Title Page

Protocol Title:		A Randomized, Multicenter, Open-label, Parallel Group Study in Postmenopausal Women With Osteoporosis to Evaluate the Noninferiority of Subject-administered Romosozumab via Autoinjector/Pen vs Healthcare Provider-administered Romosozumab via Prefilled Syringe
Short Protocol Title:		A Comparison of Subject-administered Romosozumab with Healthcare Provider-administered Romosozumab for Osteoporosis
Protocol Number:		20150120
Investigational Product:		Romosozumab
Trade Name:		Enter Trade Name
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Investigator's Agreement:

I have read the attached protocol entitled A Randomized, Multicenter, Open-label, Parallel Group Study in Postmenopausal Women With Osteoporosis to Evaluate the Noninferiority of Subject-administered Romosozumab via Autoinjector/Pen vs Healthcare Provider-administered Romosozumab via Prefilled Syringe, dated 10 August 2017, and agree to abide by all provisions set forth therein.

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I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: A Randomized, Multicenter, Open-label, Parallel Group Study in Postmenopausal Women With Osteoporosis to Evaluate the Noninferiority of Subject-administered Romosozumab via Autoinjector/Pen vs Healthcare Provider-administered Romosozumab via Prefilled Syringe

Short Protocol Title: A Comparison of Subject-administered Romosozumab with Healthcare Provider-administered Romosozumab for Osteoporosis

Study Phase: 3

Indication: osteoporosis in postmenopausal women

Rationale

Amgen is developing a 90 mg/mL concentration of romosozumab in a 1.17 mL deliverable volume (ie, 105 mg romosozumab) to be administered using prefilled syringe (PFS), as well as autoinjector/pen (AI/Pen). Both 90 mg/mL drug product presentations (PFS and AI/Pen) will use the same syringe with Crystal Zenith resin barrel as the primary container for the drug. The AI/Pen is a single-use, disposable, handheld, "spring-based", mechanical injection device that administers a fixed dose of romosozumab into the subcutaneous (SC) tissue. Unlike the PFS, the AI/Pen is being developed for home use. Designed with a hidden needle, the AI/Pen may alleviate anxiety in patients with needle phobia and potentially decrease the risk of accidental needle sticks.

The purpose of this study is to demonstrate that postmenopausal women with osteoporosis can successfully self-administer 210 mg romosozumab at 90 mg/mL once a month (QM) with 2 AI/Pens, as measured objectively by the percent change from baseline in bone mineral density (BMD) at 6 months. A comparison will be made with subjects receiving healthcare provider (HCP)-administered doses of 210 mg at 90 mg/mL with 2 PFS.

Data from this study is anticipated to support noninferiority of the 90 mg/mL concentration of romosozumab self-administered by the subject with AI/Pen compared to that administered by an HCP with PFS; it will additionally support global regulatory approval of the romosozumab AI/Pen.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the noninferiority of a 6-month treatment with 210 mg romosozumab at 90 mg/mL administered subcutaneously (SC) once a month (QM) in postmenopausal women with osteoporosis either by healthcare provider (HCP) administration with prefilled syringe (PFS) or by subject self-administration with autoinjector/pen (AI/Pen)	• Percent change from baseline in bone mineral density (BMD) at the lumbar spine, as assessed by dual-energy x-ray absorptiometry (DXA)
Secondary	
Efficacy • To evaluate the efficacy of a 6-month treatment with 210 mg romosozumab at 90 mg/mL SC QM in postmenopausal women with osteoporosis either by HCP administration with PFS or by subject self-administration with AI/Pen	• Percent changes from baseline in BMD at the total hip and femoral neck by DXA
Safety • To evaluate the safety and tolerability of a 6-month treatment with 210 mg romosozumab at 90 mg/mL SC QM by HCP administration with PFS or by subject self-administration with AI/Pen	• Incidence of treatment-emergent adverse events, serious adverse events, and adverse device effects • Incidence of subjects developing anti-romosozumab antibodies • Change from baseline in laboratory assessments and vital signs

Hypotheses

The primary hypothesis is that the mean percent change from baseline in lumbar spine DXA BMD at Month 6 in subjects (postmenopausal women with osteoporosis) self-administering 210 mg romosozumab QM with AI/Pen is not inferior to that in subjects receiving 210 mg romosozumab QM by HCP administration with PFS using a margin of -2 percentage points. It is hypothesized that the mean percent change from baseline in lumbar spine DXA BMD at Month 6 in subjects who self-administer 210 mg romosozumab QM with AI/Pen is the same as that in subjects who receive 210 mg romosozumab QM by HCP administration with PFS.

Overall Design

This is a phase 3 randomized, multicenter, open-label, noninferiority study of romosozumab in postmenopausal women with osteoporosis. The study is designed to evaluate the noninferiority of a 6-month 210 mg romosozumab SC QM treatment by subject self-administration with AI/Pen to HCP administration with PFS.

After signing the informed consent form (ICF), subjects will undergo the following periods:

- Screening period (35 days) to complete eligibility assessments
- Open-label treatment period (6 months)
- Follow-up period (3 months)

During the open-label treatment period, subjects will be randomized to receive romosozumab either via HCP administration with PFS or via self-administration with AI/Pen.

During the follow-up period, subjects will be followed for an additional 3 months to ensure appropriate follow-up for anti-romosozumab antibody formation and adverse events.

The primary analysis will be performed after all subjects have had the opportunity to complete the Month 6 visit. The final analysis will be performed after all subjects have had the opportunity to complete the Month 9 visit.

Number of Subjects

Approximately 260 subjects will be enrolled in the study and randomized 1:1 into the following treatment arms to receive 210 mg romosozumab at 90 mg/mL SC QM:

- HCP administration with PFS (approximately 130 subjects)
- Subject self-administration with AI/Pen (approximately 130 subjects)

Summary of Subject Eligibility Criteria

The study will enroll ambulatory, postmenopausal women aged $\geq$ 55 to $\leq$ 90 years with a BMD T-score of $\leq$ -2.50 at the lumbar spine, total hip, or femoral neck and at least 2 vertebrae in the L1-L4 region and at least 1 hip, evaluable by DXA. Eligible subjects should also have a history of fragility or at least 2 clinical risk factors for fracture. Subjects who have a history of osteonecrosis of the jaw, atypical femoral fracture, or metabolic or bone disease (except for osteoporosis) that may interfere with the

interpretation of the results will be excluded. Subjects taking exclusionary medication affecting bone metabolism are also excluded. Other disease-related exclusion criteria include vitamin D insufficiency, hyper- or hypothyroidism, or hyper- or hypoparathyroidism.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

During the open-label treatment period, subjects will receive 210 mg romosozumab SC QM either by HCP administration with 2 PFS or by self-administration with 2 AI/Pens.

