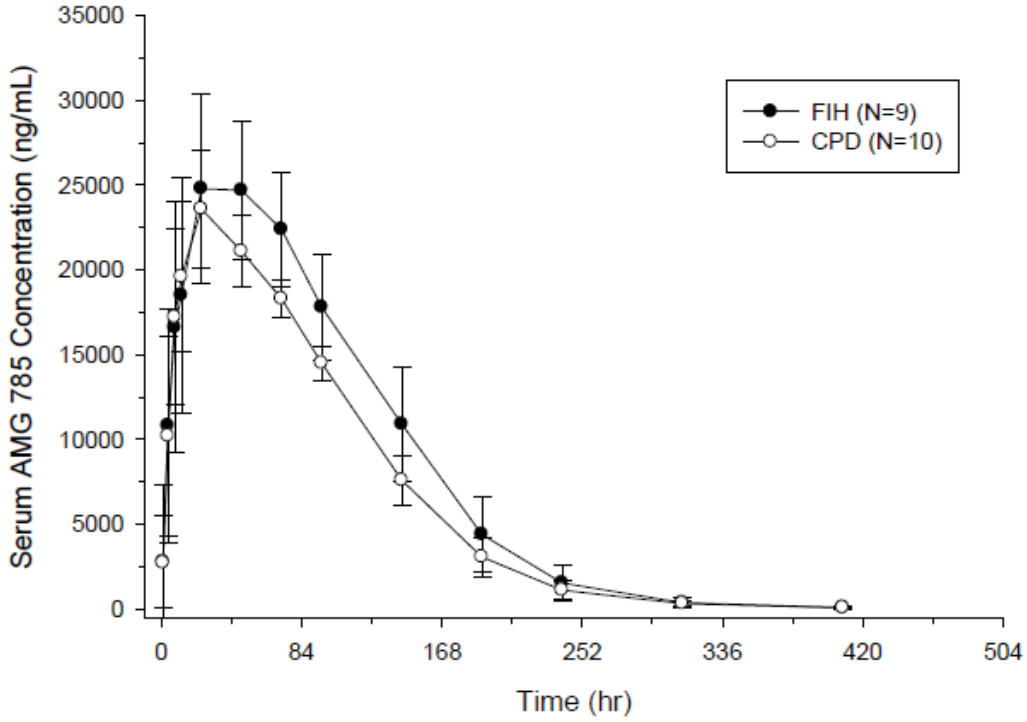


Table 2: PK parameters (absolute and dose normalized) for FIH (Process 1) and CPD (Process 2) from a single-dose PK bridging study in male monkeys

Drug Product	Dose (mg/kg)	Animal No.	Absolute PK Values				Dose Normalized PK Values		
			T_{max}	C_{max}	AUC_{last}	AUC_{inf}	C_{max}	AUC_{last}	AUC_{inf}
			h	µg/mL	µg*h/mL	µg*h/mL	µg/mL	µg*h/mL	µg*h/mL
FIH	3.0	C38468*	--	--	--	--	--	--	--
		C38912	24	26.8	2890	2890	8.9	963	964
		C38927	24	25.5	2640	2650	8.5	881	882
		C39107	24	28	3300	3310	9.3	1100	1100
		C39125	24	30.6	3210	3220	10.2	1070	1070
		C39337	48	31	4700	4710	10.3	1570	1570
		C40313	48	25.7	3290	3290	8.6	1100	1100
		C40314	48	28.3	3820	3830	9.4	1270	1280
		C40323	72	23.7	3220	3230	7.9	1070	1080
		C40330	72	18.3	2870	2870	6.1	957	958
		Mean	**43**	**26.4**	**3330**	**3330**	**8.8**	**1110**	**1110**
		SD	***20***	***3.9***	***620***	***620***	***1.29***	***200***	***200***
CPD	2.75	C38193	24	21.5	2810	2810	7.8	1020	1020
		C38195	48	19.2	2730	2730	7.0	991	990
		C38883	24	28.8	2840	2840	10.5	1030	1030
		C39047	24	24.4	2740	2750	8.9	997	1000
		C39102	24	21.2	2350	2350	7.7	853	860
		C40317	24	21.4	2530	2530	7.8	920	920
		C40321	24	22	2930	2930	8.0	1060	1070
		C40322	8	30.1	3160	3160	10.9	1150	1150
		C40328	24	23.2	2390	2400	8.4	869	870
		C40332	24	24.4	3160	3170	8.9	1150	1150
		Mean	**25**	**23.6**	**2760**	**2770**	**8.6**	**1000**	**1010**
		SD	***10***	***3.5***	***280***	***280***	***1.26***	***110***	***100***
CPD/FIH		**Ratio**	**0.58**	**0.89**	**0.83**	**0.83**	**0.98**	**0.90**	**0.91**
		% Difference	**-42%**	**-11%**	**-17%**	**-17%**	**-2.5%**	**-9.9%**	**-9.0%**

*Animal No. C38468: Serum AMG 785 concentrations were below the LLOQ for all time points; Animal was excluded from PK analysis

AUC values were rounded to 3 significant figures; calculations were performed by the sponsor using unrounded numbers

CPD/FIH Ratio was calculated using mean absolute and mean dose normalized PK parameters and expressed as a ratio of CPD/FIH values

Discussion and Conclusions

This non-GLP study was conducted to determine the relative bioavailability of AMG 785 Process 1 drug substance formulation (FIH) and AMG 785 Process 2 drug substance formulation (CPD) when administered as a single 3 mg/kg subcutaneous injection to naïve male cynomolgus monkeys. However, due to a dosing error the CPD-treated group received an AMG 785 dose of 2.75 mg/kg. Therefore, the PK parameters C_{max} and AUC were reviewed from both the perspective of absolute values as well as dose normalized values.

The differences observed between AMG 785 systemic exposures in male monkeys administered either a single SC dose of FIH at 3 mg/kg or CPD at 2.75 mg/kg were within 17% when comparing absolute C_{max} and AUC values and within 10% when C_{max} and AUC values were normalized for dose.

The study report states that "*It is likely that raw systemic exposure values between FIH and CPD treatments would have been more similar (<10% different) if equivalent doses were given. A comparison of systemic exposures parameters were made after dose normalization and expressed as a ratio. It is known that the pharmacokinetics of AMG 785 are greater than dose proportional; and thus a linear correction via dose normalization will under correct for the difference in dose and the actual difference in systemic exposure between treatments is likely less than that reflected in the ratio of dose normalized parameters*."

In the 6-month SC repeat-dose cynomolgus monkey study (Study 107426) which used the same AMG 785 Process 1 lot (i.e., Lot # 00089336) as in the current study, the results indicated that serum exposure to AMG 785 increased in a slightly greater than dose proportional manner between the doses of 3 to 100 mg/kg/day on Day 1 of dosing and that the mean T_{max} for all doses examined was 48 hours post-dose for male monkeys (see the Nonclinical review of Dr. Andreasen, IND 103077, dated June 18, 2009). It is plausible that the remaining difference in exposure between CPD and FIH after dose normalization could be a result of the greater than dose proportional PK for AMG 785, as was observed in the 6-month monkey toxicity study. Therefore, the differences observed between the systemic exposure after a single SC dose of 3 mg/kg FIH and 2.75 mg/kg CPD are considered acceptably similar from the nonclinical perspective.

Additionally, the mean T_{max} shift noted in the CPD-treated group towards an earlier time point of 24 hours fell within the T_{max} range for FIH-treated animals (i.e., 24-72 hours) and is not considered a concern at this time for a subcutaneously administered drug product.

Furthermore, the comparability between the Process 1 and Process 2 drug substance and drug product were evaluated by the Product Quality Team under the IND and NDA and the information provided was considered adequate to establish comparability between Process 1 and Process 2 drug substance formulations from the Product Quality perspective (see discussion under Section 2.3 Drug Formulation above). This provides evidence that the manufacturing and formulation changes made between Process 1 and Process 2 did not significantly alter the drug product quality.

Reference ID: 4063752

Taken together, the evidence from this non-GLP single-dose SC study in the male cynomolgus monkey provides support that AMG 785 Process 1 and Process 2 drug products are similar from the nonclinical perspective.

Reference ID: 4063752

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/s/

ANDREA BENEDICT
03/02/2017

KIMBERLY P HATFIELD
03/02/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA:	761062
Drug Name:	EVENITY® (romosozumab)
Indication(s):	Treatment of osteoporosis in postmenopausal women at high risk for fracture
Applicant:	Amgen
Date(s):	July 09, 2018 (Stamp date) January 02, 2019 (Completion date)
Safety Endpoint:	Major adverse cardiovascular events
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Tae Hyun Jung, PhD
Concurring Reviewers:	Clara Kim, PhD, Team Leader Mark Levenson, PhD, Division Director
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Jacqueline Karp, MD Theresa Kehoe, MD, Team Leader
Project Manager:	Samantha Bell, RPM

Keywords: romosozumab, major adverse cardiovascular events, positively-adjudicated cardiovascular serious adverse events, Duke University Clinical Research Institute adjudication, meta-analysis, network meta-analysis

1 EXECUTIVE SUMMARY

Romosozumab (EVENITY®) is a sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture. On July 19, 2016, Amgen submitted an original BLA, which included a 24-month phase 3 placebo-controlled fracture study (Study 337) in women with postmenopausal osteoporosis. During the review cycle, the sponsor notified the FDA of preliminary results from two studies (Studies 142, and 174) intended for a future supplement. Study 142, an active-controlled study in women, identified a higher incidence of serious cardiovascular (CV) events in the romosozumab arm (2.5%) compared to the alendronate arm (active control) (1.9%). A similar trend was observed in Study 174, a placebo control study in men with osteoporosis.

On July 13, 2017, the FDA issued a complete response letter stating that a complete analysis of Studies 142 and 174, as well as an integrated assessment of cardiovascular risk from the above phase 3 studies (Studies 337, 142 and 174) would be needed to complete the benefit-risk assessment of romosozumab. In response, on June 28, 2018, the sponsor submitted the Comprehensive Cardiovascular Report that integrated assessment of cardiovascular risk from all pivotal studies (Studies 337, 142 and 174).

The key safety endpoints were major adverse cardiac events (MACE) and cardiovascular serious events (CV SAEs) adjudicated by Duke University Research Institute. The safety analysis included events observed during the double-blind 12-month period.
The sponsor estimated the incidence and hazard ratio (HR) of MACE and CV SAE in each study. They conducted a meta-analysis, which compared romosozumab to alendronate and placebo combined. To distinguish the effect of alendronate on CV risk from the placebo effect, the reviewer conducted a network meta-analysis which compares multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of randomized controlled trials. The reviewer's analysis only included studies conducted in women with postmenopausal osteoporosis (Studies 337, and 142).
The HR in Study 337 comparing romosozumab to placebo was approximately 1.0. In contrast, in Study 142 comparing romosozumab to alendronate, the HR was 1.87 [95% confidence interval (CI): 1.11, 3.14], indicating an increased risk of MACE in the romosozumab arm compared to alendronate arm. The network meta-analysis resulted in a HR of 0.55 [95% CI: 0.27, 1.14] when comparing the risk of MACE in the alendronate arm to the placebo arm. This suggests that the large HR estimate in Study 142 might be because the incidence of MACE was low in the active control arm.

It is difficult to discern whether the increased risk of MACE identified in the romosozumab arm in Study 142 is truly a drug effect, chance finding, or because of alendronate's potential protective effect on MACE. However, because a similar trend was noted in the study of osteoporosis in men (Study 174), this signal provides corroborate evidence and should not be ignored.

Reference ID: 4370582

2 INTRODUCTION

2.1 Study Overview

Romosozumab (EVENITY®) is a sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture. The proposed dose of romosozumab is 210 mg administered subcutaneously once every month for one year. On July 19, 2016, Amgen submitted an original BLA, which included a 24-month phase 3, placebo-controlled fracture study (Study 337) in women with postmenopausal osteoporosis.

During the review cycle, the sponsor notified the FDA of preliminary results from Study 142, a phase 3 trial, intended for a future supplement. Study 142 compared romosozumab to an active control, alendronate, in women with postmenopausal osteoporosis. This study findings showed a higher incidence of serious cardiovascular (CV) events in the romosozumab arm (2.5%) compared to the alendronate arm (1.9 %) during the 12-month double-blind period of the study. Study 174, a placebo-controlled, phase 3 bone mineral density study in men with osteoporosis, also identified a higher incidence of serious CV events in the romosozumab (4.9%) arm compared to the placebo (2.5%) arm. In contrast, the incidences of serious CV events in Study 337 were similar across arms (1.3% romosozumab and 1.3% placebo).

On July 13, 2017, the FDA issued a complete response letter stating that a complete analysis of Study 142, as well as an integrated assessment of cardiovascular risk from the above phase 3 studies (Studies 337, 142 and 174) would be needed to complete the benefit-risk assessment of romosozumab. In response, the sponsor submitted the Comprehensive Cardiovascular Report (CCR) on June 28, 2018, in the current submission.

On August 17, 2018, the Division of Bone, Reproductive, and Urologic Products consulted the Division of Biometrics VII to evaluate the CV safety signal associated with romosozumab. This document is the statistical review of the CV safety of romosozumab.

Table 1. Studies included in the analysis

Study Number	Control	Treatment Period	# of Subjects per Arm	Study Population
337	placebo	12 months double-blind period + 12 months open-label denosumab treatment + 12 months optional extension period	romosozumab: 3589 placebo: 3591	Women with post-menopausal osteoporosis
142	alendronate	12 months double blind period + 12 months open-label alendronate treatment	romosozumab: 2046 alendronate: 2047	Women with post-menopausal osteoporosis
174	placebo	12 months double-blind period + 3 months follow-up	romosozumab: 163 placebo: 82	Men with osteoporosis

Source: Reviewer's summary

Reference ID: 4370582

2.2 Data Source

The data analyzed in this review are located at:
\\cdsesub1\evsprod\bla761062\0054\m5\datasets\crr\analysis\adam\datasets
The data were sufficient to perform the review.

3 STATISTICAL EVALUATION

3.1 Study Design and Population

3.1.1 Study 337

Study 337 is a randomized, double-blind, placebo-controlled, fracture study in postmenopausal women with osteoporosis. A total of 7180 subjects were randomized in a 1:1 ratio to receive either romosozumab (N = 3589) or placebo (N = 3591) for 12 months, followed by a 24-month open-label treatment period of denosumab.

3.1.2 Study 142

Study 142 is a randomized, double-blind, alendronate-controlled fracture study in postmenopausal women with osteoporosis. A total of 4093 subjects were randomized in a 1:1 ratio to receive romosozumab (N= 2046) or alendronate (N= 2047) for 12 months, followed by a 12-month open-label treatment period of alendronate. Compared to Study 337, Study 142 enrolled subjects at higher risk of fracture.

3.1.3 Study 174

Study 174 is a randomized, double-blind, placebo-controlled, bridging study that assessed changes in bone mineral density in men with osteoporosis. A total of 245 subjects were randomized in a 2:1 ratio to receive romosozumab (N = 163) or placebo (N = 82) for 12 months and followed for an additional 3 months after completion of the double-blind period for evaluation of safety and immunogenicity. No follow-on therapy was administered.

3.2 Safety Population and Endpoint

The analysis population was the safety population, which included all randomized subjects who received at least one dose of either romosozumab, placebo, or alendronate in the 12-month double-blind study period. The main safety endpoint of interest was major adverse cardiac events (MACE), defined as a composite endpoint of CV death, myocardial infarction (MI), and stroke. CV serious adverse events (CV SAEs) was the secondary endpoint of interest and was a composite endpoint of the following: death, cardiac ischemic events (MI, angina, coronary revascularization), cerebrovascular events (stroke, transient ischemic attack), noncoronary revascularization, hospitalization for heart failure, and peripheral vascular event not requiring revascularization. CV death included fatal events adjudicated as cardiovascular-related or undetermined. CV adverse events were adjudicated by the Duke University Clinical Research Institute (DCRI) and re-adjudicated by Thrombolysis in Myocardial Infarction (TIMI) Study Group. Because the DCRI and TIMI adjudications yielded similar results, the review is focused on the original DCRI-adjudication rather than the post-hoc TIMI-adjudication.

Reference ID: 4370582

3.3 Statistical Methods

The sponsor submitted a statistical analysis plan for the CCR on April 23, 2018, and submitted the CCR on June 28, 2018. The sponsor analyzed the outcome of interest, the time to the first occurrence of MACE, using a Cox regression model for each study. Subjects who did not have MACE in the double-blind period were censored either by loss to follow-up or at the end of double-blind period. In the analysis of the individual components of MACE, subjects were not censored when they experienced another type of CV event. The sponsor conducted the analysis using the double-blind 12-month period and the overall study period. The sponsor used the same model to analyze the CV SAEs. Also, the sponsor conducted a meta-analysis of the three studies, which compared the combined alendronate and placebo arms to the romosozumab group.

In addition to the sponsor's analysis, the reviewer conducted a meta-analysis only using the two studies in women (Studies 337 and 142), the indicated population. This meta-analysis did not distinguish the effect of the active control, alendronate, on the outcomes from the placebo effect, nor does it directly compare alendronate and placebo. Therefore, the reviewer conducted a network meta-analysis which compares multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of randomized controlled trials. Therefore, the analysis provides estimates that compare romosozumab to placebo and alendronate to placebo. The network meta-analyses were conducted on MACE and CV SAE events. The analysis used the same censoring criteria used in the sponsor's analyses. Additionally, the reviewer conducted network meta-analysis on individual components of MACE. The reviewer conducted two network meta-analyses based on fixed-effects models; univariate analysis with treatment group adjusted only and multivariate analysis with treatment group and age adjusted and stratified by countries.

3.4 Demographics and Baseline Characteristics

The mean age of study subjects was balanced between treatment groups within each study and ranged from 70.8 to 74.4 years old (Table 2). Cardiovascular medical histories were relatively balanced between the two trials within each study.

Table 2. Demographics and Baseline Characteristics (Studies 337, 142, 174)

	Study 337		Study 142		Study 174	
	Romosozumab	Placebo	Romosozumab	Alendronate	Romosozumab	Placebo
Number of subjects	3581	3576	2040	2014	163	81
Age (Mean (SD))	70.9 (7.0)	70.8 (6.9)	74.4 (7.5)	74.2 (7.5)	72.4 (7.4)	71.4 (6.9)
Smoking, n (%)						
Current/Former	982 (27.4)	1037 (29.0)	533 (26.1)	591 (29.3)	81 (49.7)	51 (63.0)
Never	2599 (72.6)	2539 (71.0)	1506 (73.8)	1423 (70.7)	82 (50.3)	30 (37.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Creatine	0.83	0.82	0.84	0.82	1.00	1.03

Reference ID: 4370582

Mean (SD)	(0.18)	(0.17)	(0.20)	(0.19)	(0.18)	(0.22)
Any cardiovascular related disease, n (%)	2649 (74.0)	2703 (75.6)	1618 (79.3)	1603 (79.6)	126 (77.3)	58 (71.6)
Ischemic Heart Disease, n (%)	318 (8.9)	343 (9.6)	295 (14.5)	257 (12.7)	26 (16.0)	18 (22.2)
Myocardial Infarction, n (%)	76 (2.1)	77 (2.2)	71 (3.5)	50 (2.5)	9 (5.5)	6 (7.4)
Revascularization, n (%)	51 (1.4)	48 (1.3)	40 (2.0)	42 (2.1)	10 (6.1)	11 (13.6)
Atrial fibrillation/ Atrial flutter, n (%)	58 (1.6)	76 (2.1)	93 (4.6)	76 (3.8)	7 (4.3)	4 (4.9)
Cerebrovascular, n (%)	179 (5.0)	198 (5.5)	149 (7.3)	186 (9.2)	15 (9.2)	10 (12.3)

Source: Sponsor's CCR, page 15, Table 1

3.5 Results

3.5.1 MACE

3.5.1.1 Incidence and Hazard Ratios

A total of 130 events across the three trials were adjudicated as MACE events in the 12-month double blind period; 77 MACE events in romosozumab group and 53 MACE events in placebo/alendronate group. In Study 337, the hazard ratio (HR) [95% confidence interval (CI)] of MACE comparing romosozumab to placebo was 1.03 [0.62, 1.72], indicating no difference in risk. However, the HR of MACE comparing romosozumab to alendronate was 1.87 [1.11, 3.14] in Study 142, indicating a higher risk in the romosozumab arm. The men study (Study 174) results indicated a trend in risk of MACE (HR = 1.55; [0.31, 7.69]) (Table 3).

Table 3. Number (%) and Hazard Ratios of MACE Composite and Individual Components through Month 12

	Study 337		Study 142		Study 174	
	Romosozumab N = 3581	Placebo N = 3576	Romosozumab N = 2040	Alendronate N = 2014	Romosozumab N = 163	Placebo N = 81
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
MACE	30 (0.8)	29 (0.8)	41 (2.0)	22 (1.1)	6 (3.7)	2 (2.5)
HR [95% CI]	1.03 [0.62, 1.72]		1.87 [1.11, 3.14]		1.55 [0.31, 7.69]	
CV Death	17 (0.5)	15 (0.4)	17 (0.8)	12 (0.6)	2 (1.2)	1 (1.2)
HR [95% CI]	1.13 [0.56, 2.26]		1.42 [0.68, 2.97]		1.04 [0.09, 11.46]	
MI	9 (0.3)	8 (0.2)	16 (0.8)	5 (0.2)	1 (0.6)	0 (0.0)
HR [95% CI]	1.12 [0.43, 2.91]		3.21 [1.18, 8.77]		Not Estimable	
Stroke	8 (0.2)	10 (0.3)	13 (0.6)	7 (0.3)	3 (1.8)	1 (1.2)
HR [95% CI	0.80 [0.32, 2.02]		1.86 [0.74, 4.67]		1.54 [0.16, 14.83]	

Reference ID: 4370582

Source: Sponsor's CCR, page 27, Table 5

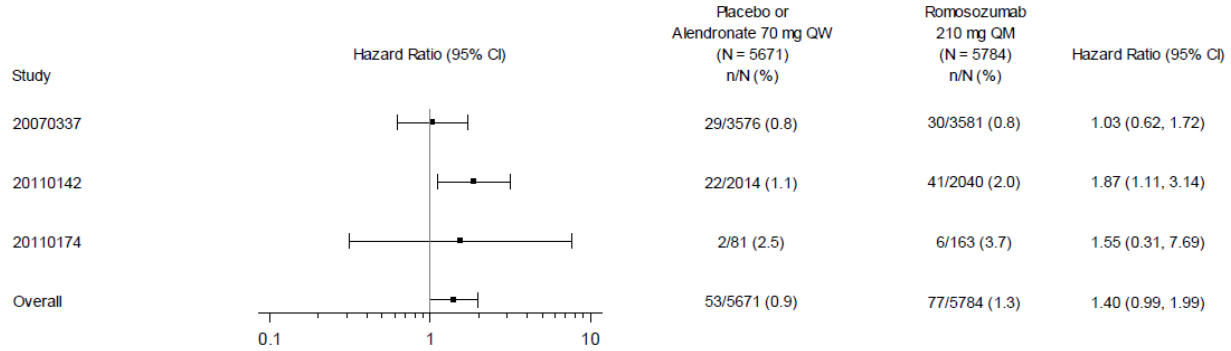
MACE: major adverse cardiac events; HR: hazard ratio; CV: cardiovascular; MI: myocardial infarction

3.5.1.2 Meta-Analysis

In the 12-month double-blind period, across the three trials, the total number (%) of MACE events was 77 (1.3%) among the romosozumab subjects and 53 (0.9%) among the control (placebo or alendronate) subjects. The HR [95% CI] of the meta-analysis of the three trials was 1.40 [0.99, 1.99] (Figure 1).

In the 12-month double blind period of the two studies in women, (Studies 337 and 142), the number (%) of MACE events was 71 (1.3%) among the romosozumab subjects and 51 (0.9%) among the control (placebo or alendronate) subjects. The HR [95% CI] of the meta-analysis was 1.38 [0.96, 1.99]. The results of the meta-analysis of the two women studies were similar to that of all three studies because of the small number of events in Study 174.

Figure 1. Time to first MACE through Month 12 (Studies 337, 142, and 174)



Source: Sponsor's CCR, page 24, Figure 2

3.5.1.3 Network Meta-Analysis

The univariate network meta-analysis of Studies 337 and 142 yielded a HR [95% CI] of 1.03 [0.62, 1.72] when comparing hazard of romosozumab arm to placebo arm. The HR was the same as that of Study 337 because only this study compared romosozumab and placebo. In contrast the HR [95% CI] comparing alendronate arm to placebo arm was 0.55 [0.27, 1.14]; although the CI included one, the estimated risk of MACE in the alendronate arm was lower compared to the placebo arm. The results, adjusted by treatment group and age and stratified by countries did not differ from the univariate analysis (Table 4).

Table 4. Network Meta-Analysis Results of MACE of Studies 337 and 142

Meta-analysis model	Treatment comparisons	HR [95% C.I]
Univariate	romosozumab vs. placebo	1.03 [0.62, 1.72]
Univariate	alendronate vs. placebo	0.55 [0.27, 1.14]

Reference ID: 4370582

Multivariate	romosozumab vs. placebo	1.02 [0.61, 1.70]
Multivariate	alendronate vs. placebo	0.55 [0.27, 1.15]

Source: Reviewer's analysis

3.5.1.4 Network Meta-Analysis of MACE Components

The HRs for CV death and MI, when comparing romosozumab to placebo were approximately 1.1, indicating a slightly higher risk in the romosozumab arm. However, that of stroke was 0.8, indicating a slightly lower risk in the romosozumab arm. The CIs for all three endpoints were wide.

When comparing the hazard of alendronate arm to placebo arm for the components, the network meta-analysis yielded HRs less than one, indicating a lower risk in the alendronate arm compared to placebo.

Table 5. Network Meta-Analysis of Components of MACE of Studies 337 and 142

Outcome	**Comparison**	**Hazard Ratio [95% CI]**
CV death	romosozumab vs. placebo	1.13 [0.56, 2.26]
	alendronate vs. placebo	0.80 [0.29, 2.20]
MI	romosozumab vs. placebo	1.12 [0.43, 2.91]
	alendronate vs. placebo	0.35 [0.09, 1.39]
Stroke	romosozumab vs. placebo	0.80 [0.32, 2.02]
	alendronate vs. placebo	0.43 [0.12, 1.58]

Source: Reviewer's analysis

3.5.2 CV SAE

3.5.2.1 Incidence and Hazard Ratio

A total of 190 events across the three trials were adjudicated as CV SAE in the 12-month double-blind period; 104 CV SAE events in the romosozumab arm and 86 CV SAE events in the placebo or alendronate arms. In Study 337, the number (%) of CV SAE events was 46 (1.3%) and 46 (1.3%), in the romosozumab and placebo arm, respectively. The HR [95% CI] of CV SAE comparing romosozumab to placebo was 1.0 [0.66, 1.50], indicating no difference in risk. The HR of CV SAE comparing romosozumab to alendronate was 1.32 [0.87, 2.01] in Study 174, indicating a numerically higher risk in the romosozumab arm. The men study results also indicated a numerically higher risk of CV SAE in the romosozumab arm compared to placebo (Table 6).

Reference ID: 4370582

Table 6. Number (%) of CV SAE events through Month 12

	Study 337		Study 142		Study 174	
	Romosozumab N = 3581	Placebo N = 3576	Romosozumab N = 2040	Alendronate N = 2014	Romosozumab N = 163	Placebo N = 81
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CV SAE	46 (1.3)	46 (1.3)	50 (2.5)	38 (1.9)	8 (4.9)	2 (2.5)
HR [95% CI]	1.0 [0.66, 1.50]		1.32 [0.87, 2.01]		2.08 [0.44, 9.80]	

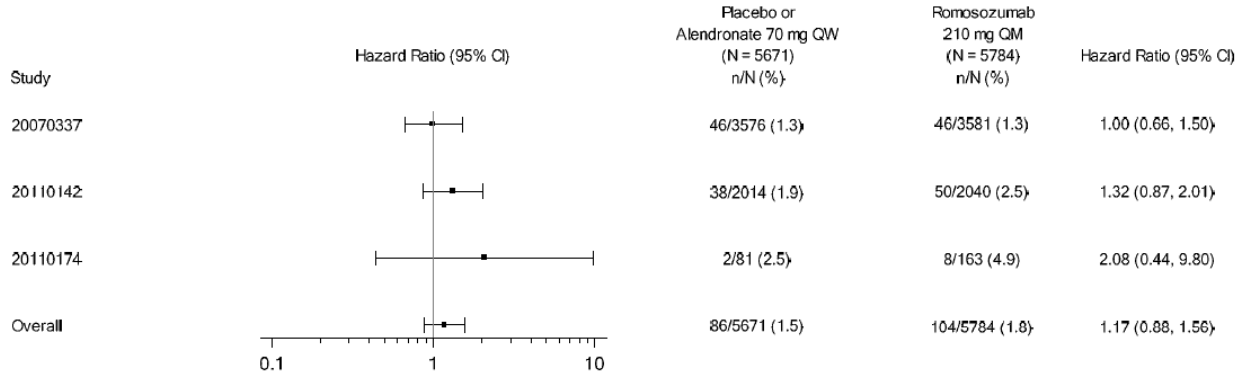
Source: Sponsor's CCR, page 51, Table 7

3.5.2.2 Meta-Analysis

In the 12-month double blind period, across the three trials, the total number (%) of CV SAE events was 104 (1.8%) in the romosozumab arm and 86 (1.5%) in the control (placebo or alendronate) arms. The HR [95% CI] of the meta-analysis of the three trials was 1.17 [0.88, 1.56] (Figure 2).

The reviewer's meta-analysis using the two studies in women (Studies 337 and 142) included 96 (1.7%) CV SAE events in the romosozumab arm and 84 (1.5%) events in the control (placebo or alendronate) arm. The HR [95% CI] of the meta-analysis was 1.14 [0.85, 1.53].

Figure 2. Time to First Occurrence of CV SAEs through Month 12



Source: Sponsor's, CCR page 3538, Figure 14-6.1.7.1.

3.5.2.3 Network Meta-Analysis

The univariate network meta-analysis of Studies 337 and 142 yielded a HR [95% CI] of 1.0 [0.66, 1.50] when comparing the hazard of the romosozumab arm to the placebo arm. The hazard ratio was the same as that of Study 337 because only this study compared romosozumab and placebo. In contrast, when comparing the hazard of the alendronate arm to the placebo arm, the HR [95% CI] was 0.76 [0.42, 1.36], which indicated a numerically lower risk in the alendronate arm compared to the placebo arm. The results, adjusted by treatment group and age and stratified by countries did not differ from the univariate analysis (Table 7).

Table 7. Network Meta-Analysis Results using CV SAE events of Studies 337 and 142

Reference ID: 4370582

Meta-analysis model	Treatment comparisons	HR (95% C.I)
Univariate	romosozumab vs. placebo	1.00 [0.66, 1.50]
Univariate	alendronate vs. placebo	0.76 [0.42, 1.36]
Multivariate	romosozumab vs. placebo	1.00 [0.66, 1.50]
Multivariate	alendronate vs. placebo	0.77 [0.43, 1.40]

Source: Reviewer's analysis

4 SUMMARY AND CONCLUSIONS

Romosozumab (EVENITY®) is a sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture. Because the study findings showed a higher incidence of serious cardiovascular (CV) events in the romosozumab arm compared to an active control (Study 142), and placebo (Study 174), the FDA issued a complete response letter on July 13, 2017, stating that a complete analysis of Study 142 and 174, as well as an integrated assessment of cardiovascular risk from the above phase 3 studies (Studies 337, 142 and 174) would be needed to complete the benefit-risk assessment of romosozumab. In response, on June 28, 2018, the sponsor submitted the CCR that integrated assessment of cardiovascular risk from all pivotal studies (Studies 337, 142 and 174).

The key safety endpoints were major adverse cardiac events (MACE) and cardiovascular serious events (CV SAEs) adjudicated by Duke University Research Institute. Events were observed during the double-blind 12-month period.

The sponsor estimated the incidence and hazard ratio (HR) of MACE and CV SAE in each study. They conducted a meta-analysis, which compared romosozumab to alendronate and placebo combined. To distinguish the effect of alendronate on CV risk from the placebo effect, the reviewer conducted a network meta-analysis which compares multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of randomized controlled trials. The reviewer's analysis only included studies conducted in women with postmenopausal osteoporosis (Studies 337 and 142).

The HR of Study 337 was approximately 1, whereas that was 1.87 [1.11, 3.14] in Study 142, indicating an increased risk of MACE in the romosozumab arm compared to alendronate arm. The network meta-analysis resulted in a HR of 0.55 [0.27, 1.14] when comparing the risk of MACE in the alendronate arm to the placebo arm. This suggests that the HR estimate in Study 142 might be because the incidence of MACE was low in the active control arm. However, the network meta-analysis had limitations because it only used two studies, which led to wide confidence interval. In addition, the HR comparing the alendronate arm to the placebo arm was estimated indirectly.

It is difficult to discern whether the increased risk of MACE identified in the romosozumab arm in Study 142 is truly a drug effect, chance finding, or because of alendronate's potential protective effect on MACE. However, because a similar trend was noted in a study of osteoporosis in men (Study 174), this signal provides corroborate evidence of risk and should not be ignored.

Reference ID: 4370582

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA Serial Number:	761062
Drug Name:	Romosozumab
Indication:	Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Applicant:	Amgen
Date(s):	Submission date: 7/19/2016
	PDUFA date: 7/19/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Jia Guo, Ph.D.
Concurring Reviewer:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive and Urologic Products
Clinical Team:	Debuene Chang, M.D., Clinical Reviewer
	Theresa Kehoe, M.D., Clinical Team Leader
Project Manager:	Samantha Bell

Keywords: incidence rate, risk reduction, relative risk, type I error , ANCOVA

Reference ID: 4077213

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1 EXECUTIVE SUMMARY

The Applicant submitted two randomized, double-blind phase 3 studies to provide evidence in support of the safety and efficacy of romosozumab 210 mg (90 mg/ml concentration) for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. One phase 3 studies was designed to demonstrate superiority of romosozumab 210 mg in 70 mg/ml concentration compared to placebo, while the second study was designed to demonstrate non-inferiority of romosozumab 210 mg in 90 mg/ml concentration, the intended dose for marketing, to romosozumab 210 mg in 70 mg/ml concentration.

The key efficacy endpoints were the reduction in the incidence of new vertebral fractures and increase in the bone mineral density (BMD) after 12 and 24 months of treatment. FDA analysis shows that treatment with romosozumab 210 mg (70 mg/ml concentration) compared to placebo reduced the risk of new vertebral fracture by 73% and 76%, at 12 and 24 month, respectively. Compared to placebo, treatment with romosozumab also significantly increased BMD at lumbar spine, total hip and femoral neck through 12 and 24 months.

The analysis further shows that romosozumab 210 mg in 90 mg/ml concentration was non-inferior to romosozumab 210 mg in 70 mg/ml concentration with respect to the percent change in BMD at lumbar spine.

The two studies provide evidence demonstrating the efficacy of romosozumab for the treatment of postmenopausal osteoporosis in women at increased risk of fracture.

2 INTRODUCTION

2.1 Overview

The Applicant, Amgen, seeks approval of EVENITY (romosozumab) injection for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. The proposed dose for marketing is 210 mg (90 mg/mL solution) subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm by a healthcare professional.

According to the Applicant:

> Romosozumab is a humanized monoclonal antibody that binds to and inhibits sclerostin, a negative regulator of bone formation. Romosozumab has a dual effect on bone, increasing bone formation and decreasing bone resorption. Romosozumab increases trabecular and cortical bone mass and improves bone structure and strength.

This statistical review is based on two pivotal phase 3 studies (20070337 and 20120156). Table 1 presents a brief summary of both studies.

Table 1: List of Studies Included in the Statistical Review

Study	Phase and Design	Treatment Period	# of Randomized Subjects per Arm	Study Population
20070337	Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled	Year 1: Placebo or romosozumab 210 mg (70 mg/ml solution) SC QM Years 2 and 3: Open-label denosumab 60 mg SC Q6M	Placebo:3591 Romosozumab: 3589	• Healthy ambulatory postmenopausal women from 55 to 90 years of age with osteoporosis. • Have a BMD T score ≤-2.5 and >-3.5 at the total hip (femoral neck) • No previous hip fracture or any severe or more than 2 moderate vertebral fractures
20120156	Phase 3 Multicenter, Randomized, Double-blind, Non-inferiority	6 months	Placebo: 53 Romosozumab 70mg/mL : 118 Romosozumab 90 mg/mL : 123	• Healthy ambulatory postmenopausal women from 55 to 90 years of age at high risk for fracture. • DXA BMD T-score of ≤ -2.50 at the lumbar spine, total hip or femoral neck. • Had a history of fragility fracture or met at least 2 clinical risk factors for fracture.

Source: Reviewer's summary.

2.2 Data Sources

The study reports, data and additional information were submitted electronically. These items are located in the Electronic Document Room at \\cdsesub1\evsprod\BLA761062 under submission dates 07/19/2016 and 03/02/2017.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Applicant submitted analysis data and statistical programs for both studies. Data sets were complete and documented. Statistical analyses of efficacy endpoints in each study were carried out following pre-specified statistical analysis plan.

3.2 Evaluation of Efficacy

This statistical review is based on both phase 3 studies listed in Table 1. Study 20070337 was designed to demonstrate superiority of romosozumab 210 mg (70 mg/ml concentration) compared to placebo, whereas study 20120156 was designed to demonstrate romosozumab 210 mg in 90 mg/ml concentration, the intended dose for marketing, is not inferior to romosozumab 210 mg in 70 mg/ml concentration.

From this point, romosozumab will be referred as romo in the rest of the review.

3.2.1 Study Design and Endpoints

Study 20070337

Study 20070337 was a multicenter, international, randomized, double-blind, placebo-controlled, phase 3 study of the safety and efficacy of romo 210 mg (in 70 mg/ml concentration) injection in ambulatory, postmenopausal women aged 55 to 90 years with osteoporosis at increased risk of fracture. Main enrollment criteria included:

- a BMD T-score $\leq$ -2.5 and > -3.50 at the total hip or femoral neck;
- at least 2 vertebrae in the L1 through L4 region and at least one hip are evaluable by DXA;
- no history of hip fracture;
- No severe or more than 2 vertebral fractures.

The study consisted of a screening period (up to 35 days), a double blind placebo-controlled period (12 months), an open-label period with denosumab (12 months) and an extension period (12 months). The extension period is currently ongoing. This review is for the first 24-month period after screening.

After screening, eligible subjects were equally randomized to receive either romo or matching placebo. Randomization was stratified by age (< 75 years, $\geq$ 75 years) and prevalent vertebral fracture (yes, no). During the 12-month double-blind study period, subjects received 3 subcutaneous (SC) injections of romo (i.e., 3 injections of 70 mg romo for a total dose of 210 mg) or matched placebo at each IP dosing visit (i.e., Day 1 study visit and monthly study visits thereafter to Month 11). During the 12-month open-label denosumab follow-up study period and the 12-month extension period, subjects received one SC injection of 60 mg denosumab Q6M in an open-label fashion. All SC injections must be administered by a healthcare professional. Calcium and vitamin D supplements were taken daily.

Efficacy assessments included evaluation by x-ray at Months 12, 24 and 36 and evaluations of bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) after 12, 24 and 36 months. Serum markers of bone metabolism, romo antibody, and patient report outcomes were also measured and recorded during the treatment period.

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The co-primary objectives of the study were

- to assess the effect of romo treatment for 12 months compared with placebo on the subject incidence of new vertebral fracture and;
- to assess the effect of romo treatment for 12 months followed by denosumab treatment for additional 12 months compared to placebo on the subject incidence of new vertebral fracture.

The co-primary endpoints were

- subject incidence of new vertebral fracture through Month 12.
- subject incidence of new vertebral fracture through Month 24.

The secondary endpoints are presented in Table 2 and assessed through Months 12 and 24, respectively.

Table 2: Study 20070337 - List of Secondary Efficacy Endpoints

Endpoint	Through Month 12	Through Month 24
Subject incidence of clinical fracture (non-vertebral fracture and clinical vertebral fracture)	√	√
Subject incidence of non-vertebral fracture	√	√
Subject incidence of new or worsening vertebral fracture	√	√
Subject incidence of major non-vertebral fracture (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip)	√	√
Subject incidence of hip fracture	√	√
Subject incidence of major osteoporotic fracture (hip, wrist, humerus, and clinical vertebral)	√	√
Subject incidence of multiple new or worsening vertebral fracture	√	√
Percent change from baseline in BMD at the lumbar spine, total hip, and femoral neck	√	√

Source: Reviewer's summary based on study protocol.

The three efficacy populations used for analyses are described below:

- Primary Analysis Set For Vertebral Fractures: all randomized subjects who had a baseline and ≥ 1 post-baseline evaluation of vertebral fracture at or before the time point under consideration. Subjects who had vertebrae with missing Genant semi quantitative scores at baseline and whose first post-baseline spinal radiograph showed no fracture on the same vertebrae were also included.

- Full Analysis Set: all randomized subjects. The full analysis set was used as the primary analysis set for non-vertebral fracture, clinical fracture, major non-vertebral fracture, major osteoporotic fracture and hip fracture efficacy endpoints.

- Primary Efficacy Analysis Set for BMD and PRO/ClinRO Endpoints: all randomized subjects who had a baseline and ≥ 1 post-baseline evaluation at or before the time point under consideration in the study period.

To control the overall type I error, the primary and secondary efficacy endpoints were tested sequentially in the following order.

1. Subject incidence of new vertebral fracture through months 12 and 24;
2. Subject incidence of clinical fracture through month 12;
3. Subject 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. Subject incidence of clinical fracture through month 24;

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5. Subject 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. Subject 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. Subject 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).

In the fixed-sequential testing procedure, the formal inferential testing was performed for a step only when the statistical significance was declared for all the endpoints tested in the previous steps. If the testing sequence was stopped at a particular step, the remaining endpoints in the testing sequence were not formally tested and were considered exploratory.

Study 20120156

Study 20120156 was a multicenter, randomized, phase 3 study to evaluate the non-inferiority of a 6-month romo 210 mg treatment at a 90 mg/mL concentration compared with a 6-month romo 210 mg treatment at a 70 mg/mL concentration in postmenopausal women with osteoporosis.

After screening, eligible subjects were randomized in a 22:5:22:5 ratios to the following treatment groups:

- romo 90 mg/mL: romo 210 mg QM, administered as 2 SC injections of a 90 mg/mL concentration in a 1.17 mL pre-filled syringe (PFS)
- placebo 90 mg/mL: placebo QM, administered as 2 SC injections of matched placebo to romo 90 mg/mL in the 1.17 mL PFS
- romo 70 mg/mL: romo 210 mg QM, administered as 3 SC injections of a 70 mg/mL concentration in a 1.0 mL PFS
- placebo 70 mg/mL: placebo QM, administered as 3 SC injections of matched placebo to romo 70 mg/mL in the 1.0 mL PFS

Randomization was double blind within the concentrations (romo 90 mg/mL and placebo 90 mg/mL; romo 70 mg/mL and placebo 70 mg/mL).

After completing a 6-month treatment period, subjects entered a 3-month follow-up period with end of study at month 9.

The primary analysis was performed after all subjects had the opportunity to complete the month 6 visit. The final analysis was performed after all subjects had the opportunity to complete the month 9 visit.

The primary endpoint was the percent change from baseline in DXA BMD at the lumbar spine (non-inferiority) and the secondary endpoints were

- percent change from baseline in DXA BMD at the total hip;
- percent change from baseline in DXA BMD at the femoral neck;
- percent change from baseline in BTMs P1NP and CTX.

The three efficacy populations used for analyses are described below:

- Primary efficacy analysis subset: all randomized subjects who had a baseline lumbar spine DXA BMD measurement and at least one post baseline lumbar spine DXA BMD measurement.

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- Hip BMD Efficacy Analysis Subset: all randomized subjects who had a baseline hip DXA BMD measurement and at least one post-baseline hip DXA BMD measurement.
- Bone Turnover Marker Efficacy Analysis Subset: all randomized subjects who had a baseline measurement and at least one post-baseline measurement for the endpoint of interest.

3.2.2 Statistical Methodologies

Study 20070337
The co-primary efficacy endpoints, the incidence of new vertebral fractures through months 12 and 24 were analyzed by a logistic regression model using the primary analysis set for vertebral fractures. The model included the treatment as the main effect and age and prevalent vertebral fracture as covariates. The odds ratio and the corresponding 95% 2-sided confidence interval and p-values using a score test were provided. Point estimates of absolute risk reduction (difference in proportions, control – treatment), risk ratio (ratio of proportions, treatment over control) and the relative risk reduction (100*(1-risk ratio)) as well as the corresponding 95% confidence intervals were also calculated via the Mantel-Haenszel method, adjusting for age and prevalent vertebral fracture strata.

The secondary fracture efficacy endpoints (i.e., incidences of non-vertebral fracture, clinical fracture, major non-vertebral fracture, major osteoporotic fracture and hip fracture) through months 12 and 24 were analyzed using the full analysis set. The cumulative incidence of fractures was summarized using the Kaplan-Meier estimates, and the hazard ratios and the confidence intervals for the risk reduction relative to placebo were based on the stratified Cox proportional hazards model.