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. Among the procedures performed, blood samples will be collected from subjects for serum chemistry, hematology, bone turnover markers, romosozumab levels, and anti-romosozumab antibodies. Bone mineral density assessments will be obtained with DXA at the lumbar spine and proximal femur.

Serious adverse events and concomitant therapies will be collected during the screening period. During the treatment period through end of study, adverse events, adverse device effects, disease-related events, and concomitant therapies will be collected.

Romosozumab will be administered to the subjects in the PFS arm as the last procedure of all applicable visits during the treatment period. For subjects in the AI/Pen arm, the self-administration of the first dose will be performed under the supervision of an HCP as the last procedure; for all subsequent doses, AI/Pens will be dispensed to subjects for self-administration without HCP supervision and outside of a professional healthcare facility.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

The primary analysis to assess the treatment difference between the PFS and AI/Pen arms in the percent change from baseline in lumbar spine DXA BMD at Month 6 will employ an analysis of covariance model. The model will have randomized treatment, baseline value of BMD, machine type, and interaction of baseline BMD value and machine type as prognostic variables. The lower bound of the one-sided 97.5% CI from mean treatment difference for the treatment arms will be compared with the noninferiority margin of -2% for assessing noninferiority. The analysis will include all

randomized subjects who have a baseline DXA BMD measurement and at least 1 post-baseline DXA BMD measurement. Subjects will be analyzed according to their randomized treatment assignment, regardless of treatment received.

To assess the robustness of the analysis for the primary endpoint, a sensitivity analysis will be performed using the per protocol analysis subset. [redacted]

[redacted]

The subject incidence of treatment-emergent adverse events and adverse device effects will be summarized by actual treatment received. Laboratory values over time will be summarized by actual treatment received. Laboratory shift tables will be provided and will compare baseline laboratory values with most extreme post-baseline values. Subject incidence of anti-romosozumab antibodies formation will be tabulated. These safety summaries will use the safety analysis subset, which will include all randomized subjects who receive at least 1 dose of investigational product.

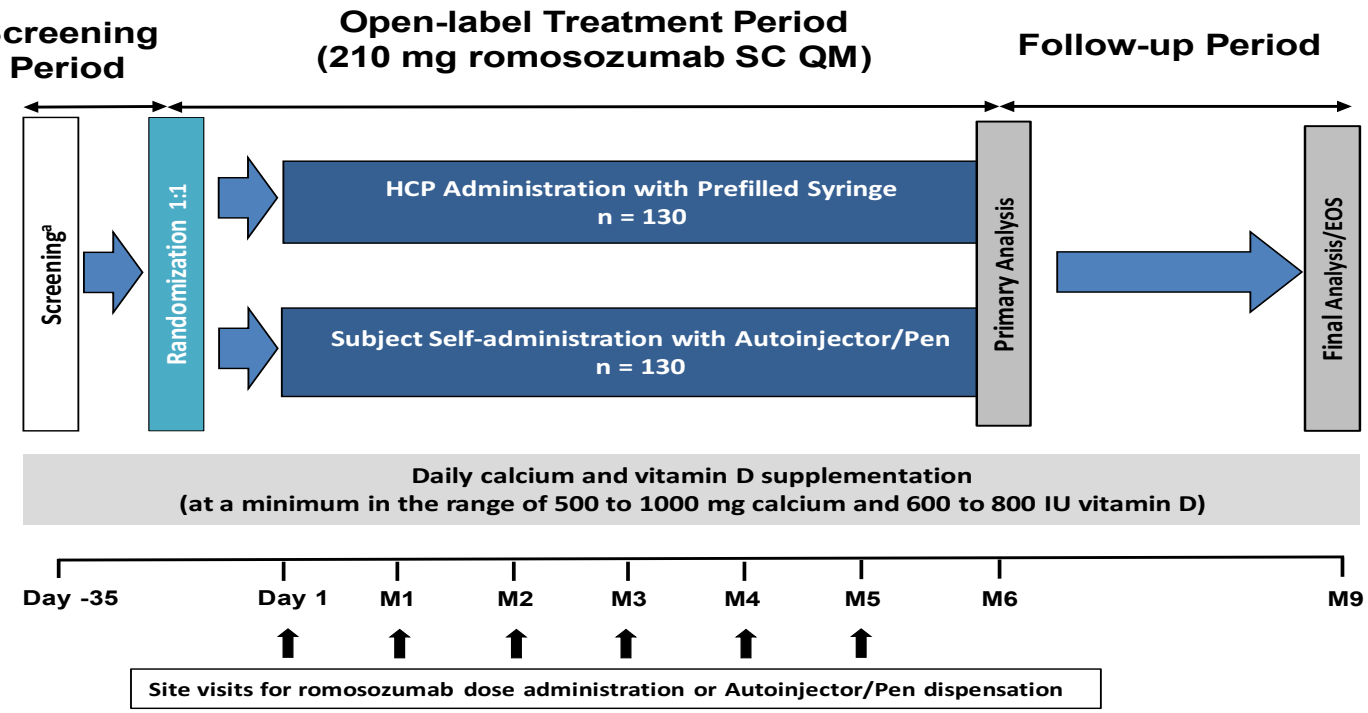
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



EOS = end of study; HCP = healthcare provider; M = month; QM = once a month; SC = subcutaneous
[a] Rescreening is permitted only once and only for subjects who fail the serum 25 (OH) vitamin D eligibility criterion.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

PROCEDURE	Screening	Treatment Period							Follow-up	Notes
	up to 35 days before Day 1	Day 1	Month 1 (±7 days)	Month 2 (±7 days)	Month 3 (±7 days)	Month 4 (±7 days)	Month 5 (±7 days)	Month 6/ ET (-7/+3 days)	Month 9/ EOS (-7/+3 days)	
GENERAL AND SAFETY ASSESSMENTS										
Informed consent	X									
Inclusion and exclusion criteria	X									
Demographics	X									
Medical and fracture history	X									
Medication history	X									
Instructions for daily calcium and vitamin D supplementation	X									
Physical examination	X				X			X		
Physical measurements	X				X			X		Height and weight
Vital signs	X				X			X		BP, heart rate, respiratory rate, and temperature
Substance use	X									Substances: alcohol, tobacco, caffeine, other
Adverse events		X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	
Adverse device effects		X	X	X	X	X	X	X	X	
Disease-related events		X	X	X	X	X	X	X	X	
Concomitant therapies review	X	X	X	X	X	X	X	X	X	

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Footnotes defined on last page of the table

Table 2-1. Schedule of Activities

PROCEDURE	Screening	Treatment Period							Follow-up	Notes
	up to 35 days before Day 1	Day 1	Month 1 (±7 days)	Month 2 (±7 days)	Month 3 (±7 days)	Month 4 (±7 days)	Month 5 (±7 days)	Month 6/ ET (-7/+3 days)	Month 9/ EOS (-7/+3 days)	
LABORATORY ASSESSMENTS (CENTRAL)										
Hematology	X	X			X			X		
Serum chemistry	X	X	X		X			X		
Serum 25 (OH) vitamin D	X									One rescreen allowed for vitamin D levels < 20 ng/mL
Hepatitis B and C testing	X									
Serum protein electrophoresis	X									
Anti-romosozumab antibody[a]		X	X		X			X	X	Collect before romosozumab administration
STUDY-SPECIFIC ASSESSMENTS										
DXA scan: lumbar spine	X							X		Perform in duplicate
DXA scan: proximal femur	X							X		
BIOMARKER ASSESSMENTS										
Bone Turnover Markers (sCTX/P1NP)		X	X					X		Obtain from subjects in fasting stage[b] and before noon
PHARMACOKINETIC ASSESSMENTS										
Romosozumab levels		X	X		X			X		
STUDY TREATMENT										
Romosozumab administration[c]										
PFS arm[d]		X	X	X	X	X	X			
AI/Pen arm[e]		X	X	X	X	X	X			
Inquiry on treatment compliance for previous dose				X	X	X	X	X		Collect only from AI/Pen arm

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Footnotes defined on next page of the table

AI/Pen = autoinjector/pen; BP = blood pressure; DXA = dual-energy x-ray absorptiometry; EOS = end of study; ET = early termination; HCP = healthcare provider; P1NP = procollagen type 1 N-telopeptide; PFS = prefilled syringe; sCTX = serum type-1 collagen C-telopeptide

[a] Subjects who test positive for neutralizing antibodies to romosozumab at the EOS or ET visit will be asked to return for anti-romosozumab antibody testing for up to 1 year after the last investigational product administration. A longer testing period may be requested in the event of safety concerns.
[b] Fasting stage is defined as overnight or, if not possible, a minimum of 8 hours.
[c] First dose should be given on day of randomization (or within 72 hours).
[d] To be administered by site staff as last procedure of each applicable visit.
[e] As last procedure of Day 1 visit, study staff will supervise self-administration of first dose. At each dosing visit thereafter, the study staff will dispense a single dose (1 box of 2 AI/Pens) to each subject for self-administration without HCP supervision and outside of a professional healthcare facility.

3. Introduction

3.1 Study Rationale

Amgen is developing a 90 mg/mL concentration of romosozumab in a 1.17 mL deliverable volume (ie, 105 mg romosozumab) to be administered using prefilled syringe (PFS), as well as autoinjector/pen (AI/Pen). Both 90 mg/mL drug product presentations (PFS and AI/Pen) will use the same syringe with Crystal Zenith resin barrel as the primary container for the drug. The AI/Pen is a single-use, disposable, handheld, "spring-based", mechanical injection device that administers a fixed dose of romosozumab into the subcutaneous (SC) tissue. Unlike the PFS, the AI/Pen is being developed for home use. Designed with a hidden needle, the AI/Pen may alleviate anxiety in patients with needle phobia and potentially decrease the risk of accidental needle sticks.

The purpose of this study is to demonstrate that postmenopausal females with osteoporosis can successfully self-administer 210 mg romosozumab at 90 mg/mL once a month (QM) with 2 AI/Pens, as measured objectively by the percent change from baseline in bone mineral density (BMD) at 6 months. A comparison will be made with subjects receiving healthcare provider (HCP)-administered doses of 210 mg at 90 mg/mL with 2 PFS.

Data from this study is anticipated to support noninferiority of the 90 mg/mL concentration of romosozumab self-administered by the subject with AI/Pen compared to that administered by an HCP with PFS; it will additionally support global regulatory approval of the romosozumab AI/Pen.

3.2 Background

3.2.1 Disease

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). Osteoporosis is a common disorder; according to the World Health Organization's current definition of osteoporosis (BMD T-score $\geq$ 2.5 standard deviations below the mean for normal young adults) (World Health Organization, 1994), the worldwide prevalence of osteoporosis has been estimated as 200 million people (Reginster and Burlet, 2006), including more than 75 million people in the United States (US), Europe, and Japan (World Health Organization, 2007). The morbidity and mortality associated with

osteoporotic-related fractures is significant in terms of disability to an individual and cost to the global economy (Cree et al, 2003; Kanis et al, 2001a; Kanis et al, 2001b).

Approved treatments for postmenopausal women with osteoporosis include inhibitors of bone resorption, such as selective estrogen receptor modulators (SERMs, eg, raloxifene), bisphosphonates (eg, alendronate [ALN], risedronate, ibandronate, and zoledronate), calcitonin, denosumab, or agents that stimulate bone formation like teriparatide (the 1-34 fragment of intact parathyroid hormone [PTH]) (Greenblatt, 2005). Antiresorptive therapies prevent osteoclasts from resorbing bone, slowing the progression of bone breakdown, increasing BMD, and lowering the risk of vertebral fractures (relative risk reduction [RRR]: 40% to 70%) and, to a lesser extent, nonvertebral fractures (RRR: 20% to 25%) (Cummings et al, 2009; Black et al, 2007; Chestnut et al, 2004; McClung et al, 2001; Chestnut et al, 2000; Ettinger et al, 1999; Harris et al, 1999; Cummings et al, 1998; Black et al, 1996). Osteoporosis is a chronic disease; and despite long-term administration of bisphosphonates, the most commonly prescribed class of antiresorptives, postmenopausal women with severe osteoporosis remain at increased risk of fracture and are in need of therapies with strong efficacy and the potential to reverse their disease condition by increasing bone formation and improving bone structure.

In contrast, bone-forming agents can promote larger improvements in bone mass and bone strength than antiresorptives and restore bone architecture, thereby addressing the need for improved protection against fractures, in particular at nonvertebral sites (Canalis, 2010; Papapoulos and Makras, 2008). Analogs of PTH (PTH 1-34 [teriparatide] and PTH 1-84) increase bone remodeling by stimulating both bone formation and bone resorption with a net gain in bone mass. As a result, there is a marked improvement in BMD, as well as indices of bone microstructure that are associated with improved mechanical strength (Borggrefe et al, 2010). Teriparatide shows a RRR of nonvertebral fractures of approximately 35% to 50% and lowers the risk of one or more new vertebral fractures by 65% (Neer et al, 2001).