The percent changes from baseline in lumbar spine, total hip and femoral neck by DXA at month 12 and month 24 were analyzed using the ANCOVA model with LOCF imputation using the primary efficacy analysis set for BMD and PRO/ClinRO endpoints. The ANCOVA model included treatment, age and prevalent vertebral fracture strata (stratification factors), and baseline value of the endpoint. Additional covariates of machine type and machine type-by-baseline value interaction were also included in the model to adjust for the effect of machine type on baseline value for parameters derived by DXA.

Study 20120156
The primary endpoint, the percent change from baseline in lumbar spine DXA BMD at Month 6 was analyzed by an analysis of covariance (ANCOVA) model using the primary efficacy analysis subset. The ANCOVA model included treatment (placebo, romo 70 mg/mL, romo 90 mg/mL) and baseline lumbar spine BMD T-score. For the evaluation of the non-inferiority hypothesis, the least squares mean of the treatment difference between romo treatment groups only (romo 90 mg/mL – romo 70mg/mL) and the corresponding lower one-sided 97.5% CI were estimated. Romo 90 mg/mL would be declared not inferior to romo 70 mg/mL if the lower bound of the one-sided 97.5% CI for the treatment difference was greater than the pre-specified NI margin of -2%.

The secondary BMD endpoints (total hip and femoral neck) were analyzed in the same way as the primary endpoint using the hip BMD efficacy subset. Least square mean estimates and two-sided 95% CIs for differences from placebo (romo 70 mg/mL – placebo, romo 90 mg/mL – placebo), and the least squares mean and corresponding two-sided 95% CI of the treatment difference between romo treatment groups only (romo90 mg/mL – romo 70 mg/mL) were provided.

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3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 20070337

Patient disposition is summarized in Table 3. In Study 20070337, a total of 7180 patients were randomized to two treatment groups. The discontinuation rate was 10.7% in the placebo group and 11.3% in the romo group. The most common reason for discontinuation was consent withdrawal.

Table 3: Study 20070337 - Summary of Patient Disposition

Double-blind period study	**Placebo n (%)**	**Romo210 mg (70 mg/ml) n (%)**	**All n (%)**
Randomized	3591 (100)	3589 (100)	7180 (100)
Completed double-blind period	3205 (89.3)	3185 (88.7)	6390 (89.0)
Discontinued study during double-blind	386 (10.7)	404 (11.3)	790 (11.0)
Consent withdrawn	253 (7.0)	261 (7.3)	514 (7.2)
Adverse event	39 (1.1)	39 (1.1)	78 (1.1)
Other	24 (0.7)	34 (0.9)	58 (0.8)
Death	20 (0.6)	27 (0.8)	47 (0.7)
Lost to follow-up	21 (0.6)	22 (0.6)	43 (0.6)
Noncompliance	16 (0.4)	9 (0.3)	25 (0.3)
Ineligibility determined	6 (0.2)	7 (0.2)	13 (0.2)
Protocol deviation	3 (<0.1)	2 (<0.1)	5 (<0.1)
Requirement for alternative therapy	2 (<0.1)	2 (<0.1)	4 (<0.1)
Administrative decision	2 (<0.1)	1 (<0.1)	3 (<0.1)

Percentages based on the number of patients randomized.
Source: Table 14-1.1 in Study 20070337 study report.

Demographic and baseline characteristics are summarized in the Appendix (Table 14 and Table 15). In Study 20070337, demographic and baseline characteristics were balanced among treatment groups. All patients were postmenopausal women aged 55 to 90 years. The mean age was 70.9 years with 31.2% of women being ≥75 years of age at enrollment. The median number of years since menopause was 20. Approximately 57% of the patients were white and 39.6% were Hispanic or Latino. The mean body mass index (BMI) was approximately 24.7 kg/m^2. About 18% of patients had prevalent vertebral fractures.

The majority of patients were from Central/Latin America (43.0%), followed by Central and Eastern Europe (29.2%), Western Europe and Australia/New Zealand (13.6%), and Asia Pacific (11.5%). However, only 1.8% of the randomized patients were from US.

Study 20120516

Patient disposition for study 20120516 is summarized in Table 4. A total of 294 patients were randomized into two treatment groups. The study discontinuation rate was 11.3% in the placebo group and about 5.8% in the two romo groups. The most common reason for discontinuation was consent withdrawal.

Table 4: Study 20120516 - Summary of Patient Disposition

	Placebo n (%)	Romo 70 mg/ml n (%)	Romo 90 mg/ml n (%)	All n (%)
Subjects who were randomized	53 (100.0)	118 (100.0)	123 (100.0)	294 (100.0)
Subjects who completed the study	47 (88.7)	110 (93.2)	117 (95.1)	274 (93.2)
Subjects who discontinued study	6 (11.3)	8 (6.8)	6 (4.9)	20 (6.8)
Withdrawal of consent of study	5 (9.4)	5 (4.2)	5 (4.1)	15 (5.1)
Protocol-specified criteria	0	1 (0.8)	0	1 (0.3)
Lost to follow up	1 (1.9)	2 (1.7)	1 (0.8)	4 (1.4)

Source: Table 14f-1.1 in study report.

Most subjects were White (99%); with only one Black (0.3%) and 2 Asian (0.7%). Overall, 277 (94.2%) subjects were not Hispanic or Latino and 17 (5.8%) subjects were Hispanic or Latino. The mean (SD) age of the subjects in this study was 67.7 (7.5) years and this was comparable across the 3 treatment groups; 61% of subjects were ≥ 65 years (see Table 16).

3.2.4 Results and Conclusions

This reviewer was able to replicate the Applicant's analysis results.

3.2.4.1 Analysis results for Study 20070337

New Vertebral Fracture

Table 5 presents the primary efficacy results for Study 20070337. The incidence of new vertebral fracture was 0.5% in the romo group compared to 1.8% in the placebo group (P-value: <0.001) through Month 12. The relative risk reduction in new vertebral fracture was 73% in patients receiving romo compared to placebo. The incidence of new vertebral fracture was 0.6% in the romo/denosumab group compared to 2.5% in the placebo/denosumab group (P-value: <0.001) through Month 24. The relative risk reduction in new vertebral fracture was 75% in patients receiving romo/denosumab compared to placebo/denosumab.

Table 5: Study 20070337 - Incidence of New Vertebral Fracture

Statistic	Through Month 12		Through Month 24	
	Placebo (N = 3591)	Romo (N = 3589)	Placebo/ Denosumab (N = 3591)	Romo / Denosumab (N = 3589)
Incidence, n/N1 (%)	59/3322 (1.8)	16/3321 (0.5)	84/3327 (2.5)	21/3325 (0.6)
Risk Comparison Estimates				
Absolute risk reduction (%)* 95% CI	1.30 (0.79, 1.80)		1.89 (1.30, 2.49)	
Relative risk reduction * 95% CI	73% (53%, 84%)		75% (60%, 84%)	
p-value†	< 0.001		< 0.001	

Source: Table 10-1 in study report.
N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures
*Based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables
†P-value is based on logistic regression

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Clinical Fracture and Non-vertebral Fracture

The study protocol pre-defined the clinical fractures as non-vertebral fractures and clinical (i.e. symptomatic) vertebral fractures. Table 6 shows that non-vertebral fractures accounted for more than 85% of clinical fractures.

The incidence of clinical fracture was 1.6% in the romo group compared to 2.5% in the placebo group (P-value: 0.008) through Month 12. Romo significantly reduced the risk of clinical fractures by 36% (95% CI: 11%, 54%) through Month 12.

Following the pre-specified testing sequence for type I error control, the incidence of non-vertebral fracture through month 12 and subject incidence of non-vertebral fracture through month 24 did not show statistically significant difference between the romo and placebo groups. No further testing on other endpoints proceeded from this point per the pre-specified testing sequence.

The incidence rate difference for clinical fractures between romo and placebo was mainly due to the difference for the clinical vertebral fractures, which were already included in the primary efficacy endpoint. Therefore, we believe that clinical fracture may not be an appropriate endpoint for fracture risk evaluation.

Table 6: Study 20070337 - Incidence of Clinical Fracture and Non-vertebral Fracture

Fracture Category /Time Point	**Incidence (n/N1 [%])**		**Absolute Risk Reduction % (95% CI)**	**Relative Risk Reduction % (95% CI)**	**Nominal p-value**	**α level**	**Statistically Significant**
Clinical	Placebo	Romo					
Month 12 [Step 1]	90/3591 (2.5)	58/3589 (1.6)	1.2% (0.4, 1.9)	36% (11, 54)	0.008	0.05	Yes
Month 24 [Step 3]	147/3591 (4.1)	99/3589 (2.8)	1.4% (0.5, 2.4)	33% (13, 48)	0.002	-	(stop testing)
Non-vertebral [Step2]	Placebo	Romo					
Month 12	75/3591 (2.1)	56/3589 (1.6)	0.8% (0.1, 1.4)	25% (-5, 47)	0.096	0.05	No
Month 24	129/3591 (3.6)	96/3589 (2.7)	1.0% (0.2, 1.9)	25% (3, 43)	0.029	0.025	No

Source: Table 10-2 in study report.
Steps 1 to 3 are the order in the testing sequence.
Relative risk reduction is calculated from the hazard ratio as 100 x (1 –hazard ratio).
Absolute risk reduction is based on inverse-weighted method adjusting for age and prevalent vertebral fracture stratification variables.
P-values are based on Cox proportional hazards model adjusting for age and prevalent vertebral fracture stratification variables.

Bone Mineral Density

Baseline bone mineral density (BMD) values were similar across all treatment groups for the total hip, femoral neck and lumbar spine (Tables 7-9). At month 12, compared with placebo, romo significantly ($p<0.001$) increased BMD at the lumbar spine by 12.7%, at total hip by 5.8%, and at femoral neck by 5.2%. Romo followed by denosumab resulted in continued increases in BMD at the lumbar spine, total hip and femoral neck at month 24. Mean differences in percent change from baseline to month 24 in BMD were significantly greater for subjects in the romo/denosumab group compared with the placebo/denosumab group ($p < 0.001$ at each site).

Table 7: Study 20070337- Summary of BMD at Lumbar Spine at Month 12 and Month 24

Location	Time Point	Statistic	Placebo/ Denosumab (N = 3591)	Romo/ Denosumab (N = 3589)
Lumbar spine	Baseline	Mean (SD)	0.8 (0.1)	0.8 (0.1)
	Month 12	% Change from baseline (SE) LS mean diff. (SE) 95% CI P-value	0.4 (0.1)	13.1 (0.1) 12.7 (0.1) (12.4, 12.9) <0.001
	Month 24	% Change from baseline (SE) LS mean diff. (SE) 95% CI P-value	5.5 (0.1)	16.6 (0.1) 11.1 (0.1) (10.8, 11.4) <0.001

Source: Reviewer's analysis, Table 10-3 in study report.
% change from baseline, LS means difference, 95% CI and P-value from ANCOVA model.

Table 8: Study 20070337- Summary of BMD at Total Hip at Month 12 and Month 24

Location	Time Point	Statistic	Placebo/ Denosumab (N = 3591)	Romo/ Denosumab (N = 3589)
Total Hip	Baseline	Mean (SD)	0.7 (0.1)	0.7 (0.1)
	Month 12	% Change from baseline (SE) LS mean diff. (SE) 95% CI P-value	0.3 (0.1)	6.0 (0.1) 5.8 (0.1) (5.6, 6.0) <0.001
	Month 24	% Change from baseline (SE) LS mean diff. (SE) 95% CI P-value	3.2 (0.1)	8.5 (0.1) 5.3 (0.1) (5.1, 5.5) <0.001

Source: Reviewer's analysis, Table 10-3 in study report.
% change from baseline, LS means difference, 95% CI and P-value from ANCOVA model.

Table 9: Study 20070337- Summary of BMD at Femoral Neck at Month 12 and Month 24

Location	Time Point	Statistic	Placebo/ Denosumab (N = 3591)	Romo/ Denosumab (N = 3589)
Femoral Neck	Baseline	Mean (SD)	0.6 (0.1)	0.6 (0.1)
	Month 12	% Change from baseline (SE) LS mean diff. (SE) 95% CI P-value	0.3 (0.1)	5.5 (0.1) 5.2 (0.1) (4.9, 5.4) <0.001
	Month 24	% Change from baseline (SE) LS mean diff. (SE) 95% CI P-value	2.3 (0.1)	7.3 (0.1) 4.9 (0.1) (4.7, 5.2) <0.001

Source: Reviewer's analysis, Table 10-3 in study report.
% change from baseline, LS means difference, 95% CI and P-value from ANCOVA model.

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3.2.4.2 Analysis results for Study 20120156

After 6 months of treatment, mean lumbar spine BMD increased 0.8%, 9.6%, and 9.2% in the placebo, romo 70 mg/mL, and romo 90 mg/mL groups, respectively (Table 10). The mean differences from placebo were 8.8% and 8.4% for the romo 70 mg/mL and romo 90 mg/mL groups, respectively (Table 10).

At lumber spine, the mean treatment difference between the romo 90 mg/mL and romo 70 mg/mL was -0.4% (-1.5%, 0.7%). Because the lower bound of the 1-sided 97.5% CI of the mean difference between the two romo groups was -1.5%, which was greater than the pre-specified limit of -2.0%, the data supports the claim of non-inferiority.

Table 10: Study 20120156 - Summary of BMD at Lumbar Spine at Month 6

Statistic	Placebo (N = 46)	Romo 70 mg/mL (N = 110)	Romo 90 mg/mL (N = 117)
Baseline (SD) % Change from baseline (SE)	0.8 (0.1) 0.8 (0.6)	0.8 (0.1) 9.6 (0.4)	0.8 (0.1) 9.2 (0.4)
LS mean diff vs. placebo (SE) 95% CI P-value vs. placebo		8.8 (0.8) (7.3, 10.3) <0.0001	8.4 (0.7) (6.9, 9.9) <0.0001
LS mean diff vs. Romo 70 mg/ml(SE) 95% CI P-value			-0.4 (-1.5, 0.7) 0.4739

Source: Reviewer's analysis, Table 10-1 in study report.
%change from baseline, LS means difference, 95% CI and P-value from ANCOVA model.

The percent change of BMD at total hip and femoral neck were also analyzed using the same approach for primary endpoint for exploratory purpose. Romo 90 mg/mL and romo 70 mg/mL, compared to placebo, showed similarly numerical treatment effect for the BMD percent change at total hip and lumbar spine at Month 6 (Tables 11 and 12).

Table 11: Study 20120156 - Summary of BMD at Total Hip at Month 6

Statistic	Placebo (N = 46)	Romo 70 mg/mL (N = 110)	Romo 90 mg/mL (N = 117)
Baseline (SD) % Change from baseline (SE)	0.7 (0.1) -0.0 (0.4)	0.7 (0.1) 3.9 (0.3)	0.7 (0.1) 3.4 (0.3)
LS mean diff vs. placebo (SE) 95% CI P-value vs. placebo		3.9 (0.5) (3.0, 4.9) <0.0001	3.5 (0.5) (2.5, 4.4) <0.0001
LS mean diff vs. Romo 70 mg/ml(SE) 95% CI P-value			-0.4 (0.4) (-1.2, 0.3) 0.2326

Source: Reviewer's analysis, Table 10-2 in study report.
%change from baseline, LS means difference, 95% CI and P-value from ANCOVA model.

Reference ID: 4077213

Table 12: Study 20120156 - Summary of BMD at Femoral Neck at Month 6

Statistic	Placebo (N = 46)	Romo 70 mg/mL (N = 110)	Romo 90 mg/mL (N = 117)
Baseline (SD) % Change from baseline (SE)	0.6 (0.1) -0.5 (0.5)	0.7 (0.1) 3.1 (0.3)	0.7 (0.1) 2.6 (0.3)
LS mean diff vs. placebo (SE) 95% CI P-value vs. placebo		3.6 (0.6) (2.4, 4.8) <0.0001	3.2 (0.6) (2.0, 4.3) <0.0001
LS mean diff vs. Romo 70 mg/ml(SE) 95% CI P-value			-0.5 (0.5) (-1.4, 0.4) 0.3014

Source: Reviewer's analysis, Table 10-3 in study report.
%change from baseline, LS means difference, 95% CI and P-value from ANCOVA model.

3.3 Evaluation of Safety

Refer to the clinical reviewer's review for evaluation of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Race, Age, and Geographic Region

The new vertebral fracture through months 12 and 24 was evaluated by subgroups of age, race, and region as defined in Table 13.

Table 13: Subgroup Categories

Grouping variable	Subgroups
Age group	< 65 years, ≥ 65 years < 75 years, ≥ 75 years
Race	White, non-white
Geographic Region	Western Europe and Australia/New Zealand, Central and Eastern Europe; Asia Pacific; North America; Central/Latin America

4.2 Other Special/Subgroup Populations

The applicant also evaluated the new vertebral fracture endpoint with each subgroup based on baseline characteristics as follows:

- prevalent vertebral fracture status (yes, no)
- history of fragility fracture (yes, no)
- history of non-vertebral fracture at age ≥55 years (yes, no)
- baseline lumbar spine BMD T-score (≤ -3, > -3 and ≤ -2.5, > -2.5)

Reference ID: 4077213

- baseline total hip or femoral neck BMD T-score ≤ -3 vs both total hip and femoral neck BMD T-score > -3
- baseline body mass index (BMI) (tertiles)
- World Health Organization Fracture Risk Assessment tool (FRAX) score for major osteoporotic fracture (tertiles)

To assess the consistency of the treatment effect in different subgroups, the incidence of new vertebral fractures was analyzed within each subgroup stratum listed above. The treatment-by-subgroup interaction was tested using a logistic regression model including treatment, age and prevalent vertebral fracture strata, individual subgroup, and treatment-by-subgroup interaction. All p-values on tests of quantitative interactions were > 0.05, and therefore, no relevant treatment-by-subgroup interactions (quantitative or qualitative) were identified through month 12 or through month 24 for any subgroup for the co-primary endpoints.

Subgroup analyses of the co-primary endpoints of subject incidence of vertebral fracture through 12 and 24 months demonstrated a consistent treatment effect (relative risk reduction romo over placebo and romo/denosumab over placebo/denosumab) in all subgroups of baseline characteristics examined (see Figures 1 and 2 in Appendix A2).

The percent changes from baseline in lumbar spine BMD and total hip BMD at month 12 and month 24 were analyzed by the following subgroups:

- baseline lumbar spine BMD T-score (≤-3, >-3 and ≤-2.5, >-2.5; for lumbar spine BMD analysis only)
- baseline total hip BMD T-score (≤-3, >-3 and ≤-2.5, >-2.5; for total hip BMD analysis only)

In the analyses of percent changes in BMD endpoints, treatment differences across the predefined subgroups (i.e., age, race and geographic region) for the lumbar spine and the total hip were consistent with the treatment differences observed for the overall population (see Figures 3 to 8 in Appendix A2).

Reviewer's comments: The applicant provided post-hoc subgroup analysis of BMD endpoint for femoral neck and for all BMD endpoints by race per reviewer's request.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were noted in this NDA.

5.2 Collective Evidence

One submitted study provides evidence that treatment with romo 210 mg (70 mg/ml concentration)

- reduced the incidence rate of new vertebral fracture compared to placebo (0.5% vs. 1.8%, P-value<0.0001) at month 12. The relative risk reduction in new vertebral fracture was 73%.
- reduced the incidence rate of new vertebral fracture compared to placebo (0.6% vs. 2.5%, P-value<0.0001) at month 24. The relative risk reduction in new vertebral fracture was 76%.
- increased bone mineral density at the total hip, femoral neck and lumbar spine by 5.8%, 5.2% and 12.7% compared to placebo at month 12.

Reference ID: 4077213

- increased bone mineral density at the total hip, femoral neck and lumbar spine by 5.3%, 4.9% and 11.1% compared to placebo at month 24.

The second study provides evidence that romo 210 mg in 90 mg/ml concentration was non-inferior to the 70 mg/ml concentration in the increase in BMD at lumbar spine.

5.3 Conclusions and Recommendations

The two studies provide evidence demonstrating the efficacy of romo for the treatment of postmenopausal osteoporosis in women at increased risk of fracture.

APPENDIX

A1. Demographics and Baseline Characteristics

Table 14: Study 20070337 Demographics and Baseline Characteristics

	Placebo/ Denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589)	All (N = 7180)
Sex - n (%)			
Female	3591 (100.0)	3589 (100.0)	7180 (100.0)
Ethnicity - n (%)			
Hispanic or Latino	1416 (39.4)	1427 (39.8)	2843 (39.6)
Not Hispanic or Latino	2175 (60.6)	2162 (60.2)	4337 (60.4)
Race - n (%)			
White	2052 (57.1)	2063 (57.5)	4115 (57.3)
Asian	441 (12.3)	425 (11.8)	866 (12.1)
Black or African American	74 (2.1)	77 (2.1)	151 (2.1)
American Indian/Alaska Native	63 (1.8)	64 (1.8)	127 (1.8)
Native Hawaiian/Other Pacific Islander	1 (<0.1)	0 (0.0)	1 (<0.1)
Multiple	59 (1.6)	60 (1.7)	119 (1.7)
Other	901 (25.1)	900 (25.1)	1801 (25.1)

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	Placebo/ Denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589)	All (N = 7180)
Age (years)			
n	3591	3589	7180
Mean	70.8	70.9	70.9
SD	6.9	7.0	7.0
Median	70.0	70.0	70.0
Min, Max	55, 90	55, 90	55, 90
Geriatric group - n (%)			
≥ 65 years	2834 (78.9)	2821 (78.6)	5655 (78.8)
≥ 75 years	1121 (31.2)	1119 (31.2)	2240 (31.2)
Weight (kg)			
n	3587	3581	7168
Mean	57.96	57.91	57.94
SD	11.10	10.83	10.96
Median	56.60	57.00	56.90
Min, Max	28.1, 133.0	22.3, 126.8	22.3, 133.0
Height (cm)			
n	3587	3580	7167
Mean	153.1	153.2	153.2
SD	7.4	7.3	7.3
Median	153.0	153.0	153.0
Min, Max	123, 182	124, 178	123, 182
BMI (kg/m^2)			
n	3587	3580	7167
Mean	24.74	24.66	24.70
SD	4.42	4.30	4.36
Median	24.30	24.20	24.20
Min, Max	13.3, 53.8	10.0, 49.5	10.0, 53.8

Source: Table 9-2 in study report.

Table 15: Study 20070337 - Key Baseline Disease Characteristics

	Placebo/ Denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589)	All (N = 7180)
Prevalent vertebral fracture - n (%)[a]			
Yes	645 (18.0)	672 (18.7)	1317 (18.3)
No	2839 (79.1)	2795 (77.9)	5634 (78.5)
Not readable	107 (3.0)	122 (3.4)	229 (3.2)
Most severe Genant semi-quantitative grade[b]			
Normal	2839 (79.1)	2795 (77.9)	5634 (78.5)
Mild	378 (10.5)	378 (10.5)	756 (10.5)
Moderate	263 (7.3)	293 (8.2)	556 (7.7)
Severe	4 (0.1)	1 (<0.1)	5 (<0.1)
Not readable/missing	107 (3.0)	122 (3.4)	229 (3.2)
Any historical fracture on/after age 45 - n (%)			
Any	1451 (40.4)	1434 (40.0)	2885 (40.2)
Osteoporotic fractures	1258 (35.0)	1270 (35.4)	2528 (35.2)
Nonvertebral fractures	782 (21.8)	778 (21.7)	1560 (21.7)
Major nonvertebral fractures	597 (16.6)	543 (15.1)	1140 (15.9)
Lumbar spine BMD T-score			
n	3481	3498	6979
Mean	-2.71	-2.72	-2.72
SD	1.04	1.04	1.04
Median	-2.78	-2.82	-2.81
Min, Max	-5.8, 2.0	-5.5, 1.8	-5.8, 2.0
Lumbar spine BMD T-score - n (%)			
≤ -3.0	1433 (39.9)	1493 (41.6)	2926 (40.8)
> -3.0 and ≤ -2.5	673 (18.7)	689 (19.2)	1362 (19.0)
> -2.5	1375 (38.3)	1316 (36.7)	2691 (37.5)
Missing	110 (3.1)	91 (2.5)	201 (2.8)
Total hip BMD T-score			
n	3590	3589	7179
Mean	-2.46	-2.48	-2.47
SD	0.47	0.47	0.47
Median	-2.52	-2.53	-2.52
Min, Max	-3.5, 0.1	-3.5, 0.1	-3.5, 0.1
Total hip BMD T-score - n (%)			
≤ -2.5	1863 (51.9)	1909 (53.2)	3772 (52.5)
> -2.5	1727 (48.1)	1680 (46.8)	3407 (47.5)
Missing	1 (<0.1)	0 (0.0)	1 (<0.1)

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	Placebo/ Denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589)	All (N = 7180)
Femoral neck BMD T-score			
n	3590	3589	7179
Mean	-2.74	-2.76	-2.75
SD	0.29	0.28	0.29
Median	-2.72	-2.73	-2.72
Min, Max	-3.5, -0.8	-3.6, -1.6	-3.6, -0.8
Femoral neck BMD T-score - n (%)			
≤ -2.5	3185 (88.7)	3217 (89.6)	6402 (89.2)
> -2.5	405 (11.3)	372 (10.4)	777 (10.8)
Missing	1 (<0.1)	0 (0.0)	1 (<0.1)
25 (OH) Vitamin D (ng/mL)			
n	3584	3581	7165
Mean	29.5	29.6	29.5
SD	11.5	10.6	11.1
Median	27.2	27.2	27.2
Min, Max	17, 320	15, 269	15, 320

Source: Table 9-3 in study report.

Table 16: Study 20120156 Demographics and Baseline Characteristics

	Placebo (N = 53)	Romosozumab 70 mg/ml (N = 118)	Romosozumab 90 mg/ml (N = 123)	All (N = 294)
Sex - n (%)				
Female	53 (100.0)	118 (100.0)	123 (100.0)	294 (100.0)
Ethnicity – n (%)				
Hispanic/Latino	2 (3.8)	6 (5.1)	9 (7.3)	17 (5.8)
Not Hispanic/Latino	51 (96.2)	112 (94.9)	114 (92.7)	277 (94.2)
Race - n (%)				
Asian	0 (0.0)	2 (1.7)	0 (0.0)	2 (0.7)
Black (or African American)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
White	53 (100.0)	115 (97.5)	123 (100.0)	291 (99.0)
Age (years)				
n	53	118	123	294
Mean	68.4	67.4	67.7	67.7
SD	8.0	7.1	7.6	7.5
Median	67.0	67.0	67.0	67.0
Q1, Q3	61.0, 75.0	61.0, 73.0	62.0, 73.0	61.0, 73.0
Min, Max	57, 85	55, 83	55, 88	55, 88
Age Group - n (%)				
< 65 years	23 (43.4)	46 (39.0)	46 (37.4)	115 (39.1)
≥ 65 years	30 (56.6)	72 (61.0)	77 (62.6)	179 (60.9)
≥ 75 years	16 (30.2)	22 (18.6)	24 (19.5)	62 (21.1)

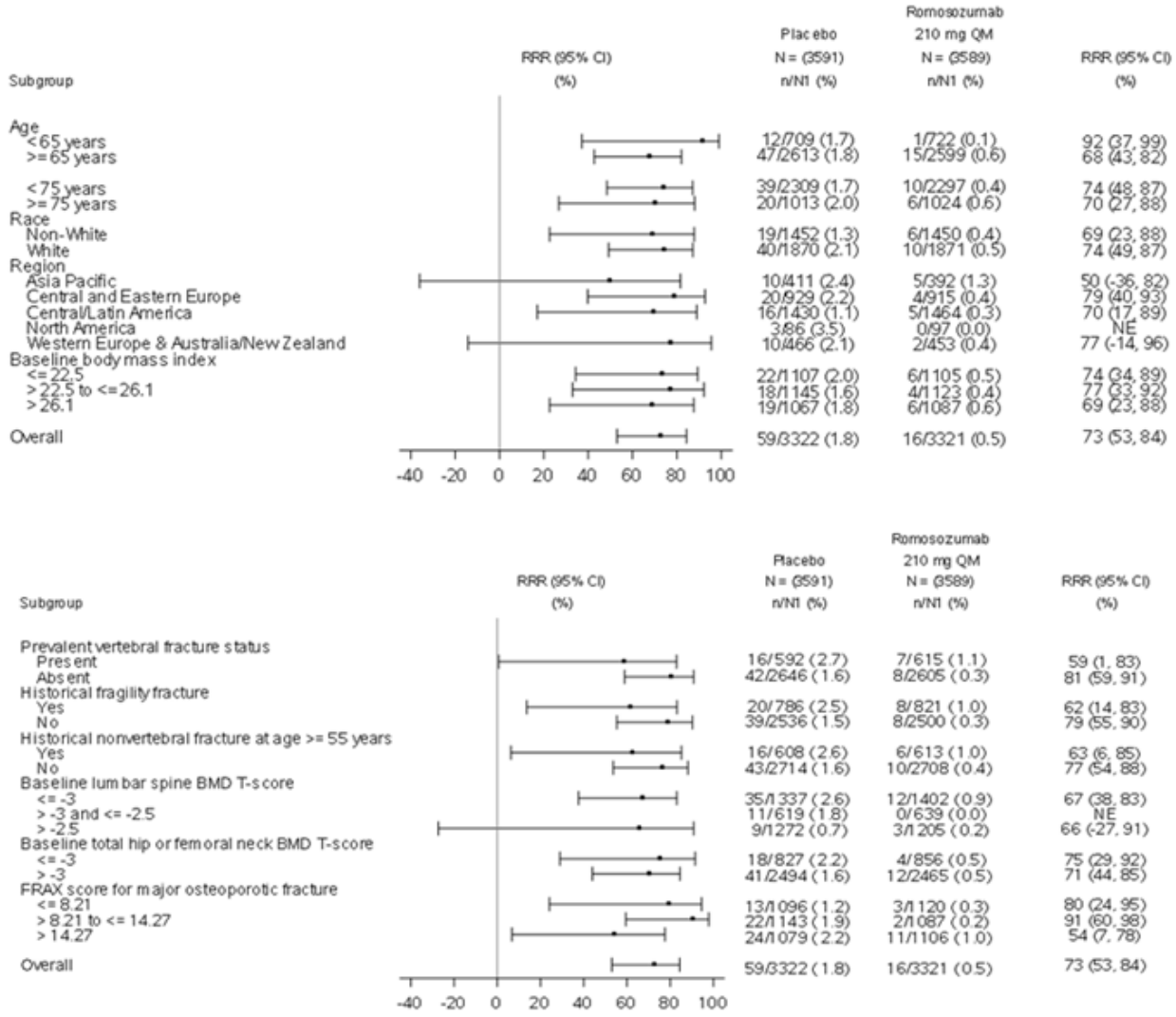
Source: Table14-2-1 in study report.

Reference ID: 4077213

A2. Subgroup Analysis Results

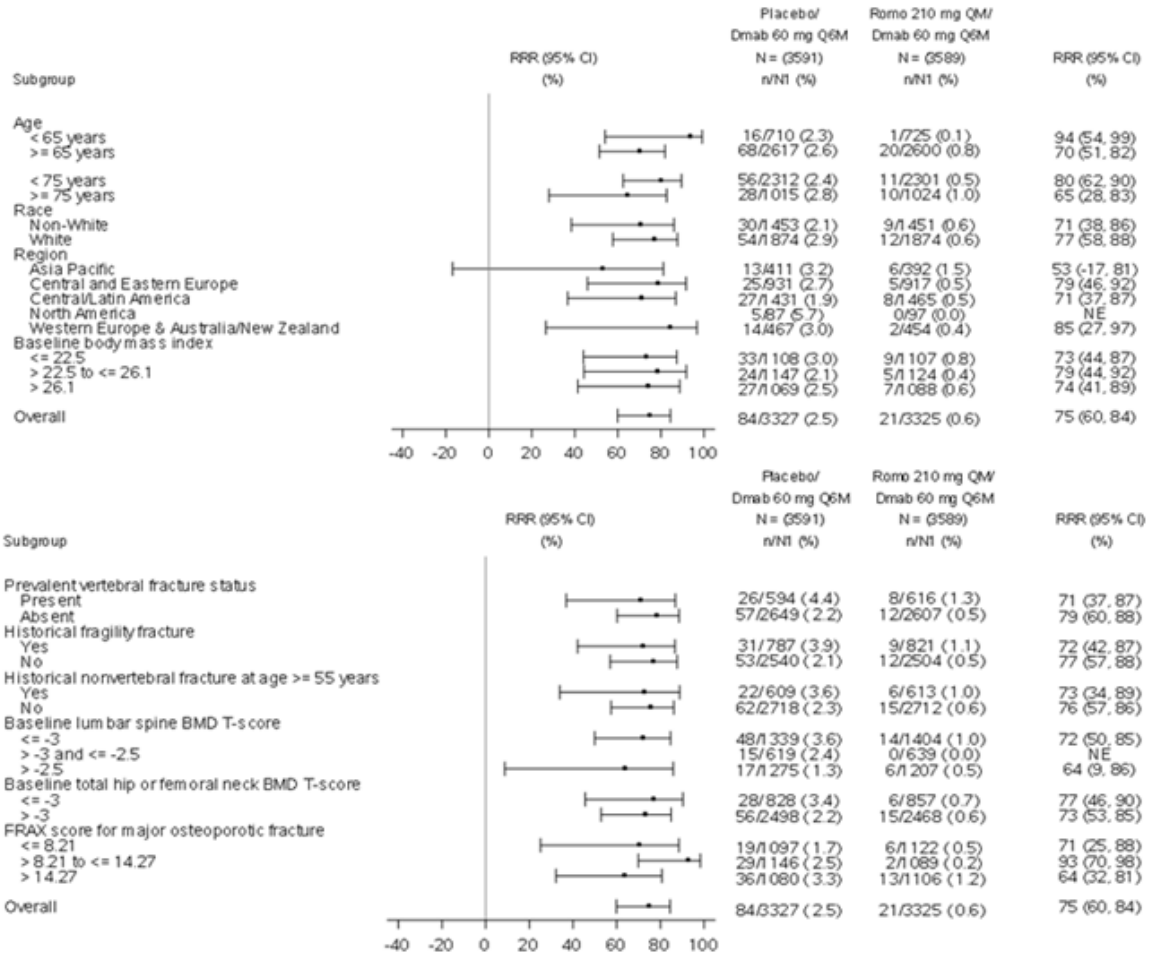
(All figures in this appendix are from the submission under 03/02/2017, response to FDA's information request)

Figure 1. Subject Incidence of New Vertebral Fracture Through Month 12 by Demographics and Baseline Characteristics (20070337 Primary Analysis Set for Vertebral Fractures, LOCF Imputation)



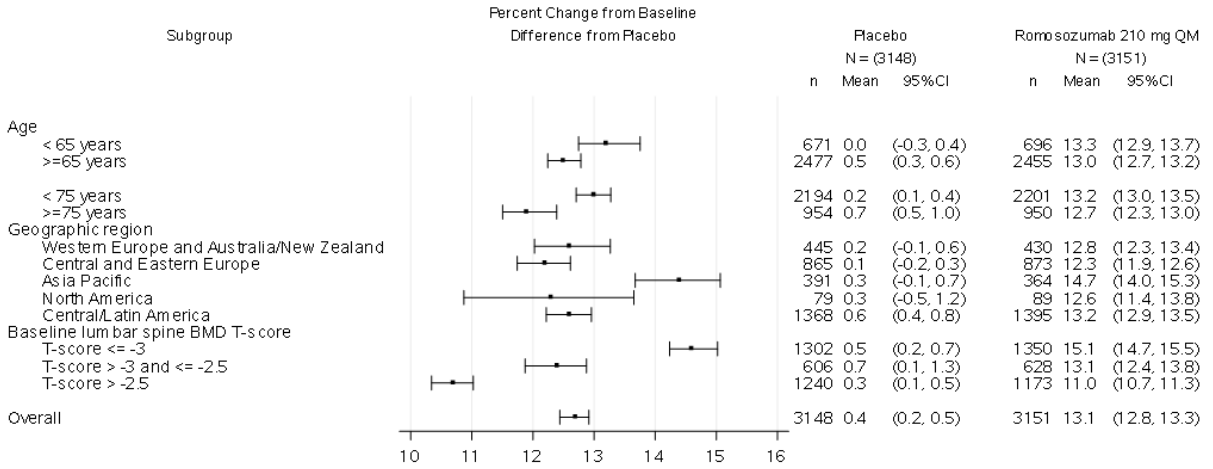
N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures
Relative risk reduction (RRR) and 95% CI based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture
Missing values are imputed by carrying forward the last non-missing post-baseline value.

Figure 2 : Subject Incidence of New Vertebral Fracture Through Month 24 by Demographics and Baseline Characteristics (20070337 Primary Analysis Set for Vertebral Fractures, LOCF Imputation)



N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures
Relative risk reduction (RRR) and 95% CI based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture
Missing values are imputed by carrying forward the last non-missing post-baseline value.

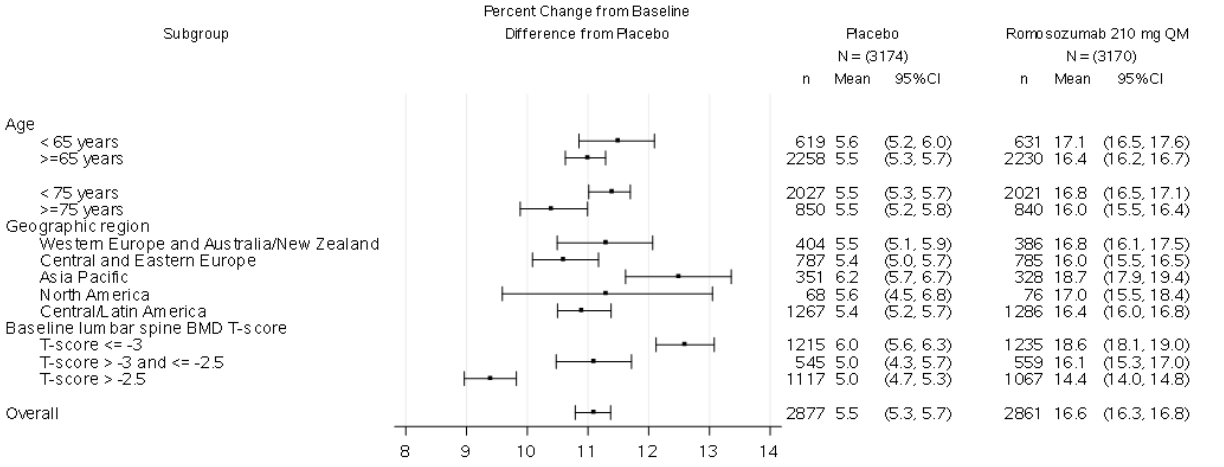
Figure 3: **Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 12 by Subgroups (20070337 Primary Analysis Set for BMD, LOCF)**



N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 12; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture, baseline value, machine type, and baseline value-by-machine type interaction; Mean = LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.

Figure 4. Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 24 by Subgroups (20070337 Primary Analysis Set for BMD, LOCF)

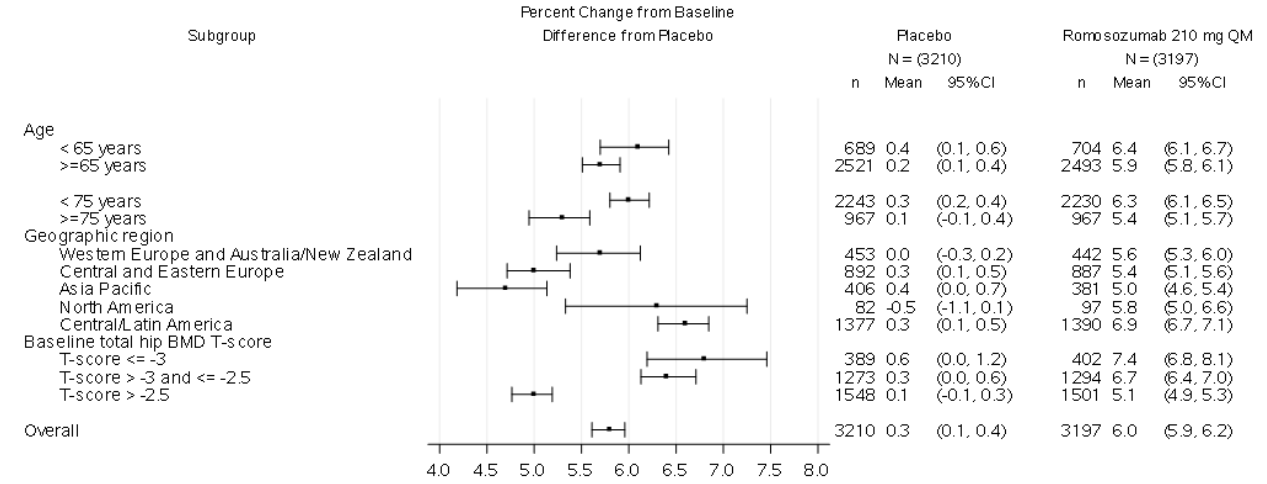


N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 12; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture, baseline value, machine type, and baseline value-by-machine type interaction; Mean = LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.

Reference ID: 4077213

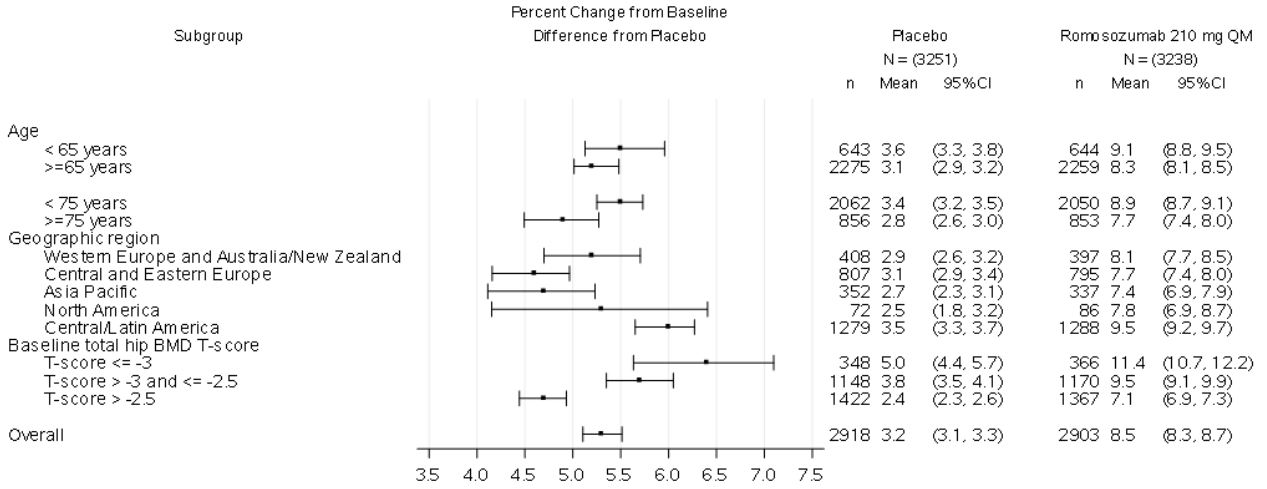
Figure 5. Total Hip Bone Mineral Density Percent Change From Baseline at Month 12 by Subgroups (20070337 Primary Analysis Set for BMD, LOCF)



N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 12; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture, baseline value, machine type, and baseline value-by-machine type interaction; Mean = LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.

Figure 6. Total Hip Bone Mineral Density Percent Change From Baseline at Month 24 by Subgroups (20070337 Primary Analysis Set for BMD, LOCF)



N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 12; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture, baseline value, machine type, and baseline value-by-machine type interaction; Mean = LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.