A novel bone-forming agent for the treatment of osteoporosis in postmenopausal women, with a different mechanism of action and the potential to reverse the features of osteoporosis by increasing bone volume and BMD and by improving bone architecture to increase bone strength and reduce the risk for fracture, would be a welcome new therapeutic option particularly for subjects with significantly compromised bone strength at high risk of fracture.

3.2.2 Amgen Investigational Product Background: Romosozumab

Sclerostin, the protein product of *SOST*, produced by the osteocyte, is an inhibitor of osteoblast-mediated bone formation (Poole et al, 2005; Van Bezooijen et al, 2004; Winkler et al, 2003; Balemans et al, 2001; Brunkow et al, 2001). Humans with inherited sclerostin deficiencies have high bone mass and BMD throughout the skeleton and are resistant to fractures (Hamersma et al, 2003; Vanhoenacker et al, 2003). Administration of a sclerostin antibody, resulting in the blocking of the inhibitory effect of sclerostin on bone formation, has been shown to increase bone formation, BMD, and bone strength in multiple animal models (normal and osteoporotic rats, monkeys) (Ominsky et al, 2010a; Ominsky et al, 2010b; Li et al, 2009; Li et al, 2007a; Li et al, 2007b).

Romosozumab is a humanized monoclonal antibody that is designed to bind and inhibit sclerostin, thereby promoting osteoblast differentiation and activity. By inhibiting sclerostin, 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.

Proof of biological activity for romosozumab has been established in a first-in-human, ascending-single-dose study in healthy men and postmenopausal women, an ascending-multiple-dose study in healthy men and postmenopausal women with low bone mass, and a phase 2 dose-ranging study in postmenopausal women with low bone mass. In all studies, treatment with romosozumab was generally well tolerated and resulted in a transient increase of the bone formation markers Procollagen Type 1 N-telopeptide (P1NP), Osteocalcin, and Bone-Specific Alkaline Phosphatase, and a decrease in the bone resorption marker serum type‑1 collagen C‑telopeptide (sCTX). Increases in BMD at the lumbar spine, total hip, and femoral neck have also been demonstrated by dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT).

Clinical studies that have been completed include the following:

- A phase 1b ALN-to-romosozumab transition study in postmenopausal women with low bone mass who had been receiving ALN or were treatment naïve

- A phase 1b multiple-dose study using peripheral QCT to evaluate the effect of romosozumab on parameters of bone quality of the forearm in postmenopausal women with low bone mass
- A phase 1 single-dose study in healthy postmenopausal Japanese women
- A phase 1 bioequivalence study to evaluate delivering 90 mg/mL romosozumab SC by PFS or AI/Pen in healthy subjects
- A phase 2a multiple-dose fracture-healing study in subjects with tibial diaphyseal fractures
- A phase 2 multiple-dose fracture-healing study in subjects with proximal femur fractures
- A phase 3 study in postmenopausal women with osteoporosis randomized to either 12 months of romosozumab or placebo followed by denosumab for 24 months in each group
- A phase 3 study in postmenopausal women with osteoporosis to evaluate the noninferiority of romosozumab at a 90 mg/mL concentration compared with a 70 mg/mL concentration

Ongoing clinical studies include the following:

- A phase 3 fracture study in postmenopausal women with osteoporosis randomized to romosozumab for 12 months followed by ALN treatment compared to ALN treatment alone
- A phase 3 study in postmenopausal Korean women with osteoporosis randomized to either romosozumab or placebo for 6 months

A detailed description of the chemistry, pharmacology, efficacy, and safety of romosozumab is provided in the Investigator's Brochure.

For additional information about the romosozumab nonclinical experience and clinical experience, refer to the Investigator's Brochure.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the noninferiority of a 6-month treatment with 210 mg romosozumab at 90 mg/mL administered subcutaneously (SC) once a month (QM) in postmenopausal women with osteoporosis either by healthcare provider (HCP) administration with prefilled syringe (PFS) or by subject self-administration with autoinjector/pen (AI/Pen)	• Percent change from baseline in bone mineral density (BMD) at the lumbar spine, as assessed by dual-energy x-ray absorptiometry (DXA)
Secondary	
Efficacy • To evaluate the efficacy of a 6-month treatment with 210 mg romosozumab at 90 mg/mL SC QM in postmenopausal women with osteoporosis either by HCP administration with PFS or by subject self-administration with AI/Pen	• Percent changes from baseline in BMD at the total hip and femoral neck by DXA
Safety • To evaluate the safety and tolerability of a 6-month treatment with 210 mg romosozumab at 90 mg/mL SC QM by HCP administration with PFS or by subject self-administration with AI/Pen	• Incidence of treatment-emergent adverse events, serious adverse events, and adverse device effects • Incidence of subjects developing anti-romosozumab antibodies • Change from baseline in laboratory assessments and vital signs

Exploratory	
[redacted]	

4.2 Hypotheses

The primary hypothesis is that the mean percent change from baseline in lumbar spine DXA BMD at Month 6 in subjects (postmenopausal women with osteoporosis) self-administering 210 mg romosozumab QM with AI/Pen is not inferior to that in subjects receiving 210 mg romosozumab QM by HCP administration with PFS using a margin of -2 percentage points. It is hypothesized that the mean percent change from baseline in lumbar spine DXA BMD at Month 6 in subjects who self-administer 210 mg romosozumab QM with AI/Pen is the same as that in subjects who receive 210 mg romosozumab QM by HCP administration with PFS.

5. Study Design

5.1 Overall Design

This is a phase 3 randomized, multicenter, open-label, noninferiority study of romosozumab in postmenopausal women with osteoporosis. The study is designed to evaluate the noninferiority of a 6-month 210 mg romosozumab SC QM treatment by subject self-administration with AI/Pen to HCP administration with PFS.

After signing the informed consent form (ICF), subjects will undergo the following periods:

- Screening period (35 days) to complete eligibility assessments
- Open-label treatment period (6 months)
- Follow-up period (3 months)

During the open-label treatment period, subjects will be randomized to receive romosozumab either via HCP administration with PFS or via self-administration with AI/Pen. Subjects in the AI/Pen arm will self-administer the first dose on Day 1 under HCP supervision; at each dosing visit thereafter, a single dose (1 box of 2 AI/Pens) will

be dispensed to each subject for self-administration without HCP supervision and outside of a professional healthcare facility.

The following events will be submitted to independent committees for adjudication:

- potential osteonecrosis of the jaw (ONJ) events
- potential cases of atypical femoral fracture (AFF)
- all deaths and serious adverse events that are deemed by the investigator to be of potential cardiovascular origin or etiology and serious adverse events with terms mapping to a pre-defined preferred term list potentially indicative of cardiovascular etiology

During the follow-up period, subjects will be followed for an additional 3 months to ensure appropriate follow-up for anti-romosozumab antibody formation (as detailed in Section 9.2.6) and adverse events.