Figure 7. Femoral Neck Bone Mineral Density Percent Change From Baseline at Month 12 by Subgroups (20070337 Primary Analysis Set for BMD, LOCF)

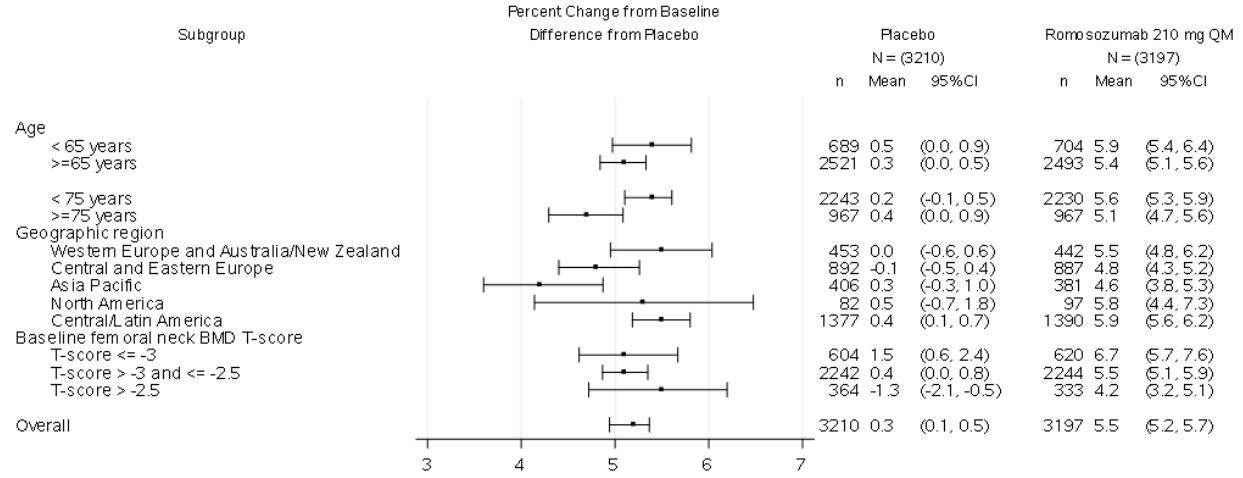
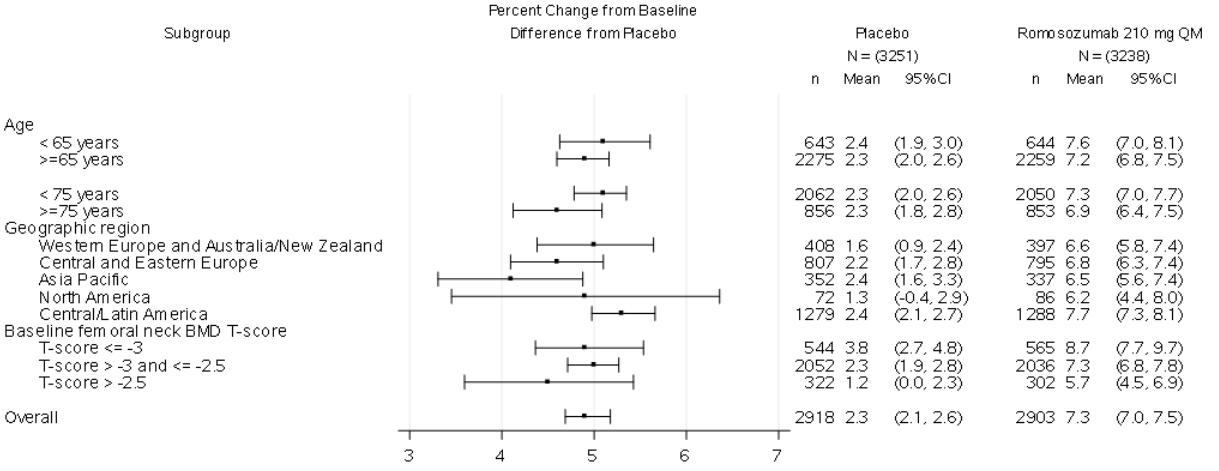


Figure 8. Femoral Neck Bone Mineral Density Percent Change From Baseline at Month 24 by Subgroups (20070337 Primary Analysis Set for BMD, LOCF)



N = Number of subjects with values at baseline and at least one post-baseline visit at or before month 12; n = Number of subjects with non-missing data

Based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture, baseline value, machine type, and baseline value-by-machine type interaction; Mean = LS Mean; Missing values are imputed by carrying forward the last non-missing post-baseline value.

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/s/

JIA GUO
03/29/2017

MAHBOOB SOBHAN
03/31/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	BLA761062 (IND 100391)
Drug Name:	EVENITY® (romosozumab) 90 mg/mL prefilled syringe (PFS) for subcutaneous injection
Indication(s):	Treatment of osteoporosis in postmenopausal women at increased risk of fracture.
Applicant:	Amgen Inc. One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA (b) (4)
Date(s):	Received 7/20/2016
Documents Reviewed:	Study 107895 (rats) was submitted on 7/20/2016 (via S001)
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Hepei Chen, Feng Zhou
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Pharmacology Team:	Gemma Kuijpers, Ph.D; Kimberly Hatfield, Ph.D
Keywords:	Carcinogenicity, Dose response

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1 Summary

This review evaluates statistically the tumorigenicity data of carcinogenicity study of romosozumab (AMG-785), 2-year study in rats. The review analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality).

Rat Study: Rats (60/sex/dose, except there were only 54 rats for male HD group) were dosed by subcutaneous injection with AMG-785 once weekly for up to 104 weeks. The AMG-785 was administered at doses of 0, 3, 10, and 50 mg/kg/day for male and female rats for at least 104 weeks. This review refers these dose groups as the vehicle control (VC), low (LD), mid (MD), and high (HD) dose groups, respectively. All surviving animals were terminated at Week 91 for males and 98 for females.

The survival analyses didn't show a statistically significant dose response relationship in mortality across control and treated groups in both male and female rats. The respective survival rates in the VC, LD, MD, and HD groups at the termination were 33%, 35%, 33%, and 30% in male rats and 33%, 35%, 40%, and 28% in female rats.

The tumor analysis did not show any statistically significant dose-response relationship in tumor incidence in tumor types tested in male rats. The pairwise comparison did show a statistically significant increase in incidence of adenoma cortical in MD groups compared to the control ($p=0.0184<0.05$) in male rats if this tumor was considered as a rare tumor; in female rats, a statistically significant positive dose response relationship was noted in adenoma islet cell for pancreas of female rats ($p=0.0323<0.05$) if this tumor was considered as a rare tumor. No other statistically significant findings were noted for female rats.

2 Background

BLA761062 is the initial biologics licensing application for romosozumab (AMG-785) for the indication of: treatment of osteoporosis in postmenopausal women at increased risk of fracture. The sponsor conducted one 24-month subcutaneous carcinogenicity study in the Sprague Dawley rats (107895). This review analyzed the SAS data sets of these studies received from the sponsor on 7/20/2016 via submission BLA761062/S0001.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the reviewing pharmacologist Dr. Gemma Kuijpers.

3 Rat Study-107895

Study Report: — 107895.pdf; SAS data: tumor.xpt

This study assessed the carcinogenic potential of AMG-785 in male and female rats. The test material (AMG-785) was administered weekly via subcutaneous injection at doses of 0, 3, 10, and 50 mg/kg/day for male rats and female rats for at least 104 weeks. This review refers these dose groups as the vehicle control (VC), low (LD), mid (MD), and high (HD) dose groups, respectively. There were 60 rats/sex/dose, except there were only 54 rats for male HD group. All surviving animals were terminated at Week 91 for males and 98 for females. Assessments of carcinogenicity included mortality, clinical observations (including mass observations), body weight, food consumption, ophthalmological evaluations, and clinical and anatomic pathology.

Text Table 1
Experimental Design

Group No.	No. of Toxicity Animals Main Study M	No. of Toxicity Animals Main Study F	Test Material	Dose Level (mg/kg/dose)
1	60	60	Reference Item	0
2	60	60	AMG 785	3
3	60	60	AMG 785	10
4	54	60	AMG 785	50

[Source: page 3108 of study report of 107895.pdf]

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

The statistical analyses for mortality data were performed for each sex separately. The survival function of each group was estimated using the Kaplan-Meier product-limit method applied on daily intervals and graphs were produced. Any animal with accidental injury that causes its death or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day.

The log-rank test was applied to the four groups in order to assess the significance of the overall group effect on mortality data. When significant differences among groups ($p \leq 0.05$) were revealed, then the significance of an overall dose-related trend in mortality across all groups was evaluated using Tarone's method.[4] Using the Multtest procedure (SAS/STAT), Tarone's test was implemented as a Peto two-sided test, with all uncensored deaths coded as 2 and all censored deaths coded as 0. The corresponding arithmetic dose level scores (0, 3, 10, and 50) was used to perform the overall trend test. Furthermore, the vehicle control group was compared to each of the other three groups using a Peto two-sided test. The sign of the statistic was used to indicate if either an increase or a decrease of the mortality rate across dose levels was observed for the trend test and each pairwise comparison.

Sponsor's concluded: The numbers of death were listed in follow table. The test results show no significance for both male and female datasets, with p-value = 0.9751 and p-value = 0.5922 respectively. Therefore, no post-hoc testing was done for these datasets, that is neither Tarone's trend test[4] nor the pairwise comparisons were performed.

Table 1 Survival of Rats

Group 1 - Vehicle Control
Group 2 - AMG 785 3 mg/kg/dose
Group 3 - AMG 785 10 mg/kg/dose
Group 4 - AMG 785 50 mg/kg/dose

Males								Sex Group	Females							
1		2		3		4			1		2		3		4	
S	%	S	%	S	%	S	%	Week	S	%	S	%	S	%	S	%
27	45	25	42	29	48	28	52	77 - 80	45	75	44	73	39	65	39	65
22	37	23	38	24	40	20	37	81 - 84	41	68	35	58	35	58	34	57
21	35	21	35	21	35	15	28	85 - 88	36	60	31	52	32	53	28	47
20	33	21	35	20	33	15	28	89 - 92 Δ	31	52	28	47	30	50	24	40
								93 - 96	21	35	22	37	24	40	17	28
								97 - 100 Ω	20	33	21	35	24	40	17	28

S Number of survivors.
% Percent of the original group size.
Δ Males termination started on 29 Jul 2013
Ω Females termination started on 17 Sep 2013
[Source: page 55 of study report of 107895.pdf]

3.1.2 Tumor Data Analysis

Neoplastic findings classified as fatal and incidental were processed using the death rate method and the prevalence method, respectively. The processing of incidental tumors was done by creating a single separate

interval for the time period following the experimental period (terminal sacrifice period) and by dividing the experimental period into the following fixed intervals: 1-52 weeks, 53-78 weeks, 79-90 weeks for males, and 1-52 weeks, 53-78 weeks, 79-92 weeks, 92-97 for females. Using the derived outcomes from the processing of both fatal and incidental tumors, a test statistic was built to perform a global survival-adjusted trend test (Peto's test) on tumor data observed in a "mortality dependent" context.[5]

For each data set within each sex, the significance of an overall linear dose-related increase in tumor occurrence rates across the four groups was evaluated using Peto's survival-adjusted one-tailed test. The corresponding arithmetic dose level scores (0, 3, 10, and 50) was used to perform the overall trend test. Furthermore, Peto's upper-tailed test was used to check if the tumor rate in each test item treated group was significantly higher than the one in the vehicle control group. When performing a pairwise comparison, only the data corresponding to the two compared groups were submitted to the statistical analysis.

Adjustment for multiple testing: As mentioned by Lin[6], the discrete permutation distribution was used to compute the corresponding p-value for each statistical test performed on a dataset containing 10 or less tumor occurrences. Each trend test (the overall trend and the pairwise comparison tests) was conducted at the 5% significance level but was discussed in the statistical report according to the tumor prevalence classification (common or rare) and the FDA's recommendations. More precisely, given that this chronic study is in only one species, significance of the results for common and rare tumors were respectively discussed at 0.01 and 0.05 levels for the overall trend test, and at 0.025 and 0.10 levels for the pairwise comparisons.

Sponsor's concluded: There was no neoplastic change attributed to the weekly administration of AMG 785.

There was a statistically significant increase in renal lipoma, a rare tumor, by trend test (p =0.0486 versus cutoff of p<=0.05), in females only. The incidence of renal lipoma was marginally increased in females at 50 mg/kg/dose compared to concurrent control and marginally above the testing facility historical data range and reported literature. However, this finding was not considered AMG-785 related based on low incidence, lack of preneoplasic precursors lesions and comparable nature and morphology to the renal lipoma in the concurrent control female.

The slight increased incidence of adrenal cortical adenoma, a common tumor, noted in males only at 10 mg/kg dose was statistically significant (p = 0.0169 versus cutoff of p<= 0.025) by pairwise comparison test. However, this finding was not considered AMG 785-related based on the incidence being within historical control data range, the absence of a dose-related trend, and the absence of a precursor preneoplastic change.

Text Table 4
(*p*-values ≤ 0.10 but > 0.025 are flagged as # while *p*-values ≤ 0.025 are flagged as ##)

Organ Name	Tumor Name	Comparison	*P*-value	Flag
--- *MALES* ---				
Adrenal	Adenoma: cortical	1 vs 3	0.0169	##
Pancreas	Adenoma/carcinoma, islet cell	1 vs 3	0.0549	#
Skin Tissues (Combination)	Keratoacanthoma	1 vs 3	0.0972	#
--- *FEMALES* ---				
Adrenal	Benign pheochromocytoma	1 vs 2	0.0432	#
Pancreas	Adenoma: islet cell	1 vs 4	0.0998	#
Thyroid	Adenoma: C-cell	1 vs 2	0.0607	#

[Source: page 3111 of study report of 107895.pdf]

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 7/20/2016 via submission BLA761062/eCTD S-0001.

3.2.1 Survival Analysis

The survival distributions of rats in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings: All surviving animals were terminated at Week 91 for males and 98 for females. This reviewer's analysis showed the numbers (percent) of death were 40 (67%), 41 (68%), 40 (67%), and 38 (70%) in male rats and 40 (67%), 39 (65%), 36 (60%), and 43 (72%) in female rats in the VC, LD, MD, and HD groups, respectively. The tests did not show any statistically significant dose response relationships or pairwise comparisons in mortality in male or female rats.

3.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier [1] and Bieler and Williams [2]. In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two chronic studies in species, and a significance level α=0.01 for common tumors and α=0.05 for rare tumors for a submission with one chronic study species in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the FDA guidance suggested the use of test levels α=0.01 for common tumors and α=0.05 for rare tumors for a submission with two chronic studies in two species, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman [3]. In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Lin and Rahman [3] showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

Reviewer's findings: The following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationship or for pairwise comparisons of treated groups and vehicle control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Vehicle Controls in Male and Female Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	50 mg High (H) P - C vs. H
Male-Adrenal	Adenoma: Cortical	0/60 (25)	2/60 (25)	6/60 (29)	2/54 (25)
		0.4382	0.2449	0.0184 $	0.2449
Female-Adrenal	Benign Pheochromocytoma	2/60 (38)	8/60 (39)	2/60 (36)	0/60 (34)
		0.9884	0.0473 @	0.6719	0.7250
	Malignant Pheochromocytoma	0/60 (38)	2/60 (38)	0/60 (36)	0/60 (34)
		0.7308	0.2467	NC	NC
	Benign Pheochromocytoma/ Malignant Pheochromocytoma	2/60 (38)	10/60 (40)	2/60 (36)	0/60 (34)
		0.9942	0.0159 @	0.6719	0.7250
Female-Kidney	Lipoma	1/60 (38)	0/60 (37)	0/60 (36)	3/60 (35)
		0.0429 @	0.4933	0.4865	0.2766
Female-Pancreas	Adenoma: Islet Cell	0/60 (38)	0/60 (37)	3/60 (38)	3/60 (35)
		0.0323 $	NC	0.1200	0.1052

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
$ = Statistically significant at 0 05 level in rare tumor for test of dose response relationship /pairwise comparisons;
@ = Not statistically significant at 0 01 level in common tumor for test of dose response relationship /pairwise comparisons;
NC = Not calculable

Based on the criteria of adjustment for multiple testing discussed above, there was no tumor types or combined tumor types which were considered to have a statistically significant positive dose response relationship in male rats. The pairwise comparison did show a statistically significant increase in incidence of adenoma cortical in Adrenal (which was considered as a rare tumor) in MD groups compared to the control ($p=0.0184<0.05$).

In female rats, a statistically significant positive dose response relationship was noted in adenoma islet cell for pancreas of female rats ($p=0.0323<0.05$) if this tumor was considered as a rare tumor. No other statistically significant findings were noted for female rats.

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Mathematical Statisticians

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cc:
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4 Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	8	13.33	12	20.00	5	8.33	4	7.41
53 - 78	21	48.33	21	55.00	23	46.67	19	42.59
79 - 91	11	66.67	6	65.00	12	66.67	15	70.37
Terminal sacrifice	20	33.33	21	35.00	20	33.33	16	29.63
Total	60		60		60		54	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.8131	0.8069	0.8764	0.8954
Homogeneity (Log-Rank)	0.9749	0.8051	0.8748	0.8937

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	3	5.00	1	1.67	4	6.67	1	1.67
53 - 78	11	23.33	11	20.00	15	31.67	19	33.33
79 - 91	14	46.67	18	50.00	10	48.33	16	60.00
92 - 100	12	20.00	9	15.00	7	11.67	7	11.67
Terminal sacrifice	20	33.33	21	35.00	24	40.00	17	28.33
Total	60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.2189	0.9224	0.8225	0.2996
Homogeneity (Log-Rank)	0.6033	0.9211	0.8200	0.2899

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 3A: Tumor Rates and P-Values for Trends and Pairwise Comparisons – Male Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	50 mg High (H) P - C vs. H
Adrenal	Adenoma: Cortical	0/60 (25)	2/60 (25)	6/60 (29)	2/54 (25)
		0.4382	0.2449	0.0184 $	0.2449
	Benign Pheochromocytoma	4/60 (27)	3/60 (25)	6/60 (28)	3/54 (25)
		0.6042	0.4553	0.3886	0.4553
	Malignant Pheochromocytoma	1/60 (26)	2/60 (25)	1/60 (27)	0/54 (24)
		0.8235	0.4850	0.2547	0.4800
	Benign Pheochromocytoma/ Malignant Pheochromocytoma	5/60 (27)	5/60 (26)	7/60 (29)	3/54 (25)
		0.7867	0.6110	0.4274	0.6028
Bone-Tibia	Osteosarcoma	0/60 (25)	0/60 (24)	0/59 (26)	1/54 (25)
		0.2500	NC	NC	0.5000
Bone Miscellaneous	Osteosarcoma	0/12 (6)	0/3 (2)	0/9 (6)	1/10 (7)
		0.3333	NC	NC	0.5385
Bone-Tibia/ Bone Miscellaneous	Osteosarcoma	0/60 (25)	0/60 (24)	0/59 (26)	2/54 (25)
		0.0606	NC	NC	0.2449
Hemolym. Tissue	Histiocytic Sarcoma	0/60 (25)	1/60 (25)	0/60 (26)	0/54 (24)
		0.5000	0.5000	NC	NC
	Malignant Lymphoma	3/60 (27)	1/60 (24)	5/60 (30)	0/54 (24)
		0.9262	0.6489	0.4152	0.8595
I.S. Interscapular	Fibroma	0/60 (25)	0/60 (24)	1/60 (27)	0/54 (24)
		0.2400	NC	0.5192	NC
I.S. Scapular, Lef	Fibroma	1/60 (26)	0/60 (24)	1/60 (27)	0/54 (24)
		0.6184	0.4800	0.2547	0.4800
	Fibrosarcoma	1/60 (26)	0/60 (24)	0/60 (26)	0/54 (24)
		0.7400	0.4800	0.5000	0.4800
	Fibroma/Fibrosarcoma	2/60 (26)	0/60 (24)	1/60 (27)	0/54 (24)
		0.8297	0.7347	0.5144	0.7347
	Lipoma	0/60 (25)	0/60 (24)	1/60 (27)	0/54 (24)
		0.2400	NC	0.5192	NC
	Trichoepithelioma	0/60 (25)	0/60 (24)	1/60 (27)	0/54 (24)
		0.2400	NC	0.5192	NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trends and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	50 mg High (H) P - C vs. H
Kidney	Adenoma: Tubular Cell	0/60 (25)	1/60 (24)	0/60 (26)	0/54 (24)
		0.5051	0.4898	NC	NC
	Carcinoma: Transitional Cell	0/60 (25)	1/60 (25)	0/60 (26)	0/54 (24)
		0.5000	0.5000	NC	NC
	Adenoma: Tubular Cell/ Carcinoma: Tubular Cell	1/60 (26)	1/60 (24)	0/60 (26)	0/54 (24)
		0.8083	0.7347	0.5000	0.4800
	Carcinoma: Tubular Cell	1/60 (26)	0/60 (24)	0/60 (26)	0/54 (24)
		0.7400	0.4800	0.5000	0.4800
	Lipoma	0/60 (25)	0/60 (24)	0/60 (26)	1/54 (25)
		0.2500	NC	NC	0.5000
L. Node Mandibular	Hemangioma	0/60 (25)	0/60 (24)	0/59 (26)	1/52 (25)
		0.2500	NC	NC	0.5000
L.Node Mesenteric	Hemangioma	0/60 (25)	2/60 (24)	0/60 (26)	1/54 (25)
		0.4433	0.2347	NC	0.5000
	Hemangiosarcoma	0/60 (25)	2/60 (24)	1/60 (26)	0/54 (24)
		0.6876	0.2347	0.5098	NC
	Hemangioma/Hemangiosarcoma	0/60 (25)	4/60 (25)	1/60 (26)	1/54 (25)
		0.6528	0.0549	0.5098	0.5000
	Lipoma	0/60 (25)	1/60 (24)	0/60 (26)	0/54 (24)
		0.5051	0.4898	NC	NC
Liver	Adenoma: Hepatocellular	0/60 (25)	3/60 (26)	1/60 (26)	0/54 (24)
		0.8062	0.1248	0.5098	NC
	Carcinoma: Hepatocellular	2/60 (26)	2/60 (25)	1/60 (26)	0/54 (24)
		0.9121	0.6801	0.5000	0.7347
	Adenoma: Hepatocellular/ Carcinoma: Hepatocellular	2/60 (26)	5/60 (27)	2/60 (27)	0/54 (24)
		0.9689	0.2259	0.3196	0.7347
Mammary Gland	Adenocarcinoma	1/49 (21)	0/55 (22)	0/51 (23)	0/47 (21)
		0.7586	0.5116	0.5227	0.5000
	Fibroadenoma	1/49 (21)	0/55 (22)	0/51 (23)	2/47 (22)
		0.1530	0.5116	0.5227	0.5179

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trends and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	50 mg High (H) P - C vs. H
Pancreas	Adenoma: Acinar Cell	0/60 (25)	0/60 (24)	3/60 (27)	2/54 (25)
		0.1066	NC	0.1324	0.2449
	Adenoma: Islet Cell	1/60 (26)	1/60 (24)	3/60 (27)	4/54 (26)
		0.0644	0.7347	0.3196	0.1749
	Carcinoma: Islet Cell	0/60 (25)	0/60 (24)	3/60 (27)	2/54 (25)
		0.1066	NC	0.1324	0.2449
	Adenoma: Islet Cell/ Carcinoma: Islet Cell	1/60 (26)	1/60 (24)	6/60 (28)	5/54 (27)
		0.0767	0.7347	0.0620	0.1043
Parathyroid Gland	Adenoma	0/56 (23)	0/54 (21)	0/58 (25)	1/51 (23)
		0.2500	NC	NC	0.5000
Pituitary	Adenoma: Pars Distalis	27/60 (39)	16/60 (32)	25/60 (39)	23/54 (36)
		0.4255	0.9201	0.5948	0.5971
	Adenoma: Pars Intermedia	2/60 (26)	0/60 (24)	0/60 (26)	0/54 (24)
		0.9343	0.7347	0.7549	0.7347
	Carcinoma: Pars Distalis	0/60 (25)	0/60 (24)	0/60 (26)	1/54 (25)
		0.2500	NC	NC	0.5000
	Adenoma: Pars Distalis/ Adenoma: Pars Intermedia/ Carcinoma: Pars Distalis	29/60 (40)	16/60 (32)	25/60 (39)	24/54 (37)
		0.4559	0.9568	0.7122	0.6832
Skin Miscellaneous	Adenoma: Basal Cell	1/19 (11)	0/21 (9)	0/22 (13)	0/19 (9)
		0.7381	0.4500	0.5417	0.4500
	Adenoma: Sebaceous	0/19 (10)	1/21 (9)	1/22 (13)	0/19 (9)
		0.4902	0.4737	0.5652	NC
	Papilloma: Squamous Cell	0/19 (10)	2/21 (10)	1/22 (13)	1/19 (9)
		0.3912	0.2368	0.5652	0.4737
	Carcinoma: Squamous Cell	2/19 (11)	2/21 (10)	3/22 (14)	0/19 (9)
		0.8865	0.6692	0.6217	0.7105
	Keratoacanthoma	2/19 (11)	1/21 (10)	7/22 (15)	0/19 (9)
		0.9134	0.4624	0.1375	0.7105
	Carcinoma: Squamous Cell/ Papilloma: Squamous Cell/ Keratoacanthoma	4/19 (13)	5/21 (12)	9/22 (16)	1/19 (9)
		0.9302	0.4400	0.1597	0.7068
Spleen	Hemangiosarcoma	1/60 (26)	1/60 (24)	1/60 (26)	0/54 (24)
		0.7262	0.7347	NC	0.4800

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trends and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - C vs. L	10 mg Mid (M) P - C vs. M	50 mg High (H) P - C vs. H
Testis	Adenoma: Interstitial Cell	0/60 (25)	0/60 (24)	0/60 (26)	1/53 (25)
		0.2500	NC	NC	0.5000
	Mesothelioma(M)	0/60 (25)	1/60 (24)	0/60 (26)	0/53 (24)
		0.5051	0.4898	NC	NC
Thymus	Benign Thymoma	0/59 (25)	0/57 (22)	0/59 (25)	1/53 (25)
		0.2577	NC	NC	0.5000
	Malignant Schwannoma	0/59 (25)	0/57 (22)	0/59 (25)	1/53 (25)
		0.2577	NC	NC	0.5000
Thyroid	Adenoma: C-Cell	8/60 (29)	10/60 (27)	4/60 (28)	6/54 (27)
		0.7449	0.3191	0.8172	0.5604
	Carcinoma: C-Cell	0/60 (25)	0/60 (24)	2/60 (27)	0/54 (24)
		0.4242	NC	0.2647	NC
	Adenoma: C-Cell/ Carcinoma: C-Cell	8/60 (29)	10/60 (27)	6/60 (29)	6/54 (27)
		0.7742	0.3191	0.6201	0.5604
	Adenoma: Follicular Cell	6/60 (28)	4/60 (25)	0/60 (26)	0/54 (24)
		0.9996	0.5586	0.9854	0.9815

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 3B: Tumor Rates and P-Values for Trends and Pairwise Comparisons – Female Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	50 mg High (H) P - H vs. C
Adrenal	Adenoma: Cortical	6/60 (39)	3/60 (38)	1/60 (36)	7/60 (37)
		0.0936	0.7466	0.9331	0.4580
	Carcinoma: Cortical	1/60 (38)	0/60 (37)	0/60 (36)	0/60 (34)
		0.7379	0.4933	0.4865	0.4722
	Adenoma: Cortical/ Carcinoma: Cortical	7/60 (39)	3/60 (38)	1/60 (36)	7/60 (37)
		0.1313	0.8344	0.9635	0.5732
	Benign Pheochromocytoma	2/60 (38)	8/60 (39)	2/60 (36)	0/60 (34)
		0.9884	0.0473	0.6719	0.7250
	Malignant Pheochromocytoma	0/60 (38)	2/60 (38)	0/60 (36)	0/60 (34)
		0.7308	0.2467	NC	NC
	Benign Pheochromocytoma/ Malignant Pheochromocytoma	2/60 (38)	10/60 (40)	2/60 (36)	0/60 (34)
		0.9942	0.0159	0.6719	0.7250
Cecum	Leiomyoma	1/60 (38)	0/60 (37)	0/60 (36)	0/60 (34)
		0.7379	0.4933	0.4865	0.4722
Cervix	Benign Schwannoma	0/60 (38)	1/60 (38)	0/60 (36)	0/60 (34)
		0.4795	0.5000	NC	NC
	Malignant Schwannoma	0/60 (38)	0/60 (37)	0/60 (36)	1/60 (34)
		0.2345	NC	NC	0.4722
	Benign Schwannoma/ Malignant Schwannoma	0/60 (38)	1/60 (38)	0/60 (36)	1/60 (34)
		0.2907	0.5000	NC	0.4722
	Hemangioma	1/60 (38)	0/60 (37)	0/60 (36)	0/60 (34)
		0.7379	0.4933	0.4865	0.4722
	Leiomyoma	1/60 (38)	1/60 (37)	0/60 (36)	0/60 (34)
		0.7980	0.7467	0.4865	0.4722
Fat	Mesothelioma(M)	0/3 (1)	0/3 (2)	1/2 (2)	0/3 (2)
		0.2857	NC	0.6667	NC
Hemolym. Tissue	Histiocytic Sarcoma	1/60 (38)	1/60 (38)	2/60 (37)	1/60 (35)
		0.4095	NC	0.4899	0.7325
	Malignant Lymphoma	2/60 (38)	0/60 (37)	0/60 (36)	0/60 (34)
		0.9327	0.7467	0.7397	0.7250
I.S. Interscapular	Fibroma	1/60 (38)	0/60 (37)	1/60 (36)	0/60 (34)
		0.6032	0.4933	0.7397	0.4722
Kidney	Lipoma	1/60 (38)	0/60 (37)	0/60 (36)	3/60 (35)
		0.0429	0.4933	0.4865	0.2766

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Reference ID: 4074652

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	50 mg High (H) P - H vs. C
Liver	Adenoma: Hepatocellular	1/60 (38)	1/60 (37)	0/60 (36)	1/60 (34)
		0.5062	0.7467	0.4865	0.7250
	Carcinoma: Hepatocellular	1/60 (38)	0/60 (37)	0/60 (36)	0/60 (34)
		0.7379	0.4933	0.4865	0.4722
	Adenoma: Hepatocellular/ Carcinoma: Hepatocellular	2/60 (38)	1/60 (37)	0/60 (36)	1/60 (34)
		0.5947	0.4899	0.7397	0.4578
Lymph Node	Sarcoma (Not Otherwise Specified)	0/26 (17)	0/25 (16)	1/25 (17)	0/21 (12)
		0.1935	NC	0.5000	NC
Mammary Gland	Adenocarcinoma	15/60 (42)	15/60 (43)	16/59 (42)	18/60 (43)
		0.2446	0.4418	0.5000	0.3601
	Adenoma	2/60 (38)	1/60 (38)	1/59 (37)	0/60 (34)
		0.8616	0.5000	0.4899	0.7250
	Carcinoma: Squamous Cell	0/60 (38)	0/60 (37)	1/59 (36)	0/60 (34)
		0.2345	NC	0.4865	NC
	Fibroadenoma	41/60 (50)	44/60 (51)	36/59 (48)	35/60 (47)
		0.8780	0.3763	0.7249	0.7432
	Fibrosarcoma	0/60 (38)	0/60 (37)	1/59 (37)	0/60 (34)
		0.2329	NC	0.4933	NC
Ovary	Adenoma: Sertoliform Tubular	0/60 (38)	0/60 (37)	1/60 (37)	0/60 (34)
		0.2329	NC	0.4933	NC
	Carcinoma: Tubulostromal	1/60 (38)	0/60 (37)	0/60 (36)	0/60 (34)
		0.7379	0.4933	0.4865	0.4722
Pancreas	Adenoma: Acinar Cell	0/60 (38)	0/60 (37)	1/60 (36)	0/60 (34)
		0.2345	NC	0.4865	NC
	Adenoma: Islet Cell	0/60 (38)	0/60 (37)	3/60 (38)	3/60 (35)
		0.0323	NC	0.1200	0.1052
	Carcinoma: Islet Cell	1/60 (38)	0/60 (37)	1/60 (36)	0/60 (34)
		0.6032	0.4933	0.7397	0.4722
	Adenoma: Islet Cell/ Carcinoma: Islet Cell	1/60 (38)	0/60 (37)	4/60 (38)	3/60 (35)
		0.0985	0.4933	0.1790	0.2766
Parathyroid Gland	Adenoma	0/57 (35)	0/55 (34)	1/59 (37)	1/58 (33)
		0.1824	NC	0.5139	0.4853

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Reference ID: 4074652

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	50 mg High (H) P - H vs. C
Pituitary	Adenoma: Pars Distalis	36/60 (51)	32/60 (49)	40/60 (52)	39/59 (51)
		0.1840	0.6375	0.3063	0.3270
	Carcinoma: Pars Distalis	1/60 (38)	3/60 (38)	0/60 (36)	1/59 (34)
		0.6602	0.3074	0.4865	0.7250
	Adenoma: Pars Distalis/ Carcinoma: Pars Distalis	37/60 (51)	35/60 (50)	40/60 (52)	40/59 (51)
		0.2023	0.5253	0.3882	0.3229
	Sarcoma (Not Otherwise Specified)	0/60 (38)	1/60 (38)	0/60 (36)	0/59 (34)
		0.4795	0.5000	NC	NC
Skin Miscellaneous	Carcinoma: Squamous Cell	2/29 (22)	2/33 (22)	1/30 (20)	1/34 (23)
		0.7159	NC	0.4634	0.5171
	Keratoacanthoma	0/29 (20)	1/33 (21)	0/30 (20)	1/34 (23)
		0.3431	0.5122	NC	0.5349
	Carcinoma: Squamous Cell/ Keratoacanthoma	2/29 (22)	3/33 (22)	1/30 (20)	2/34 (24)
		0.5917	0.5000	0.4634	0.3380
Spleen	Hemangioma	0/59 (37)	0/60 (37)	1/60 (36)	0/60 (34)
		0.2361	NC	0.4932	NC
Stomach	Leiomyosarcoma	1/60 (38)	0/60 (37)	0/60 (36)	0/60 (34)
		0.7379	0.4933	0.4865	0.4722
Thymus	Benign Thymoma	1/58 (37)	2/57 (36)	0/59 (35)	0/60 (34)
		0.8822	0.4896	0.4861	0.4789
	Malignant Thymoma	0/58 (37)	1/57 (36)	0/59 (35)	0/60 (34)
		0.4859	0.4932	NC	NC
	Benign Thymoma/ Malignant Thymoma	1/58 (37)	3/57 (37)	0/59 (35)	0/60 (34)
		0.9351	0.3073	0.4861	0.4789

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Reference ID: 4074652

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	3 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	50 mg High (H) P - H vs. C
Thyroid	Adenoma: C-Cell	5/60 (39)	11/60 (40)	8/60 (38)	8/60 (37)
		0.3958	0.0890	0.2552	0.2380
	Carcinoma: C-Cell	1/60 (38)	1/60 (37)	1/60 (37)	0/60 (34)
		0.7135	0.7467	0.7467	0.4722
	Adenoma: C-Cell/ Carcinoma: C-Cell	6/60 (39)	12/60 (40)	9/60 (39)	8/60 (37)
		0.5165	0.0998	0.2834	0.3428
	Adenoma: Follicular Cell	0/60 (38)	2/60 (38)	1/60 (36)	2/60 (34)
		0.1701	0.2467	0.4865	0.2195
	Carcinoma: Follicular Cell	0/60 (38)	0/60 (37)	1/60 (36)	0/60 (34)
		0.2345	NC	0.4865	NC
	Adenoma: Follicular Cell/ Carcinoma: Follicular Cel	0/60 (38)	2/60 (38)	2/60 (36)	2/60 (34)
		0.1873	0.2467	0.2332	0.2195
	Neuroendocrine Tumor	0/60 (38)	0/60 (37)	0/60 (36)	1/60 (34)
		0.2345	NC	NC	0.4722
Tooth	Odontoma	4/60 (39)	6/60 (40)	6/60 (38)	3/60 (36)
		0.7437	0.3850	0.3514	0.4544
Uterus	Adenocarcinoma: Endometrial	1/60 (38)	0/60 (37)	1/60 (36)	0/60 (34)
		0.6032	0.4933	0.7397	0.4722
	Polyp: Endometrial Stromal	3/60 (39)	4/60 (39)	4/60 (37)	5/60 (36)
		0.2132	0.5000	0.4700	0.3109
	Sarcoma: Endometrial Stromal	1/60 (38)	0/60 (37)	1/60 (37)	0/60 (34)
		0.6050	0.4933	0.7467	0.4722
	Adenocarcinoma: Endometrial/ Polyp: Endometrial Stromal/ Sarcoma: Endometrial Stromal	4/60 (39)	4/60 (39)	4/60 (37)	5/60 (36)
		0.2826	NC	0.6141	0.4480
	Hemangioma	1/60 (38)	0/60 (37)	0/60 (36)	0/60 (34)
		0.7379	0.4933	0.4865	0.4722
Vagina	Benign Schwannoma	0/60 (38)	1/60 (38)	0/60 (36)	0/60 (34)
		0.4795	0.5000	NC	NC
	Malignant Schwannoma	0/60 (38)	0/60 (37)	0/60 (36)	1/60 (35)
		0.2397	NC	NC	0.4795
	Benign Schwannoma/ Malignant Schwannoma	0/60 (38)	1/60 (38)	0/60 (36)	1/60 (35)
		0.2968	0.5000	NC	0.4795

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

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Figure 1A: Kaplan-Meier Survival Functions for Male Rats

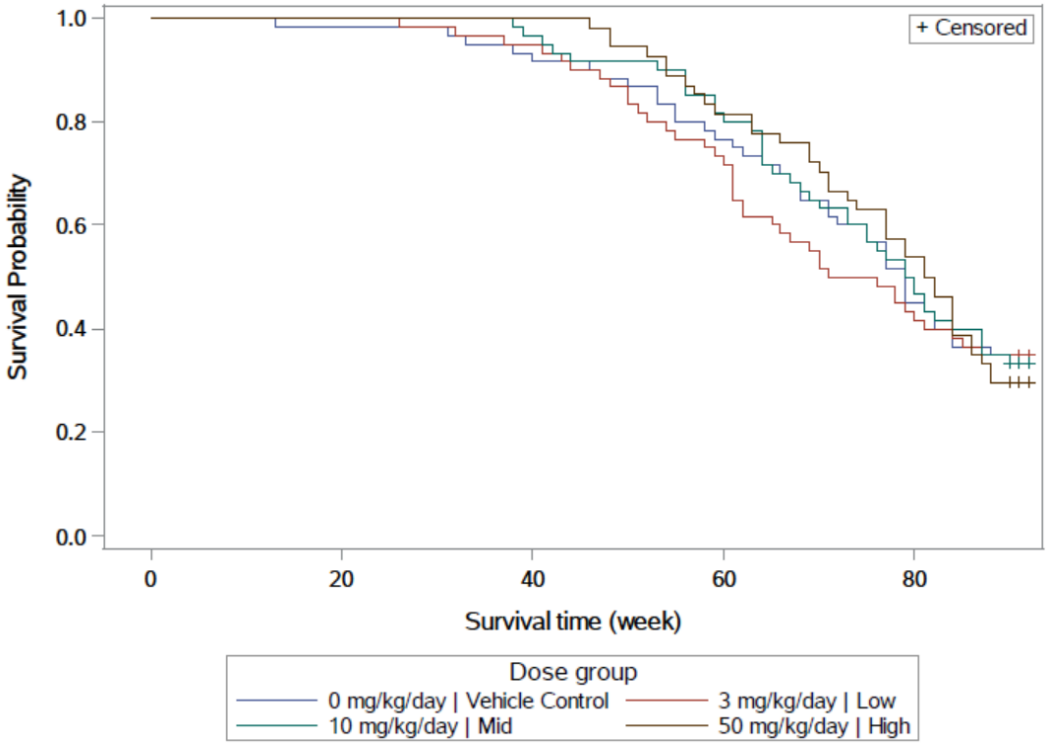
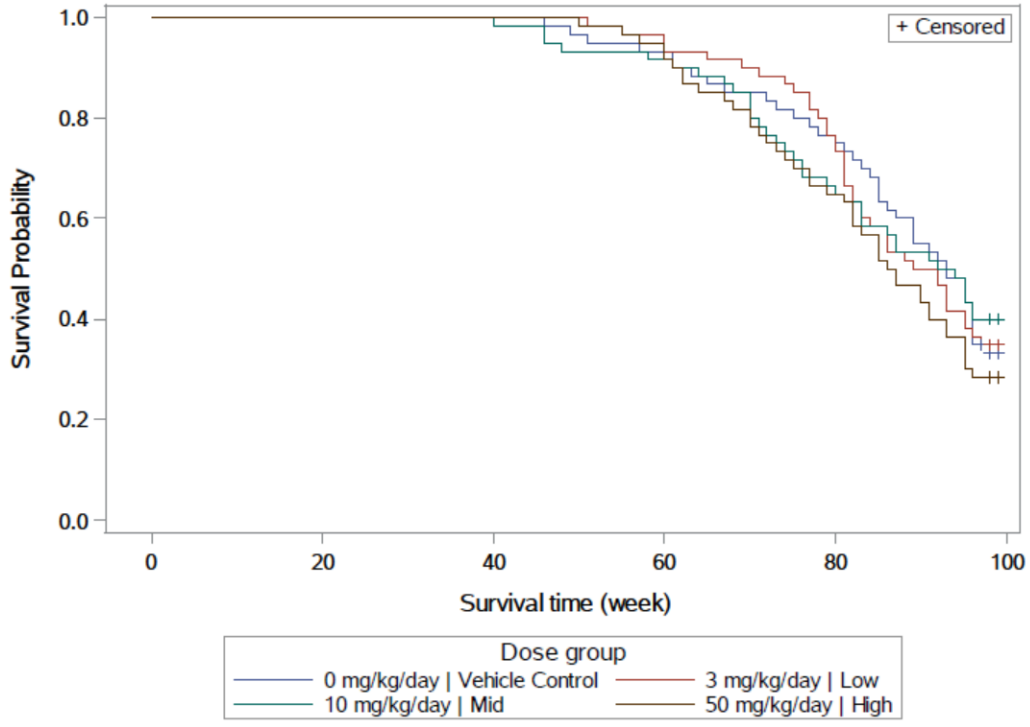


Figure 1B: Kaplan-Meier Survival Functions for Female Rats



Reference ID: 4074652

5 References

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.

2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.

3. Lin K.K. and Rahman M.A.," Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics*, 8(1), 1-15, 1998.

4. Tarone RE, "Test for trend in life table analysis", *Biometrika* 1975, 62: 679-82

5. Peto R, Pike MC, day NE, Gray RG, Lee PN, Parish S, Peto J, Richards S, and Wahrendorf J, "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments," Long-term and short-term screening assays for carcinogens: a critical appraisal, ed. IARC Monographs, Supplement 2, IARC, (Lyon, 1980), 311-426.

6. Guidance for industry: Statistical aspects of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals. Draft guidelines May 2001. Rockville (MD): US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).

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Reference ID: 4074652

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/s/

HEPEI CHEN
03/24/2017

KARL K LIN
03/24/2017
Concur with review.

FENG ZHOU
03/24/2017

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

BLA:	761062
Drug Name:	Romosozumab
Topic for the Addendum:	Site inspection for pivotal BE study
Submissions involved:	Response to IR letter dated April 26, 2017 (SDN 42)
	Response to IR letter dated May 15, 2017 (SDN 46)
Goal Date:	07/19/17
Applicant	Amgen, Inc.
Primary Reviewer	Lin Zhou, Ph.D.
Secondary Reviewer	Yow-Ming Wang, Ph.D.
OCP Division	DCP III
OND Division	OND/ODEIII/DBRUP

1. CONCLUSION

The bioanalytical portion of pivotal pharmacokinetic (PK) comparability study (Study 20120277) is acceptable from a clinical pharmacology perspective.

2. BACKGROUND

After filing of BLA 761062 (Romosozuamb), we sent a consult to office of study integrity and surveillance (OSIS) requesting inspections on sites that analyzed PK samples for pivotal PK comparability studies 20120277 and 20150197.

During inspections conducted by scientists Mohsen Rajabi Abhari and Stanley Au, significant issues were observed for one of the analytical sites for Study 20120277 (One Amgen Center Driver, Thousand Oaks, CA) and Form FDA-483 containing inspectional findings (concern over freeze-thaw stability of samples) was issued on February 17, 2017.

Amgen sent OSIS their response to the FDA-483 on March 9, 2017.

After reviewing Amgen's initial response to FDA-483 dated March 9, 2017, both OSIS and we found that the response was not adequate to support the —freeze-thaw stability of the PK samples. We discussed the issue with the Applicant during the late-cycle meeting on April 5, 2017. In addition, IR letters related to how to resolve the issue were sent to the Applicant on April 7 and 18, 2017.

Amgen provided response to April 7 and 18, 2017 IR letters on April 26, 2017. After OSIS reviewed the data, another IR went to the Applicant on May 3, 2017 and Amgen responded on May 15, 2017.

Based on all the information submitted, OSIS concluded that the freeze-thaw stability of romosozumab PK samples was supported and we agree with their assessment.

Reference ID: 4124393

Except the consult form sent to OSIS (Attachment 1), details about the aforementioned communications can be found in OSIS reviews written by Dr. Mohsen Rajabi Abhari, dated 04/18/2017 and 06/05/2017.

3 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Reference ID: 4124393

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/s/

LIN ZHOU
07/14/2017

YOW-MING C WANG
07/14/2017

Office of Clinical Pharmacology Review

BLA Number	761,062
Link to EDR	\\CDSESUB1\evsprod\BLA761062\761062.enx [SDN 1 (eCTD 0001), SDN 8 (eCTD 0009), SDN 13 (eCTD 0013), and SDN 22 (eCTD 0019)]
Submission Date	July 19, 2016
Submission Type	Standard
Brand Name	EVENITY®
Generic Name	Romosozumab
Dosage Form and Strength	Single-use prefilled syringe: 105 mg of romosozumab in 1.17 mL solution (90 mg/mL).
Dosage and Administration	Administer 210 mg subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm. A full dose of 210 mg EVENITY requires two single-use prefilled syringes. EVENITY should be administered by a healthcare provider.
Proposed Indication	For the treatment of osteoporosis in postmenopausal women at increased risk of fracture
Applicant	Amgen, Inc.
Associated IND	IND 100391
OCP Review Team	Lin Zhou, PhD Yow-Ming Wang, PhD Luning Zhuang, PhD Jeffry Florian, PhD
OCP Final Signatory	Hae Young Ahn, PhD Division Deputy Director Division of Clinical Pharmacology 3

Reference ID: 4076576

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Reference ID: 4076576

1. EXECUTIVE SUMMARY

The Applicant is seeking the approval of EVENITY® (romosozumab) for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Romosozumab is a humanized IgG2 monoclonal antibody that binds and inhibits sclerostin. By blocking sclerostin, romosozumab increases bone formation due to the activation of bone lining cells, increased bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells. Additionally, romosozumab results in changes to expression of osteoclast mediators, thereby decreasing bone resorption.

Romosozumab is administered by subcutaneous injection. The proposed dosing regimen is 210 mg monthly for 12 months. EVENITY® should be administered by a healthcare professional and a full dose of EVENITY® requires two single-use prefilled syringes, each delivering 105 mg of romosozumab. The 210 mg monthly dosing for 12 months was selected for Phase 3 studies based on a Phase 2 dose ranging study. The Applicant additionally submitted results of 8 clinical pharmacology studies in healthy subjects, subjects with low bone mineral density, and postmenopausal women with osteoporosis (PMO) to support the pharmacokinetics (PK) and pharmacodynamics (PD) of romosozumab.

1.1 Recommendations

The Divisions of Clinical Pharmacology 3 and Pharmacometrics have reviewed the information contained in BLA 761,062. The review team recommends approval of this BLA from a clinical pharmacology perspective if inspection results of the analytical and clinical sites of the two pivotal PK comparability studies (Study 20120277 and 20150197) are acceptable (The inspection results will become available on 04/19/17). The key review issues with specific recommendations and/or comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal Phase 3 study 20070337 (n = 7157) provides the primary evidence of effectiveness. Subjects treated with romosozumab (12 months) followed by denosumab (12 months) had a reduced risk of fracture at Month 12 and Month 24 compared to subjects treated with placebo (12 months) followed by denosumab (12 months). In addition, romosozumab/denosumab treatment is associated with an increased bone mineral density in lumbrar spine, total hip, and femoral neck compared to placebo/denosumab at Month 12 and Month 24. The Phase 2 dose ranging Study 20060326 provides supportive evidence.

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General dosing instructions	The proposed dosing recommendation is 210 mg monthly for 12 months. The dose-response relationship for efficacy from the Phase 2 dose-finding study and the efficacy data from the pivotal Phase 3 study, which evaluated only one dose level, support the dosing recommendation.
Dosing in patient subgroups	No dose individualization is recommended based on intrinsic or extrinsic factors.
Drug interactions	Disease-drug-drug interactions are not applicable because postmenopausal women with osteoporosis do not have much elevated proinflammatory cytokins based on the current understanding.
Immunogenicity	Immunogenicity has a negative impact on systemic exposure of romosozumab. But it does not appear to impact efficacy and safety of romosozumab following 12 monthly dosing in the pivotal Phase 3 study.
Bridge between the to-be-marketed and clinical trial formulations	The drug product tested in the pivotal Phase 3 study is the single-use glass prefilled syringe (PFS) containing 70 mg/mL romosozumab and the proposed to-be-marketed formulation is the single-use (b) (4) PFS containing 90 mg/mL romosozumab. In addition, romosozumab containing drug substance (DS) manufactured at Amgen Thousand Oaks (ATO) was evaluated in the pivotal Phase 3 study 20070337. The commercial DS is being manufactured at Amgen Rhode Island (ARI). We found the bridge between the to-be-marketed product and the clinical trial product established based on the PK comparability studies 20120277 (70 mg/mL PFS vs. 90 mg/mL PFS) and 20150197 (ATO vs. ARI). Inspection reports for analytical and clinical sites for both studies are pending.
Labeling	The proposed labeling was generally acceptable. The Clinical Pharmacology review team has recommendations for specific content and formatting changes.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Romosozumab is a humanized IgG2 monoclonal antibody that binds and inhibits sclerostin. By blocking sclerostin, romosozumab increases bone formation due to the activation of bone lining cells, increased bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells. Additionally, romosozumab results in changes to expression of osteoclast mediators, thereby decreasing bone resorption.

The following is a summary of clinical pharmacokinetics of romosozumab:

Romosozumab exhibited nonlinear pharmacokinetics across the SC and IV dose ranges of 0.1 to 10 mg/kg and 1 to 5 mg/kg, respectively. Exposure increased greater than dose proportionally (e.g., 550-fold increase in mean AUC from time 0 to infinity [AUCinf] for the 100-fold increase in SC dose from 0.1 to 10 mg/kg).

Absorption:

Administration of a single dose of 210 mg romosozumab in healthy male and female subjects (n = 90, age range: 21 to 65 years) resulted in a mean (standard deviation [SD]) maximum serum concentration (Cmax) of 22.2 (5.8) mcg/mL and a mean area under the concentration-time curve (AUC) of 389 (127) mcg*day/mL. The median time to maximum romosozumab concentration (Tmax) was 5 days (range: 2 to 7 days). Steady-state concentrations were achieved by month 3 following the monthly administration of 210 mg to postmenopausal women. Trough serum romosozumab mean concentration values from samples collected prior to dosing at months 3, 6, 9, and 12 ranged from 8.46 to 9.78 mcg/mL.

For a 210-mg SC dose of romosozumab, the estimated bioavailability was 81%.

Distribution:

The population PK analysis estimated volume of distribution at steady-state was 3.92L.

Eliminaiton:

The metabolic pathway of romosozumab has not been characterized. The clearance of romosozumab decreased as dose increased. Mean systemic clearance (CL/F) of romosozumab

was estimated to be 0.383 mL/hr/kg, following a single SC administration of 3 mg/kg. The mean effective t1/2 was 12.8 days after 3 SC doses of Q4W 3 mg/kg.

Development of ADA was associated with reduced serum romosozumab concentrations. One subject tested neutralizing antibody positive in the first in human single dose Phase 1 study had a rapid decline in romosozumab serum concentrations after retreatment. After a single dose of 1mg/kg, romosozumab serum concentration rose to 2010 ng/ml on Day 5 dropped below the lower limit of quantification (BQL = 50 ng/mL) on Day 7 and remained BQL through the PK sampling window up to 168 days, despite continued dosing once every two weeks. In the Phase 3 studies, the presence of binding ADAs appeared to decrease romosozumab exposure up to 25% at months 3, 6, and 9. The exposures became comparable (approximate 10% difference in mean values) at month 12 between ADA positive and ADA negative subjects.

Intrinsic Factors:

Based on a population pharmacokinetic analysis, no notable difference in pharmacokinetics with age (20–89 years), gender, race, or disease state (low bone mass or osteoporosis) was shown. The exposure of romosozumab decreased with increasing body weight.

Specific Populations:

Renal Impairment: Following a single 210 mg dose of romosozumab in a clinical study of 16 patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (ESRD) requiring hemodialysis, mean Cmax and AUC were 29% and 44% higher in patients with severe renal impairment as compared to healthy subjects. Mean romosozumab exposure was similar between patients with ESRD requiring hemodialysis and healthy subjects. PK of romosozumab was not evulated in ESRD patients without dialysis. A population pharmacokinetic analysis indicated an increase in romosozumab exposure with increasing severity of renal impairment.

Prior exposure to alendronate: The pharmacokinetics of romosozumab was similar in patients transitioning from alendronate therapy.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen is 210 mg monthly for 12 months.

The dose-response relationship for efficacy from the Phase 2 dose-finding study and the efficacy data from the pivotal Phase 3 study, where only one dose level was studied, support a recommendation of the 210 mg monthly dosing.

EVENITY should be administered by a healthcare professional and a full dose of EVENITY requires two single-use prefilled syringes (one after another), each delivering 105 mg of romosozumab.

2.2.2 Therapeutic individualization

Therapeutic individualization is not recommended at this time.

No dose individualization is recommended based on intrinsic or extrinsic factors although renal function (as measured by eGFR) and body weight have been identified as significant covariates in the population PK modeling analysis. However, use of romosozumab in patients with severe renal impairment and with ESRD requiring or without dialysis should be carefully monitored for hypocalcemia.

Renal function

Population pharmacokinetic analysis indicated an increase in romosozumab exposure with increasing severity of renal impairment. The dedicated renal impairment study also showed that mean Cmax and AUC were 29% and 44% higher in patients with severe renal impairment as compared to healthy subjects while mean romosozumab exposure was similar between patients with ESRD requiring hemodialysis and healthy subjects. Dose adjustment based on renal function is not warranted for the following two reasons: 1) the fixed dosing regimen (210 mg) was given to all subjects, including 10 subjects with severe renal impairment in the Phase 3 study and had an acceptable safety profile, and 2) data from the dedicated renal impairment study indicated that the incidence of hypocalcemia was associated with severity of renal impairment, but not with exposure of romosozumab. The number of subjects reported hypocalcemia was 0/8 in healthy subjects, 1/8 in subjects with severe renal impairment, and 4/8 in subjects had ESRD requiring hemodialysis.

Body weight

The population PK model predicts increasing exposure for decreasing body weight. The predicted exposure for subjects in the lowest quartile of body weight was ~50% higher than that in the highest quartile of body weight. Because the fixed dosing regimen (210 mg) was given to all subjects in the Phase 3 study and had an acceptable safety profile, dose adjustment based on body weight is not warranted.

See *Section 3.3.3* for more information.

2.3 Outstanding Issues

None from a Clinical Pharmacology's perspective.

2.4 Summary of Labeling Recommendations

In general the Applicant has provided adequate clinical pharmacology information to support the product labeling. We recommend including the following labeling concepts in the product labeling:

- **6.2 Immunogenicity**: Add a summary statement about impact of immunogenicity on PK of romosozumab. Detailed PK data will be presented in Section 12.3.
- **7. Drug Interactions:** Delete the whole section because no drug interaction study was conducted.
- **8.6 Hepatic Impairment:** Delete the whole section because no hepatic impairment study was conducted.
- **12.3 Pharmacokinetics:** PK information presented in this section is reorganized as subsections of Absorption, Distribution, Elimination, Intrinsice factors and Special populations. (b) (4) (b) (4) .

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The Product

Romosozumab is a humanized IgG2 kappa monoclonal antibody that binds to sclerostin with high affinity. Romosozumab has an approximate molecular weight of 145 kDa.

EVENITY (romosozumab) Injection is supplied as a sterile, preservative free, clear to opalescent, colorless to light yellow solution for subcutaneous injection in a single-use prefilled syringe. Each single use prefilled syringe delivers 1.17 mL of solution containing 105 mg of romosozumab (90 mg/mL), acetate (3.8 (b) (4) mg) , calcium (0.61 mg), sucrose (70 mg), and polysorbate 20 (0.07 mg) in Water for Injection, USP. Sodium hydroxide (b) (4) to a pH of 5.2.

A full dose of EVENITY (210 mg) requires two single-use prefilled syringes.

Available Treatments for Osteoporosis

Treatment for osteoporosis and the prevention of osteoporotic fractures consist of 1 class of bone-forming agents and several types of antiresorptive therapies, including bisphosphonates (Table 1).

Table 1. Pharmacologic Therapies for Postmenopausal Osteoporosis (Source: Table 1 of module 2.5 Clinical overview)

Category	Drug[a]	Route and Frequency of Administration
Bone forming therapies		
PTH analogs	teriparatide (Forteo®/Forsteo®)	subcutaneous injection, daily
Antiresorptive therapies		
Bisphosphonates	alendronate (Fosamax®)	oral, daily or weekly
	ibandronate (Boniva®)	oral, daily or monthly; IV, every 3 months
	risedronate (Actonel®, Atelvia®)	oral, daily, weekly, or monthly
	zoledronic acid (Reclast®)	IV, yearly
Calcitonin	calcitonin (Fortical®, Miacalcin®)	nasal spray, daily
SERM	raloxifene (Evista®)	oral, daily
RANKL inhibitor	denosumab (Prolia®)	subcutaneous injection, every 6 months

IV = intravenous; PTH = parathyroid hormone; RANKL = Receptor activator of nuclear factor kappa-B ligand; SERM = selective estrogen receptor modulator

[a] Not all therapies listed are available in every region

The Clinical Development Program

The BLA contained 9 Phase 1 studies, 2 Phase 2 sutdies, and 4 Phase 3 studies. Studies are listed below.

Phase 1 (Except Study 20090153 and 201101253, more details about other Phase 1 Studies can be found in Section 4.4):

- Study 20120277 and 20150197 were the two pivotal PK comparability studies to bridge the drug product tested in Phase 3 studies (the single-use glass prefilled syringe (PFS) containing 70 mg/mL romosozumab) and the proposed drug product for marketing (the single-use [redacted] (b) (4) PFS containing 90 mg/mL romosozumab). Details of these two studies can be found in Section 4.3.
- Study 20060220 was the first-in-human study for romosozumab in which single ascending doses of romosozumab up to 10 mg/kg for SC and 5 mg/kg for IV were tested in healthy men and postmenopausal women.
- Study 20060221 was the first multiple-dose study in patients with low bone mass. Subjects enrolled in this study were treated with placeo, 1 mg/kg Q2W, 2 mg/kg Q2W, 2 mg/kg Q4W, or 3 mg/kg Q4W for 3 months, all by SC administration.
- Study 20110227 was the dedicated renal impairment study.This study was conducted because of the following reasons: 1) Despite the large molecular weight, eGFR was found to be a significant factor in the PK of several monoclonal antibodies (Zhu et al, 2009; Frey et al, 2010; Struemper et al, 2013). 2) Additionally, chronic kidney disease (CKD) has been implicated with disturbances of the Wnt pathway with an elevated level of serum sclerostin reported in CKD subjects (de Oliveira et al, 2013; Brandenbury et al, 2013; Drueke and Lafage-Proust, 2011). An inverse relationship was found between serum sclerostin and eGFR in CKD subjects (Pelletier et al, 2013; Cejka et al, 2014).
- Study 20060223 was a single-dose study in postmenopausal women with low bone mass who had been receiving alendronate for at least 1 year and in postmenopausal women with low bone mass who were treatment-naïve for osteoporosis/bone loss. The objective of the study was to investiage PK, PD, safety and tolerability of romosozumab in subjects transitioning from alendronate to romosozumab study.
- In addition, Study 20090153 and 20110253 also provided supportive PK information of romosozuamb while the primary objectives of these two studies were to evaluate the PD of romosozumab. Study 20090153 was designed to evaluate the effect of romosozumab on parameters of bone quality of the forearm using peripheral quantitative computed tomography and Study 20110253 invesitgated the percent change from baseline in lumbar spine BMD after 3 months of romosozumab administration in postmenopausal women with low bone mineral density previously treated with alendronate.

Phase 2: Study 20060326 was the primary dose-finding study with a retreatment period from Month 36 to 48. Study 20101291 was the dose finding study in the Japanese population, which was a short study with fewer dosing arms compared to Study 20060326. More details about Study 20060326 can be found in Section 4.3.

Phase 3: Study 20070337 was the pivotal Phase 3 study, enrolled 7180 subjects. Study 20120156 was a placebo-controlled noninferiority study in PMO subjects comparing two romosozumab formulations, i.e., a formulation with 90 mg/mL (QM, 2 x 1.17mL subcutaneous [SC]) concentration to another formulation with 70 mg/mL (QM, 3 x 1mL SC) concentrations, and Study 20080289 was a Phase 3 teriparatide-controlled study in PMO subjects transitioning from oral bisphosphonates. Study 20110142 (the 4th study) is an alendronate-controlled, fracture outcome trial that is ongoing and not included in this BLA. More details about Study 20070337 can be found in Section 4.3.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Romosozumab is a humanized IgG2 monoclonal antibody that binds and inhibits sclerostin. By blocking sclerostin, romosozumab increases bone formation due to the activation of bone lining cells, the increased bone matrix production by osteoblasts, and the recruitment of osteoprogenitor cells. Additionally, romosozumab results in changes to expression of osteoclast mediators, thereby decreasing bone resorption.
Pharmacodynamics	Results from the pivotal Phase 3 trial (20070337) in postmenopausal women with osteoporosis showed that EVENITY increased the bone formation marker P1NP early in treatment, with a peak increase of approximately 145% relative to placebo 2 weeks after initiating treatment, followed by a return to comparable levels as the placebo treatment at Month 9, and a decline to approximately 15% below placebo at Month 12. EVENITY decreased the bone resorption marker CTX-I with a maximal reduction of approximately 55% relative to placebo 2 weeks after initiating treatment. CTX-I levels in the EVENITY treated group remained below those of placebo treated group and by approximately 25% at Month 12. Results from the primary Phase 2 dose finding study (20060326) showed that after discontinuation of EVENITY therapy, P1NP levels returned to baseline within 12 months; CTX-I increased above baseline levels within 3 months and returned toward baseline levels by Month 12, reflecting reversibility of effect. Upon retreatment with EVENITY after being off-treatment for 12 months, the level of increase in P1NP and decrease in CTX-I by EVENITY was similar to that observed during the initial treatment. Please note that bone turnover markers (BTM) are not validated

	biomarker for either fracture (the clinical endpoint for treatment of osteoporosis) or BMD (the surrogate maker for clinical outcome used for dose-finding purpose).
General Information	
Bioanalysis	Romosozumab concentrations in human serum were quantified by a validated enzyme-linked immunosorbent assay (ELISA) using specific anti-idiotype antibodies for capture and detection of romosozumab. Briefly, microplate wells were coated with mouse anti-human-romosozumab antibody to capture romosozumab. Unbound materials were removed by washing the wells. Horseradish peroxidase-labelled mouse anti-human-romosozumab antibody was used for the detection of the captured romosozumab. The nominal assay range for lower limits of quantification and upper limits of quantification was 50.0 to 2500 ng/mL, and the dilution linearity was established for up to 1:10000 dilution. See Section 4.1 for more information.
PK model	The PK of romosozumab was described by a three-compartment PK model with linear distribution to peripheral compartments, parallel linear elimination in the central compartment and target-mediated non-linear elimination in the peripheral compartments.
Heathy subjects vs PMO patients	Population PK analysis indicated no significant differences in PK between PMO patients and healthy subjects when body weight has been accounted for.
Drug exposure at steady state	Steady-state concentrations were achieved by Month 3 following the monthly administration of 210 mg dose in the pivotal Phase 3 study 20070337. The mean values of trough serum romosozumab concentration ranged from 8460 to 9780 ng/mL in samples collected prior to dosing at Months 3, 6, 9, and 12.
Dose Linearity	Romosozumab exhibited nonlinear pharmacokinetics across the SC and IV dose ranges of 0.1 to 10 mg/kg and 1 to 5 mg/kg, respectively. Exposure increased greater than dose proportionally (e.g., 550-fold increase in mean AUC from time 0 to infinity [AUCinf] for the 100-fold increase in SC dose from 0.1 to 10 mg/kg).
Body weight	Romosozumab trough concentrtions were higher in subjects with lower body weight. The predicted exposure for subjects in the lowest quartile of body weight was ~50% higher than that in the highest quartile of

	body weight.
Renal Impairment	Mean romosozumab exposure, as measured by Cmax and AUC values, in subjects with severe renal impairmentcohort was numerically greater than the healthy subject cohort (29% for Cmax and 44% for AUC, respectively) based on data from a dedicated study; however, most of the subjects (6-7 of 8 subjects in the cohort) with severe renal impairment had values that were within the range of healthy subjects. Mean romosozumab exposure was similar between subjects with ESRD requiring hemodialysis and healthy subjects. Romosozumab PK in subjects with ESRD not on dialysis has not been evaluated. The PopPK analysis showed that renal impairment has an effect on the CL of romosozumab. See section 3.3.3 and 4.5 for additional details.
Hepatic Impairment	No formal trial was conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of romosozumab.
Prior exposure to Alendronate	Compared to subjects with osteoporosis/low bone mass who are treatment-naïve, postmenopausal women with low bone mass who had been receiving alendronate for at least 1 year had similar extent of exposure after treatment with one single dose (210 mg) of romosozumab. Mean Cmax values differed by less than 4% between prior exposure to alendronate group and treatment naïve group and median tmax values were similar (4.9 days and 4.5 days). Mean AUClast and AUCinf were also similar (< 12% difference) and mean terminal half-life was approximately 7.5 days for both groups. PopPK analysis also concluded that prior exposure to alendronate did not have a significant impact on the exposure of romosozumab.
ADME	
Absorption	Administration of a single dose of 210 mg romosozumab in healthy male and female subjects (n = 90, age range: 21 to 65 years) resulted in a mean (SD) maximum serum concentration (Cmax) of 22.2 (5.8) mcg/mL and a mean area under the concentration-time curve (AUC) of 389 (127) mcg*day/mL. The median time to maximum romosozumab concentration (Tmax) was 5 days (range: 2 to 7 days). Steady-state concentrations were achieved by month 3 following the monthly administration of 210 mg in postmenopausal women. Trough

	serum romosozumab mean concentration values from samples collected prior to dosing at months 3, 6, 9, and 12 ranged from 8.46 to 9.78 mcg/mL. For a 210-mg SC dose of romosozumab the bioavailability was estimated to be 81%.
Distribution	The population PK analysis estimated volume of distribution at steady-state was 3.92L.
Elimination	The clearance of romosozumab decreased as dose increased. Mean systemic clearance (CL/F) of romosozumab was estimated to be 0.383 mL/hr/kg, following a single SC administration of 3 mg/kg. The mean effective t1/2 was 12.8 days after 3 SC doses of Q4W 3 mg/kg.
Metabolism	The metabolic pathway of romosozumab has not been characterized.
Excretion	Romosozuamb is a humanized monoclonal antibody of the IgG2 subclass and has a molecular weight of approximately 145 kDa; therefore, intact romosozumab are unlikely to be filtered by kidney or excreted in urine.
Immunogenicity	
Incidence	In Phase 1 studies, about 7.9% (66 of 832) of subjects developed binding antibodies after at least 1 dose of romosozumab. All positive subjects showed a persistent binding response with a positive result at the last time point tested. Neutralizing antibodies were detected in 27.3% (18 of 66) of binding antibody positive subjects. The incidence of anti-romosozumab binding ntibodies in clinical studies with repeated dosing was higher than the antibody incidence following a single dose. About 20% (852 of 4289) of subjects exposed to romosozumab in the Phase 2 and 3 studies developed binding antibodies. The antibody responses were transient (i.e., became negative by the last time point tested) for 48.6% (414 of 852) of the binding antibody positive subjects. Neutralizing antibodies were detected in 5.4% (46 of 852) of binding antibody positive subjects, 23.9% of which (11 of 46) were transient. The incidence of binding and neutralizing antibodies in subject dosed with 210 mg QM was 19.1% (758 of 3959) and 4.1% (31 of 758),

	respective; which were similar to the incidences in the overall studies.
Impact on PK	Development of anti-drug antibodies (ADA) was associated with reduced serum romosozumab concentrations.
Impact on efficacy	Overall, ADA appeared to have no impact on efficacy. While it is not feasible to draw a definitive conclusion on the impact of ADA on fracture, due to the small number of subjects who had fracture in the Phase 3 trial. In addition, ADA did not affect romosozumab treatment effect on BMD.
Impact on safety	No associations could be made between the presence of anti-romosozumab binding and/or neutralizing antibodies and the worsening of immune mediated symptoms even after multiple dosing with romosozumab. Notable association was observed in the development of injection site reactions with romosozumab dosing when compared to placebo, however, this was irrespective of the immunogenicity.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology information provides supportive evidence of effectiveness. Romosozumab treatment produced pharmacodynamic effects in changes of bone turnover markers (an increase in P1NP and a reduction in CTX-I) as well as an increase in the bone mineral density (BMD). During clinical development multiple studies evaluated these PD effects, including two Phase 3 studies (Study 20080289 and Study 20120156) that had bone mineral density (BMD) at Month 6 as the primary efficay endpoint and the pivotal Phase 3 study (Study 20070337) which had BMD and bone turnover markers as secondary endpoints.

The pivotal evidence of effectiveness is from the Phase 3 pivotal trial (Study 20070337) which is a randomized double-blind placebo-controlled study with 2-year fracture data.

The following sub-sections further provide details of the fracture data, the BMD data, and the data for bone turnover markers.

Primary efficacy (fracuture) results in Phase 3 trials

Study 20070337 was a randomized double-blind placebo-controlled study with 2-year fracture data. A total of 7180 women were randomized in a 1:1 ratio to receive either romosozumab 210 mg SC QM or matched placebo in a blinded fashion for the duration of the 12-month double-blind, placebo controlled study period. After the double-blind period, subjects entered a 12-month denosumab follow-on study period in which they received denosumab 60 mg SC Q6M

in an open-label fashion while remaining blinded to their initial treatment assignment. The primary analysis was conducted after all subjects completed the 24-month visist. The co-primary efficacy endpoints were subject incidence of new vertebral fracture through Month 12 and Month 24.

The applicant's analysis showed that romosozumab significantly reduced the risk of new vertebral fractures compared with placebo through Month 12 (odds ratio = 0.27, $p < 0.001$), with a relative risk reduction of 73% (risk ratio = 0.27 [95% CI: 0.16, 0.47]). After an additional 12 months of treatment with denosumab, vertebral fracture risk reduction persisted over the 24-month study period for subjects initially randomized to romosozumab compared to subjects initially treated with placebo (odds ratio = 0.24, $p < 0.001$), with a relative risk reduction of 75% (risk ratio = 0.25 [95% CI: 0.16, 0.40]). See Table 2 for more details.

Table 2. Subject Incidence Rates of New Vertebral Fracture Through Month 12 and Through Month 24 (Primary Efficacy Analysis Set, LOCF Imputation) (20070337 24-Month Primary Analysis Period)

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

LOCF = last observation carried forward; RRR = relative risk reduction; N = Number of subjects randomized; N1 = Number of subjects in the primary analysis set for vertebral fractures.
Source: Table 10-1 of 02-csr-2007-0337-rpt-body.pdf

Efficacy (BMD) results in Phase 2 and 3 trials

Lumbar spine, total hip, and femoral neck BMD were secondary efficacy endpoints for the pivotal Phase 3 study (20070337) and lumbar spine BMD was the primary efficacy endpoint for Phase 2 dose-finding studies. While BMD is not a qualified surrogate marker for fracture, lumbar

spine BMD is considered an acceptable marker for dose-finding in osteoporosis development programs.

In Study 20070337, romosozumab significantly increased BMD at the lumbar spine, total hip, and femoral neck compared with placebo at Month 12. Romosozumab followed by denosumab resulted in continued increases in BMD at the lumbar spine, total hip, and femoral neck at Month 24. The mean percent change from baseline to Month 24 in BMD were significantly greater for subjects in the romosozumab/denosumab group compared with the placebo/denosumab group ($p < 0.001$ at each site). Only lumbar spine BMD data are show in Table 3. For more details, please see Table 10-3 of the clinical study report for Study 20070337.

Table 3. Lumbar Spine Density Percent Change from Baseline at Month 12 and Month 24 (ANCOVA Model) (Primary Efficacy Analysis Set for BMD, LOCF)(20070337 24-Month Primary Anslyis Period)

	Placebo/ Denosumab 60 mg Q6M (N = 3591)	Romosozumab 210 mg QM/ Denosumab 60 mg Q6M (N = 3589)	Difference from Placebo/Denosumab 60 mg Q6M[a]
Lumbar spine			
Month 12			
n	3148	3151	
LS mean	0.4	13.1	12.7
SE	0.1	0.1	0.1
(95% CI)	(0.2, 0.5)	(12.8, 13.3)	(12.4, 12.9)
p-value	-	-	<0.001
Month 24			
n	2877	2861	
LS mean	5.5	16.6	11.1
SE	0.1	0.1	0.1
(95% CI)	(5.3, 5.7)	(16.3, 16.8)	(10.8, 11.4)
p-value	-	-	<0.001

ANCOVA = analysis of covariance; LOCF = last observation carried forward; LS = least squares; N = number of randomized subjects; n = number of subjects with values at baseline and at the time point of interest. *Source: Table 10-3 of 02-csr-2007-0337-rpt-body.pdf*

The lumbar spine BMD results of Phase 2 dose-ranging study 20060326 and 20101291 also supported the effectiveness of romosozumab 210 mg monthly for 12 months for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. See *Sections 3.3.2* and *4.7.3* for more information.

Pharmacodynamics (bone turnover markers) results from Phase 2 and 3 studies

In the pivotal Phase 3 study 20070337, romosozumab increased the bone formation marker P1NP early in treatment, with a peak increase of approximately 145% relative to placebo 2 weeks after initiating treatment, followed by a return to placebo levels at Month 9 and a decline to approximately 15% below placebo at Month 12. EVENITY decreased the bone resorption marker (CTX-I with a maximal reduction of approximately 55% relative to placebo 2 weeks after initiating treatment. After EVENITY treatment, CTX-I levels remained below placebo and were approximately 25% below placebo at Month 12.

Results from the primary Phase 2 dose finding study (20060326) showed that after discontinuation of romosozumab therapy, P1NP levels returned to baseline within 12 months; CTX-I increased above baseline levels within 3 months and returned toward baseline levels by Month 12. Upon retreatment with romosozumab after 12 months off treatment, the level of increase in P1NP and decrease in CTX-I by romosozuamb was similar to that observed during the initial treatment.

It should be noted that bone turnover markers are not validated biomarker for either fracture (the clinical endpoint for treatment of osteoporosis) or BMD (the endpoint for clinical outcome used for dose-finding purpose). See details about the CTX-I and PINP assays in Section 4.1.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate. The dose-response relationship for efficacy from the Phase 2 dose-finding study (Study 20060326) and the efficacy data from the pivotal Phase 3 study (Study 20070337), where only one dose level was studies, support a recommendation of the 210 mg monthly dosing for 12 months.

Study 20060326 was a multicenter, international, randomized, placebo-controlled, parallel-group study in postmenopausal women with low BMD at the lumbar spine, total hip, or femoral neck. The study included the following treatment phases:

1. a 24-month treatment phase (Months 1-24), during which subjects received 1 of 5 doses of romosozumab (70 mg SC QM, 140 mg SC QM, 210 mg SC QM, 140 mg SC Q3M, and 210 mg SC Q3M), placebo, or active controls [alendronate (ALN) 70 mg PO QW for 12 months + denosumab 60 mg SC Q6M for 12 months or teriparatide (TPTD) 20 mcg SC QD for 12 months only].
2. followed by re-randomization to a 12-month extension phase (months 24-36) with either denosumab SC 60 mg or placebo SC Q6M treatment
3. followed by a 12-month retreatment phase (months 36-48)with romosozumab. Subjects initially randomized to romosozumab or placebo received romosozumab 210 SC QM. Subjects who initially received ALN ended their participation at month 36 and were not retreated with romosozumab

4. followed by a 24-month follow-on phase (months 48 to 72) with 1 dose level of zoledronic acid or no intervention.

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

At Month 12, as shown in Table 4, the increase in mean percent change in BMD at the lumbar spine was statistically significant for all romosozumab dose groups when compared with placebo ($p < 0.0001$). The romosozumab 140 mg QM and 210 mg QM dose groups also demonstrated statistically significant increases when compared with ALN ($p < 0.0001$) and TPTD ($p \leq 0.0276$).

Table 4. DXA Lumbar Spine BMD Percent Change From Baseline to Month 12 – Linear Mixed Effect Model Showing Each of Romosozumab Groups (Primary Efficacy Subset) (20060326 12-Month Primary Analysis) ***(Source: Table 10-2 of 02-csr-20060326-rpt-body.pdf)***

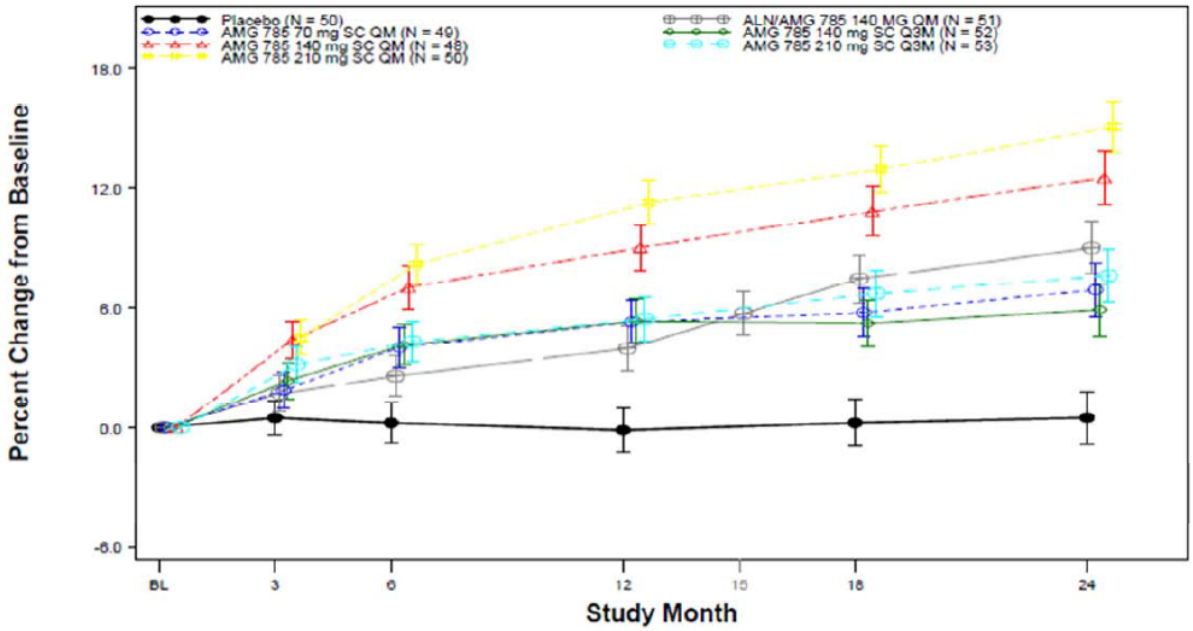
	Placebo	ALN PO	TPTD SC	Romosozumab SC				
	Total (N = 50)	70 mg QW (N = 51)	20 µg QD (N = 49)	70 mg QM (N = 49)	140 mg Q3M (N = 52)	140 mg QM (N = 48)	210 mg Q3M (N = 53)	210 mg QM (N = 50)
Month 12								
n	47	47	46	44	49	46	51	49
LS Mean	-0.1	4.1	7.1	5.4	5.4	9.1	5.5	11.3
95% CI	(-1.2, 0.9)	(3.0, 5.1)	(6.1, 8.2)	(4.3, 6.4)	(4.4, 6.5)	(8.0, 10.2)	(4.4, 6.6)	(10.3, 12.4)
Difference from placebo[a]								
LS Mean				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, 7.1)	(10.0, 12.9)
p-value				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Difference from ALN[b]								
LS Mean				1.3	1.4	5.0	1.5	7.3
95% CI				(-0.2, 2.8)	(-0.1, 2.8)	(3.6, 6.5)	(0.0, 2.9)	(5.8, 8.7)
p-value				0.0853	0.0853	<0.0001	0.0853	<0.0001
Difference from TPTD[c]								
LS Mean				-1.8	-1.7	2.0	-1.6	4.2
95% CI				(-3.3, -0.3)	(-3.2, -0.2)	(0.5, 3.4)	(-3.1, -0.2)	(2.7, 5.6)
p-value				0.0276	0.0276	0.0276	0.0276	<0.0001

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

Lumbar spine BMD continued to increase from Month 12 to Month 24 in all but the 140 mg Q3M romosozumab dosing group; the BMD increases were greatest in the 210 mg QM group (Figure 1.) Compared with the placebo group, each of the romosozumab groups showed a significantly increased lumbar spine BMD ($p < 0.0001$) at month 18 and 24. Subjects randomized to the ALN-to-romosozumab transition group (ALN/romosozumab) began treatment with romosozumab 140 mg QM at Month 12. Increases in lumbar spine BMD improved with

romosozumab treatment during months 12 to 24. Note: Subjects assigned to TPTD SC PO 20 mcg QD arm only received TPTD for 12 months and there was no data on this dosing arm beyond 12 months.

Figure 1. Least Square Means (95% CI) of Percent Change From Baseline in DXA Lumbar Spine BMD by Visit (Primary Efficacy Subset) based on Month 24 Interim Analysis of Study 20060326 ***(Source: Figure 10-8 of 02-csr-20060326-rpt-body.pdf)***



ALN = alendronate; AMG 785 = romosozumab; BL = baseline; BMD = bone mineral density; CI = confidence interval; DXA = dual-energy X-ray absorptiometry; N = Number of subjects randomized and have baseline and at least one post baseline BMD measurements on or prior to the Month 12.

The dose and dosing regimen selected for the pivotal Phase 3 study is 210 mg QM for 12 months for the following reasons: 1) Dosing arm 210 QM showed the highest increased in mean percent change in BMD at the lumbar spine compared to other dosing arms. At the End of Phase 2 meeting, the Agency recommended that the sponsor test both 140 mg QM and 210 mg QM in their pivotal Phase 3 trials because 140 mg QM also showed reasonable amount increase in lumbar BMD after 12-month treatment and the Applicant decided to study only one dose level in the pivotal Phase 3 study. 2) The increase in BMD slowed down between Month 12 and Month 24. 3) There are uncertainties about the safety of long-term treatment (>18 months) of an anabolic agent based on data from TPTD.

Fracture and BMD data from the pivotal Phase 3 study (20070337) support the proposed dose and dosing regimen of romosozumab 210 mg QM for 12 months. See Section 3.3.1 for details.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. There is no need for alternative dosing regimen for subpopulations based on the intrinsic factors. The proposed dosing regimen with a fixed dose of 210 mg given monthly is appropriate for the general indicated population.

However, use of romosozumab in patients with severe renal impairment and with ESRD requiring or without dialysis should be carefully monitored for hypocalcemia.

The applicant conducted a dedicated renal impairment study investigating PK of romosozumab in healthy subjects (n=8), subjects with severe renal impairment (n=8), and subjects who have ESRD requiring hemodialysis (n=8). Subjects have ESRD without dialysis was not enrolled into this study. The exposure in patients with severe renal impairment was higher than that in healthy subjects. Mean Cmax and AUC were 29% and 44% higher in patients with severe renal impairment as compared to healthy subjects. However, the exposure range in these two groups have substantial overlap. Most of the subjects with severe renal impairment had values that were within the range of healthy subjects, specifically, Cmax in 7 out of 8 subjects and AUC in 6 out of 8 subjects. Meanwhile, romosozumab PK was similar between healthy subjects and ESRD subjects requiring hemodialysis. The scientific explanations behind this observation are unclear at this time. When it comes to safety, the most frequently reported treatment-emergent adverse events in the dedicated renal impairment study was hypocalcemia. Data suggested that the incidence of hypocalcemia was associated with severity of renal impairment, but not with exposure of romosozumab. The number of subjects reported hypocalcemia was 0/8 in healthy subjects, 1/8 in subjects with severe RI, and 4/8 in subjects had ESRD requiring hemodialysis.

Based on the population PK (PopPK) analysis (Section 4.5), no significant impact of gender, age, race (Japanese/non-Japanese), prior alendronate, and drug product manufacturing process on romosozumab exposure were identified. However, body weight and severity of renal impairment would affect PK of romosozumab. The impact on romosozumab exposure are listed in Table 5 (Source: Section 4.5 Table 6) .

Table 5. Impact of Body Weight and Renal Function on AUC for 210 mg QM Dosing Based on Population PK Predictions for Patients in Study 20070337 (n=434) or Simulations*

Parameter	Category/Quantile	n	$AUC_{330-360}$ (µg·day/mL) (mean, 95% CI)
Body Weight (kg)	1st quantile (35.4 -50.2)	110	701.9 (523.8-787.2)
	2nd quantile (50.2-56.3)	106	587.3 (515.0-661.0)
	3rd quantile (56.3-63.2)	108	482.7 (398.2-557.7)
	4th quantile (63.2-95.9)	110	467.9 (369.4-512.2)
eGFR (mL/min/1.73m^2)	Normal (≥90)	49	527.1 (387.1-591.9)
	Mild (60-90)	290	558.2 (436.0-631.9)
	Moderate (30-60)	93	585.9 (491.1-671.7)
	Severe (15-30)*	-*	837.4 (707.0-967.9)*

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Note: The AUC data were summarized from the predicted AUC value for each individual subject in the PK substudy of Phase 3 study 20070337. The AUC prediction was based on the individual estimated PopPK model parameters which were obtained based on modeling the trough concentration data .
**Simulation with 2910 number of patients, which represents demorgraphic of the phase 3 population based on Reviewer's updated population PK model with a dose of 210 mg QM. There were only two subjects with severe renal function in the Phase 3 study 20070337.*

In the Phase 3 study only Ctrough were collected, therefore the AUC data in Table 5 were predicted for the PK substudy population using the population model parameters estimated for each individual. Furthermore, due to the small number of subjects with severe renal impairment study 20070337, the reviewer simulated exposures in severe renal impairment using the same covariate model to evaluate the effect of renal impairment. The covariate model was developed based on a total of 10 subjects with severe renal impairment (8 from the dedicated renal impairment study and 2 from the pivotal phase 3 study 20070337). Please note, Study 20070337 had 10 subjects with severe renal impairment but only 2 of them had PK data.

An increasing exposure was also predicted for decreasing eGFR. In particular, the predicted exposure for patients with severe renal impairment was ~60% higher than subjects with normal renal function; which is consistent with what observed in the dedicated renal impairment study (Study 20110227). In the dedicated renal impairment study, mean AUC were 44% higher in patients with severe renal impairment as compared to healthy subjects.

Dose adjustment based on renal function is not warranted for the following two reasons: 1) the fixed dosing regimen (210 mg) was given to all subjects, including 10 subjects with severe renal impairment in the Phase 3 study and had an acceptable safety profile (Section 4.6), and 2) data from the dedicated renal impairment study indicated that the incidence of hypocalcemia was associated with severity of renal impairment, but not with exposure of romosozumab.

An increasing exposure was predicted for decreasing body weight. In particular, the predicted exposure for subjects in the lowest quartile of body weight was ~50% than that in the highest quartile of body weight; which could have the potential to affect the safety profile. However, the fixed dosing regimen (210 mg) was given to all subjects in the pivotal Phase 3 study and had an acceptable safety profile. Therefore, dose adjustment based on body weight is not warranted (Section 4.6).

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug interactions are not applicable as romosozumab is administered by SC injection.

Disease-drug-drug interactions are not applicable because postmenopausal women with osteoporosis do have not much elevated proinflammatory cytokins based on the current understanding.

4. APPENDICES

4.1 Summary of Bioanalytical Methods

4.1.1 Romosozumab assay

The romosozumab serum concentrations were analyzed using an enzyme linked immunosorbent assay (ELISA) using specific anti-idiotype antibodies for capture and detection of romosozumab. The method was developed and validated (validation number 108298) at Amgen Inc. (Thousand Oaks, CA) and was subsequently transferred (b) (4) (b) (4) where the method underwent partial method validations at each laboratory; validation number 108763 at (b) (4) and validation number 117101 at (b) (4)

Briefly, microplate wells were coated with mouse anti-human-romosozumab antibody (Clone 2.59, Amgen Inc., Thousand Oaks, CA) to capture romosozumab. Unbound materials were removed by washing the wells. Horseradish peroxidase-labelled mouse anti-human-romosozumab antibody (Clone 2.5, Amgen Inc., Thousand Oaks, CA) was used for the detection of the captured romosozumab.

Validation reports for all three sites appear to be acceptable. Validated parameters from validation number 108298 is listed here as an example (Table 4.1.1).

Table 4.1.1 Validation Summary Table for Serum Romosozumab Assay *(Source: Study 108298)*

Standard Curve Fit	4 Parameter Logistic (Auto-Estimate) with a weighing factor of 1
Assay Range (nominal)	50 to 2496 ng/mL
LLOQ (nominal)	50 ng/mL
ULOQ (nominal)	2496 ng/mL
% Diff for STDs	Within ± 15%
% Diff for all QCs	Within ± 20%
% CV for STDs and QCs	≤ 15%
% CV for Study Sample	≤ 15%
Selectivity	No matrix effect was observed in 20 individual serum lots (10 males and 10 postmenopausal females, aged between 45 -59 years old). No unspiked serum lots had detectable level of AMG 785.
Specificity	Interference from human recombinant sclerostin, and polyclonal rabbit anti-AMG 785 antibodies were tested. Human recombinant sclerostin at the concentration up to 1 µg/mL did not interfere in the measurement of AMG 785. Polyclonal rabbit anti- AMG 785 at concentration > 10 ng/mL interfered in the measurement of AMG 785.
Dilutional Linearity	Linear from 1:2 to 1:10000 dilution
Hook Effect	Not observed
Robustness/Ruggedness	Verified by using different instruments, different analysts, different incubation times and running the method on different

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	days. These conditions were included in the accuracy and precision experiments, from which results the acceptance criteria were determined. Robustness of the procedure to run 3 plates simultaneously was tested during validation and study.
Coated Plate Stability	Plate coating stability established at 2° to 8°C for up to 72 hours. Plate blocking stability established at 22° to 28°C from 1 to 3 hour.
Freeze-Thaw Stability	5 cycles
Bench-Top Stability	Stability was demonstrated as follows: 1. At 2° to 8° C for up to 27 hour in 100% serum 2. At ambient room temperature (ART) for 6 hours in 100% serum 3. At ART for 6 hours after pretreatment
Long Term Storage Stability	Long-term stability was demonstrated up to 539 days at -60° to -80°C (ongoing) and up to 190 days at -15° to -25°C.
Incurred Sample Reanalysis	Reproducibility of the method was demonstrated using 76 samples (complete profiles from 4 patients).
Parallelism	Tested in 4 pooled samples. Parallelism was demonstrated in all pooled samples.