The primary analysis will be performed after all subjects have had the opportunity to complete the Month 6 visit. The final analysis will be performed after all subjects have had the opportunity to complete the Month 9 visit.

From screening to end of study (EOS), subjects will receive daily calcium and vitamin D supplementation that at a minimum should be in the range of 500 to 1000 mg elemental calcium and 600 to 800 IU vitamin D.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 260 subjects will be enrolled in the study and randomized 1:1 into the following treatment arms to receive 210 mg romosozumab at 90 mg/mL SC QM:

- HCP administration with PFS (approximately 130 subjects)
- Subject self-administration with AI/Pen (approximately 130 subjects)

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

Approximately 30 investigative sites in the United States and Europe will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for the Month 6 visit.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination [ET] of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The EOS date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

5.3.2 Study Duration for Subjects

After signing the informed consent, subjects must be randomized within 35 days (or within 70 days for subjects who are rescreened).

After randomization, individual subjects will participate in the study for up to 9 months, including a 6-month treatment period and a 3-month follow-up period.

For individual subjects, the Month 9 visit is the EOS visit. Subjects who test positive for neutralizing antibodies to romosozumab at the EOS visit or the ET visit will be asked to return for anti-romosozumab antibody testing for up to 1 year after the last investigational product administration. A longer testing period may be requested in the event of safety concerns.

5.4 Justification for Investigational Product Dose

The proposed treatment regimen of 210 mg romosozumab QM for 6 months is expected to achieve substantial increases in BMD in subjects who are treatment naïve. This was demonstrated by the observation of substantial increases in BMD at the lumbar spine,

total hip, and femoral neck during 6 months of romosozumab administration in the phase 3 placebo-controlled fracture study, in which BMD increased from baseline of 9.7 % with 95% CI (7.9%, 10.8%) at the lumbar spine and 4.7 % with 95% CI (3.2%, 5.5%) at the total hip (Cosman et al, 2016).

This 210-mg romosozumab QM dosing regimen was also used in another phase 3 study, in which postmenopausal women with osteoporosis were randomized to either romosozumab for 12 months followed by ALN treatment or to ALN treatment alone.

6. Study Population

The population for the study is postmenopausal women with osteoporosis at high risk for fracture who are not currently taking any exclusionary medication affecting bone metabolism.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent/assent prior to initiation of any study-specific activities/procedures, or subject's legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the Investigator, may compromise the ability of the subject to give written informed consent.

102 Postmenopausal female (postmenopausal status is defined as no vaginal bleeding or spotting for 12 consecutive months prior to screening)

103 ≥ 55 to ≤ 90 years of age at the time of informed consent

104 Ambulatory

105 BMD T-score ≤ -2.50 at the lumbar spine, total hip, or femoral neck, as assessed by the central imaging vendor at the time of screening, based on DXA scans

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

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

108 Subject has history of fragility (ie, osteoporosis-related fracture) or subject meets at least 2 of the following clinical risk factors for fracture

- ≥ 70 years of age at the time of informed consent
- BMD T-score ≤ -3.00 at the lumbar spine, total hip, or femoral neck, as assessed by the central imaging vendor at the time of screening, based on DXA scans
- current smoker
- consumption of ≥ 3 glasses of alcohol a day
- parental history of fragility (ie, osteoporosis-related) fracture
- body weight ≤ 125 pounds/56 kilogram

109 Ability to follow and understand instructions and the ability to self-inject, per investigator judgement

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

Disease-Related

201 History of ONJ and/or AFF

202 History of metabolic or bone disease (except osteoporosis) that may interfere with the interpretation of the results, such as sclerosteosis, Paget's disease, rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, Cushing's disease, hyperprolactinemia, and malabsorption syndrome

203 Subject with reported history of hearing loss associated with cranial nerve VIII compression due to excessive bone growth (eg, as seen in conditions such as Paget's disease, sclerosteosis and osteopetrosis)

204 Vitamin D insufficiency [defined as serum 25 (OH) vitamin D levels < 20 ng/mL], as determined by the central laboratory. Vitamin D repletion will be permitted and subjects may be rescreened.

205 Current hyperthyroidism (unless well controlled on stable antithyroid therapy) by subject report or by chart review, per principal investigator evaluation

206 Current clinical hypothyroidism (unless well controlled on stable thyroid replacement therapy) by subject report or by chart review, per principal investigator evaluation

207 Current, uncontrolled hyper- or hypoparathyroidism, defined as PTH outside the normal range, per subject medical history. Uncontrolled hyperparathyroidism is defined as: parathyroid hormone (PTH) outside the normal range in subjects with concurrent hypercalcemia; or PTH values > 20% above the upper limit of normal (ULN) in normocalcemic subjects.

208 Current hyper- or hypocalcemia, defined as albumin-adjusted serum calcium outside the normal range, as assessed by the central laboratory. Serum calcium levels may be retested once in case of an elevated serum calcium level within 1.1x the ULN as assessed by the central laboratory

Other Medical Conditions

209 Malignancy, except non-melanoma skin cancers or cervical or breast ductal carcinoma in situ within the last 5 years

210 Possible diagnosis of multiple myeloma or related lymphoproliferative disorder, as assessed by serum protein electrophoresis performed by the central laboratory and interpreted by the investigator

211 Evidence of acute or chronic hepatitis B or hepatitis C virus. Hepatitis status will be evaluated by testing for hepatitis B surface antigen (HepBsAg), total hepatitis B core antibody (HepBcAb) and hepatitis C antibody by the central laboratory at initial screening. Polymerase chain reaction (PCR) should be performed to confirm active disease only if total HepBcAb is positive and HepBsAg is negative or if C antibody is positive.

212 Positive for Human Immunodeficiency Virus, per subject report or chart review

Prior/Concomitant Therapy

213 Strontium ranelate or fluoride (for osteoporosis): more than 1 month of cumulative use within 5 years prior to randomization

214 Intravenous (IV) bisphosphonates

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

215 Dose received within the past 18 months prior to randomization: denosumab or any cathepsin K inhibitor, such as odanacatib (MK-0822)

216 Teriparatide or any PTH analogs

- any dose received within 3 months prior to randomization
- more than 1 month of cumulative use between 3 and 12 months prior to randomization

217 Oral bisphosphonates

- 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

218 Dose received within the past 6 months prior to randomization: systemic oral or transdermal estrogen or SERMs (up to 1 month of cumulative use is allowed)

219 More than 1 month of cumulative use of activated vitamin D3 or vitamin K2 within 6 months prior to randomization

220 Dose received within the past 6 months prior to randomization: hormonal ablation therapy (up to 1 month of cumulative use is allowed)

221 Dose received within the past 3 months prior to randomization: tibolone, calcitonin, or cinacalcet

222 Dose received within the past 3 months prior to randomization: systemic glucocorticosteroids (≥ 5 mg prednisone equivalent per day for more than 14 days

223 Subject has previously received a sclerostin antibody product within the past 12 months prior to randomization

Prior/Concurrent Clinical Study Experience

224 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies).