The methods used for each study was listed in Table 4.1.2.

Table 4.1.2. Bioanalytical Methods and Validation Reports for Quantification of Serum Romosuzumab *(Source: Table 9 of Module 2.7.1)*

Assay Study No.	Method	Assay Validated (Site)	Assay Range (ng/mL)	Amgen Study No.
Serum Romosozumab				
108298	(b) (4)	Yes (Amgen)	50 - 2496	20060220
108298		Yes (Amgen)	50 - 2490	20120277
108298		Yes (Amgen)	50 - 2492	20101180
108763		Yes (b) (4)	50 - 2500	20060221 20060223
108763		Yes	50 - 2496	20120274 20090378 20090153 20110253
117101		Yes	50 - 2500	20110227
108763		Yes	50 - 2496	20070337
108763		Yes	50 - 2496	20060326
117101		Yes	50 - 2500	20101291
108763		Yes	50 - 2500	20090418 20150197

4.1.2 Bone Turnover Marker (Serum CTX-I and P1NP) Assays

On October 21, 2016, the Applicant submitted bioanalytical methods for all the BTM markers tested in the clinical development program (SN 0009), in response to FDA 06 October 2016 Information Request. The Applicant evaluated multiple bone turnover markers, including CTX-I, P1NP, Bone Specific Alkaline Phosphatase (BSAP), Osteocalcin, and Tartrate-Resistant Acid Phosphaotase-5b (TRACP-5b). Since CTX-I and P1NP are the more common ones than the others and language related to changes in CTX-I and P1NP from Study 20070337 and Study 20060326 were proposed in the labeling, our review focuses on the serum CTX-I and P1NP assays for Study 20060326 and 20070337. Validation reports for the four assays (Table 4.1.3) were requested in an Information Request (IR) sent to the applicant on 03/10/17.

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Table 4.1.3. Bioanalytical Methods and Supported Contract Laboratories of CTX-I and P1NPs in Human Serum for Study 20070337 and 20060326 ***(Source: Table 2 of Response to FDA 06 October 2016 Information Request)***

Serum Marker	Method	Supported Contract Lab	Amgen Study No.
CTX-1	[redacted] (b) (4)		20060326
			20070337
P1NP			20060326
			20070337

4.1.2.1 Assays for Study 20060326

Validation reports for assays measuring CTX-I and P1NP in Human Serum for Study 20060326 are adequate.

Determination of serum CTX-I concentration in samples from Study 20060326 used a kit called "Serum CrossLaps® ELISA" [redacted] (b) (4) (b) (4). The Serum CrossLaps® ELISA is an enzyme-linked immunosorbent assay based on the capture of the analyte (CTX-I) and its revelation by two highly specific monoclonal antibodies, one is biotinylated and the other is conjugated with peroxidase. The complex Mab1-CTX-I-Mab2 generated binds to streptavidin coated on microwell surface an dthe addition of a chromogenic substrate allows to obtaina color reaction. The CTX-I concentration in the sample is determined spectrophotometrically and calculated from a standard calibration curve. Validated parameters for "Serum CrossLaps® ELISA" are summarized in Table 4.1.4.

Table 4.1.4 Validation Summary Table for Serum CTX-1 Assay for Study 20060326 ***(Source: [redacted] (b) (4) .pdf submitted on 03/15/17 in response to IR sent on 03/10/17)***

Standard Curve Fit	The calibration curve is obtained by plotting the mean absorbances of the 6 standards in ordinate against the corresponding CTX-I concentrations in abscissa. The fitting of the calibration curve is performed by the "MultiCalc" software using the "4 PL" mathematical model which calculates and fits a curve through all the experimental points.
Assay Range (nominal)	0.05 to 2.45 ng/mL
LLOQ (nominal)	0.052 ng/mL
ULOQ (nominal)	2.45 ng/mL
% of recovery	[redacted] (b) (4) %
With-assay precision	< 6 %
Between-assay precision	< 10 %
Stability	For a conservation of 1 week the serum will be stored at -20°C.

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	For a longer period at -70°C minimum. A maximum of 4 freez and thaw cycles is acceptable.

Determination of serum P1NP concentration in samples from Study 20060326 used a kit called "Intact P1NP RIA Kit" (b) (4). The assay is based on a competitive radioimmunoassay technique. The P1NP to meaure competes with P1NP -^{125}I for a liminted number of high affinity binding sites of a polyclonal antibody. After the separation of the free P1NP from the P1NP-antibody complex, the radioactivity of the latter is counted and is reversely proportional to the amount of P1NP in the reaction mixture. The concentration in the sample is calculated with a standard curve. Validation of the assay was conducted by (b) (4). Validated parameters for "Intact P1NP RIA Kit" are summarized in Table 4.1.5.

Table 4.1.5 Validation Summary Table for Serum P1NP Assay for Study 20060326
(Source: (b) (4).pdf submitted on 03/15/17 in response to IR sent on 03/10/17)

Standard Curve Fit	The fitting of the calibration curve is performed by Riasmart™ software using the "Logistic Four Parameters" mathematical model.
Assay Range (nominal)	2.8 to 190 ng/mL
LLOQ (nominal)	2.8 ng/mL
ULOQ (nominal)	190 ng/mL
% of recovery	(b) (4)%
With-assay precision	< 8 %
Between-assay precision	< 7 %
Stability	For a conservation of 2 weeks the serum will be stored at -20°C. For a longer period at -70°C minimum. A maximum of 6 freez and thaw cycles is acceptable.

4.1.2.2 Assays for Study 20070337

Validation reports for assays measuring CTX-I and P1NP in Human Serum for Study 20070337 are adequate.

Determination of serum CTX-I concentration in samples from Study 20070337 used the (b) (4) CTX-I (CrossLaps®) Assay. This CTX-I assay is based on chemiluminescence techonology. Two highly specific monoclonal antibodies are used. The antibodies are against the amino acid sequence of EKAHD-β-GGR, where the aspartic acid residue is (D) β-isomerized. In order to obtain a specific signal in (b) (4) CTX-I assay, two chains of EKAHD-β-GGR must be cross-linked.

Samples are incubated with both labelled antibodies for a period of time. Streptavidin coated magnetic particles are then added and following a further incubation step, the particles are "captured" using a magnet. After a washing step and addition of trigger reagents, the light emitted by the acridinium label is directly proportional to the concentration of CTX-I in the

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original sample. Validated parameters for "(b) (4) CTX-1 assay" are summarized in Table 4.1.6.

Table 4.1.6 Validation Summary Table for Serum CTX-1 Assay for Study 20070337
(Source: (b) (4) .pdf submitted on 03/15/17 in response to IR sent on 03/10/17)

Assay Range (nominal)	0.043 to 6 ng/mL
LLOQ (nominal)	0.043 ng/mL
ULOQ (nominal)	6 ng/mL
Intra- & inter-assay accuracy for QCs	Within ± 10%
Intra- & inter-assay precision for QCs	Within ± 10%
Intra- & inter-assay precision for samples	Within ± 10%
Hook effect	Not observed
Dilutional linearity	Linearity validation was considered acceptable up to a dilution of 4X.
Stability	Room temperature stability was acceptable for up to 72 h, and refrigerated and frozen (<-10°C) stabiligy acceptable for up to 7 days. Long term frozen stability (-20, -80, and -150°C) for up to 3 years has been reported but not tested in this validation exercise. Freeze/thaw stability was acceptable for up to 6 freeze/thaw cycles.

Determination of serum P1NP concentration in samples from Study 20070337 used a kit called "UniQTM PINP 100 test kit" (b) (4). Based on the product number, the kit is the same as what was used for Study 20060326 and a description of the assay can be found above Table 4.1.5. The validation report was done by (b) (4). Validated parameters for "UniQTM PINP 100 test kit" are summarized in Table 4.1.7 and 4.1.8.

Table 4.1.7 Validation Summary Table for Serum P1NP Assay for Study 20070337
(Source: PINP Method Validation Report CCLS_24March2017 submitted on 03/24/17 in response to IR dated 03/10/17)

Assay Range (nominal)	4.9 to 250 ng/mL
LLOQ (nominal)	4.9 ng/mL
ULOQ (nominal)	250 ng/mL, can measure up to 5000 ng/mL with 1:20 dilution
Accuracy/Recovery	Acceptable
With-assay precision	< 4 %
Between-assay precision	< 12 %
Stability	A maximum of 3 freeze and thaw cycles is acceptable. Ambient (18-26°C): 4 days Refridgerated (2-8°C): 7 days -20 °C Frozen: 7 years (kit manufacturer documentation)

The accuracy of the PINP assay was established using UniQ™ PINP Kit Control Levels 1 & 2 assayed in 10 replicates. The achieved means were acceptable within manufacturer's ranges for both levels of QC (Table 4.1.7).

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Table 4.1.8. Accuracy Summary for Serum P1NP Assay for Study 20070337 (*Source: Table 5.6.1 in PINP Method Validation Report CCLS_24March2017 submitted on 03/24/17 in response to IR sent on 03/10/17*)

UniQ™ PINP Kit Control	Manufacturer's Mean (µg/L)	Achieved Mean (µg/L)
Level 1 QC	42.4 (range 33.4 to 48.0)	42.6
Level 2 QC	121.0 (range 92.0 to 136.0)	121.5

4.1.3 Bioanalytical assays for immunogenicity assessment

Two validated assays were used to detect the presence of anti-romosozumab antibodies in human serum. Samples were first tested in an ECL-based bridging immunoassay to detect antibodies capable of binding to romosozumab (binding antibody [Bab] assay). Samples confirmed to be positive for binding antibodies were subsequently tested in a non-cell-based assay to determine neutralizing activity against romosozumab (neutralizing antibody [Nab] assay) for all studies. If a sample was positive for binding antibodies and demonstrated neutralizing activity, the sample was defined as positive for neutralizing antibodies. See Product Quality Review (immunogenicity section) for more detailed information regarding the immunogenicity assay validations.

This section provides a summary of assay information relevant to clinical pharmacology assessments.

4.1.3.1 Binding Antibody Assay

This ECL-based homogenous bridging immunoassay method is based on the bivalent characteristics of the antibody binding and utilizes the Meso Scale Discovery (MSD) platform. The testing strategy follows a two-tiered assay approach consisting of a screening assay and a specificity assay. The screening assay is performed to detect the presence of binding antibodies to romosozumab. Samples with a signal-to-noise (S/N) value greater than the assay cut-point are then tested to confirm the specificity of the response. Samples from drug-treated subjects tested in the specificity assay that deplete in the presence of excess soluble drug are reported as positive for the presence of anti-romosozumab antibodies.

Samples are treated with acetic acid to enable antibody complex dissociation before the analysis. Samples are then incubated overnight with conjugate/neutralization mixture consisting of biotinylated romosozumab: ruthenylated romosozumab (50:50), Tris pH 9.5, and soluble drug (only in the specificity assay). During this overnight incubation, the 2 antigen binding sites of anti-romosozumab antibodies are able to form a bridge between the labeled romosozumab molecules. The biotinylated-romosozumab molecule binds to the streptavidin-coated surface of the well resulting in the immobilization of the bridged ADA-conjugate complex. The plate is then washed, treated with tripropylamine MSD read buffer, and read on a MSD plate reader. The result is a luminescent signal from a series of electrically induced oxidation-reduction reactions

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involving ruthenium (from the captured complex) and tripropylamine. The consequent ECL signal is measured by photodiodes and is quantified as ECL units. The amount of ECL signal is proportional to the amount of anti-romosozumab antibodies in the sample.

The binding antibody assay sensitivity and drug tolerance in human serum are provided in Table 4.1.4.

Table 4.1.4. Summary of Assay Parameters: Binding Antibody Assay for Romosozuamb
(Source: Table 2 of the Applicant's Integrated Immunogenicity Report)

Assay Sensitivity (ng/mL)	Drug Tolerance	
	Anti-romoaozumab Ab Concentration (mcg/mL)	Romosozumab Concentration (mcg/mL)
5	(b) (4)	

In the pivotal Phase 3 study, afte 210 mg monthly dosing, trough serum romosozumab mean concentration values from samples collected prior to dosing at months 3, 6, 9, and 12 ranged from 8460 to 9780 ng/mL. In the same study, samples for anti-romosozumab antibody were collected at baseline, months 1, 3, 6, 9, 12, 15 and 24. Except for the sample taken at Month 1, the expected romosozumab levels are lower than the drug tolerance level, and do not interfere with the measurement of anti-romosozumab antibody in the immunogenicity samples.

4.1.3.1 Neutralizing Antibody Assay

To detect the presence of antibodies that are capable of disrupting the binding of romosozumab to sclerostin in serum samples, an ECL-based competitive target binding assay was developed. This assay utilizes the MSD platform and follows a tiered, two-assay approach consisting of a screening assay and a confirmatory assay. Samples that show reactivity in the screening assay are placed in a confirmatory assay that confirms that the interruption of the binding between romosozumab and sclerostin observed in the screening assay is due to the presence of anti-romosozumab neutralizing antibodies. The combined results of the screening assay and confirmatory assay are used to determine if a sample is positive or negative for neutralizing antibodies against romosozumab.

The method for the detection of anti-romosozumab neutralizing antibodies uses ruthenylated romosozumab and biotinylated sclerostin. In this assay, the anti-romosozumab antibody-containing sample is incubated with ruthenylated romosozumab and biotinylated sclerostin and allowed to form a binding complex. The binding complex is captured on an avidin-coated MSD plate. The plate is then washed and read on a MSD plate reader. The result is a luminescent signal from a series of electrically induced oxidation-reduction reactions involving ruthenium (from the captured complex) and tripropylamine. The consequent ECL signal is measured by photodiodes and is quantified as ECL units. If there are anti-romosozumab neutralizing

antibodies present in the sample, they will compete with biotinylated sclerostin for the binding to the ruthenylated romosozumab; therefore, the amount of binding complex captured on the plate is reduced and the result is a decrease in ECL signal in the assay. To confirm that a sample contains anti-romosozumab-specific neutralizing antibodies, an excess amount of romosozumab is added exogenously to the sample, which will bind to anti-romosozumab antibodies and reduce the amount of anti-romosozumab antibodies available to bind to ruthenylated romosozumab, thus resulting in an increase in ECL signal in the assay.

The assay sensitivity and drug tolerance for human serum for romosozumab bioassay are listed in Table 4.1.5.

Table 4.1.5. Summary of Assay Parameters: Neutralizing Antibody Assay for Romosozuamb *(Source: Table 3 of the Applicant's Integrated Immunogenicity Report)*

Assay Sensitivity (mcg/mL)	Drug Tolerance	
	Anti-romoaozumab Ab Concentration (mcg/mL)	Romosozumab Concentration (mcg/mL)
0.75	(b) (4)	

In the pivotal Phase 3 study, samples for anti-romosozumab antibody were collected at baseline, months 1, 3, 6, 9, 12, 15 and 24. Due to the low drug tolerance level of the neutralizing assay, only samples taken at Month 15 and Month 24 can have a reliable reading.

Samples have high concentration of neutralizing antibody can still be detected as positive for neutralizing antibody even when the romosozumab level in the samples are higher than the tolerance level.

4.2 Biopharmaceutics: Comparative PK Studies

A summary outlining the use of romosozumab drug substance and drug product in the clinical program is provided in Table 4.2.1.

Table 4.2.1. Romosozuamb Drug Substance and Drug Product used in the different stage of clinical development. ***(Source: Reviewer's filing memo for BLA 761062)***

	Romosozumab Drug Substance and Drug Product					
Drug substance	Process 1 ATO	Process 2 ATO			Process 2 ARI	
Drug product	#1	#2	#3	#4	#5 (To be marketed)	#6
Formulation Strength	70 mg/mL	70 mg/mL	90 mg/mL	120 mg/mL	(b) (4)	90 mg/mL
Presentation	Glass vial	Glass PFS	(b) (4) PFS	Glass PFS	PFS	Autoinjector (AI)
Phase 1 PK/PD studies	20060220 20060221 20060223 20060326 20090378 20090153	20110253				
Phase 1 BE/BA studies		***20120277***	***20120277***			
			20150197		***20150197***	
			20101180	20101180		
					20090418	20090418
		20110227 20120274				
Phase 2 studies	20060326	20060326 20101291				
Phase 3 studies		20070337 20080289 20120156	20120156			

AI = autoinjector, ARI = Amgen Rhode Island; ATO = Amgen Thousand Oaks; CZ = Crystal Zenith; PFS = prefilled syringe.

The pivotal Phase 3 postmenopausal osteoporosis clinical study (20070337) and the active-comparator-controlled study (20080289) used 70 mg/mL glass PFS presentations containing Process 2 ATO drug substance. The planned commercial product will be a (b) (4) PFS with 90 mg/mL romosozumab containing Process 2 ARI drug substance. The Applicant conducted the following 2 single-dose, randomized pharmacokinetic equivalence studies to bridge the product used in the Phase 3 studies and the to-be-marketed product:

- Study 20120277 compared the pharmacokinetic profile after administration of a single 210-mg SC romosozumab dose, delivered as either three 1.0-mL PFS injections of 70-mg/mL concentration (Process 2 ATO), or two 1.17-mL PFS injections of 90-mg/mL concentration (Process 2 ATO). – *Drug product #2 vs.#3*

- Study 20150197 compared the pharmacokinetic profile after administration of a single 210-mg SC romosozumab dose of the romosozumab 90-mg/mL concentration (administered as two 1.17-mL PFS injections) using drug substance produced at ATO (Process 2, (b) (4) scale) versus at ARI (Process 2, (b) (4) scale). – *Drug product #3 vs. #5.*

Note: The applicant is not seeking marketing authorization for the AI presentation of romosozumab in this marketing application.

Table 4.2.1 contains study design information for Study 20120277 and Study 20150197. Table 4.2.2 contains the Cmax, AUC0-t, AUC0-inf data and the statistical comparisons of these parameters between the test product and the reference product for both studies. Figure 4.2.3 shows the PK profiles.

Table 4.2.1. Summary of Study Design Infor for Comparative PK Studies 20120277 and 20150197

Study number	**20120277**		**20150197**	
Pruducts compared	*Reference*: Product #2 (70 mg/mL) *Test*: Product #3 (90 mg/mL)		*Reference*: Product #3 (ATO) *Test*: Product #5 (ARI)	
Lots tested	1037281 and 1038445		1065063 and 1064897	
Study design	Parallel group, open-label		Parallel group, open-blind	
Study population	Healthy men or women (18-65 yo); body weight at screening (45-95 kg)		Healthy men or women (18-65 yo)	
# of subjects randomized and completed the study	Reference: 87	Test: 85	Reference: 96	Test: 92
# of sujects included BE analysis	Reference: 82	Test: 84	Reference: 96	Test: 90
Criteria for exclusion	None of the PK parameters (AUCinf, AUClast, Cmax) could be adequately estimated in non-compartmental analysis			
Romosozuamb dose	210 mg single dose		210 mg single dose	
Administration route	SC		SC	
Primary endpoints	AUC_{last}, AUC_{inf}, C_{max}		AUC_{last}, AUC_{inf},C_{max}	
PK sampling timepoints	Day 1 (pre-dose), 2, 3, 4, 6, 8, 11, 15, 18, 22, 29, 36, 43, 57, 85.		Day 1 (pre-dose), 2, 3, 4, 6, 8, 11, 15, 18, 22, 29, 36, 43, 57, 85.	
Study sites	A single center in USA		Three centers in USA	
Study period	03/01/2013-09/13/2013		12/07/2015-02/04/2016	

Reference ID: 4076576

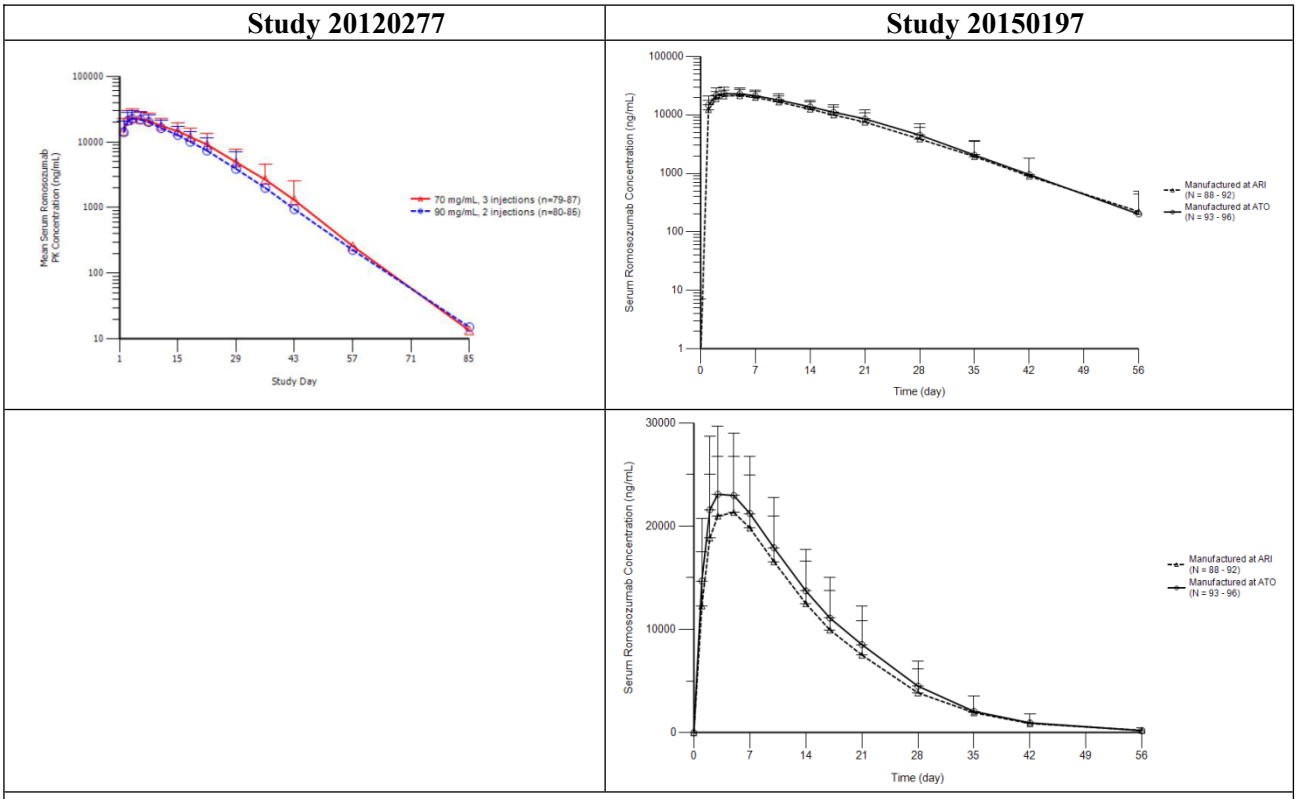


Figure 4.2.1. Mean (SD) Serum Romosozumab Concentration-time Profiles Following Single SC Doses from Two Comparative PK studies of Romosozumab *(Source: Figure 11-1 in CSR Study 20120277 and Figure 11-1 in CSR Study 20150197)*

Table 4.2.2. Pharmacokinetic Parameters for BioequivalenceTesting and Statistical Summary. ***(Source of Data: Table 11-2 in CSR Study 20120277 and Table 11-2 in CSR Study 20150197)***

Study number	Comparison	Reference	Test	Geometric Mean Ratio of Test/Reference	90% CI
20120277	N	82	84		--
	C_{max} (mcg/mL)	22753.645	22568.183	0.992	(0.909 to 1.082)
	AUC_{last} (mg*d/L)	405790.848	363935.655	0.897	(0.814 to 0.989)
	AUC_{inf} (mg*d/L)	407765.090	363935.405	0.896	(0.813 to 0.987)
20150197	N	96	90	--	--
	C_{max} (ng/mL)	23398.97	21442.74	0.92	(0.86 to 0.98)
	AUC_{last} (ng*d/L)	399643.23	364019.92	0.91	(0.84 to 0.99)
	AUC_{inf} (ng*d/L)	406243.05	367291.55	0.90	(0.83 to 0.98)

Reviewer's analysis:

- Study 20120277
  The sponsor's BE analysis excluded 6 subjects (Subjects (b) (6) (b) (6)) using the criteria of "The PK parameter analysis set included subjects for

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whom at least one of the PK parameters (AUCinf, AUClast, Cmax) could be adequately estimated for the purpose of primary analysis". The sponsor's analysis showed that the lower bound of 90% CI for AUCinf was 0.813. When the reviewer repeated the analysis in Pheonix 64, only two subjects need to be excluded (Subject (b) (6) due to protocol violation and Subject (b) (6) had %AUCinf extrapolated close to 50%). Reviewer's analyis showed that the lower bound of 90% CI for AUCinf was 0.799 and 90% CI for Cmax and AUClast both fall within the range of 0.8 to 1.25.

Although 0.799 barely missed the cutoff of 0.800, we consider that the PK comparability between the reference and test products in this study is established because 1) AUCinf was extrapolated and the extrapolation method may not be the most appropriate one for romosozumab, which has target mediated drug disposition and 2) The small difference in AUCinf is not expected to have any clinical implications.

- Study 20150197
  Reviewer's analysis confirmed the sponsor's analysis. The PK comparability using BE criteria between the reference and test products in this study is established.

- Overall, we found the bridge between the to-be-marketed formulation (90 mg/mL (b) (4) (b) (4) PFS (Process 2 ARI) and clinical trial formulation (70 mg/mL glass PFS (Process 2 ATO) established based on data from the two PK comparability studies, Study 20120277 and 20150197.

- Inspection reports for analytical and clinical sites for both studies are pending.

4.3 Pharmacokinetics: Individual Study Summary

4.3.1. Study 20120277 and 20150197 (The Two Pivotal PK Comparability Studies)

Study 20120277 compared the pharmacokinetic profile after administration of a single 210-mg SC romosozumab dose, delivered as either three 1.0-mL PFS injections of 70-mg/mL concentration (Process 2 ATO), or two 1.17-mL PFS injections of 90-mg/mL concentration (Process 2 ATO).

Study 20150197 compared the pharmacokinetic profile after administration of a single 210-mg SC romosozumab dose of the romosozumab [(b) (4)] concentration (administered as two 1.17-mL PFS injections) using drug substance produced at ATO (Process 2, [(b) (4)] scale) versus at ARI (Process 2, [(b) (4)] scale).

Detailed information of these two studies are listed in Section 4.2 Biopharmaceutics: Comparative PK Studies.

4.3.2 Study 20060220 (The First in Human Study)

Study 20060220 was a randomized, double-blind, placebo-controlled, single ascending dose Phase 1 study conducted in healthy men and postmenopausal women. Subjects received romosozumab SC (0.1, 0.3, 1, 3, 5, and 10 mg/kg) or romosozumab IV (1 and 5 mg/kg).

The romosozumab concentration-time profiles by treatment groups are shown in Figure 4.3.1 and Figure 4.3.2. PK parameters estimated by non-compartment analysis are listed in Table 4.3.1 and Table 4.3.2. The exposure (AUC) of romosozuamb increased in a greater than dose-proportional manner, indicating the concentration-dependent nature of drug clearance.

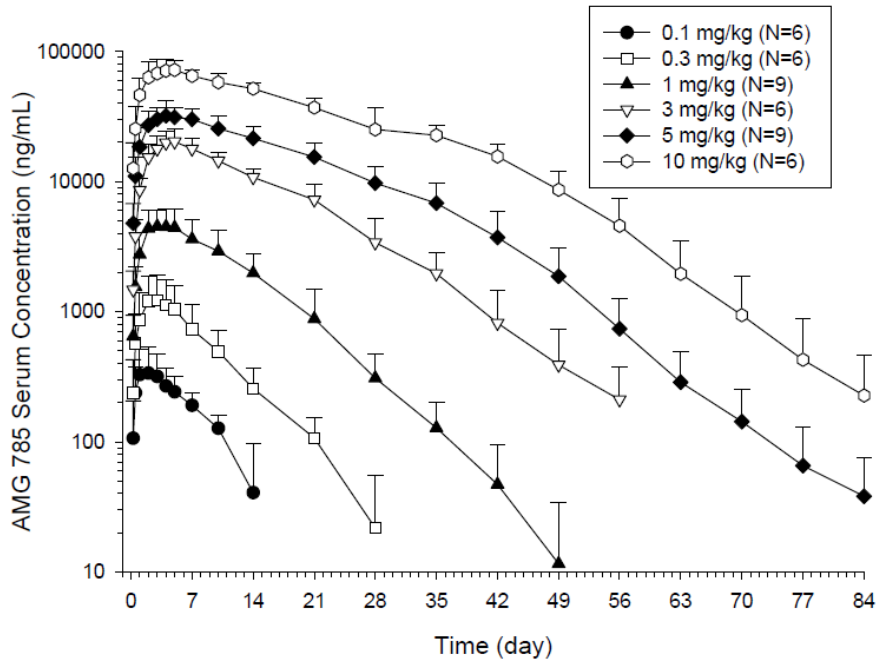


Figure 4.3.1. Mean (+SD) Serum Concentration-time Profiles Following a Single Subcutaneous Administration of Romosozumab to Healthy Postmenopausal Women and Healthy Men *(Source: Figure 10-1 of CSR Study 20060220)*

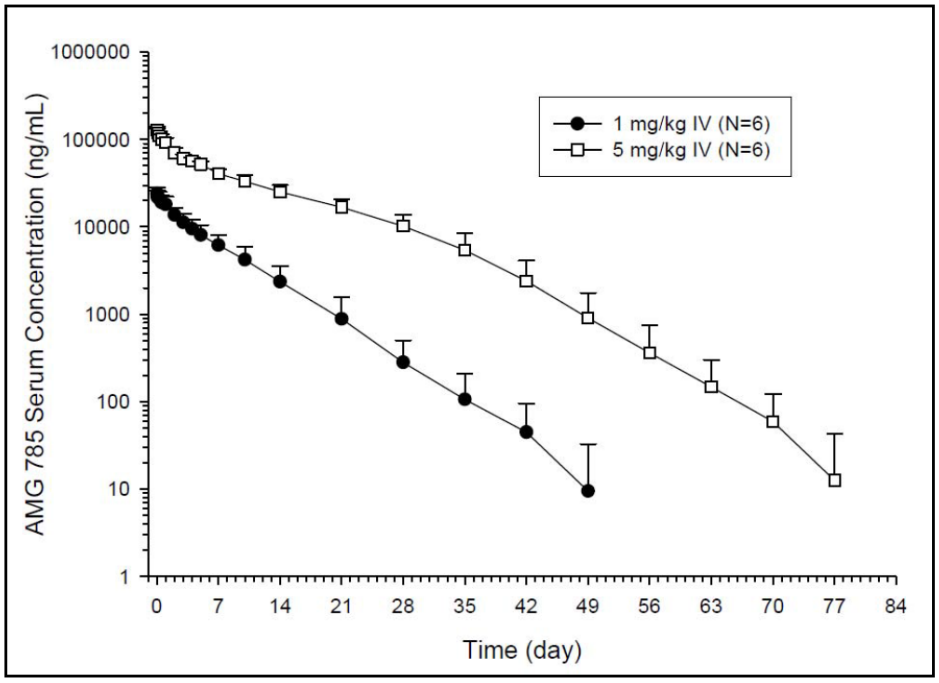


Figure 4.3.2. Mean (+SD) Serum Concentration-time Profiles Following a Single Intravenous Administration of Romosozumab to Healthy Postmenopausal Women and Healthy Men *(Source: Figure 10-2 of CSR Study 20060220)*

Dose (mg/kg)	$t_{1/2}$ β[a] (day)	$t_{1/2}$ γ[b] (day)	T_{max}[c] (day)	C_{max}[d] (ng/mL)	$AUC_{0\text{-}inf}$[e] (μg*hr/mL)	CL/F[f] (mL/hr/kg)
0.1 (n=6)	N/A	5.20 (1.36)	1.5 (0.5-7)	375 (182)	78.5 (22.6)	1.39 (0.489)
0.3 (n=6)	N/A	5.13 (0.640)	2.5 (2-5)	1280 (653)	288 (144)	1.35 (0.841)
1 (n=9)	N/A	5.50 (0.322)	3 (2-14)	4890 (1780)	1480 (605)	0.873 (0.647)
3 (n=6)	11.1 (3.70)	6.68 (0.961)	5 (4-7)	21300 (5170)	8170 (1810)	0.383 (0.0901)
5 (n=9)	12.9 (3.14)	5.81 (0.874)	5 (3-7)	33500 (8290)	16900 (4350)	0.319 (0.0998)
10 (n=6)	18.0 (3.54)	5.88 (1.60)	4.5 (2-7)	75200 (15900)	43400 (8550)	0.236 (0.0370)

Values are reported as 3 significant figures except for T_{max}
[a]Half life associated with the beta (plateau) phase of elimination
[b]Half-life associated with the gamma (terminal) phase of elimination
[c]Time of maximum concentration reported as median and range
[d]Maximum concentration
[e]Area under the serum concentration time curve from time zero to infinity
[f]Apparent clearance

Table 4.3.1. Mean (SD) Noncompartmental Parameter Estimates Following a Single SC Administration of Romosozumab to Healthy Postmenopausal Women and Healthy Men ***(Source:Table 10-1 of CSR Study 20060220)***

Dose (mg/kg)	$t_{1/2}$ β[a] (day)	$t_{1/2}$ γ[b] (day)	C_0[c] (ng/mL)	$AUC_{0\text{-}inf}$[d] (μg*hr/mL)	CL[e] (mL/hr/kg)
1 (n=6)	N/A	4.49 (0.974)	24900 (4670)	3020 (989)	0.362 (0.117)
5 (n=6)	10.6 (1.70)	4.93 (0.639)	132000 (13700)	24400 (4400)	0.210 (0.0361)

Values are reported as 3 significant figures
[a]Half life associated with the beta (plateau) phase of elimination
[b]Half-life associated with the gamma (terminal) phase of elimination
[c]Initial concentration
[d]Area under the serum concentration time curve from time zero to infinity
[e]Clearance

Table 4.3.2. Mean (SD) Noncompartmental Parameter Estimates Following a Single IV Administration of Romosozumab to Healthy Postmenopausal Women and Healthy Men ***(Source: Figure 10-2 of CSR Study 20060220)***

4.3.2. Study 20090387 (The PK Study in Japansese Population)

Study 20090387 was a randomized, double-blind, placebo-controlled, single-dose Phase 1 study conducted in healthy postmenopausal women and non-Japanese women residing in the United States. Subjects received romosozumab SC (1, 3, or 5 mg/kg).

The romosozumab PK parameters estimated following single-dose SC administration are shown in Table 4.3.3. At the 3-mg/kg dose, the PK profile was not substantially different for healthy postmenopausal Japanese and non-Japanese women.

	Mean (SD)						
Dose (mg/kg)	t_{max}[a] (day)	C_{max} (ng/mL)	AUC_{last} (µg*hr/mL)	AUC_{inf} (µg*hr/mL)	CL/F (mL/day/kg)	$t_{1/2}\beta$ (day)	$t_{1/2}\gamma$ (day)
1 mg/kg (n = 6)	5.0 (5.0-8.0)	4.06 (1.45)	64.0 (27.0)	64.7 (26.8)	18.6 (10.0)	-	5.82 (1.05)
3 mg/kg (n = 6)	5.0 (3.0-12)	17.1 (4.7)	344 (90)	347 (90)	9.27 (2.64)	15.1 (NA)	6.31 (1.14)
3 mg/kg Non-Japanese Subjects (n = 4)	5.0 (5.0-7.0)	18.6 (1.1)	412 (136)	421 (147)	7.91 (2.68)	15.3 (6.2)	6.81 (2.69)
5 mg/kg (n = 6)	5.0 (5.0-7.0)	33.8 (8.1)	804 (320)	806 (323)	6.98 (2.35)	16.2 (4.1)	7.19 (1.55)

Table 4.3.3. Noncompartmental Parameter Estimates Following Subcutaneous Administration of Romosozumab to Healthy Postmenopausal Japanese and Non- Japanese Women (3 mg/kg only) ***(Source: Table 10-3 of CSR Study 20090378)***

4.3.3. Study 20060221 (The First Multiple-dose Study)

Study 20060221 was a randomized, double-blinded, placebo-controlled, ascending multiple dose study in healthy men and postmenopausal women with low bone mass. Forty-eight subjects were enrolled into 1 of 6 cohorts as shown in Table 4.3.4.

	Total No. Subjects Randomized	No. Subjects Received Romo/Placebo	Romo Dose Received	Total No. of Doses Received
Cohort 1	8	6/2	1 mg/kg SC Q2W	6
Cohort 2	8	6/2	2 mg/kg SC Q4W	3
Cohort 3	8	6/2	2 mg/kg SC Q2W	6
Cohort 4	8	6/2	3 mg/kg SC Q4W	3
Cohort 5	8	6/2	1 mg/kg SC Q2W	6
Cohort 6	8	6/2	3 mg/kg SC Q4W	3
Total	**48**	**36/12**		

Table 4.3.4. Subjects Randomization Scheme for Study 20060221 ***(Source: Section 2.2.1.2, Summary of Clinial Pharmacology Studies)***

The romosozumab concentration-time profiles are shown in Figure 4.3.3 and Figure 4.3.4. The PK parameter estimates from noncompartmental analysis are shown in Table 4.3.5 and Table 4.3.6. For the Q2W dose groups, mean C_{max} and $AUC_{0\text{-}14}$ days values increased 2.0- to 2.3-fold, respectively, for the 2-fold increase in dose (1 mg/kg to 2 mg/kg). For the Q4W dose groups, mean values of C_{max} and $AUC_{0\text{-}28\ days}$ increased approximately 1.8- to 2-fold, respectively, for the 1.5-fold increase in dose (2 mg/kg to 3 mg/kg). No marked (≥ 2-fold) accumulation was observed with Q4W dosing.

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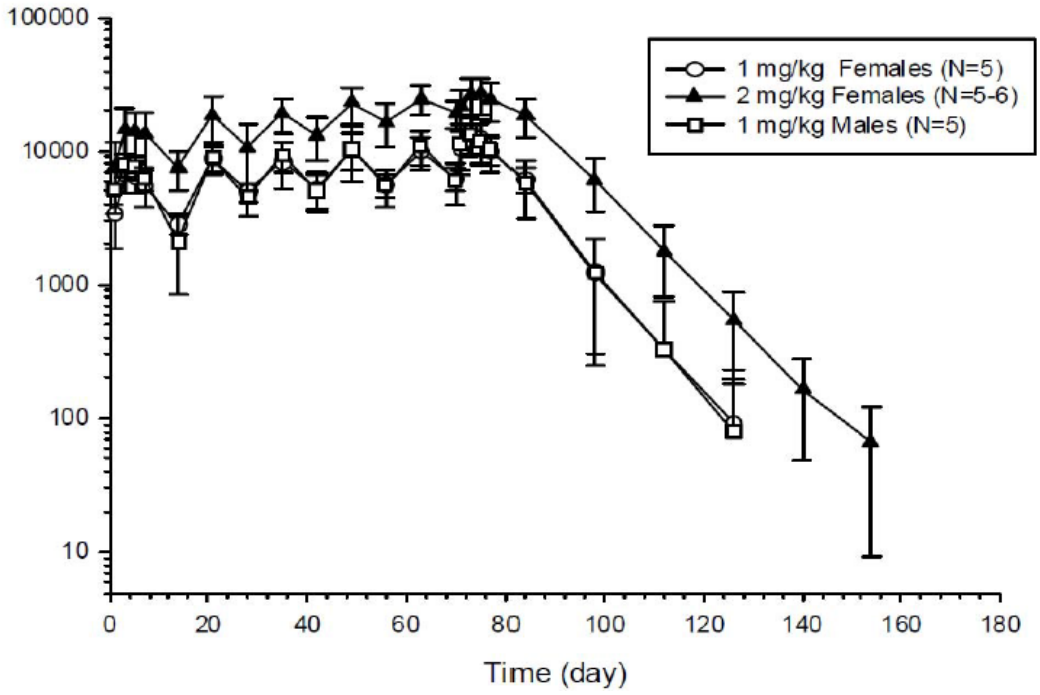


Figure 4.3.3. Mean (SD) Serum Romosozumab Concentration-time Profiles Following a SC Administration of 6 Q2W Doses of Romosozumab to Healthy Men and Postmenopausal Women With Low Bone Mass (Study 20060221) ***(Source: Figure 10-1 of CSR Study 20060221)***

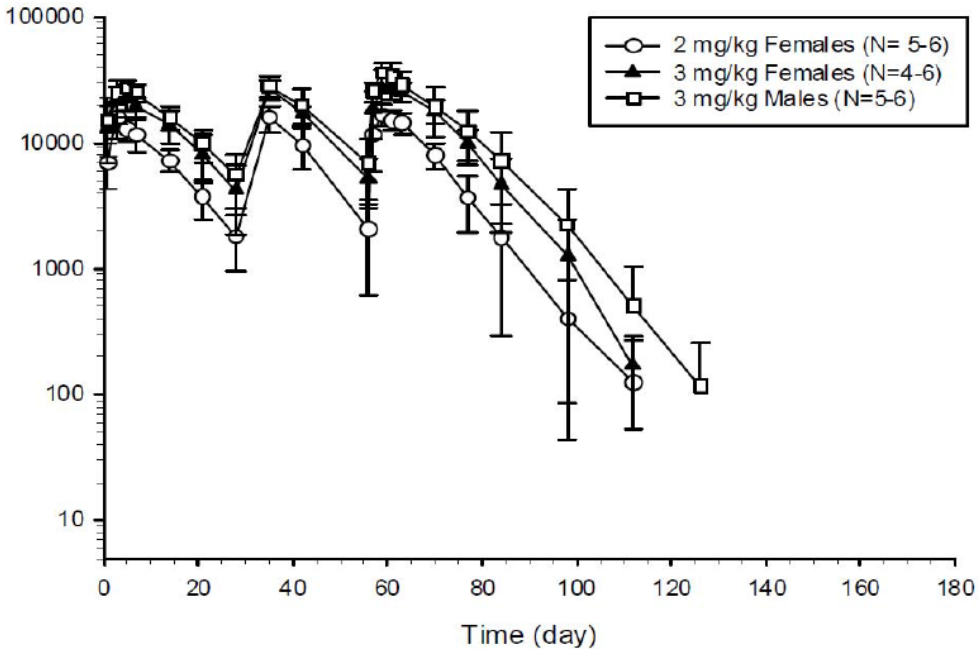


Figure 4.3.4. Mean (SD) Serum Romosozumab Concentration-time Profiles Following a SC Administration of 3 Q4W Doses of Romosozumab to Healthy Men and Postmenopausal Women With Low Bone Mass (Study 20060221) ***(Source: Figure 10-2 of CSR Study 20060221)***

Treatment	First Dose			Last Dose				
	t_{max} (day)	C_{max} (μg/mL)	$AUC_{0\text{-}14\ days}$ (μg *day/mL)	t_{max} (day)	C_{max} (μg /mL)	$AUC_{0\text{-}14\ days}$ (μg *day/mL)	$t_{1/2}$ (day)	AR
1 mg/kg SC (Women)	3.0	6.80	65.5	3.0	14.2	141	7.02	2.15
(N = 5)	(2.0 - 5.0)	(1.86)	(15.6)	(0.0 - 5.0)	(4.3)	(41)	(3.52)	(0.45)
1 mg/kg SC (Men)	3.0	8.06	71.3	3.0	13.4	136	6.77	1.90
(N = 5)	(3.0 - 5.0)	(1.57)	(11.8)	(3.0 - 5.0)	(4.4)	(42)	(1.92)	(0.49)
2 mg/kg SC (Women)	4.5	14.8	152	3.5	27.8	321	9.32	2.35
(N = 5 - 6)	(3.0 - 7.0)	(6.0)	(63)	(3.0 - 5.0)	(8.4)	(97)	(1.88)	(0.90)

Table 4.3.5. Mean (SD) Noncompartmental Parameter Estimates Following SC Administration of 6 Q2W Doses of AMG 785 to Healthy Men and Postmenopausal Women with Low Bone Mass *(Source: Table 10-1, CSR of Study 20060221)*

Treatment	First Dose			Last Dose				
	t_{max} (day)	C_{max} (μg/mL)	$AUC_{0\text{-}28\ days}$ (μg *day/mL)	t_{max} (day)	C_{max} (μg /mL)	$AUC_{0\text{-}28\ days}$ (μg *day/mL)	$t_{1/2}$ (day)	AR
2 mg/kg SC (Women)	3.0	15.7	202	3.0	16.7	231	6.51	1.17
(N= 6)	(3.0 - 5.0)	(4.6)	(48)	(1.0 - 4.0)	(3.3)	(58)	(1.37)	(0.26)
3 mg/kg SC (Women)	3.0	24.5	340	5.0	29.5	462	6.84	1.35[a]
(N = 5)	(3.0 – 5.0)	(6.8)	(73)	(2.0 - 7.0)	(8.7)	(97)	(1.79)	(0.19)
3 mg/kg SC (Men)	5.0	27.7	434	3.0	37.1	555	6.07	1.26
(N = 6)	(3.0 - 5.0)	(4.2)	(81)	(3.0 - 5.0)	(8.1)	(181)	(1.50)	(0.23)

[a] N=4

Table 4.3.6. Mean (SD) Noncompartmental Parameter Estimates Following SC Administration of 3 Q4W Doses of AMG 785 to Healthy Men and Postmenopausal Women with Low Bone Mass *(Source: Table 10-2, CSR of Study 20060221)*

4.3.4. Study 20110227 (The Dedicated Renal Impairment Study)

Study 20110227 was an open-label, single-dose, parallel group Phase 1 Study of romosozumab in healthy subjects and subjects with Stage 4 renal impairment (RI) or Stage 5 renal impairment (ESRD) requiring hemodialysis. A total of 24 subjects (8 subjects with stage 4 RI, 8 subjects with ESRD requiring hemodialysis, and 8 healthy subjects) were enrolled in parallel into 1 of 3 treatment groups and each received a single 210 mg SC romosozumab dose.