225 Subject has previously entered this study

226 Other investigational procedures while participating in this study are excluded

Other Exclusions

227 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 3 months after the last dose of romosozumab.

228 Subject has known sensitivity to any of the products or components to be administered during dosing.

229 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

230 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (which begins after the ICF is signed) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the IVRS/IWRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who fail to meet the vitamin D entry criteria, ie, subjects with a serum 25 (OH) vitamin D level < 20 ng/mL may rescreen 1 time. Subjects who fail any other eligibility criteria are not permitted to be rescreened.

During the rescreening period, the subject should receive vitamin D repletion following a protocol defined by the principal investigator. A serum 25 (OH) vitamin D level ≥ 20 ng/mL must be confirmed by the central laboratory before the subject will be randomized. While it is possible to repeat the serum 25 (OH) vitamin D test during the

rescreening period, vitamin D eligibility must be confirmed by the central laboratory and the subject must be randomized within the 35-day rescreening window.

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to, or used by a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

Study Treatment Name	**Amgen Investigational Product:** Romosozumab[a] in PFS	**Amgen Investigational Product:** Romosozumab[a] in AI/Pen
Dosage Formulation	Romosozumab will be presented in a box containing 2 PFS. Each PFS will contain 1.17 mL of 90 mg/mL romosozumab.	Romosozumab will be presented in a box containing 2 AI/Pens. Each AI/Pen will contain 1.17 mL of 90 mg/mL romosozumab.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	210 mg QM (2 PFS)	210 mg QM (2 AI/Pens)
Route of Administration	SC injection	SC injection
Accountability	The amount administered, date and time of administration, and box number of romosozumab are to be recorded on each subject's CRF.	The amount dispensed, amount returned, amount self-administered (ie, full, partial, none, unknown), date dispensed, date returned, the date of self-administration, and box number of romosozumab are to be recorded on each subject's CRF.

Study Treatment Name	**Amgen Investigational Product:** Romosozumab[a] in PFS	**Amgen Investigational Product:** Romosozumab[a] in AI/Pen
Dosing Instructions	Injections of romosozumab will be administered by an HCP into different sites on the subject's anterior abdominal wall, thigh, or upper arm. The injection should not be administered in the same arm from which blood is drawn. The SC injection must be administered as the last procedure after all other study visit procedures have been completed. A physician must be available during administration of romosozumab. It is recommended that all subjects be closely observed for approximately 30 minutes after dosing. The first dose should be administered on the day of randomization. If this is not possible, it must be administered within 72 hours of randomization. All efforts should be made to administer romosozumab within the defined study visit windows (refer to Table 2-1). In case of an out-of-window visit, romosozumab can be administered ± 2 weeks of the target visit date, ie, calculated from the Day 1 visit, as described in Section 9.1.2. If romosozumab cannot be administered ± 2 weeks of the target visit date, the dose is to be considered missed.	The first dose will be self-administered into the subject's anterior abdominal wall or thigh under the supervision of an HCP. The SC injection must be administered as the last procedure after all other study visit procedures have been completed. For all subsequent injections, the subjects will self-administer the dose into different sites on their anterior abdominal wall or thigh without HCP supervision and outside of a professional healthcare facility. The first dose should be self-administered on the day of randomization. If this is not possible, it must be self-administered within 72 hours of randomization. All efforts should be made to dispense and self-administer the romosozumab AI/Pens within the defined study visit windows (refer to Table 2-1). In case of an out-of-window visit, romosozumab can be dispensed and self-administered ± 2 weeks of the target visit date, ie, calculated from the Day 1 visit, as described in Section 9.1.2. If the romosozumab AI/Pens cannot be dispensed and self-administered ± 2 weeks of the target visit date, the dose is to be considered missed.
Device	PFS	AI/Pen

AI/Pen = autoinjector/pen; CRF = case report form; HCP = healthcare provider; PFS = prefilled syringe; QM = once a month; SC = subcutaneous
[a] Romosozumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Medical Devices

The investigational medical device(s) provided by Amgen for use in this study are the PFS and AI/Pen (Table 7-1).

The romosozumab AI/Pen is a single-use disposable, handheld, “spring-based”, mechanical injection device for the SC injection of a fixed dose of 105 mg in a 1.17 mL deliverable volume. A full dose of 210 mg comprises 2 AI/Pens.

The romosozumab PFS is a single-use, disposable, handheld manual injection device for the SC injection of a fixed dose of 105 mg in a 1.17 mL deliverable volume. A full dose of 210 mg comprises 2 PFS.

Additional details are provided in the IPIM.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices, that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

7.1.3 Other Protocol-required Therapies

Other protocol-required therapies (calcium and vitamin D supplements) that are commercially available are not provided but will be reimbursed by Amgen. The investigator will be responsible for obtaining supplies of these protocol-required therapies.

From screening to EOS, subjects will receive daily calcium and vitamin D supplementation that, at a minimum, should be in the range of 500 to 1000 mg elemental calcium and 600 to 800 IU vitamin D.

Where available, vitamin D3 preparations should be used; if vitamin D3 is not available, use of vitamin D2 preparations is acceptable.

If a subject develops hypercalcemia over the course of the study, the principal investigator may use his/her medical judgment and reduce the calcium and/or vitamin D supplementation to maintain serum calcium concentration within the normal range.

If a subject develops hypocalcemia over the course of the study, appropriate additional supplementation should be instituted as deemed acceptable by local guidelines, to maintain serum calcium concentration within the normal range.

If a subject is unable to tolerate the daily calcium or vitamin D supplementation, the formulation may be changed or the dose lowered. The intolerance as well as the resolution (ie, change in formulation or dosage) should be documented in the subject chart.

Additional details regarding these protocol-required therapies are provided in the IPIM.

7.1.4 Other Treatment Procedures

This is not applicable to this study.