The romosozumab concentration-time profiles by renal function group are shown in Figure 4.3.5. Descriptive statistics of PK parameter estimates by renal function group are presented in Table 4.3.7. A comparison of the PK parameters (tmax, Cmax, and AUC) between subjects with stage 4 RI (group 1), subjects with ESRD requiring hemodialysis (group 2), and healthy subjects (group 3) dosed at 210 mg SC are presented in Table 4.3.8 and Table 4.3.9. Individual PK parameters (Cmax and AUC) plot by group are presented in Figure 4.3.6.

Mean romosozumab exposure, as measured by Cmax and AUC values, in the stage 4 RI cohort was greater than the healthy cohort; mean Cmax and AUC were 29% and 44% higher in patients

Reference ID: 4076576

with severe renal impairment as compared to healthy subjects. However, the exposure range in these two groups have substantial overlap. Most of the subjects with stage 4 RI had values that were within the range of healthy subjects, specifically, Cmax in 7 out of 8 subjects and AUC in 6 out of 8 subjects. In addition, mean romosozumab exposure was similar between subjects with ESRD requiring hemodialysis and healthy subjects.

The geometric least square mean point estimates and 90% CIs for the ratio of Cmax in subjects in stage 4 RI or subjects with ESRD requiring hemodialysis compared with healthy subjects were 1.313 (0.945, 1.824) (Table 4.2.8) and 0.895 (0.638, 1.256) (Table 4.3.9), respectively.

We note that, mechanistically speaking, it is unclear how the renal function/hemodialysis affects the exposure of romosozumab.

When it comes to safety, the most frequently reported treatment-emergent adverse events in the dedicated RI study was hypocalcemia. Data suggested that the incidence of hypocalcemia was associated with severity of RI, but not with exposure of romosozumab. The number of subjects reported hypocalcemia was 0/8 in healthy subjects, 1/8 in subjects with severe RI, and 4/8 in subjects had ESRD requiring hemodialysis.

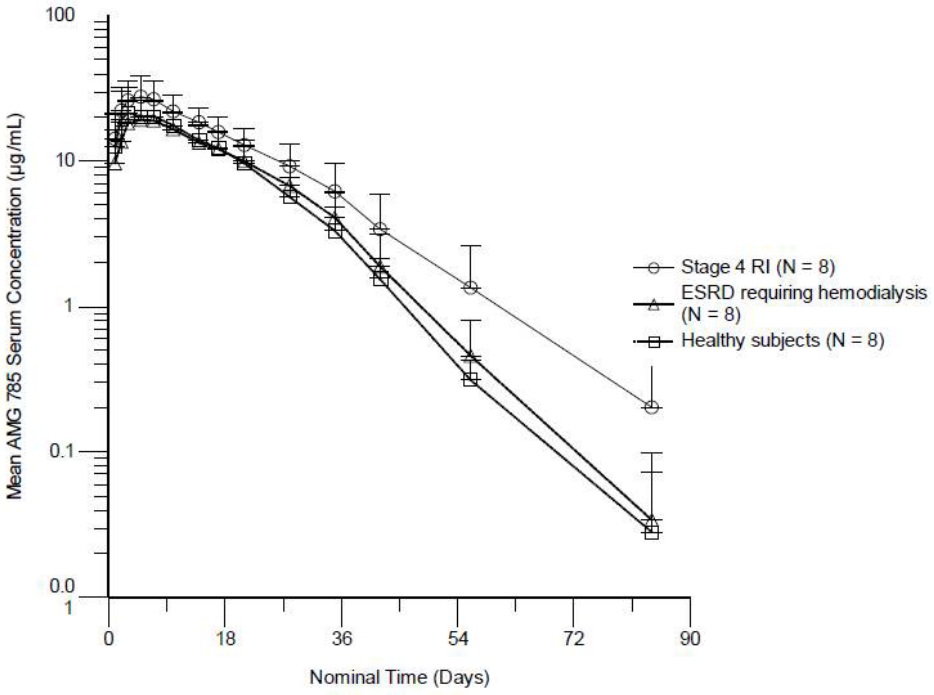


Figure 4.3.5. Mean (+SD) Serum Romosozumab Concentration-time Profiles After SC Administration of 210 mg Romosozumab in Subjects with Stage 4 RI, Subjects with ESRD Requiring Hemodialysis, and Healthy Subjects. (Source: Figure 11-6 of CSR Study 20110227)

Reference ID: 4076576

PK Parameter	Stage 4 RI (Group 1) (n = 8)	ESRD Requiring Hemodialysis (Group 2) (n = 8)	Healthy Subjects (Group 3) (n = 8)
t_{max} (day)	5.0 [3.0 - 7.0]	5.0 [3.0 – 7.0]	5.0 [3.0 - 7.0]
C_{max} (μg/mL)	28.9 (10.8) [14.8 – 51.5]	19.8 (7.3) [9.39 – 31.9]	22.4 (10.3) [13.5 – 45.2]
AUC_{last} (day•μg/mL)	637 (218) [323 – 983]	444 (154) [216 – 643]	443 (143) [264 – 700]
AUC_{inf} (day•μg/mL)	642 (221) [326 – 987]	447 (154) [218 – 647]	445 (143) [265 – 703]

Table 4.3.7. Descriptive Statistics of Romosozumab PK Parameter Estimates After SC Administration of 210 mg Romosozumab in Subjects with Stage 4 RI, Subjects with ESRD Requiring Hemodialysis, and Healthy Subjects. The data are presented as Mean (SD), [Min-Max]. (Source: Table 11-1 of CSR Study 20110227)

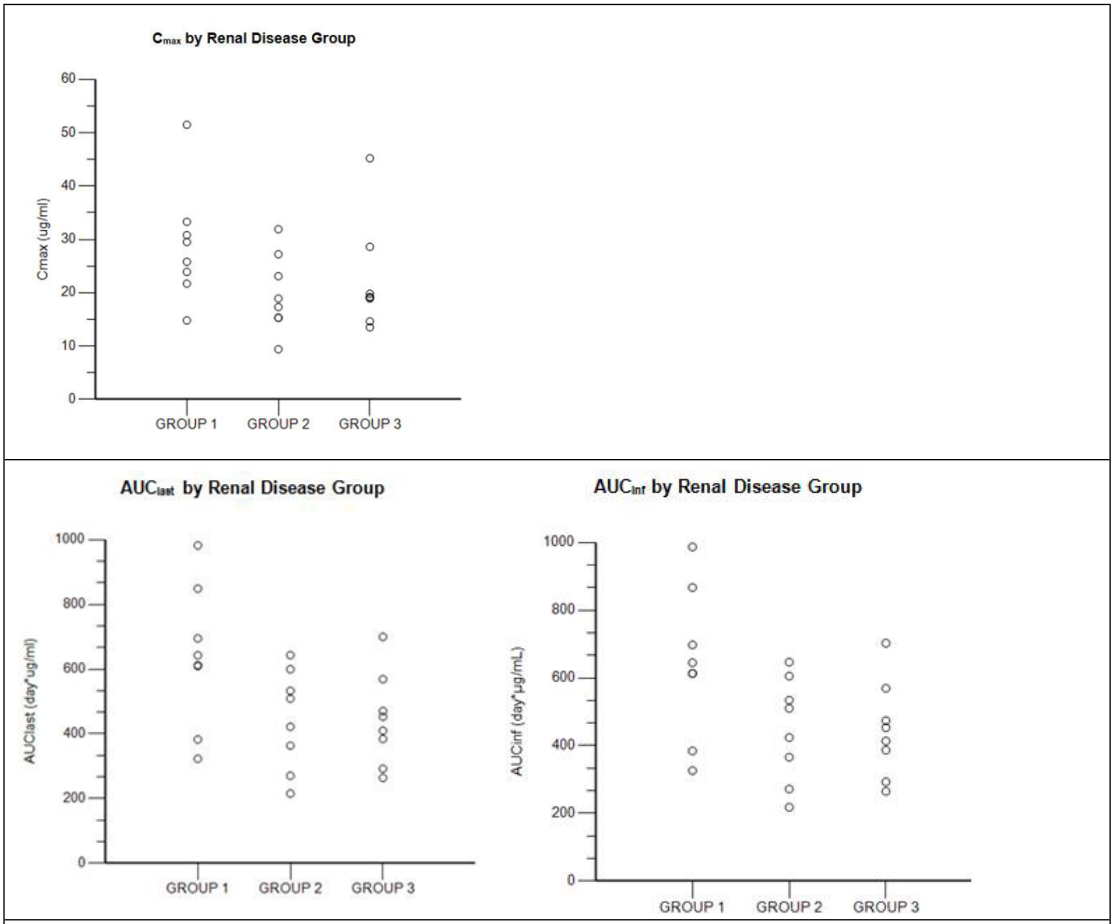


Figure 4.3.6. Individual Romosozumab Pharmacokinetic Parameter (Cmax, AUClast and AUCinf) Plots After SC Administration of 210 mg Romosozumab in Subjects with Stage 4 RI (Group 1), Subjects with ESRD Requiring Hemodialysis (Group 2), and Healthy Subjects (Group 3). (Source: Figure 11-8 of CSR Study 20110227)

Parameter (Unit)	Group 1 Stage 4 RI (Test) N	Group 1 Stage 4 RI (Test) Geometric Means	Group 3 Healthy Subjects (Ref) N	Group 3 Healthy Subjects (Ref) Geometric Means	Ratio of Test/Ref	Confidence Interval of Ratio Lower 90%	Confidence Interval of Ratio Upper 90%
C_{max} (μg/mL)	8	27.300	8	20.795	1.313	0.945	1.824
AUC_{inf} (day•μg/mL)	8	605.879	8	425.208	1.425	1.048	1.937
AUC_{last} (day•μg/mL)	8	601.695	8	423.247	1.422	1.046	1.933

AUC_{inf} = area under the concentration-time curve from time 0 to infinity; AUC_{last} = area under the concentration-time curve from time 0 to time of last quantifiable concentration; C_{max} = maximum observed serum concentration; eGFR = estimated glomerular filtration rate; PK = pharmacokinetics;
RI = renal impairment
Planned total dose for all the groups was 210 mg.
Group 1 Stage 4 RI (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2).
Group 3 Healthy subjects (eGFR ≥ 80 mL/min/1.73 m^2).
The ratio and CI were based on natural log scale data converted back to the original scale.

Table 4.3.8. Least Squares Geometric Means of Pharmacokinetic Parameter Estimates of Romosozumab After Subcutaneous Administration of Romosozumab - Comparison of Group 1 With Group 3 ***(Source: Table 11-2 of CSR Study 20060227)***

Parameter (Unit)	Group 2 ESRD (Test) N	Group 2 ESRD (Test) Geometric Means	Group 3 Healthy Subjects (Ref) N	Group 3 Healthy Subjects (Ref) Geometric Means	Ratio of Test/Ref	Confidence Interval of Ratio Lower 90%	Confidence Interval of Ratio Upper 90%
C_{max} (μg/mL)	8	18.613	8	20.795	0.895	0.638	1.256
AUC_{inf} (day•μg/mL)	8	420.521	8	425.208	0.989	0.723	1.354
AUC_{last} (day•μg/mL)	8	418.157	8	423.247	0.988	0.721	1.354

AUC_{inf} = area under the concentration-time curve from time 0 to infinity; AUC_{last} = area under the concentration-time curve from time 0 to time of last quantifiable concentration; C_{max} = maximum observed serum concentration; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease;
PK = pharmacokinetics
Planned total dose for all the groups was 210 mg.
Group 2 ESRD requiring hemodialysis
Group 3 Healthy subjects (eGFR ≥ 80 mL/min/1.73 m^2).
The ratio and CI were based on natural log scale data converted back to the original scale.

Table 4.3.9. Least Squares Geometric Means of Pharmacokinetic Parameter Estimates of Romosozumab After Subcutaneous Administration of Romosozumab - Comparison of Group 2 With Group 3 ***(Source: Table 11-3 of CSR Study 20110227)***

4.3.5. Study 20060223 (Transitioning from Alendronate to Romosozumab Study)

Study 20060223 was a randomized, open-lable, single-dose study in postmenopausal women with low bone mass who had been receiving alendronate for at least 1 year and in

postmenopausal women with low bone mass who were treatment-naïve for osteoporosis/bone loss. Subjects were to 1 of 3 groups as shown below.

- Group A: Subjects who had been receiving alendronate for at least 1 year and continued receiving alendronate (12 weekly dose of 70 mg alendronate or equivalent), beginning on day 1
- Group B: Subjects who had been receiving alendronate for at least 1 year and discontinued alendronate and received a single 3-mg/kg SC dose of romosozumab on day 1
- Group C: treatment-naïve subjects who received a single 3 mg/kg dose of romosozumab on day 1.

The romosozumab serum concentration-time profiles are shown in Figure 4.3.7. Descriptive statistics of PK parameter estimates by treatment group are presented in Table 4.3.10.

Mean Cmax values differed by less than 4% between groups B and C and median tmax values were similar (4.9 days and 4.5 days). The extents of exposure as measured by mean AUClast and AUCinf were also similar (< 12% difference) and mean terminal half-life was approximately 7.5 days for both groups.

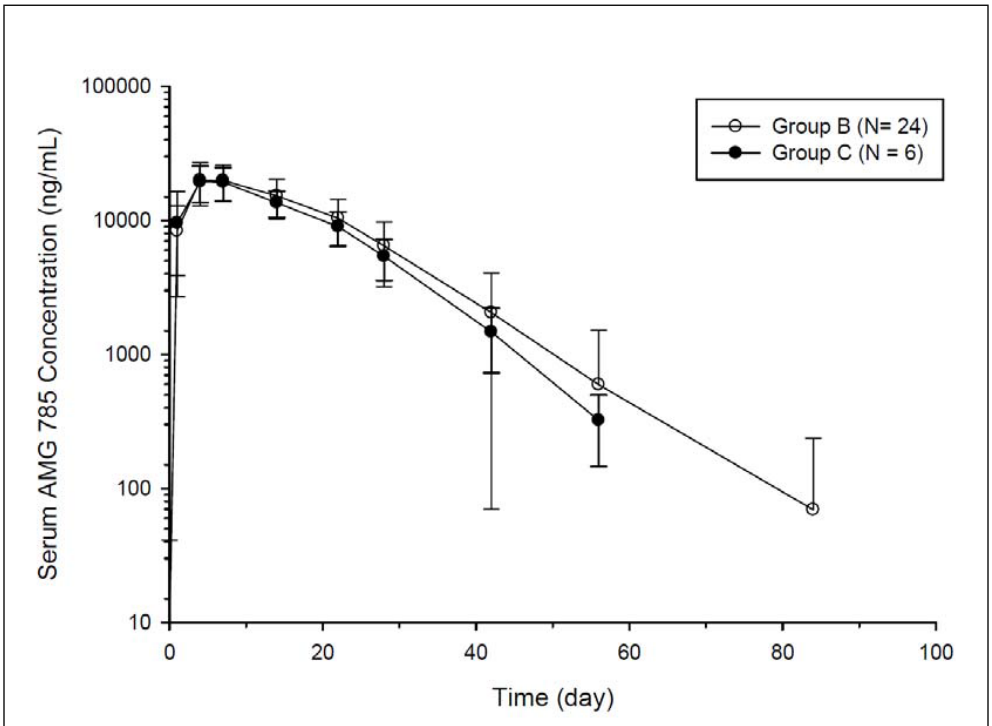


Figure 4.3.7. Mean (SD) Serum Romosozumab Concentration-time Profiles After SC Administration of Romosozumab 3 mg/kg in Postmenopausal Women with Low Bone Mass. Group B: Alendronate switch to Romosozuamb; Group C: Treatment-naïve Subjects ***(Source: Figure 12 of CSR Study 20060223)***

	Group B					Group C				
	t_{max} (day)	C_{max} (μg/mL)	AUC_{0-t} (day*μg/mL)	AUC_{0-inf} (day*μg/mL)	$t_{1/2}$ (day)	t_{max} (day)	C_{max} (μg/mL)	AUC_{0-t} (day*μg/mL)	AUC_{0-inf} (day*μg/mL)	$t_{1/2}$ (day)
N	24	24	24	24	24	6	6	6	6	6
Mean	5.5	20.9	449	452	7.49	5.2	20.1	404	406	7.53
SD	1.4	6.7	176	178	1.72	1.5	5.9	116	117	1.51
Min	4.0	8.49	189	190	3.87	4.0	12.2	226	227	6.12
Median	4.9	22.2	430	431	7.08	4.5	21.8	454	455	7.10
Max	7.0	33.2	920	933	11.8	7.0	27.4	505	507	9.98
%CV	26	32.2	39.2	39.3	22.9	29	29.2	28.8	28.8	20.1

Table 4.3.10. Summary Statistics for Noncompartmental PK Estimates Following a Single SC Administration of 3 mg/kg Romosozumab to Postmenopausal Women with Low Bone Mass. Group B: Alendronate switch to Romosozuamb; Group C: Treatment-naïve Subjects *(Source: Table 10-3 of CSR Study 20060223)*

4.3.6. Study 20060326 (The Dose-finding and Retreatment Study)

Study 20060326 was a randomized, placebo-controlled Phase 2 study to determine the effect of treatment with romosozumab versus placebo on lumar spine BMD in postmenopausal women with low BMD. The study included a 24-month initial treatment phase during which subjects received romosozumab (419 subjects randomized to receive 70 mg, 140 mg, or 210 mg), placebo, or active control. Romosozumab and placebo were given QM or Q3M; one active control group received alendronate for the first 12 months followed by romosozumab for another 12 months, and the other active control group only received teriparatide 20 mcg QD for 12 months. Following initial treatment, subjects were re-randomized to a 12-month extension phase with denosumab or placebo; followed by a 12-month retreatment phase with romosozumab (the same dose regimen as in the initial treatment); followed by a 24-month follow-on phase with zoledronic acid or no intervention. Study design and treament schema of Study 20060326 are shown in Figure 4.3.8 and 4.3.9.

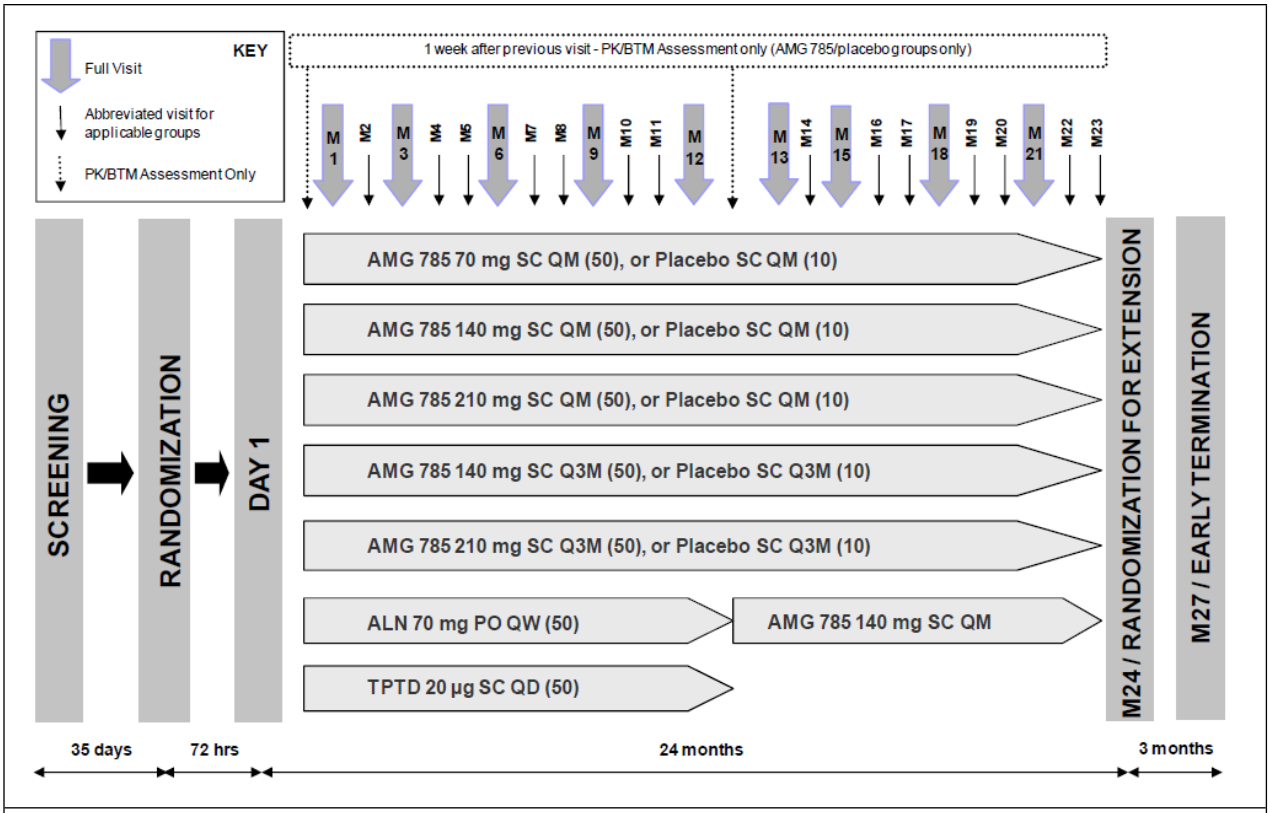


Figure 4.3.8. Study Design and Treatment Schema_Study Day 1 to Month 24) ***(Source: Figure 8-1 of CSR Study 20060326)***

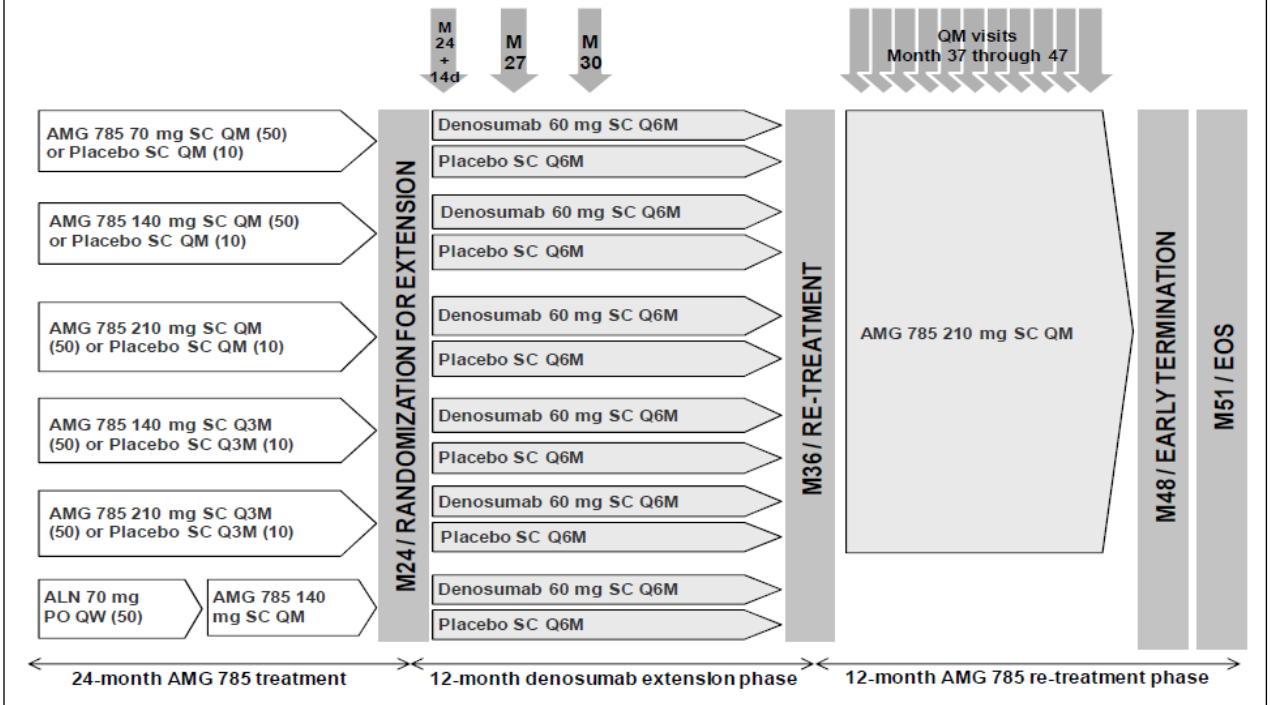


Figure 4.3.9. Study Design and Treatment Schema_12-Month Denosumab Extension Phase and 12-Month Romosozumab Retreatment Phase) ***(Source: Figure 8-2 of CSR Study 20060326)***

ALN = alendronate; AMG785 = romosozumab; EOS = end of study; PO = orally; QD = every day; QM

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= every month; Q3M = every 3 months; Q6M = every 6 months; QW = every week; All subjects were to take at least 1000 mg elemental calcium and 800 IU vitamin D daily.
Note: Numbersin parentheses represented planned enrollment numbs, not actual. End of study is at 72 months.

Serum concentration-time profiles during 24-month romosozumab treatment phase followed by 12-Month Denosumab Extension Phase and a 12-Month Romosozumab Retreatment Phase are shown in Figure 4.3.10. Brief summaries of the PK results in each treatment phase is provided below.

- 24-month romosozumab treatment phase

For the QM cohorts, the peak serum romosozumab concentrations increased 3.7-fold after the first dose and 4.4-fold after the 12th dose for the 3-fold increase in dose from 70 to 210 mg. The peak concentration after the 12th dose ranged from 1.2- to 1.5-fold greater than the peak after the first dose for the 70, 140, and 210 mg QM doses.

Pharmacokinetic data for the QM cohorts were available before dosing, i.e., at trough concentration (Ctrough) time points at months 1, 2, 3, 6, 9, and 12 during the first year and ranged from 675 to 1070 ng/mL at the 70 mg QM dose, 2780 to 4770 ng/mL at the 140 mg QM dose, and 5640 to 9320 ng/mL at the 210 mg QM dose. During the second year, Ctrough data were collected at months 13, 14, 15, 18, 21, and 24, and ranged from 757 to 1120 ng/mL, 4880 to 6320 ng/mL, and 8310 to 10900 ng/mL, at the 70, 140, and 210 mg QM doses, respectively. Trough concentration values increased greater than dose proportionally. At Month 12 and Month 24, mean Ctrough at the 210 mg QM dose were 10-fold greater than concentrations at the 70 mg QM dose. Overall, the data indicate a greater extent of accumulation for 210 mg QM dosing than at 70 mg QM dosing.

For the Q3M cohorts, accumulation was minimal. The peak serum romosozumab concentrations increased 1.6-fold after the first dose and after the 12th dose for the 1.5-fold increase in dose from 140 to 210 mg. Mean romosozumab concentrations at trough time points for Q3M cohorts were below the quantitation limit (BQL).

The mean peak concentrations after the first dose of romosozumab at 140 mg QM for the cohort that received ALN treatment for the first year and for the cohort that received 24 months of romosozumab at 140 mg QM were similar at 12500 and 12400 ng/mL, respectively. Serum romosozumab Ctrough values ranged from 2590 to 5150 ng/mL for the ALN cohort and ranged from 2780 to 4770 ng/mL for the romosozumab 140 mg QM cohort. Mean Ctrough values after 12 doses of romosozumab at 140 mg in both groups were similar.

- Month 24 to 36 (denosumab extension) and month 36 to 48 (romosozumab retreatment)

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After receiving denosumab or placebo during the third year of the study, subjects across all cohorts showed similar exposure during the retreatment phase regardless of their various treatments for the first 2 years.

For the cohort of subjects who received romosozumab treatment at 210 mg QM during the initial 2-year treatment followed by 12 months of denosumab prior to romosozumab retreatment, the average Ctrough values at steady state during the first 2 years of treatment (average concentration of the last 3 time points-months 18, 21, and 24) and average retreatment Ctrough at steady-state (average of concentrations at months 42, 45, and 48) were similar at 8940 ng/mL and 9420 ng/mL, respectively.

For the cohort that received romosozumab treatment at 210 mg QM during the initial 2-year treatment followed by 12 months of placebo prior to romosozumab retreatment, the average Ctrough values at steady state during the first 2 years and the average Ctrough at steady state during the retreatment phase were similar at 11300 ng/mL and 10900 ng/mL, respectively.

The average Ctrough value of the last 3 time points for the cohort that received placebo QM or Q3M during the initial 2-year treatment followed by 12 months of denosumab prior to romosozumab 210 mg QM in the retreatment period was 13900 ng/mL, 1.5-fold greater than the average Ctrough value over the last 3 time points of the first 2 years of romosozumab 210 mg treatment.

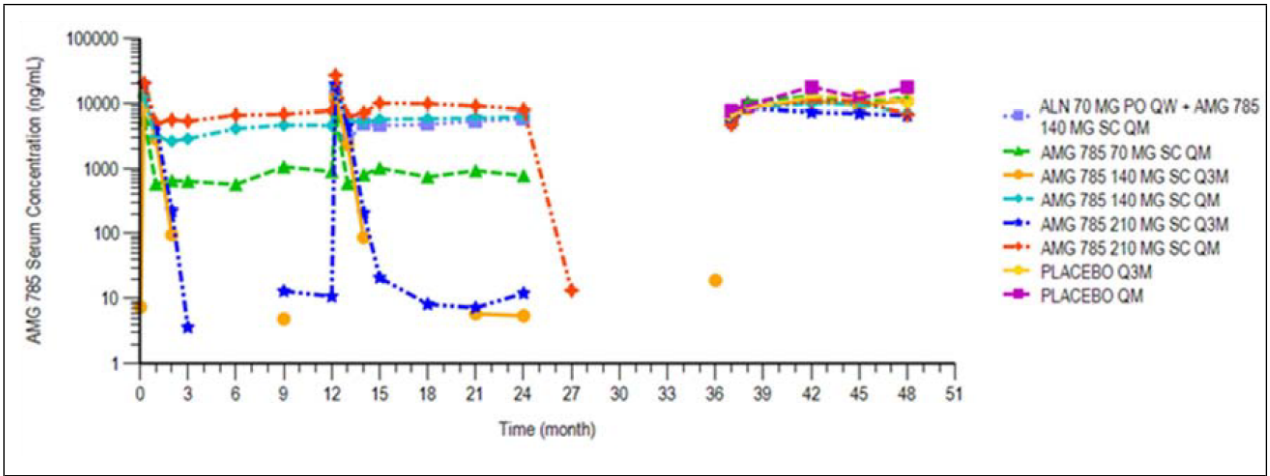


Figure 4.3.10. Mean Serum Romosozuamb Concentration-time Profiles during 24-month romosozumab treatment phase followed by 12-Month Denosumab Extension Phase and a 12-Month Romosozumab Retreatment Phase ***(Source: Fgiure 11-2 of Study 20060326)***

4.3.7. Study 20101291 (The Dose Finding Study in Japanese Population)

Study 20101291 was a double-blind, randomized, placebo-controlled, multiple dose Phase 2 study in Japanese women with postmenopausal osteoporosis. Subjects received placebo or romosozumab 70 mg, 140 mg, or 210 mg by SC injection QM for 12 months.

The concentration-time profile of romosozumab is shown in Figure 4.3.11. Peak romosozumab concentrations increased 3.6-fold over the romosozumab 70 to 210 mg dose range (3-fold increase in dose). Mean serum concentrations measured 1 week after the administration of the first dose of romosozumab (day 8) were 7150, 16500, and 25600 ng/mL for the romosozumab 70, 140, and 210 mg groups, respectively. Trough serum romosozumab mean concentration values (from samples collected before dose administration at months 1, 2, 3, 6, 9, and 12) after multiple administrations with romosozumab ranged from 777 to 911 ng/mL, 3730 to 4590 ng/mL, and 6060 to 10400 ng/mL in the romosozumab 70, 140, and 210 mg groups, respectively. Trough concentrations demonstrated greater than dose proportional increases with ascending dose in the dose range of 70 mg to 210 mg, with the Month 12 time point exhibiting a 12-fold increase in concentration for a 3-fold increase in dose. Steady state was generally achieved by month 3 for all dose levels.

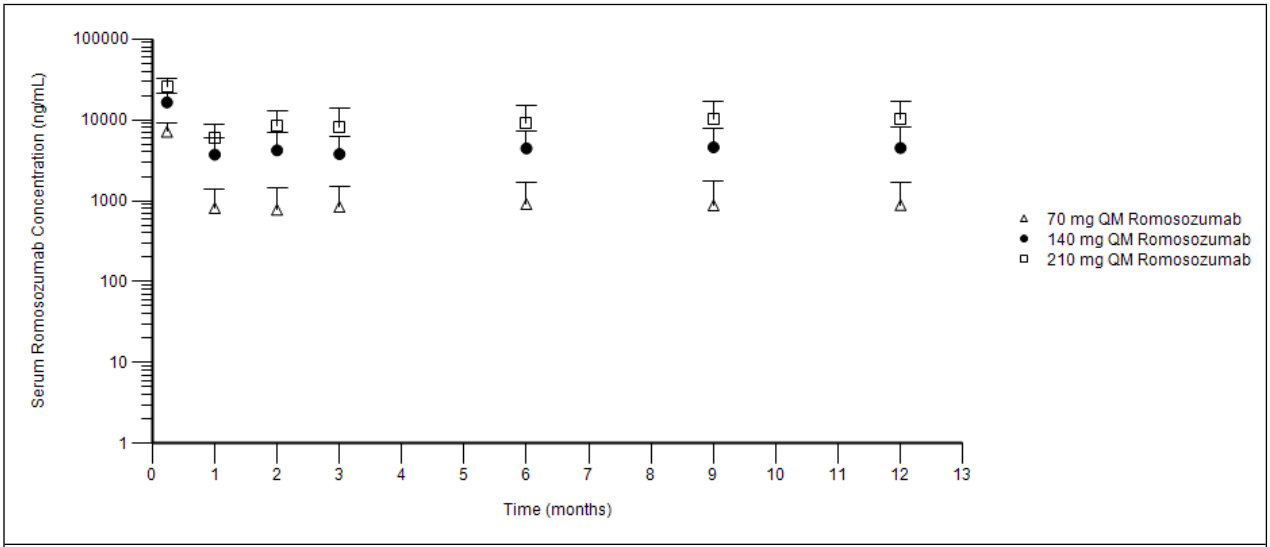


Figure 4.3.11. Mean (SD) Serum Concentration-time Profiles After SC Administrations of 70, 140, or 210 mg QM Romosozumab to Japanese Subjects with Postmenopausal Osteoporosis ***(Source: Figure 11-1, CSR of Study 20101291)***

4.3.8. Study 20070337 (The Pivotal Phase 3 Trial)

Study 20070337 was a multicenter, international, randomized, double-blind, placebo-controlled, parallel group study in postmenopausal women with osteoporosis, to assess the effect of romosozumab treatment for 12 months compared with placebo on the incidence of vertebral and other fractures, and to assess the effect of romosozumab treatment for 12 months followed by

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denosumab treatment for 12 months compared to placebo followed by denosumab treatment on the incidence of vertebral and other fractures (N = 7180).

Romosozumab PK were assessed in a PK substudy (931 subjects: romosozumab = 466, placebo = 465) to allow a PopPK analysis. Romosozumab serum concentrations were measured at day 1, day 14, month 1, month 3, month 3 + 14 days, month 6, month 6 + 14 days, month 9, month 12, and month 13.

After monthly administrations of romosozumab 210 mg to postmenopausal women with osteoporosis, exposure appeared to reach steady-state by month 3. Mean Ctrough from samples collected prior to dosing at months 3, 6, 9, and 12 ranged from 8050 to 9780 ng/mL. Two weeks after the fourth and seventh doses of romosozumab (month 3 plus 14 days and month 6 plus 14 days, respectively), peak concentrations were evaluated. Mean serum concentrations ranged from 21200 to 21900 ng/mL and were comparable after steady-state was reached.

Descriptive statistics of peak and trough serum romosozumab concentration-time data are shown in Table 4.3.11.

	Romosozumab 210 mg SC QM								
Statistic	Day 1 Predose	Day 14	Month 1 Predose	Month 3 Predose	Month 3 + 14 Days	Month 6 Predose	Month 6 + 14 Days	Month 9 Predose	Month 12
N	469	125	325	324	51	366	54	362	381
Mean	37.3	16700	5930	8050	21900	8460	21200	9510	9780
SD	574	5730	3480	5510	9940	6150	11600	6370	6900
Min	0.00	5010	87.9	123	1090	0.00	4770	0.00	0.00
Median	0.00	16500	5420	7510	19900	7550	19500	8840	8620
Max	10200	33900	20300	40700	54300	38300	67900	36100	55900
CV%	1541.0	34.3	58.7	68.4	45.4	72.8	54.7	67.0	70.5

Table 4.3.11. Descriptive Statistics of Peak and Trough Serum Romosozumab Concentration-Time Data (ng/mL) After Subcutaneous Administrations of Romosozumab 210 mg QM to Postmenopausal Women with Osteoporosis *(Source: Table 11-3, CSR of Study 20070337)*

4.4 Immunogenicity

4.4.1. Immunogenicity incidences of ADA and NAb

In Phase 1 studies, about 7.9% (66 of 832) of subjects developed binding antibodies after at least 1 dose of romosozumab. All ADA positive subjects showed a persistent binding response with a positive result at the last time point tested. Neutralizing antibodies were detected in 2.1% (18 of 832) of all romosozumab dosed subjects, which is 27.3% (18/66) of all ADA+ subjects. See more detailed in Table 7 of Integrated Immunogenicity Report.

The incidence of anti-romosozumab binding antibodies in clinical studies with repeated dosing was higher than the antibody incidence following a single dose. About 20% (852 of 4289) of subjects exposed to romosozumab in the Phase 2 and 3 studies (Study 20070337, 20060326, 20101291, 20120156 and 20080289) developed binding antibodies. The antibody responses were transient (i.e., became negative by the last time point tested) for 9.7% (414 of 4289) of the overall dosed subjects. Neutralizing antibodies were detected in 1.1% (46 of 4289) of overall dosed subjects, 0.3% of which (11 of 4289) were transient. The percentage of ADA+ subjects who were NAb positive was 5.4% (46/852). See more detailed in Table 9 of Integrated Immunogenicity Report.

The incidence of binding and neutralizing antibodies in subject dosed with 210 mg QM was 19.1% (758 of 3959) and 0.8% (31 of 3959), respective. The percentage of ADA+ subjects who were NAb positive was 4.1% (31/758). This was similar to the incidences in the overall Phase 2 and 3 studies. See more detailed in Table 9 of Integrated Immunogenicity Report.

4.4.2. Impact of ADA on PK

Overall, development of ADA was associated with reduced serum romosozumab concentrations.

4.4.2.1 Impact of ADA on PK based on ADA+/ADA- status

In the Applicant's initial submission, the impact of immunogenicity on PK exposures was assessed by comparing romosozumab concentrations in subjects with anti-romosozumab antibodies to antibody-negative subjects in studies 20060326, 20101291 and 20070337.

In these 3 studies, romosozumab levels were reduced in some subjects with binding antibodies (approximately 25% lower exposure at months 3, 6, and/or 9 and comparable to each other with approximate 10% difference in mean values) at Month 12 (Table 4.4.1). Greater reduction in romosozumab levels at same time points were observed for subjects with neutralizing antibodies (Table 4.4.2).

Table 4.4.1. Summary of Trough Concentrations at Steady-state After Administration of Romosozumab 210 mg QM SC to Postmenopausal Women With Low BMD or

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Osteoporosis (Studies 20060326, 20101291, and 20070337) Stratified by Binding Antibody Status *(Source: Table 18 of Summary of Clinical Pharmacology Studies)*

	Month 3 Predose		Month 6 Predose		Month 9 Predose		Month 12	
	All Negative	Binding Positive	All Negative	Binding Positive	All Negative	Binding Positive	All Negative	Binding Positive
N	339	80	379	85	369	93	392	89
Mean	8230	6400	8810	6630	9820	8030	10000	8980
SD	5620	4440	6130	5400	6350	5540	6700	7000
Min	123	396	111	0.00	0.00	211	0.00	139
Median	7480	5570	7740	5320	9100	7070	8750	7540
Max	40700	18800	38300	32600	36100	32000	55900	46200
%CV	68.2	69.3	69.6	81.4	64.7	69.0	66.9	77.9

BMD = bone mineral density; %CV = percent coefficient of variation; min = minimum; max = maximum.

Table 4.4.2. Summary of Trough Concentrations at Steady-state After Multiple QM SC Administrations of 210 mg Romosozumab to Postmenopausal Women With Low BMD or Osteoporosis (Studies 20060326, 20101291 , and 20070337) Stratified by Neutralizing Antibody Status *(Source: Table 19 of Summary of Clinical Pharmacology Studies)*

	Month 3 Predose			Month 6 Predose			Month 9 Predose			Month 12 Predose		
	All Negative	Binding Positive, Neutralizing Negative	Binding Positive, Neutralizing Positive	All Negative	Binding Positive, Neutralizing Negative	Binding Positive, Neutralizing Positive	All Negative	Binding Positive, Neutralizing Negative	Binding Positive, Neutralizing Positive	All Negative	Binding Positive, Neutralizing Negative	Binding Positive, Neutralizing Positive
N	339	77	3	379	79	6	369	88	5	392	83	6
Mean	8230	6470	4760	8810	6850	3750	9820	8230	4610	10000	9290	4750
SD	5620	4500	1860	6130	5490	3110	6350	5570	4160	6700	7070	4390
Min	123	396	2760	111	0.00	848	0.00	384	211	0.00	743	139
Median	7480	5580	5060	7740	5330	2990	9100	7200	4020	8750	7550	3940
Max	40700	18800	6450	38300	32600	8560	36100	32000	10500	55900	46200	10100
%CV	68.2	69.6	39.2	69.6	80.1	82.9	64.7	67.6	90.3	66.9	76.1	92.3

BMD = bone mineral density; %CV = coefficient of variation; min = minimum; max = maximum; QM = monthly; SC = subcutaneous.

In Study 20060326, an initial 24-month treatment phase with romosozumab, placebo, or active control was followed by a 12-month extension phase with denosumab or placebo, which was then followed by a 12-month retreatment phase with romosozumab. Thirteen subjects who developed ADAs during the first 2 years, participated in the extension and re-treatment phases and tested for ADA again during year 4. The year 4 mean Ctrough in these 13 subjects were 26% to 30% lower at months 6, 9, and 12 than the exposure observed in subjects without ADA detected during the entire 4-year treatment (Table 4.4.3).

Table 4.4.3 Summary of Year 4 Trough Concentrations at Steady-state After Multiple QM SC Administrations of 210 mg Romosozumab to Postmenopausal Women With Low BMD or Osteoporosis (Study 20060326) Stratified by Varying Antibody Statuses Across Year 1, 2, and 4 *(Source: Table 20 of Summary of Clinical Pharmacology Studies)*

	Binding Antibody Negative through Year 2 and in Year 4			Binding Antibody Positive through Year 2 and Negative in Year 4			Binding Antibody Positive through Year 2 and Positive in Year 4			Binding Antibody Negative through Year 2 and Positive in Year 4		
	Month 6[a] Predose	Month 9[a] Predose	Month 12[a]	Month 6[a] Predose	Month 9[a] Predose	Month 12[a]	Month 6[a] Predose	Month 9[a] Predose	Month 12[a]	Month 6[a] Predose	Month 9[a] Predose	Month 12[a]
N	108	98	94	18	14	18	13	11	11	7	6	7
Mean	11000	10400	10600	10900	9740	9480	7880	7270	7840	4010	4620	4600
SD	7940	6860	7140	5340	5260	5580	5500	4950	5020	2440	3820	2720
Min	457	714	501	3370	2730	2900	468	1470	579	1480	1950	1190
Median	9620	8880	9480	9790	8660	7950	7490	5970	7730	2980	3120	3670
Max	40500	37800	32500	22000	24500	21100	17100	17600	16400	7560	11800	9240
%CV	72.1	65.9	67.5	49.1	54.1	58.9	69.8	68.0	64.0	60.7	82.6	59.1

BMD = bone mineral density; %CV = percent coefficient of variation; min = minimum; max = maximum; QM = monthly; SC = subcutaneous.
[a] Months 6, 9, and 12 refer to the fourth year of treatment; therefore, month 6 corresponds with month 42 after the first dose, month 9 corresponds with month 45 after the first dose, and month 12 refers to month 48 after the first dose.