7.1.5 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) include romosozumab, PFS, and AI/Pen.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or drug-device combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.6 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Medications listed below will be proscribed during the study, as these medications are known or suspected to affect bone metabolism:

- strontium (including strontium ranelate and over the counter strontium preparations)
- fluoride (for treatment of osteoporosis)
- Vitamin K and vitamin K analogs (for treatment of osteoporosis)
- Activated vitamin D (1,25-di(OH) vitamin D, or 1 (OH) vitamin D)
- IV bisphosphonates
- oral bisphosphonates (cumulative dosing regimens of $\leq$ 1 month are acceptable)
- denosumab
- teriparatide or any PTH analogs
- systemic oral or transdermal estrogen (cumulative dosing regimens of $\leq$ 1 month are acceptable, vaginal preparations and estrogen creams will be allowed at any time)

- SERMs (cumulative dosing regimens of ≤ 1 month are acceptable)
- calcitonin (cumulative dosing regimens of ≤ 1 month are acceptable)
- tibolone (cumulative dosing regimens of ≤ 1 month are acceptable)
- cinacalcet
- prolonged (ie, > 3 months) oral glucocorticoid therapy at a prednisone equivalent dose of ≥ 5.0 mg/day (tapering glucocorticoid courses of ≤ 1 month duration are permitted regardless of dose; inhaled or topical glucocorticoids are permitted)
- hormonal ablation therapy

If a subject discontinues the investigational product and begins an approved alternative osteoporosis therapy, every effort should be made to have the subject continue participation in the study and complete all scheduled assessments (ie, withdrawal of partial consent, see Section 8).

7.2 Method of Treatment Assignment

Subjects will be randomized in a 1:1 allocation ratio to either the PFS or AI/Pen arm in an open-label manner on a randomization schedule prepared by the Amgen Global Randomization and Blinding Group before the start of the study.

The randomization will be performed by IVRS/IWRS, and the randomization number will be provided through the IVRS/IWRS.

A subject may only be randomized once, and each randomization number may only be assigned once. A subject will be considered enrolled once a randomization number is assigned by the IVRS/IWRS.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

7.4.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

7.4.1.1 Amgen Investigational Product: Romosozumab

No dosing adjustments for romosozumab will be permitted.

For subjects in the PFS arm, all efforts should be made to administer romosozumab within the defined study visit windows (refer to Table 2-1). In case of an out-of-window visit, romosozumab can be administered ± 2 weeks of the target visit date, ie, calculated

from the Day 1 visit. If romosozumab cannot be administered ± 2 weeks of the target visit date, the dose is considered missed.

For subjects in the AI/Pen arm, all efforts should be made to dispense and self-administer the romosozumab AI/Pens within the defined study visit windows (refer to Table 2-1). In case of an out-of-window visit, AI/Pens can be dispensed and self-administered ± 2 weeks of the target visit date, ie, calculated from the Day 1 visit. If AI/Pens cannot be dispensed and self-administered ± 2 weeks of the target visit date, the dose is to be considered missed.

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product, other protocol-required therapies, or devices during the study are provided in the IPIM for site staff and the Instructions for Use (IFU) document for subjects.

7.6 Treatment Compliance

Subjects in the AI/Pen arm will be asked to bring in all used and unused packages dispensed for their unsupervised self-administration at their next site visit (ie, Month 2, 3, 4, 5, and 6 visits) in a plastic box provided by Amgen. In the case that the subject forgets, he or she should be advised to bring them in at the following site visit. The investigational site staff will count the number of used and unused AI/Pens. The amount dispensed, amount returned, the amount self-administered (ie, full, partial, none, unknown), date dispensed, date returned, the date of self-administration, and box number of romosozumab are to be recorded on each subject's CRF.

7.7 Treatment of Overdose

Overdose with this product has not been reported. Neither the effects of overdose of romosozumab nor an antidote to overdose are known. The maximum amount of romosozumab that can be safely administered in a single dose has not been determined, and there is currently insufficient information to draw any conclusions about the safety of doses higher than those studied in clinical trials. The highest single dose of

romosozumab tested in clinical trials is 10 mg/kg SC. Subjects who have received higher than protocol-defined doses should be carefully monitored for adverse events.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies affecting bone metabolism that were being taken/used from 5 years prior to screening through randomization will be collected. The therapy name, indication, dose, unit, frequency, start date, and stop date will be recorded.

For the following prior therapies, collect whether the therapy was being taken before screening through randomization: therapies for cardiovascular conditions. The therapy name, indication, dose, unit, frequency, start date, and stop date will be recorded.

A detailed history will also be collected of other prior therapies taken from 30 days prior to study enrollment through randomization. The therapy name, indication, start date, and stop date will be recorded.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.6.

Concomitant therapies are to be collected from randomization through EOS. For concomitant therapies, collect therapy name, indication, dose, unit, frequency, start date, and stop date.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the

investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, disease-related events, and device-related events, as applicable and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Requirement for alternative therapy
- Pregnancy

8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the

subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in, or Invasive Procedures

This is not applicable to this study.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will register the subject in the IVRS/IWRS and screen the subject in order to assess eligibility for participation. Screening procedures may be performed on multiple days but must be completed within a 35-day screening window.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Rescreening is permitted only once, and only for subjects who fail the serum 25 (OH) vitamin D eligibility criterion, ie, subjects with a serum 25 (OH) vitamin D level < 20 ng/mL. Subjects who fail any other eligibility criteria are not permitted to be rescreened.

Rescreen subjects must first be registered as screen failures in IVRS/IWRS and subsequently registered as rescreens on the same day. Subjects not entered into the IVRS/IWRS as a rescreen will not be eligible for randomization. Once the subject is registered as rescreened, a new 35-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening.

9.1.1.1 Screening Bone Mineral Density Assessment

To determine eligibility based on BMD T-score, lumbar spine and proximal femur DXA scans will be analyzed by the central imaging vendor.

For screening purposes, DXA scans of the lumbar spine and proximal femur taken up to 35 days prior to the beginning of the screening period may be used if all of the following criteria are met:

- Images were obtained as part of the routine standard of care, or following appropriate informed consent procedures
- Images were obtained by a trained technician, using the parameters specified by the central imaging vendor for this study (refer to the appropriate imaging manuals provided by the central imaging vendor)
- DXA images were obtained using the same DXA scanner that will be used for this study

To be eligible for the study, subjects must have at least 2 lumbar vertebrae and at least 1 proximal femur, evaluable by DXA (as determined by the principal investigator or designee).

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1) during the treatment period from Day 1 through Month 6.

Day 1 is defined as the date on which the first dose of romosozumab is administered. All on-study visits (ie, visits after Day 1) are calculated from the Day 1 visit. If a subject's visit is delayed, their subsequent visit date is not to be shifted and is always to be calculated from the Day 1 visit. Month is defined as a calendar month.

For subjects in the PFS arm, romosozumab is to be administered as the last procedure during each dosing visit. Subjects in the AI/Pen arm will self-administer their first dose under HCP supervision as the last procedure of their Day 1 visit; at each dosing visit thereafter, a single dose will be dispensed to each subject for self-administration without HCP supervision and outside of a professional healthcare facility.