4.4.2.2 Impact of ADA on PK based on signal-to-noise (S/N) ratio

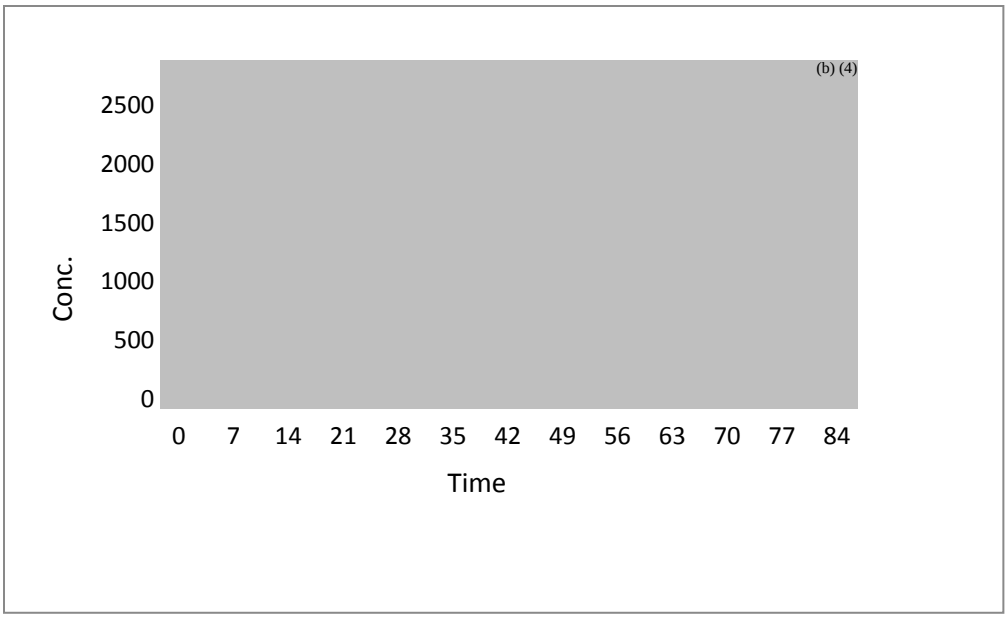
During the review cycle, the clinical pharmacology review team requested that the Applicant conduct further analysis regarding the relationship between titer and romosozumab concentration. The applicant did not have titer of immunogenicity samples and proposed to conduct the analysis between S/N ratio and romosozumab concentration. The new analysis was conducted based on data from Subject (b) (6) in Phase 1, the Phase 2 dose finding study (20060326), and the pivotal Phase 3 study (20070337). The scope of the analysis was decided for the following reasons: 1) Subject (b) (6) showed significant impact of immunogenicity on PK. 2) Study 20060326 had a retreatment period after subjects were off romosozumab for 12 months and, therefore, provided a good opportunity of investigating immunogenicity after retreatment. 3) The pivotal Phase 3 Study 20070337 enrolled 7180 postmenopausal women with osteoporosis, which represents about 80% of the entire patient population in this submission. In general, the higher S/N ratio is, the lower the romosozumab exposure is.

Impact of immunogenicity on PK based on S/N ratio is summarized as follows:

- One of the neutralizing antibody positive subjects (Subject (b) (6)) from Phase 1 study 20060220 was inadvertently enrolled and dosed in a subsequent ascending multi-dose pharmacology/pharmacodynamic study 20060221. A rapid decline in romosozumab serum concentrations was observed in this subject after the first dose in study 20060221, and serum concentrations were not measurable after day 6, despite continued dosing once every two weeks (Figure 4.4.1).

  Figure 4.4.1 Serum Romosozumab Concentration (ng/mL) following 6 SC Q2W 1mg/kg doses (Subject (b) (6) in Study 20060221) ***(Source of data: Appendix Table 1.3-2 of CSR-20060221)***

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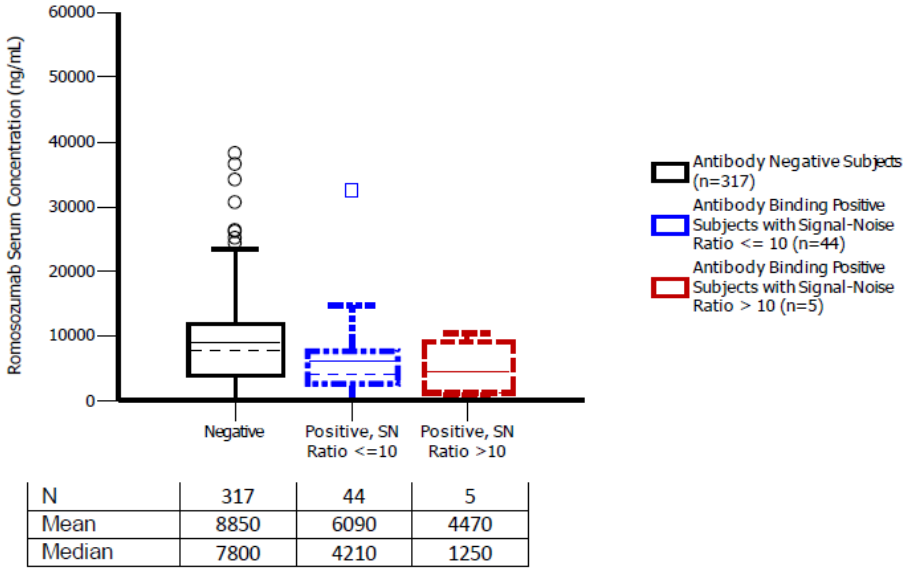
Subject (b) (6) had high signal-to-noise (S/N) ratio. Despite the intereference from romosozumab in the sample, she was tested positive for neutralizing antibodies. Below is the narrative on this subject from the applicant,

Subject (b) (6) received an initial single dose of romosozumab at 10 mg/kg subcutaneous (SC) on (b) (6) in the romosozumab first-in-human Study 20060220. Of note, 10 mg/kg was the highest dose tested in the romosozumab clinical development program. On (b) (6), a non-serious adverse event of injection site erythema was reported as mild in severity, related to study drug and resolved on (b) (6) with no further action taken. The subject was positive for binding antibodies on (b) (6) (study day 57; S/N value = 1.61) and for neutralizing antibodies on (b) (6) (b) (6) (end of study [study day 85]; S/N value = 37.30). The subject returned for follow-up antibody testing as specified in the protocol. Prior to re-exposure of romosozumab in study 20060221, the subject's S/N values ranged from 382.05 to 1019.50. The subject was still positive for neutralizing antibodies when, in violation with the protocol in/exclusion criteria, she enrolled in romosozumab Study 20060221 (subject number (b) (6)) and received a second dose of romosozumab at 1 mg/kg SC on (b) (6) (b) (6) and then every 2 weeks until (b) (6). At the time the subject was enrolled into Study 20060221, the investigator was not aware of her prior participation in the first-in-human study. The subject was tested for anti-romosozumab antibodies as per protocol, every month during Study 20060221 and approximately every 3 months after last dose: she remained positive for neutralizing antibodies as of (b) (6) and was then lost to follow up. Throughout the study, the range of S/N for subject (b) (6) was between 333.40 (before first dose) and 7,454.68; following the peak S/N value of 7,454.68 on study day 141, the values decreased over time to 639.83 at the subject's last follow-up visit.

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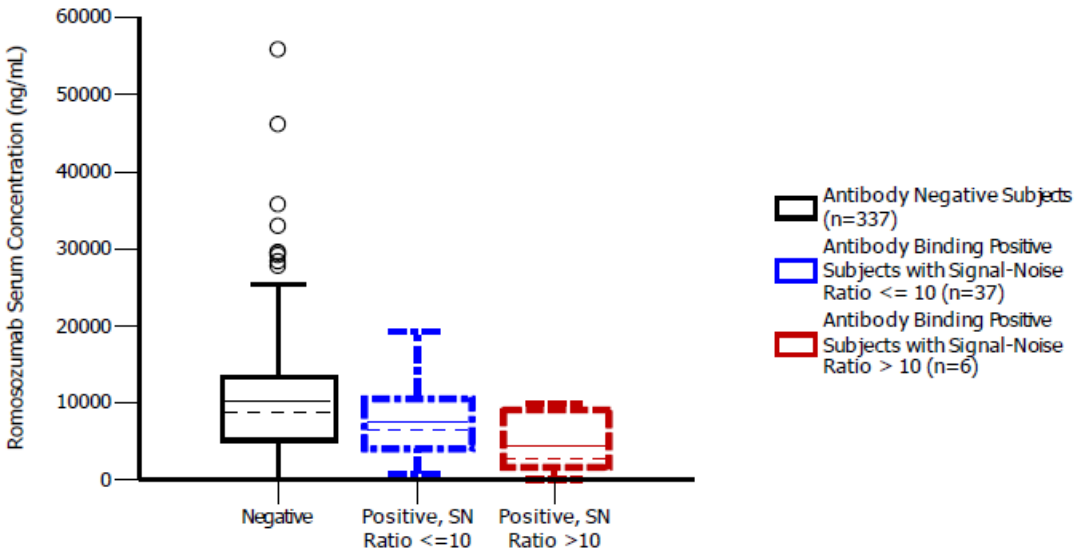
- Among a total of 478 subjects enrolled in the PK substudy of 20070337, 95 subjects tested positive for anti-romosozumab binding antibodies at one or more time points post-baseline. Among the subjects with evaluable PK information, 9 subjects had S/N ratios > 10 at Month 6 or 12, and their mean romosozumab serum concentrations were lower at these visits compared with the concentration values in subjects who tested negative for anti-romosozumab antibodies (Figure 4.4.2 and Figure 4.4.3)

Figure 4.4.2. Serum Romosozuamb Concentration Versus S/N ratio at Month 6 in Antibody Binding Positive Subjects (Study 20070337) ***(Source: Figure 2 of Applicant's Supplemental Integrated Immunogenicity Report submitted on 2/15/17)***



N	317	44	5
Mean	8850	6090	4470
Median	7800	4210	1250

Figure 4.4.3. Serum Romosozuamb Concentration Versus S/N ratio at Month 12 in Antibody Binding Positive Subjects (Study 20070337) ***(Source: Figure 3 of Applicant's Supplemental Integrated Immunogenicity Report submitted on 2/15/17)***



N	337	37	6
Mean	10100	7460	4460
Median	8800	6630	2790

4.4.3. Impact of ADA on efficacy

Overall, ADA appeared to have no impact on efficacy. It is not feasible to draw a definitive conclusion on the impact of ADA on fracture, due to the small number of subjects who were ADA positive and fractured. There is lack of impact of ADA positive on BMD changes. Although the presence of ADA appeared to have a negatie impact on bone turnover markers, the correlation between BTM and BMD, or between BTM and fracture is unclear.

4.4.3.1 Impact of ADA on efficacy based on ADA+/ADA- status

In the Applicant's initial submission, the impact of immunogenicity on BMD was assessed by comparing romosozumab concentrations in subjects with anti-romosozumab antibodies to antibody-negative subjects in studies 20060326, 20101291 and 20070337. In each of these three studies, the effect of ADA on BMD change is similar for ADA positive and negative subjects. See Section 7 of Integrated Immunogenicity Report for more details.

4.4.3.2 Impact of ADA on efficacy based on signal-to-noise (S/N) ratio

During the review cycle, we requested that the Applicant conduct further analysis regarding the relationship between titer and efficacy of romosozumab. The applicant did not have titer of immunogenicity samples and proposed to conduct the analysis between S/N ratio and efficacy of romosozumab. The scope of the new analysis is listed in Section 4.4.2.2 of this review.

The impacts of immunogenicity on efficacy based on S/N ratio are summarized below:

- Subjects experiencing a new vertebral fracture through Month 24 had an incidence of anti-romosozumab antibodies consistent with the overall patient population [4/21 (19.0%)]. The 4 subjects who tested positive for anti-romosozumab binding antibodies had S/N values ranging from 1.42 to 7.61 and tested negative for neutralizing antibodies.

- Analysis focused on the relationship between the immunoassay S/N values from Study 20070337 with percent change in BMD from baseline at months 12 and 24, showed no impact of the magnitude of the anti-romosozumab binding antibody response on BMD change from baseline across all anatomical sties and timepoints. Lumbar spine BMD data are listed as an example (Table 4.4.4).

- Consistent with those pharmacokinetic data shown in Figure 4.4.1, Subject (b) (6) had no notable changes in pharmacodynamic markers (ie, increases in P1NP and BMD) in Study 20060221.

Table 4.4.4. Lumbar Spine Bone Mineral Density Percent Change from Baseline by Visit by Maximum Observed Immunoassay Signal-to-Noise Through Month 15 (Descriptive Statistics, Observed Data) (Romosozumab Arm in Primary Analysis Set for BMD (20070337 M24 Analysis) ***(Source of Data: Table 4 of Applicant's Supplemental Integrated Immunogenicity Report submitted on 2/15/17)***

Romosozumab 210mg QM			
	ADA Negative	ADA Positive	
Lumbar spine BMD at Month 12		S/N Ratio ≤ 10	S/N Ratio > 10
N	2550	553	67
n	2525	549	67
Mean±SD	13.1±6.0	13.1±5.8	13.1±6.9
Median	12.9	12.9	13.0
Q1, Q3	8.9, 16.9	9.2, 16.5	8.4, 18.1
Min, Max	-6.1, 44.9	-3.2, 32.9	-1.5, 29.7
Lumbar spine BMD at Month 24			
n	2282	509	64
Mean±SD	5.5±4.6	5.7±4.6	5.6±5.3
Median	5.2	5.0	5.7
Q1, Q3	2.5, 8.2	2.8, 8.3	2.5, 9.2
Min, Max	-13.8, 46.9	-7.3, 27.9	-7.2, 30.9

N = Number of subjects randomized to romosozumab, with BMD values at baseline and at least one post-baseline visit at or before Month 24 and with at least one post-baseline positive binding anti-romosozumab antibody data through month 15; n = Number of subjects with evaluable data at the time point of interest;

4.4.4 Impact of ADA on safety

Overall, ADA appeared to have no impact on safety. We defer to the clinical team regarding the impact of ADA on safety.

4.4.4.1 Impact of ADA on safety based on ADA+/ADA- status

In the Applicant's initial submission, the impact of ADA on safety was based on data from the pivotal placebo-controlled Phase 3 study (20070337), with additional safety data coming from an active-controlled Phase 3 study with teriparatide (20080289), a dose-ranging placebo- and active-controlled (teriparatide or alendronate) study (20060326), a dose-ranging placebo-controlled study in Japanese women (20101291), and a placebo-controlled noninferiority study (20120156).

The following adverse events were evaluated for the timing of antibody onset and the corresponding antibody status: hypersensitivity, injection site reactions and autoimmune disorders. No associations could be made related to presence of anti-romosozumab binding and neutralizing antibodies and the worsening of immune mediated symptoms even after multiple dosing with romosozumab. Notable association was observed in the development of injection site reactions with romosozumab dosing when compared to placebo, however this was irrespective of the immunogenicity. See Table 14-8.3.7 of Module 5.3.5.3 – Integrated Summary of Safety for more details.

4.4.4.2 Impact of ADA on safety based on signal-to-noise (S/N) ratio

In response to our information request described above, the Applicant further evaluated the impact of ADA on safety based on S/N ratio and safety data from Study 20070337. The pivotal Phase 3 Study 20070337 enrolled 7180 postmenopausal women with osteoporosis, which represents about 80% of the entire patient population in this submission.

There were no notable differences in adverse reactions between subjects with S/N values > 10 and placebo subjects, anti-romosozumab antibody negative subjects, or anti-romosozumab antibody positive subjects with S/N values ≤ 10 (Table 4.4.5). While the incidence of autoimmune disorders was slightly higher in the subset of antibody positive subjects with a S/N > 10, this is likely due to the small size of this subset, as the 2 reported disorders (chronic gastritis and type IIa hyperlipidaemia) are unlikely to be a consequence of anti-drug antibodies.

Table 4.4.5 Subject Incidence of Treatment-emergent Injection Site Reaction, Hypersensitivity, and Autoimmune Disorders in the 12-Month Double-blind Period by Maximum Observed Immunoassay Signal-to-Noise Antibody Status Through Month 15 (Safety Analysis Set) (20070337 M24 Analysis) ***(Source: Table 3 of Supplemental Integrated***

Reference ID: 4076576

Immunogenicity Report)

Adverse Event Category Preferred Term	Placebo Total (N = 3576) n (%)	Romosozumab 210 mg QM			
			Binding Antibody Positive		
		Antibody Negative (N = 2747) n (%)	Signal-to-Noise Ratio ≤ 10 (N = 583) n (%)	Signal-to-Noise Ratio > 10 (N = 69) n (%)	Total (N = 652) n (%)
No. of subjects reporting treatment-emergent adverse events	363 (10.2)	329 (12.0)	76 (13.0)	11 (15.9)	87 (13.3)
Hypersensitivity	245 (6.9)	191 (7.0)	44 (7.5)	4 (5.8)	48 (7.4)
Injection site reactions	104 (2.9)	140 (5.1)	38 (6.5)	5 (7.2)	43 (6.6)
Autoimmune disorders	32 (0.9)	25 (0.9)	3 (0.5)	2 (2.9)	5 (0.8)

N (Placebo) = Number of subjects who received at least one dose of investigational product in the 12-month double-blind period; N (Romosozumab) = Number of subjects who received at least one dose of romosozumab and with at least one post-baseline anti-romosozumab antibody data through month 15; QM = month.

Anti-romosozumab antibodies were not tested in subjects randomized to placebo.

Adverse events were coded using the MedDRA dictionary version 18.1.

Hypersensitivity includes only treatment-emergent adverse events as a result of a narrow search/scope in standardized MedDRA queries (SMQ).

Injection site reaction includes only treatment-emergent adverse events as a result of Amgen-defined MedDRA search strategies.

Autoimmune disorder includes only treatment-emergent adverse events from the MedDRA high level group term of Autoimmune disorders

4.5 Population PK Analyses

The population PK review is comprised of two parts: first part is the Applicant's analysis (Section 4.5.1) and the second part is the Reviewer's comments and analysis (Section 4.5.2).

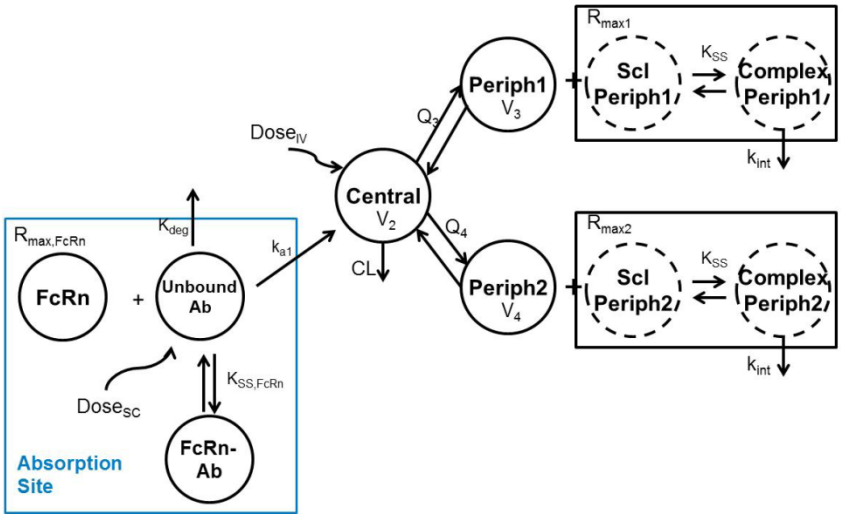
4.5.1 Applicant's analysis

A population PK analysis was conducted by the Applicant to characterize the pharmacokinetics of romosozumab administered IV or SC in healthy subjects and postmenopausal women with low BMD or osteoporosis. The clinically relevant covariates which may explain the variability of the PK parameters were explored and the individual exposure estimates were computed for the subsequent exposure-response analyses.

Overall, 11 clinical studies were pooled for population PK analysis including 8 Phase 1 studies (20060220, 20060221, 20060223, 20090378, 20101180, 20120277, 20110227, and 20110253), 2 Phase 2 studies (20060326 and 20101291), and 1 pivotal Phase 3 studies (20070337). In these studies, romosozumab was administered as a single IV dose (N=12 subjects) of 1 mg/kg or 5 mg/kg; a single SC dose (N=359 subjects) of 0.1 mg/kg to 10 mg/kg or 210 mg; or as multiple SC doses (N=1098 subjects) ranging from 1 to 3 mg/kg given every 2 or 4 weeks or fixed doses of 70, 140, or 210 mg given every month or 3 months for up to 48 months.

A nonlinear mixed effect modeling approach was implemented to characterize the population PK of romosozumab using NONMEM 7.2. A three-compartment PK model with linear distribution to peripheral compartments and parallel linear elimination in the central compartment and target-mediated non-linear elimination in the peripheral compartments was selected as the structural model. A saturable FcRn-mediated absorption process was used to describe romosozumab absorption and bioavailability after SC administration. The model schematic and parameters are shown in Figure 1.

Figure 1 Model Schematic for Romosozumab PKPD



Source: Applicant's population PK report, Figure 13-12, Page 96.

Reference ID: 4076576

The covariates considered for the analysis were demographic factors, including sex, age, race (Japanese vs non-Japanese), body weight; renal function estimated using the Modification of Diet in Renal Disease (MDRD) formula, prior alendronate administration, and drug product manufacturing process (1: clinical process; 2: commercial process). The summary statistics of covariates by study were listed in Table 1. The final dataset contained 13346 serum concentrations of romosozumab from 1459 subjects, including 341 (138 male, 203 female) healthy subjects, 35 (12 male, 23 female) with low BMD, and 419 osteopenic or 664 osteoporotic postmenopausal women. The median body weight was 61 kg and ranged from 33 to 109 kg. The overall median age was 66 years and ranged from 20 to 89 years. The median eGFR was 80 mL/min/1.73 m^2 and ranged from 7 to 144 mL/min/1.73 m^2. The majority of subjects were Caucasian (51%), 14% Japanese, 7% Hispanic, 4% Black, and rest from other races.

Table 1 Summary Statistics of Covariates by Clinical Study

Study	N	Sex[a] (M/F) (%F)	Race[b] (W/B/H/J/O)	Subject Type[c] (H/L/On/Os)	Body Weight (kg)	Age (years)	eGFR (mL/min/1.73 m^2)	BMD LS (g/cm^2)	ADA Status[d] (N/B/BN)	Process (1/2)	Prior ALN (N/Y)
						Mean (SD)	Median [Min-Max]				
20060220	53	12/41 (77%)	2/1/50/0/0	53/0/0/0	70.3 (9.2) 70.8 [52.6-89.3]	52.8 (3.9) 52 [46-60]	93 (16.7) 92 [60-140]	1.11 (0.1) 1.09 [0.96-1.37]	47/4/2	53/0	53/0
20060221	34	11/23 (68%)	21/1/12/0/0	0/34/0/0	72.2 (12.5) 72 [52-99.5]	59 (8.4) 56 [46-78]	90 (18.3) 90 [59-136]	1.01 (0.11) 1.01 [0.79-1.41]	22/10/2	34/0	34/0
20060223	30	0/30 (100%)	30/0/0/0/0	0/0/30/0	65.8 (12) 65.6 [50.9-109.4]	67.4 (6.9) 67 [54-82]	86.8 (19.4) 83 [34-132]	0.84 (0.07) 0.82 [0.68-0.96]	23/5/2	30/0	30/0
20090378	22	0/22 (100%)	4/0/0/18/0	22/0/0/0	55.6 (9.1) 53 [43.8-83.2]	59.7 (5.5) 60 [49-68]	89.1 (12.7) 90 [64-118]	0.93 (0.1) 0.92 [0.79-1.15]	22/0/0	22/0	22/0
20101180	70	25/45 (64%)	69/1/0/0/0	70/0/0/0	75.3 (10.4) 76.6 [51-90]	49.1 (12.2) 53 [20-65]	78 (13.7) 78 [50-106]	-	59/8/3	0/70	70/0
20110227	24	10/14 (58%)	18/5/0/0/1	24/0/0/0	77.6 (9.9) 78 [55.9-100.5]	65.4 (7.8) 66 [53-80]	41.7 (36.3) 28 [7-105]	1.03 (0.14) 1.03 [0.93-1.13]	23/1/0	0/24	24/0
20110253	60	0/60 (100%)	50/0/0/0/10	0/0/60/0	62.4 (10.8) 60.5 [45-103.5]	66.6 (7.9) 66 [55-84]	81.5 (18.8) 77 [52-132]	0.8 (0.11) 0.78 [0.54-1.09]	56/4/0	0/60	0/60
20120277	172	91/81 (47%)	102/51/0/0/19	172/0/0/0	74.7 (11.3) 75.6 [48.6-95.5]	46.7 (11.7) 50 [22-65]	93.8 (17.2) 92 [65-144]	-	156/12/4	0/172	172/0
20060326	328	0/328 (100%)	282/2/39/1/4	0/0/328/0	64.3 (10.1) 64.1 [39.5-98.2]	67.2 (6.4) 67 [55-85]	81.5 (17.9) 77 [33-136]	0.82 (0.09) 0.8 [0.66-1.31]	248/69/11	301/27	281/47
20101291	189	0/189 (100%)	0/0/0/189/0	0/0/0/189	49.3 (7.1) 48.8 [32.5-73.1]	68.2 (6.1) 67 [56-84]	91.5 (16.7) 89 [58-135]	0.66 (0.07) 0.66 [0.53-1.02]	135/49/5	0/189	189/0
20070337	475	0/475 (100%)	164/3/0/16/0/292	0/0/0/475	57.3 (10.4) 56.5 [35-96.9]	71.5 (7) 72 [55-89]	75.5 (17) 75 [30-133]	0.81 (0.12) 0.8 [0.54-1.28]	383/90/2	0/475	475/0
All studies[f] (final dataset)		150/1309	743/64/102/30/ 208/312	341/35/ 419/664	62.3 (13) 60.905 [32.5-109.35]	64.6 (11.6) 66 [20-89]	82.3 (19.6) 80 [7-144]	0.81 (0.14) 0.8 [0.53-1.41]	1176/252/31	442/1017	1351/108

[a] For sex, M: Male; F: Female
[b] For race, W: White; B: Black; H: Hispanic; J: Japanese; O: Other, including Asian, American Indian or Alaskan Native, Hawaiian or Pacific Islander groups
[c] For subject type, H: healthy; L: low BMD; On: osteopenia; Os: osteoporosis
[d] For ADA status: N: Negative; B: Binding positive; BN: Binding and neutralizing positive
[e] For race, W: White; B: Black; H: Hispanic; A: Asian; J: Japanese; O: Other, including American Indian or Alaskan Native, Hawaiian or Pacific Islander groups
[f] Includes 2 subjects (b) (6) who were excluded in the index dataset due to having only 1 post dose PK.

Source: Applicant's population PK report, Table 12-7, Page 65.

The final covariate model included effects of baseline body weight, eGFR, Japanese race, and manufacturing process on CL and baseline body weight, age, and sex on V2. Prior alendronate or postmenopausal osteoporosis (PMO) treatments, patient populations (eg, healthy/low-BMD, osteopenic, and osteoporotic), and baseline sclerostin had no significant association with romosozumab PK parameters. Therefore, these covariates had no impact on romosozumab exposures or dosing. The final parameters and their precision are shown in Table 2.

Reference ID: 4076576

Table 2 Parameter Estimates for the Final Covariate Model

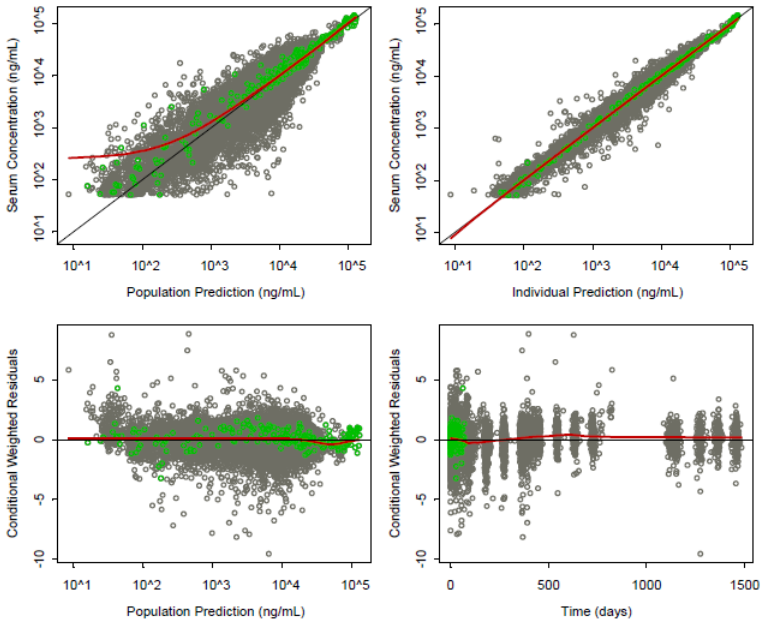
		Final Dataset	
	Parameter (unit)	**Mean (%RSE[d])**	**Bootstrap 95% PI[e]**
Linear Clearance[b]	CL (L/d)	0.293 (4.71%)	[0.265, 0.313]
• Exponent body weight scaling factor	-	1.07 (5%)	[0.956, 1.16]
• eGFR	-	0.189 (20.8%)	[0.117, 0.256]
• Japanese	-	1.110 (2.85%)	[1.05, 1.16]
• Manufacturing process #2 (commercial process development)	-	0.886 (1.56%)	[0.862, 0.917]
Volume of distribution for central compartment	V_2 (L)	2.91 (2.37)	[2.82, 3.03]
• Exponent body weight scaling factor	-	1.07 (6.54)	[1.02, 1.29]
• Age	-	0.713 (11.2)	[0.613, 0.893]
• Female	-	1.24 (2.8)	[1.11, 1.3]
Intercompartmental clearance between central and 1st peripheral compartment	Q_3 (L/d)	0.177 (11.5)	[0.163, 0.201]
Volume of distribution for 1st peripheral compartment	V_3 (L)	0.645 (15.8)	[0.437, 0.761]
Intercompartmental clearance between central and 2nd peripheral compartment	Q_4 (L/d)	0.277 (12.8)	[0.245, 0.346]
Volume of distribution for 2nd peripheral compartment	V_4 (L)	0.722 (7.85)	[0.671, 0.812]
Apparent density of total target in 1st peripheral compartment	R_{max1} (ng/mL)	19300 (5.7)	[6690, 21600]
Apparent density of total target in 2nd peripheral compartment	R_{max2} (ng/mL)	8990 (26.3)	[6210, 17600]
Elimination of romosozumab-target complex	k_{int} (1/d)	0.054 (6.63)	[0.0507, 0.0572]
Quasi-steady state constant in peripheral compartment	K_{SS} (ng/mL)	149 (9.53)	[133, 162]
Apparent density of total FcRn at absorption site	$R_{max,FcRn}$ (ng)	5120 (6.52)	[4470, 5870]
Degradation rate constant of unbound romosozumab at absorption site	k_{deg} (1/d)	0.041 (22.3)	[0.0259, 0.0599]
Quasi-steady state constant for FcRn binding	$K_{ss,FcRn}$ (ng)	66.4 (13.9)	[48.2, 88.1]
Absorption rate constant of unbound romosozumab at absorption site	k_{a1} (1/d)	0.240 (2.48)	[0.221, 0.257]
Inter-subject variability in CL	ωCL (%)	32.2 (5.34)	[30, 34.1]
Inter-subject variability in V_2	ωV_2 (%)	29.0 (19.9)	[25.7, 32.6]
Inter-subject variability in k_{a1}	ωka_1 (%)	43.8 (15.9)	[38.9, 51.4]
Proportional residual error			
Studies 20060326, 20070337, 20101291, 20090378 and 20110253	σ_{prop1} (%)	30.7 (2.93)	[28.9, 32.3]
All other studies	σ_{prop2} (%)	15.3 (3.63)	14.3-16.5

Source: Applicant's population PK report, Table 12-14, Page 74.

The diagnostic plots and VPC are presented in Figure 2,

Figure 3 and Figure 4 demonstrating good predictability.

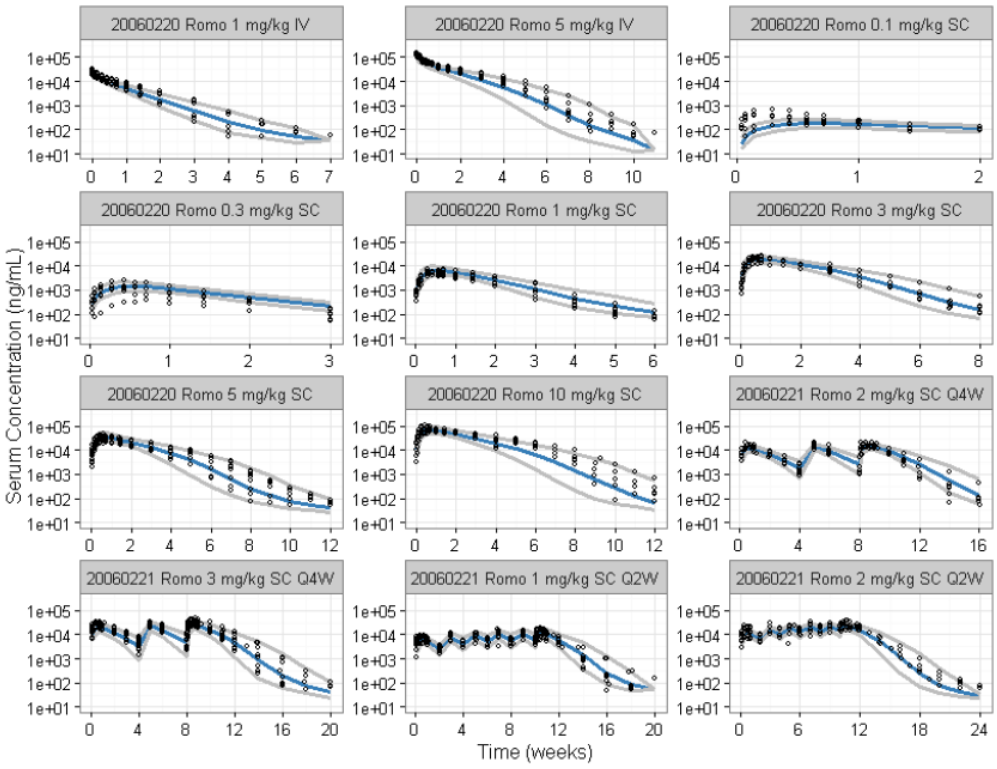
Figure 2 Goodness of Fit Plot for the Final Population PK Model

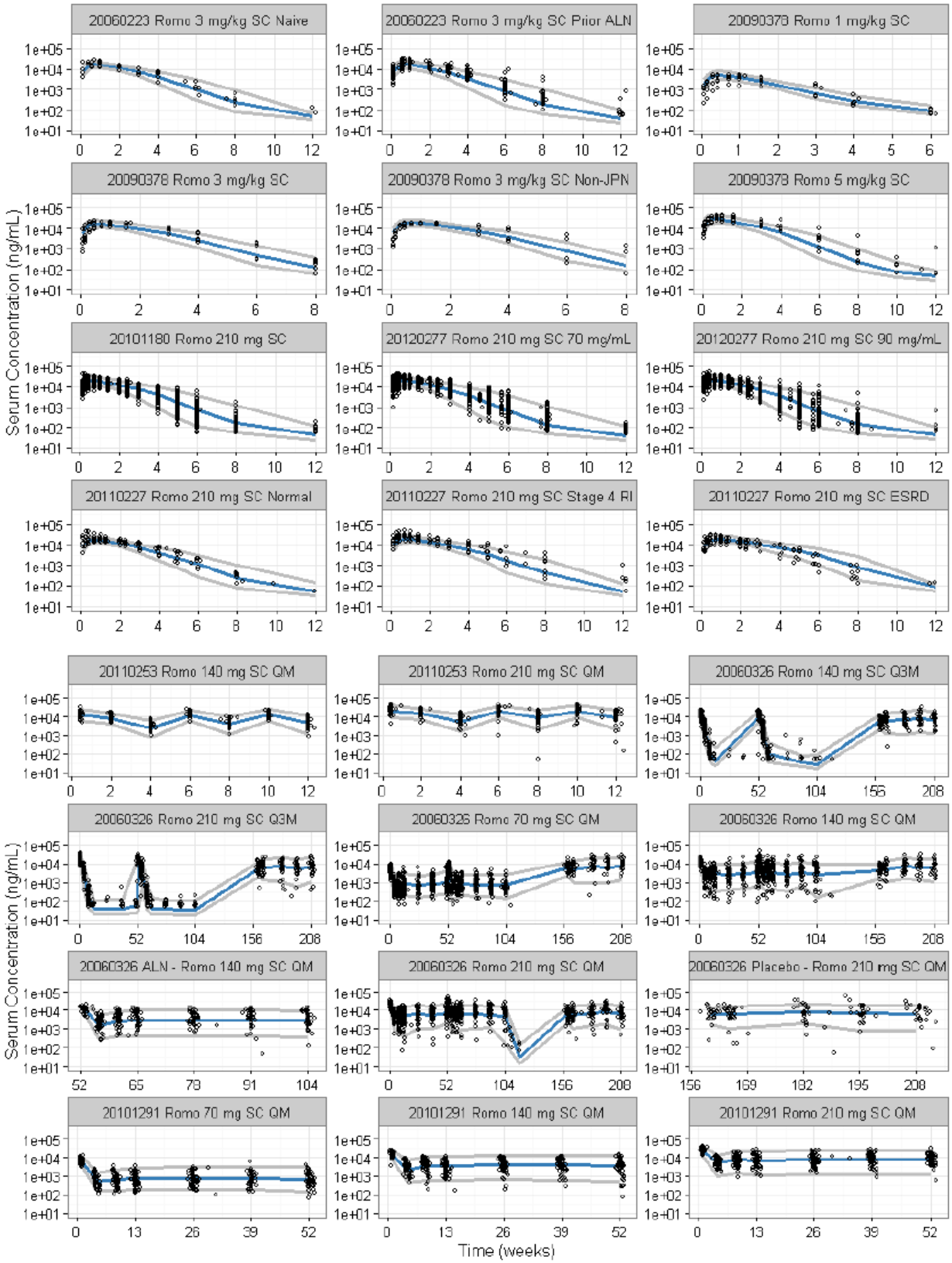


Green and grey data points reflect observations following IV and SC dosing, respectively.

Source: Applicant's population PK report, Figure 13-25, Page 117.

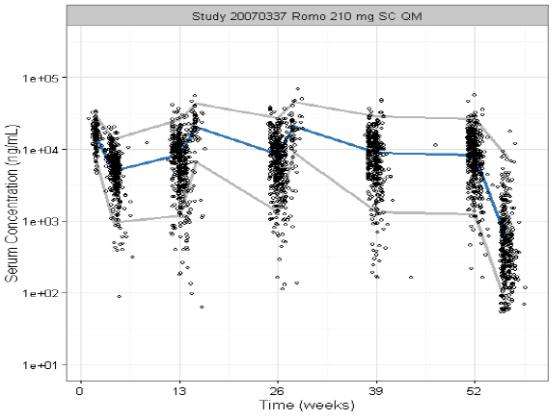
Figure 3 Visual Predictive Check for the Final Population PK Model for Phase 1 and 2 studies by dose





Source: Applicant's population PK report, Figure 13-29, Page 124.

Figure 4 Visual Predictive Check for the Final Population PK Model for Phase 3 study



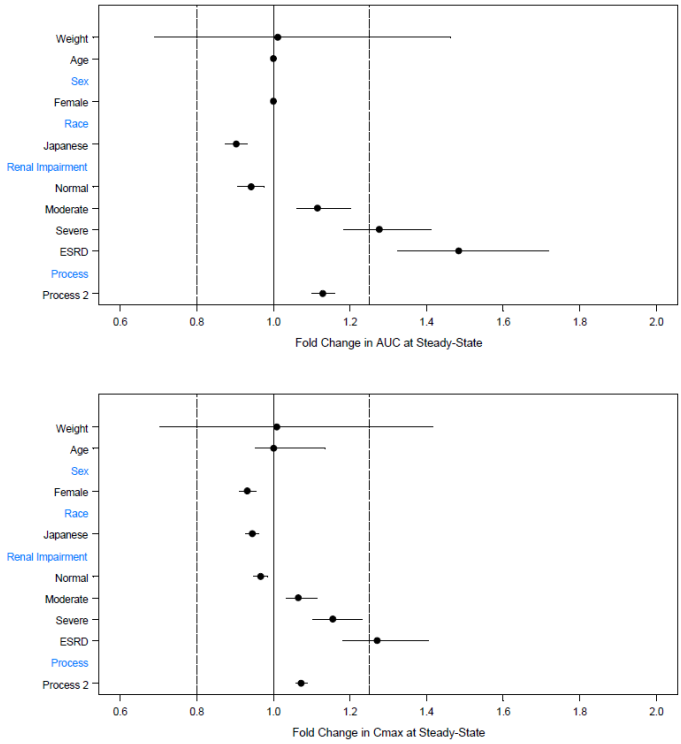
Source: Applicant's population PK report, Figure 13-29, Page 125.

The final population PK model was used to evaluate the impact of covariates on romosozumab exposure and compare the fixed dosing with body weight based dosing.

1. Impact of covariates on romosozumab exposure

The impact of other covariates, in addition to body weight, on steady-state romosozumab exposure parameters (AUCss and Cmax,ss) after a clinical dose of 210 mg SC QM is shown using a forest plot (Figure 5).

Figure 5 Fold Change and 95%PI in Steady-state AUC and Cmax across the Range of Covariates:



Vertical reference lines refer to 0.8, 1.0 and 1.25 fold-changes in median model predicted AUC and Cmax at steady state, compared to the reference subject. Renal function based on eGFR: normal (≥90 mL/min/1.73 m²), mild (60 to<90 mL/min/1.73 m²), moderate (30 to <60 mL/min/1.73 m²), severe (15 to <30 mL/min/1.73 m²), ESRD (5 to <15 mL/min/1.73 m²).

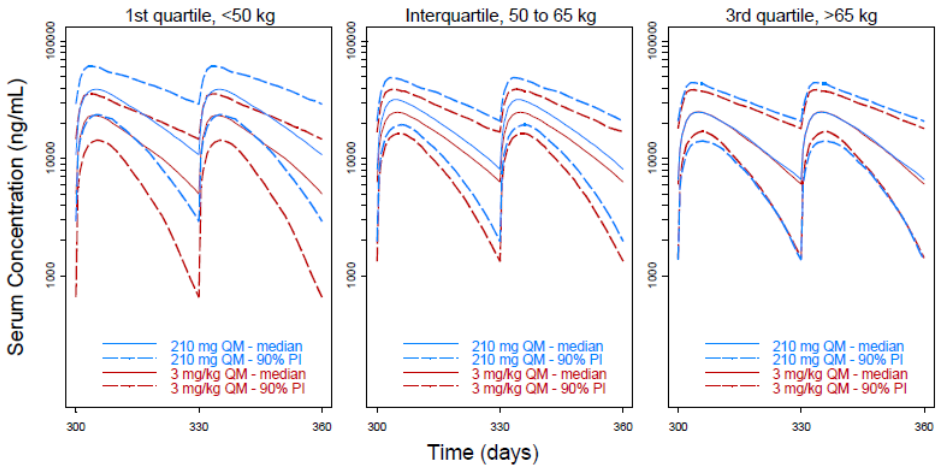
Source: Applicant's population PK report, Figure 13-30, Page 126.

The reference subject is a subject with weight of 61 kg, age of 66 years, mild renal function, male, race of non-Japanese, and using the formulation utilized in the clinical studies. Although these covariates have significant associations with romosozumab PK parameters, the distributions of romosozumab AUCss and Cmax,ss fold change with respect to the reference subject overlapped greatly across covariate ranges, suggesting their impact on overall PK variability is small and resulted in less than 20% difference in exposure for most covariates. Body weight and advanced renal impairment (severe renal impairment and ESRD without hemodialysis) showed PK changes beyond the empirically defined region of clinical importance (0.8 -1.25).

2. Justification of a non-weight Based Dosing for Clinical use in PMO Patients

The median and 90% prediction interval of the simulated serum concentration-time profile of romosozumab after 210 mg QM or 3 mg/kg SC QM is shown in Figure 6 for PMO subjects with a body weight range from 33 to 98 kg.

Figure 6 Model-based Simulation of the Time Course of Romosozumab Serum Concentration at Steady-state for 3 mg/kg or 210 mg Every Month Dosing in PMO Patients with a Body Weight Range of 33 to 98 kg



Source: Applicant's population PK report, Figure 13-31, Page 127.

In addition, Table 3 provides the mean and the standard deviation of the AUCss, Cmax, Tmax for the 1st and 12th dose stratified by low (1st quartile, <50 kg), mid (2nd and 3rd quantile , 50 kg ≤ weight ≤ 65 kg) and high (4th quartile, >65 kg) body weight, as well as the accumulation ratio. The fixed dosing regimen of 210 mg SC QM had approximately 27% and 28% increase in median AUCss and Cmax,ss in the 2nd and

3rd quantile of body weight compared to a weight-based regimen of 3 mg/kg SC QM. Compared to PMO subjects with body weight in the 2nd and 3rd quantile, a romosozumab fixed dose of 210 mg administered to PMO patients with body weight lower than 50 kg resulted in a 27% and 23% increase in median AUCss and Cmax,ss, respectively. Conversely, in PMO patients with body weight higher than 67 kg, a fixed dose of 210 mg resulted in a 19% and 21% lower median AUCss and Cmax,ss respectively, Additionally, 210 mg QM dosing does not result in a substantial increase in variability. The percent CV for low versus high body weight quartiles with 3 mg/kg dosing are 33.9 and 34.3, whereas that using fixed dosing (210 mg) are 38.5 and 39.1 respectively.

Table 3 Impact of Weight Based (3 mg/kg) or Fixed Dosing (210 mg) on Romosozumab Exposures in PMO Subjects

	Weight-based dosing 3 mg/kg QM			Fixed dosing 210 mg QM		
	Body Weight			Body Weight		
PK Exposure Parameters	<53 kg	53-61 kg	>61 kg	<53 kg	53-61 kg	>61 kg
N	247	506	247	247	506	247
AUC 1st month (µg·day/mL)	281 (23.6) 278	323 (24.2) 316	341 (23.1) 328	507 (23.8) 488	418 (23%) 413	342 (28.3) 326
AUC 12th month (µg·day/mL)	445 (33.9%) 427	500 (35.1%) 472	513 (34.3%) 473	802 (38.5%) 757	633 (33.3%) 597	525 (39.1%) 485
AUC Ratio	1.56 (18.9%) 1.51	1.53 (20.6%) 1.45	1.49 (20.3%) 1.4	1.56 (23.8%) 1.49	1.5 (17.7%) 1.43	1.51 (20.1%) 1.44
C_{max} 1st month (µg/mL)	17.3 (28.8%) 17	18.7 (30%) 17.8	19.1 (27.7%) 18.6	28 (29%) 26.7	23.4 (28.3%) 22.9	18.8 (31.8%) 17.9
C_{max} 12th month (µg/mL)	24.2 (26.7%) 23.9	26.4 (28.7%) 25.1	26.7 (27.1%) 25.3	41.1 (30.1%) 39.3	33 (27.5%) 32	26.8 (32.8%) 25.2
C_{max} Ratio	1.43 (18.8%) 1.37	1.44 (20.3%) 1.37	1.42 (19.7%) 1.34	1.5 (23%) 1.44	1.43 (17.5%) 1.38	1.44 (19.6%) 1.38
T_{max} 1st month (day)	4.56 (32%) 4	5.04 (32.4%) 5	5.44 (30%) 5	5.17 (34.4%) 5	5.21 (32%) 5	5.63 (30.1%) 5
T_{max} 12th month (day)	4.91 (27.9%) 5	5.12 (26.6%) 5	5.34 (23.8%) 5	4.94 (26.2%) 5	5.1 (26%) 5	5.45 (24.6%) 5

Numbers are mean (CV%) median.

Source: Applicant's population PK report, Figure 12-16, Page 77.

To conclude, prior alendronate or PMO treatments, patient populations (eg, healthy/low-BMD, osteopenic, and osteoporotic), antibody status (eg, negative, binding vs. neutralizing), and baseline sclerostin had no significant association with romosozumab PK parameters. Therefore, these covariates had no impact on romosozumab exposures and no dose adjustments are proposed based on these factors. Body weight and renal function (as measured by eGFR) were significant covariates with increasing exposure predicted for decreasing body weight or eGFR. Considering the fixed dosing regimen was given to Phase 3 study with an acceptable safety profile, dose adjustment based on body weight or renal function is not warranted.

4.5.2 Reviewer's comments:

The reviewer found the Applicant's population PK model structure for romosozumab reasonable. The applicant's population PK dataset included ESRD patients with hemodialysis from study 20110227 (the dedicated renal impairment study) When the reviewer reran the population PK analysis, these patients were removed for the following reasons.

1. *Data from the dedicated renal impairment study showed that the exposure in severe renal impairment subjects was 44% higher than that in subject with normal renal function, whereas the exposure in ESRD subjects with hemodialysis was comparable to that in subjects with normal function (Table 4). The reason behind the scene is unknown as hemodialysis does hardly remove large molecules. In the dedicated renal impairment study, PK samples were intensively collected over 85 days after a single dose of 210 mg. When hemodialysis occurred on a day of sample collection, sample collections were performed before hemodialysis. The frequency of hemodialysis in ESRD patients was not specified. It appears that the impact of hemodialysis on PK of romosozumab is inconclusive.*
2. *On the other hand, the VPC plot (Figure 3) from study 20110227 shows that the observations of severe renal impairment subjects were slightly under-predicted and observations of ESRD subjects with hemodialysis were slightly over-predicted.*

Table 4 Descriptive Statistics of Romosozumab Pharmacokinetic Parameter Estimates After Subcutaneous Administration of 210 mg Romosozumab in Subjects With Stage 4 RI, Subjects With ESRD Requiring Hemodialysis, and Healthy Subjects

PK Parameter	Stage 4 RI (Group 1) (n = 8)	ESRD Requiring Hemodialysis (Group 2) (n = 8)	Healthy Subjects (Group 3) (n = 8)
t_{max} (day)	5.0 [3.0 - 7.0]	5.0 [3.0 – 7.0]	5.0 [3.0 - 7.0]
C_{max} (µg/mL)	28.9 (10.8) [14.8 – 51.5]	19.8 (7.3) [9.39 – 31.9]	22.4 (10.3) [13.5 – 45.2]
AUC_{last} (day•µg/mL)	637 (218) [323 – 983]	444 (154) [216 – 643]	443 (143) [264 – 700]
AUC_{inf} (day•µg/mL)	642 (221) [326 – 987]	447 (154) [218 – 647]	445 (143) [265 – 703]

Source: Applicant's dedicated renal impairment study (20110227) report, Table 11-1, Page 51.

When reviewer reran the population PK analysis without the ESRD subjects, the parameter estimates were consistent with Applicant's results except that the power-law coefficient estimate of estimated glomerular filtration rate (eGFR) was changed from 0.189 to 0.219[1]*.*

One thing to mention, the eGFR values used in the Applicant's population PK model was calculated using the following equation:

[1] Impact of creatinine clearance (eGFR) was presented as power function centralized by 80 mL/min/1.73m^2, which is median eGFR value from final population PK data.

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$$eGFR = 186 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times 0.742(Female) \times 1.212(Black)$$

The coefficient (186) was different from the value (175) used in the Phase 3 dataset (adbase.xpt). The coefficient of 175 is recommended in FDA guidance with regard to dedicated renal impairment study (http://www.fda.gov/downloads/Drugs/Guidances/UCM204959.pdf). However, the difference is not expected to result in significant change in population PK results. Thus, the reviewer used the dataset as provided by the Applicant.

Based on the reviewer's assessment, except bodyweight and renal function, other covariats , including gender, age, race (Japanese/non-Japanese), prior alendronate, and drug product manufacturing process do have not signifant impact on romosozumab exposure.

The impact of body weight and renal function were independently evaluated by the Reviewer using the updated population PK model. Summary values based on these covariates for the Phase 3 data are provided below in Table 5. The reviewer is presenting information in this manner so that it is easier to compare exposures differ between patients with various degrees of renal impairment to exposures in patients with normal renal function.

Table 5 Impact of body weight and renal function based on Phase 3 study (n=434) or simulation from Reviewer's population PK model with a dose of 210 mg QM

Parameter	*Category/Quantile*	*n*	*$AUC_{330-360}$ (µg·day/mL) (mean, 95% CI)*
Body Weight (kg)	*1st quantile (35.4 -50.2)*	*110*	*701.9 (523.8-787.2)*
	2nd quantile (50.2-56.3)	*106*	*587.3 (515.0-661.0)*
	3rd quantile (56.3-63.2)	*108*	*482.7 (398.2-557.7)*
	4th quantile (63.2-95.9)	*110*	*467.9 (369.4-512.2)*
eGFR (mL/min/1.73m²)	*Normal (≥90)*	*49*	*527.1 (387.1-591.9)*
	Mild (60-90)	*290*	*558.2 (436.0-631.9)*
	Moderate (30-60)	*93*	*585.9 (491.1-671.7)*
	*Severe (15-30)**	*-**	*837.4 (707.0-967.9)**

Note: The AUC data were summarized from the predicted AUC value for each individual subject in the PK substudy of Phase 3 study 20070337. The AUC prediction was based on the individual estimated PopPK model parameters which were obtained based on modeling the trough concentration data .
**Simulation with 2910 number of patients, which represents demorgraphic of the phase 3 population based on Reviewer's updated population PK model with a dose of 210 mg QM. There were only two subjects with severe renal function in the Phase 3 study 20070337.*

Source: Reviewer's independent analysis.

The results elucidate that the exposures were relatively higher in low body weight patients and lower in high body weight patients, but the magnitude of difference between 1st and 4th quantile will be less than 1.5-fold. The difference in exposure across body weight is considered as relatively small and not clinically significant. Thus, no dose adjustment is necessary based on body weight.

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The exposures were comparable for normal, mild and moderate renal impairment patients. The exposure in severe renal impairment patients was imprecise due to the limited number of patients with severe renal impairment included in the Phase 3 trials. According the simulation, the exposure in severe renal impairment are expected to be 1.6-fold higher than that in normal renal function patients, respectively. Considering the fixed dosing regimen was given to Phase 3 study with an acceptable safety profile, no dose adjustment is needed for patients based on renal impairment.

4.6 Exposure-Response Analyses

In each subsection, the applicant's analysis is presented first and the reveiwer's comments and analysis follow.

4.6.1 Dose-BMD analysis

The effect of romosozumab dose regimen on the time course of bone mineral density (BMD) change in postmenopausal women with osteoporosis was analyzed by the Applicant. Data from two Phase 2 studies (20060326 and 20101291) one Phase 3 study (20070337) were used in the romosozumab dose-BMD analysis. A summary of the study designs is provided in Table 6.

Table 6 Summary of Clinical Studies

Study	Type	Cohorts and Doses	BMD Measurement
Phase 2			
20060326	Low BMD	Placebo SC 70, 140, 210 mg QM SC 140, 210 mg Q3M PO ALN 70 mg QW SC TPT 20 µg QD	Baseline, 3, 6, 12, 15 (for ALN cohort only), 18, 24, 27, 36, 39, 42 and 48 months
20101291	Ost	Placebo SC 70, 140 210 mg QM	Baseline, 6 and 12 months
Phase 3			
20070337	Ost	Placebo SC 210 mg QM	Baseline, 6, 12, 18, and 24 months BMD sub-study (142 subjects with non-missing sCTX, and P1NP):

Ost = osteoporosis

Source: Applicant's dose-BMD analysis report, Table 12-1, Page 39.

Study 20060326: A total of 393 subjects with low BMD were randomized to placebo, teriparatide 20 µg SC QD, alendronate 70 mg PO QW, or romosozumab 70 mg SC QM, 140 mg SC QM, 210 mg SC QM, 140 mg SC Q3M or 210 mg SC Q3M. After 12 months on study, subjects in the teriparatide cohort discontinued from the study and subjects in the alendronate cohort were transitioned to romosozumab 140 mg SC QM; subjects in the other cohorts continued receiving their original treatment for an additional 12 months. After 24 months, subjects were either followed for 3 more months (27 months on study), or transitioned to placebo or denosumab 60 mg SC Q6M for an additional 12 months. After 36 months, subjects were discontinued or transitioned to romosozumab 210 mg SC QM for an additional 12 months. BMD at lumbar spine and total hip were collected for up to 48 months.

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Study 20101291: A total of 241 Japanese PMO subjects were randomized to placebo, 70 mg SC QM, 140 mg SC QM, or 210 mg SC QM romosozumab (n = 63 per cohort). BMD at lumbar spine and total hip data were collected for up to 12 months.

Study 20070337: A total of 7180 PMO subjects were randomized to receive placebo (n = 3591) or romosozumab 210 mg SC QM (n = 3589) for up to 12 months. After 12 months, all subjects were transitioned to denosumab 60 mg SC QM for an additional 12 months. BMD at lumbar spine and total hip were collected for up to 24 months. Only subjects with non-missing measurements of bone turn-over markers at baseline (P1NP and sCTx-I) were included in the analysis as they were found to be significant covariates in the initial model based on the index dataset (n=142).

Summary statistics for continuous and categorical covariates are presented in Table 7.

Table 7 Summary Statistics of Race, Body Weight, Age, Years since Menopause, BMD Lumbar Spine and Total Hip, P1NP and sCTX-I by Clinical Study

Study	N	Race (G/J)	Weight (kg)	Age (years)	Years Menopause	BMD LS (g/cm^2)	BMD TH (g/cm^2)	P1NP (ng/mL)	sCTX (ng/mL)
All	776	534/242	58.7 (11.5) 58 [32.5-104.3]	68 (6.8) 67.4 [55.1-88.8]	19.4 (8.7) 19 [1-55]	0.77 (0.12) 0.76 [0.53-1.31]	0.72 (0.09) 0.71 [0.49-1.06]	52.2 (22.8) 49.6 [7.3-373.9]	0.52 (0.3) 0.48 [0.04-4.6]
20060326	393	392/1	64.4 (10.1) 64.4 [35.5-98.2]	67.3 (6.5) 67 [55-85]	19.4 (8.5) 19 [2-50]	0.83 (0.09) 0.81 [0.66-1.31]	0.77 (0.08) 0.77 [0.54-1.07]	52.6 (20.2) 49.4 (15.8-179)	0.54 (0.26) 0.50 (0.07-2.49)
20101291	241	0/241	49.3 (6.93) 48.7 [32.5-73.1]	68.4 (6.5) 68 [56-85]	18.5 (8.4) 18 [1-45]	0.67 (0.067) 0.66 [0.53-1.02]	0.65 (0.07) 0.65 [0.49-0.98]	50.7 (18.1) 50.3 [8.4-161]	0.47 (0.26) 0.41 [0.04-1.59]
20070337	142	142/0	59 (11.1) 58.4 [37.5-104.3]	69.5 (7.9) 68.3 [55.1-88.8]	20.8 (9.7) 21 [3-55]	0.79 (0.12) 0.79 [0.54-1.2]	0.68 (0.07) 0.68 [0.53-0.9]	53.46 (33.98) 49.05 [7.3-373.9]	0.55 (0.44) 0.49 [0.04-4.6]

Numbers are mean (SD) median [min-max].
For race, G: Global/non-Japanese; J: Japanese
LS: Lumbar spine; TH: Total hip

Source: Applicant's dose-BMD analysis report, Table 12-6, Page 45.

A previously published time-varying dose-BMD model of postmenopausal osteoporosis treatments was modified to describe the percent change from baseline in BMD at lumbar spine and total hip after SC administration of monthly and quarterly romosozumab dosing schedules to postmenopausal women with osteoporosis. The model parameters for the final model are presented in Table 8. Romosozumab maximal response was estimated to be 11.4% (95%CI: 10.5 to 12.2) for lumbar spine and 6.0% (95%CI: 5.1 to 6.7) for total hip. The time to achieve 50% of E_{max} for romosozumab for the lumbar spine was estimated to be 5.4 months (bootstrap 95% prediction interval: 4.5 to 6.7), whereas that for total hip was 8.25 months (bootstrap 95% prediction interval: 6.1 to 10.9).

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Table 8 Parameter Estimates for the Final Model

Model Parameters	Lumbar Spine			Total Hip		
	Estimate (%RSE)	Bootstrap		Estimate	Bootstrap	
		Median	95% PI		Median	95% PI
Placebo Response						
Study 2006326						
$E_{0\ (t = 3\ mos)}$, %	0.453	0.422	0.238, 0.932	-0.331	-0.355	-0.479, -0.079
$E_{0\ (t = 6\ mos)}$, %	0.639	0.595	0.400, 1.144	-0.478	-0.520	-0.653, -0.219
$E_{0\ (t = 12\ mos)}$, %	0.196	0.367	0.109, 0.822	-0.613	-0.669	-0.792, -0.308
$E_{0\ (t = 15\ mos)}$, %	0.590	0.657	0.264, 1.261	-0.789	-0.672	-0.941, -0.316
$E_{0\ (t = 18\ mos)}$, %	0.549	0.551	0.317, 1.196	-0.943	-0.972	-1.11, -0.568
$E_{0\ (t = 24\ mos)}$, %	1.140	1.191	0.826, 1.871	-0.996	-1.018	-1.2, -0.615
$E_{0\ (t = 27\ mos)}$, %	0.050	0.083	0.001, 1.102	-1.230	-1.235	-1.68, -0.564
$E_{0\ (t = 30\ mos)}$, %	0.637	0.580	0.205, 1.343	-1.100	-1.106	-1.35, -0.651
$E_{0\ (t = 36\ mos)}$, %	0.672	0.629	0.307, 1.362	-1.570	-1.599	-1.84, -1.14
$E_{0\ (t = 39\ mos)}$, %	1.080	1.090	0.595, 1.962	-1.560	-1.580	-1.86, -1.15
$E_{0\ (t = 42\ mos)}$, %	0.955	0.958	0.362, 2.055	-1.500	-1.532	-1.8, -1.04
$E_{0\ (t = 48\ mos)}$, %	1.990	2.021	0.997, 3.356	-1.660	-1.674	-2.02, -1.05
Study 20101291						
$E_{0\ (t = 6\ mos)}$, %	1.550	1.591	1.591, 1.094	0.466	0.572	0.203, 0.796
$E_{0\ (t = 12\ mos)}$, %	0.893	0.873	0.873, 0.359	0.513	0.634	0.152, 0.928
$E_{0\ (t = 6\ mos)}$, %	0.988	1.01	0.581, 1.78	0.663	0.689	0.351, 1.2
$E_{0\ (t = 12\ mos)}$, %	0.580	0.607	0.344, 1.37	0.153	0.226	0.00267, 0.762
$E_{0\ (t = 18\ mos)}$, %	0.356	0.242	0.142, 1.3	0.468	0.474	0.12, 1.16
$E_{0\ (t = 24\ mos)}$, %	0.663	0.186	0.351, 1.2	1.000	1.01	0.881, 1.13
Study 20070337						
Dose-BMD Model Parameters						
E^{ss}_{max}, %	31.7	31.5	26.2, 41.4	17.0	17.0	14.1, 22.9
k, $month^{-1}$	0.128	0.128	0.103, 0.153	0.084	0.0833	0.0635, 0.113
ED_{50}, mg QM	244	243	189, 373	Same as lumbar spine		
Alendronate treatment on k	0.279	0.275	0.175, 0.388	0.204	0.194	0.0938, 0.341
Denosumab treatment on k	0.076	0.0751	0.0169, 0.148	0 Fixed	0 Fixed	0 Fixed
Japanese on E_{max}	1.230	1.24	1.1, 1.39	0.752	0.725	0.581, 0.917
sCTX on E_{max}	0.307	0.31	0.205, 0.401	0.307	0.44	0.331, 0.56
Weight on E_{max}	-0.271	-0.284	-0.496, -0.0871	NE	NE	NE
Study 20070337 on E_{max}	1.000	1.01	0.881, 1.13	1.200	1.18	0.967, 1.44
Inter-individual Variability						
ω, %	3.1	3.1	2.8, 3.4	2.2	1.6	1.2, 1.8
Residual Error						
σ, %	2.5	2.5	2.4, 2.6	1.6	1.6	1.55, 1.72

Source: Applicant's dose-BMD analysis report, Table 12-10, Page 50.

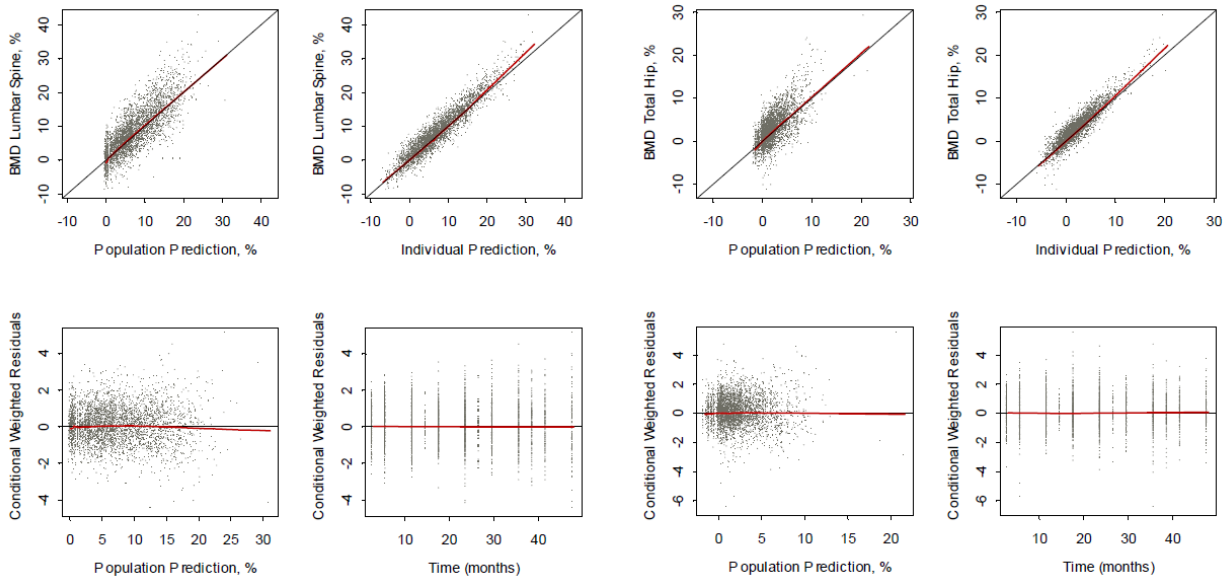
Subjects who were on prior alendronate treatment had a slower rate of onset for romosozumab treatment effect (19.1 months at lumbar spine and 40 months at total hip). Subjects who were on prior denosumab treatment had a slower rate of onset for romosozumab treatment effect at lumbar spine (6.2 months) but showed no total hip gain when transitioned to romosozumab. The BMD gain during the romosozumab retreatment after off-treatment period were similar to that in naïve subjects.

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In the final model, the proportional effect for Japanese subjects on E_{max} was estimated to be 1.23 (95%CI: 1.1 to 1.3) for the lumbar spine and 0.752 (95%CI: 0.581 to 0.917) for total hip. Study effect (Japanese study) and sCX on E_{max} for lumbar spine and total hip, and body weight on E_{max} for lumbar spine were identified as significant covariates in the final model.

Figure 7 show the goodness-of-fit plots for BMD lumbar spine and total hip, respectively, for the final model fit to the dataset. The observed versus predicted plots (upper panels) show random normal scatter around the identity line, indicating the absence of major systematic bias and the adequacy of the model to describe the data. In addition, conditional weighted residuals (middle panels) also show random normal scatter around a value of 0 over time and the range of predicted values with no specific pattern suggesting model misspecification.

Figure 7 Goodness of Fit Plots for BMD at Lumbar Spine (Left) and Total Hip (Right) for the Final Model

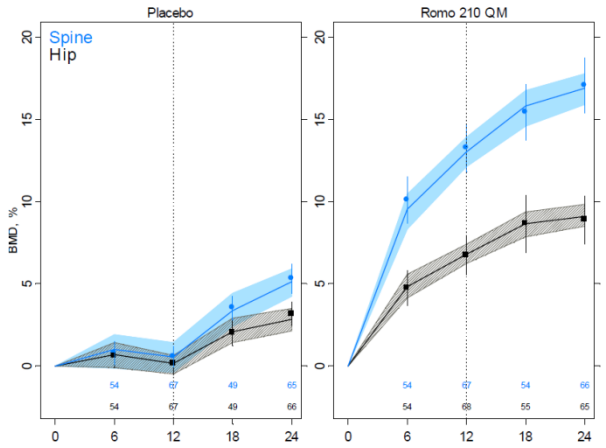


Source: Applicant's dose-BMD analysis report, Figure 13-16 and Figure 13-17, Page 73-74.

The internal evaluation of the final model using visual predictive check (VPC) demonstrated good predictability of the final model to describe the time course of the mean (and 95% confidence interval) BMD change from baseline at lumbar spine and total hip in each of the cohorts (Figure 8 for study 20070337). The observed mean (95% CI) shown in points and error bars were within the corresponding simulation-based 95%CI shown in shaded areas, across all studies and cohorts.

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Figure 8 Visual Predictive Check for the Final Model Stratified by 20070337 Study Cohort



Source: Applicant's dose-BMD analysis report, Figure 13-23, Page 81.

To conclude, a dosing regimen of 210 mg SC QM provided the greatest and fastest BMD gain compared to the other dosing regimens evaluated with predicted mean placebo corrected BMD gains at lumbar spine and total hip at 12 months of 11.4% (95%CI: 10.5 to 12.2) and 6.0% (95%CI: 5.1 to 6.7), respectively.

Reviewer's comments:

The reviewer reviewed the dose-BMD model. The dose-response model can well describe the observations under different dosing regimens and switch between on-treatment and off-treatment.

4.6.2 Exposure-BMD analysis

The effect of romosozumab concentrations on the time course of BMD changes in postmenopausal women with osteoporosis was analyzed by the Applicant. The studies included in this PK/PD analysis are:

Protocol 20060326: A multi-center, international, randomized, placebo-controlled, parallel group study in approximately 400 postmenopausal women with low BMD at the lumbar spine, total hip or femoral neck. The study consisted of three phases: 1) 24-month romosozumab treatment phase (day 1 to Month 24); 2) 12-month denosumab/placebo phase (Month 24 to month 36); 3) 12-month romosozumab retreatment phase (month 36 to month 48).

Protocol 20101291: A multi-center, randomized, double-blind, placebo-controlled, parallel-group study in Japanese women with osteoporosis defined as low BMD at the lumbar spine, total hip or femoral neck. Approximately 220 subjects were to be randomized 1:1:1:1 to receive either70 mg, 140 mg or 210 mg romosozumab SC QM or matched placebo SC QM for the duration of the 12-month treatment period.

Patient demographics at screening are summarized in Table 9 and Table 10. The study population consisted of 522 females with ages ranging from 55.3 to 84.8 years, PMO ranging from 1 to 45 years,

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and weights ranging from 32.5 to 95.9 kg. There were 301 non-Japanese and 251 Japanese subjects, and all but one Japanese subject was enrolled in study 1291.

Table 9 Summary of Categorical Covariates by Study

Study	Stat	non-Japanese	Japanese	Hologic	Lunar	Placebo	70 mg SC QM	140 mg SC Q3M	140 mg SC QM	210 mg SC Q3M	210 mg SC QM
All	Number	301	251	462	90	111	112	52	111	53	113
All	Percentage	54.5	45.5	83.7	16.3	20.1	20.3	9.4	20.1	9.6	20.5
1291	Number		250	240	10	61	63		63		63
1291	Percentage		100	96	4	24.4	25.2		25.2		25.2
60326	Number	301	1	222	80	50	49	52	48	53	50
60326	Percentage	99.7	0.3	73.5	26.5	16.6	16.2	17.2	15.9	17.5	16.6

Source: Applicant's exposure-BMD analysis report, Table 1, Page 42

Table 10 Summary of Continuous Covariates by Study

Study	covariate	N	minimum	maximum	median	mean	sd
All	Weight (kg)	552	32.500	95.90	55.700	57.500	11.4000
All	Age (yr)	552	55.300	84.80	66.900	67.700	6.5200
All	Post Menopause Onset (yr)	552	1.000	45.00	18.000	18.900	8.4100
All	Baseline BMD (g/cm3)	552	0.529	1.31	0.737	0.750	0.1150
All	Baseline P1NP (ng/mL)	552	8.440	161.00	50.100	51.700	19.1000
All	Baseline CTX (ng/mL)	552	0.043	2.48	0.469	0.511	0.2660
1291	Weight (kg)	250	32.500	73.10	48.800	49.400	7.0100
1291	Age (yr)	250	55.500	84.60	67.400	68.300	6.3800
1291	Post Menopause Onset (yr)	250	1.000	45.00	18.000	18.400	8.3600
1291	Baseline BMD (g/cm3)	250	0.529	1.02	0.657	0.664	0.0668
1291	Baseline P1NP (ng/mL)	250	8.440	161.00	50.400	51.100	18.2000
1291	Baseline CTX (ng/mL)	250	0.043	1.59	0.409	0.473	0.2600
60326	Weight (kg)	302	39.500	95.90	64.000	64.300	9.7900
60326	Age (yr)	302	55.300	84.80	66.700	67.300	6.6200
60326	Post Menopause Onset (yr)	302	2.000	44.00	19.000	19.300	8.4300
60326	Baseline BMD (g/cm3)	302	0.662	1.31	0.803	0.821	0.0961
60326	Baseline P1NP (ng/mL)	302	15.800	158.00	49.800	52.200	19.7000
60326	Baseline CTX (ng/mL)	302	0.073	2.48	0.512	0.542	0.2670

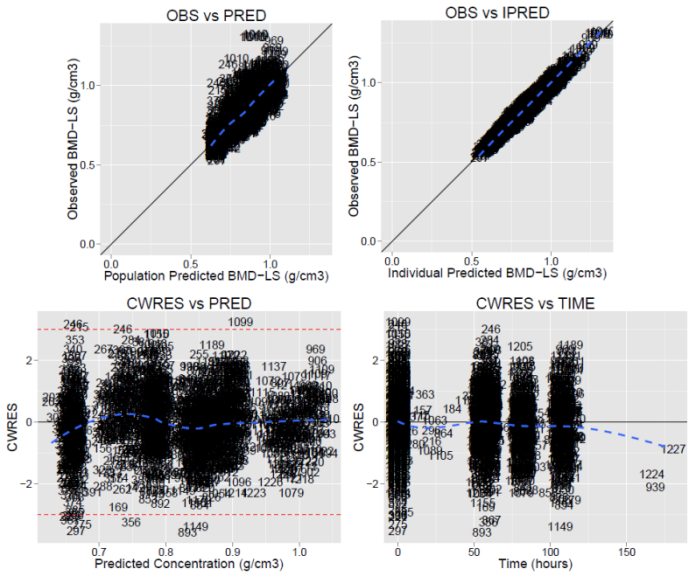
Source: Applicant's exposure-BMD analysis report, Table 2, Page 43

Initial modeling was performed using the mechanistic PK/PD model developed to describe the on-treatment PD efficacy (BMD) effects of romosozumab using the 24-month initial treatment phase Study 60326 and 12-month Study 1291 data. Individual romosozumab PK parameter estimates for PK/PD modeling were derived in population PK analysis (*section 4.5*). The effects of study (1291 vs. 60326) on baseline BMD were included in the base model. The base model also included an effect of DXA (hologic vs. lunar) machine type on baseline BMD.

In the final model, the body weight and PMO were added to the population PK/PD model. Diagnostic plots revealed that the model was consistent with the observed data and little systematic bias was evident (Figure 9). The VPC results revealed that the full model for two-year efficacy provided a reliable description of the data with adequate precision of structural model and variance parameter estimates (Figure 10). Parameter estimates are listed in Table 11. The population mean estimate for logit(Ima x) was -0.812 (67.0%), corresponding to an I_{max} value of 0.307. Estimates for IC_{50} and SC_{50} were 70.4 ng/mL and 22,600 ng/mL. Differences in baseline BMD for study 1291 subjects (approximately 15% lower) and lunar machine measurements (15% higher) were identified.

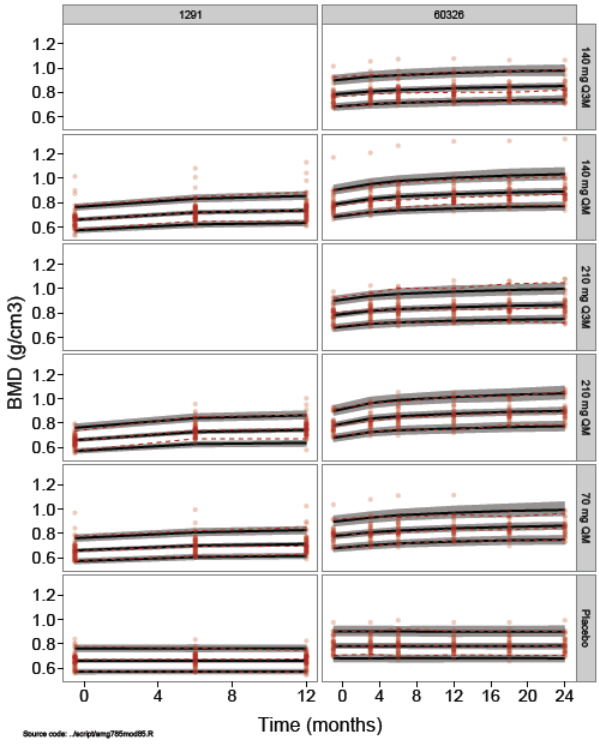
Reference ID: 4076576

Figure 9 Diagnostic plots for PK/PD model based on BMD



Source: Applicant's exposure-BMD analysis report, Figure 26-27, 29 and 31, Page 78—83

Figure 10 BMD Visual Predictive Check: Hologic. Results from 500 simulated trials are summarized as the median, 5th, and 95 h percentiles (solid black lines) with associated 95% CIs. Observed values are plotted as red circles, with observed median, 5th, and 95th percentiles (dashed red lines)



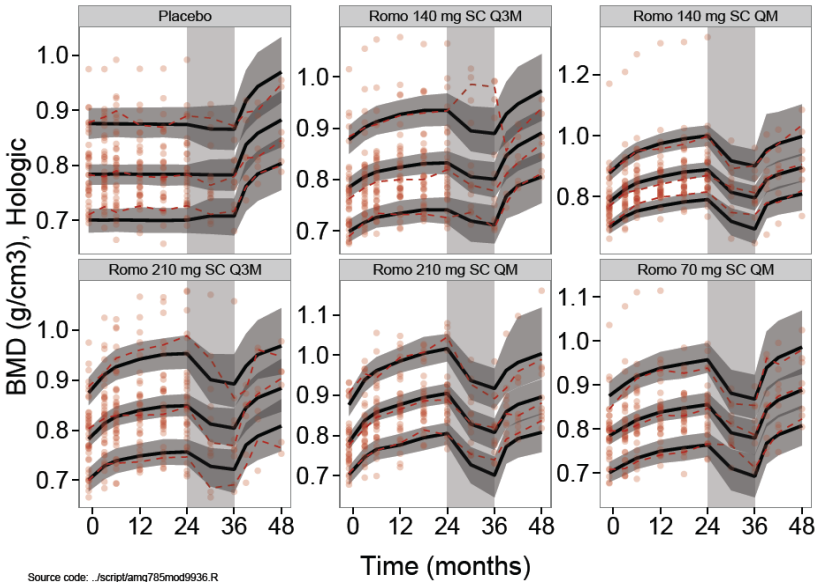
Source: Applicant's exposure-BMD analysis report, Figure 108, Page 160

Table 11 Parameter Estimates from Full Covariate Population PK-PD Model

Description	Model	Estimate	RSE	95% CI	Variability
lifespan resorption cavities	$LSRC \sim \theta_1$	1.53 $week$	fixed	fixed	
lifespan collagen formation	$LSCF \sim \theta_2$	2.13 $week$	2.99	(2.01, 2.25)	
disease progression	$DP \sim \theta_3 + \eta_6$	0.0120 $1/yr$	96.7	(-0.0108, 0.0348)	
concentration to achieve half maximum effect	$IC50 \sim \theta_4$	70.4 ng/mL	11.7	(54.2, 86.6)	
maximum effect	$I_{max} \sim \exp(\theta_5 + \eta_4)/(1 + \exp(\theta_5 + \eta_{4}))$	-0.812	6.99	(-0.923, -0.701)	
concentration to achieve half maximum effect	$SC_{50} \sim \theta_6$	22600 ng/mL	23.1	(12400, 32800)	
bone modeling input rate	$K_0 \sim \theta_7 \cdot \exp^{\eta_5}$	3.41 $BMU/week$	15.9	(2.35, 4.47)	
feedback factor	$FB \sim \theta_8 \cdot \exp^{\eta_7}$	26.3	2.92	(24.8, 27.8)	
baseline P1NP	$P1NP_0 \sim \theta_9 \cdot \exp^{\eta_{10}}$	43.9 ng/mL	1.92	(42.3, 45.5)	
baseline CTX	$CTX_0 \sim \theta_{10} \cdot \exp^{\eta_{11}}$	0.466 ng/mL	2.96	(0.439, 0.493)	
baseline BMD	$BMD_0 \sim \theta_{11} \cdot \text{STUDYEFF} \cdot \text{MTYPEFF} \cdot \exp^{\eta_{12}}$	0.775 $g/cm3$	0.760	(0.763, 0.787)	
study effect on baseline BMD	$\text{STUDYEFF} \sim \theta_{12\text{STUDY}}$	0.854	0.977	(0.838, 0.87)	
machine type effect on baseline BMD	$\text{MTYPEFF} \sim \theta_{13\text{MTYP}}$	1.15	1.15	(1.12, 1.18)	
lifespan mineralisation	$LSM \sim \theta_{14} \cdot \exp^{\eta_8}$	216 $week$	2.48	(205, 227)	
weight effect on I_{max}	$WT_{Imax} \sim \theta_{15}$	0.525	40.7	(0.106, 0.944)	
PMO effect on I_{max}	$PMO_{Imax} \sim \theta_{16}$	0.0683	130	(-0.105, 0.242)	
weight effect on K_0	$WT_{K0} \sim \theta_{17}$	-0.359	39.2	(-0.635, -0.0829)	
PMO effect on K_0	$PMO_{K0} \sim \theta_{18}$	-0.0546	94.0	(-0.155, 0.046)	
weight effect on $P1NP_0$	$WT_{P1NP0} \sim \theta_{19}$	-0.0413	157	(-0.168, 0.0856)	
PMO effect on $P1NP_0$	$PMO_{P1NP0} \sim \theta_{20}$	-0.113	27.7	(-0.174, -0.052)	
weight effect on CTX_0	$WT_{CTX0} \sim \theta_{21}$	0.00219	4420	(-0.188, 0.192)	
PMO effect on CTX_0	$PMO_{CTXP0} \sim \theta_{22}$	-0.153	29.8	(-0.242, -0.0638)	
weight effect on BMD_0	$WT_{BMD0} \sim \theta_{23}$	0.0444	36.6	(0.0126, 0.0762)	
PMO effect on BMD_0	$PMO_{BMD0} \sim \theta_{24}$	0.0169	50.6	(0.00011, 0.0337)	
interindividual variability of $P1NP_0$	$IIV_{P1NP0} \sim \Omega_{1,1}$	0.105	6.21	(0.0922, 0.118)	%CV = 33.3
interindividual $P1NP_0$-CTX_0 covariance	$cov_{P1NP0,CTX0} \sim \Omega_{2,1}$	0.136	6.93	(0.118, 0.154)	cor = 0.858
interindividual variability of CTX_0	$IIV_{CTX0} \sim \Omega_{2,2}$	0.239	6.30	(0.209, 0.269)	%CV = 52.0
interindividual $P1NP_0$-BMD_0 covariance	$cov_{P1NP0,BMD0} \sim \Omega_{3,1}$	-0.000600	237	(-0.00339, 0.00219)	cor = -0.0208
interindividual CTX_0-BMD_0 covariance	$cov_{CTX0,BMD0} \sim \Omega_{3,2}$	-0.00293	71.7	(-0.00704, 0.00118)	cor = -0.0671
interindividual variability of BMD_0	$IIV_{BMD0} \sim \Omega_{3,3}$	0.00794	5.13	(0.00714, 0.00874)	%CV = 8.93
interindividual variability of I_{max}	$IIV_{IMAX} \sim \Omega_{4,4}$	0.371	14.8	(0.263, 0.479)	%CV = 67.0
interindividual I_{max}-K_0 covariance	$cov_{IMAX,K0} \sim \Omega_{5,4}$	0.0875	19.4	(0.0543, 0.121)	cor = 0.581
interindividual variability of K_0	$IIV_{K0} \sim \Omega_{5,5}$	0.0613	21.5	(0.0354, 0.0872)	%CV = 25.1
interindividual variability of DP	$IIV_{DP} \sim \Omega_{6,6}$	0.0332	9.63	(0.0269, 0.0395)	%CV = 18.4
interindividual variability of FB	$IIV_{FB} \sim \Omega_{7,7}$	0.120	14.2	(0.0867, 0.153)	%CV = 35.7
interindividual variability of LSM	$IIV_{LSM} \sim \Omega_{8,8}$	0.0325	30.2	(0.0133, 0.0517)	%CV = 18.2
P1NP proportional error	$err_{prop} \sim \Sigma_{1,1}$	0.0328	0.722	(0.0323, 0.0333)	%CV = 18.1
CTX proportional error	$err_{prop} \sim \Sigma_{2,2}$	0.0847	1.22	(0.0827, 0.0867)	%CV = 29.1
LS additive error	$err_{add} \sim \Sigma_{3,3}$	0.000420	3.39	(0.000392, 0.000448)	SD = 0.0205

Source: Applicant's exposure-BMD analysis report, Table 4, Page 45

Figure 11 Re-Treatment Model BMD Visual Predictive Check for Hologic Machine: All Data. Results from 500 simulated trials are summarized as the median, 5t h, and 95t h percentiles (solid black lines) with associated 95% CIs. Observed values are plotted as red circles, with observed median, 5th, and 95th percentiles (dashed red lines)



Source: Applicant's exposure-BMD analysis report, Figure 139, Page 191

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Once a suitable population PK/PD model was developed, an extension to the base model was developed to describe the on-treatment, off-treatment and re-treatment PD efficacy (BMD) effects of romosozumab using only Study 60326 data that included the off-treatment (nominal months 24-36) and romosozumab re-treatment. Additional model development was driven by deviances between the model-predicted and observed markers for the off-treatment and re-treatment periods. The final model was updated by adding a rebound and rebound precursor pool with the precursor affecting the resorption cavity input. VPC results for the re-treatment model are presented in Figure 11. These VPC plots were stratified by the romosozumab dose regimen that was administered prior to the off-treatment period. Results were presented for the entire study period (0-48 months), the off-treatment phase only (24-36 months), and the re-treatment phase only (36-48 months).

To conclude, the two-year efficacy of romosozumab was described by exposure-BMD model. The model provides a reasonable representation of the effects of romosozumab on BMD.

Reviewer's comments:

The reviewer reviewed the exposure-BMD analysis conducted by Applicant and the results show that the data can be reasonably characterized by the PK/PD model.

The reviewer conducted an independent analysis for BMD percentage change from baseline (%CFB) and new vertebral facture separated by body weight and renal function. The information was summarized at 12 and 24 month from Phase 3 studies and listed in Table 12 and Table 13.

Table 12 Summary of BMD %CFB at Lumbar Spine across body weight and renal functions based on Phase 3 study (n=3157)

	Category/Quantile	No. of Sub, 12 mon; N	BMD %CFB, 12 mon Median (min-max)	No. of Sub, 24 mon; N	BMD %CFB, 24 mon Median (min-max)
Lumbar Spine					
Body Weight (kg)	22.3 -50.0	732	14.8 (-3.6-44.9)	657	18.9 (-6.1-56.2)
	50.0-57.0	821	13.7 (-6.1-34.7)	764	17.2 (-4.8-42.2)
	57.0-64.2	810	12.4 (-2.9-32.3)	747	16.0 (-2.1-41.1)
	64.2-126.8	843	10.8 (-3.9-37.6)	756	14.1 (-3.2-33.9)
eGFR ($mL/min/1.73m^2$)	Normal (≥90)	377	14.0 (-3.6-32.9)	335	17.2 (-3.5-44.5)
	Moderate (60-90)	2145	13.1 (-3.9-44.9)	1973	16.6 (-4.8-56.2)
	Moderate (30-60)	628	11.5 (-6.1-29.3)	568	14.6 (-6.1-36.0)
	Severe (15-30)	7	11.5 (6.2-20.5)	4	15.1 (12.0-20.4)
	ESRD (<15)	-	-	-	-

Source: Reviewer's independent analysis.

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Table 13 Summary of New Vertebral Fracture rate across body weight and renal functions based on Phase 3 study (n=3326)

	Category/Quantile	New Vertebral fracture, 12 mon; n/N (%)	New Vertebral fracture, 24 mon; n/N (%)
Body Weight (kg)	22.3 -50.0	5/785 (0.60)	10/785 (1.19)
	50.0-57.0	3/866 (0.37)	3/866 (0.37)
	57.0-64.2	3/839 (0.38)	3/839 (0.38)
	64.2-126.8	5/836 (0.56)	6/836 (0.68)
eGFR (mL/min/1.73m^2)	Normal (≥90)	2/402 (0.50)	4/402 (1.00)
	Moderate (60-90)	10/2248 (0.44)	12/2248 (0.53)
	Moderate (30-60)	4/667 (0.60)	6/667 (0.90)
	Severe (15-30)	0/9 (-)	0/9 (-)
	ESRD (<15)	-	-

Source: Reviewer's independent analysis.

The results indicate that the BMD is comparable across renal function categories. The similar conclusion can be drawn based on the primary efficacy endpoint, new vertebral fracture. There is no trend that the BMD %CFB and/or new vertebral fracture rate would be increased in more severe renal impairment patients. On the other side, BMD %CFB was decreased around 37% and 34% for 12 and 24 month in highest body weight group compared to that in lowest body weight group. However, this difference did not result in any clinically significant differences in incident rates of new vertebral fracture across body weight range. All these results demonstrate that no dose adjustment is necessary based on body weight and renal function from efficacy perspective.

From safety perspective, only one subject with hypocalcemia was identified in the Phase 3 study. In the dedicated renal impairment study (Study 20110227), hypocalcemia were reported to 5 subjects, 1 severe renal impairment subject and 4 ESRD subjects with hemodialysis. Based on Table 4 in section 4.5, the exposure in ESRD subjects with hemodialysis was comparable to that in normal renal function subject. Thus, the higher event rate of hypocalcemia is not driven by the exposure, which further support that no dose adjustment is necessary based on renal function.

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