Subjects who discontinue the study before the Month 6 visit should undergo all the procedures for the Month 6 visit, as indicated in the Schedule of Activities (Table 2-1).

9.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the end of the last dosing interval of investigational product.

9.1.4 End of Study

The EOS visit is the Month 9 visit. Subjects will return to the site for the EOS visit for the procedures specified in the Schedule of Activities (Table 2-1).

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

9.2.1.3 Medical History

The Investigator or designee will collect a complete medical history that started prior to screening through administration of the first dose of romosozumab. Medical history will include information on the subject's prior or current medical conditions. Record all findings on the medical history CRF.

In addition to the medical history above, osteoporosis history must date back to the original diagnosis. Fracture history will be collected from the age of 45 through administration of the first dose of romosozumab. Fracture history will include date of fracture, anatomical site(s) of fracture(s), and degree of trauma involved. Record all findings on the fracture history CRF.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

9.2.1.5 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

9.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of alcohol, tobacco, caffeine, or other.

9.2.2 Efficacy Assessments

9.2.2.1 Dual-energy X-ray Absorptiometry

Bone density measurements will be performed by DXA. Only Lunar or Hologic bone densitometers will be allowed for the study. The same DXA machine must be used for all study procedures for a particular subject for the duration of the study. All DXA scans will be submitted to and analyzed by the central imaging vendor. A separate procedure manual provided by the central imaging vendor will give specific instructions for acquisition of scans as well as performance of Instrument Quality Control.

Bone density will be measured at the lumbar spine and the proximal femur. DXA scans of the lumbar spine will be performed in duplicate, ie, subjects will be removed from the table in between scans. Lumbar spine scans must include L1 through L4. For proximal femur DXA scans, the left side should be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a subject fractures the hip that has been scanned during the study up to the time of fracture, no further scans will be obtained for the affected location.

All DXA scan data will be submitted electronically to the central imaging vendor for analysis. Sites unable to submit data electronically can submit on CD or other media as specified in the DXA Procedural Manual, but electronic submission is preferred.

After analysis by the central imaging vendor, the study site may be asked to re-acquire a scan due to malpositioning or other technical reasons. The investigative sites must comply with the requests from the central imaging vendor. Repeat scans must be performed as soon as possible after the request is received.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Disease-related Events

Disease-related events are defined in Appendix 4.

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment/protocol-required therapies through EOS are reported using the Event CRF.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events.

Disease-related events pre-defined for this study include: fractures (serious or non-serious), as they are anticipated to occur in the study population due to the underlying disease.

9.2.3.1.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product(s) through EOS are reported using the Event CRF.

9.2.3.1.1.3 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through EOS, ET, or 30 days after the last dose of investigational product (whichever is longer) are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.4 Adverse Events and Serious Adverse Events Requiring Adjudication

The following events will be submitted to independent committees for adjudication:

- potential ONJ events
- potential cases of AFF
- all deaths and serious adverse events that are deemed by the investigator to be of potential cardiovascular origin or etiology and serious adverse events with terms mapping to a pre-defined preferred term list potentially indicative of cardiovascular etiology

9.2.3.1.1.5 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after EOS. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, adverse device effects, disease-related events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

As a means to not introduce bias when detecting adverse events and/or serious adverse events, open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects will be collected after the start of study treatment and until 3 months after the end of treatment with romosozumab.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.1.6 Adverse Device Effects

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures in the event CRF.

Product complaints are described in Section 7.1.5.

Further details regarding adverse device effects can be found in Appendix 4.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. The position selected for a subject should be the same as that is used throughout the study and documented on the vital sign CRF.

The temperature location selected for a subject should be the same as that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment)

are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event in the event CRF.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

9.2.4.1 Pregnancy Testing

Pregnancy testing is not relevant to this study because the study population is postmenopausal women with osteoporosis.

9.2.4.2 Hepatitis B and C Testing

Hepatitis testing will be performed at initial screening to confirm subject eligibility. Subjects should be excluded if they have a positive HepBsAg or if PCR is positive for hepatitis B or hepatitis C virus. Hepatitis testing will be performed by the central laboratory.

The following laboratory testing will be performed:

- HepBsAg and total HepBcAb
- Hepatitis B Virus DNA Real-Time PCR will be only performed if total HepBcAb is positive and HepBsAg is negative
- Hepatitis C virus antibody
- Hepatitis C Virus RNA Real-Time PCR will be only performed if hepatitis C virus antibody is positive

9.2.4.3 Prespecified Biomarker Assessments

Subjects will have blood drawn at visits specified in the Schedule of Activities (Table 2-1) for analysis of bone turnover markers (BTMs), P1NP and sCTX.

Blood draws for BTMs must be obtained from subjects in fasting stage and before noon. Fasting stage is defined as overnight fasting. If overnight fasting is not feasible, a minimum of 8 hours fasting is required.

9.2.5 Pharmacokinetic Assessments

All subjects will have pharmacokinetic samples assessed.

Whole blood samples of approximately 5 mL per each applicable visit will be collected for measurement of serum concentrations of romosozumab as specified in the Schedule of Activities (Table 2-1). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

9.2.6 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Table 2-1) for the measurement of anti-romosozumab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized. Additional blood samples may be obtained to rule out anti-romosozumab antibodies during the study.

Subjects who test positive for neutralizing antibodies to romosozumab at the final scheduled study visit defined as the EOS visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result until: (1) neutralizing antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of romosozumab. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive romosozumab.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-romosozumab antibody response may also be asked to return for additional follow-up testing. Refer to the Schedule of Activities (Table 2-1), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.

10. Statistical Considerations

10.1 Sample Size Determination

The noninferiority margin is calculated on the basis of the comparison of 210 mg QM romosozumab at a 90 mg/mL concentration administered by an HCP using PFS with placebo on percent change from baseline in lumbar spine at Month 6 in postmenopausal women with low bone mass (Study 20120156).

[redacted]

[redacted]

[redacted] This result assumes a 5% dropout rate during the 6-month treatment period, no expected difference in mean percent changes in lumbar spine DXA BMD from baseline at Month 6 between the 2 groups, and a common standard deviation of 4.3 percentage points.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

10.2.1.1 Full Analysis Set

The full analysis set includes all randomized subjects. Subjects in this set will be analyzed according to their randomized treatment assignment, regardless of treatment received.

10.2.1.2 Primary Efficacy Analysis Subset

The primary efficacy analysis subset will include all randomized subjects who have a baseline lumbar spine DXA BMD measurement and at least 1 post-baseline lumbar spine DXA BMD measurement. Data from subjects in this subset will be analyzed according to randomized treatment groups, regardless of treatment received.

10.2.1.3 Hip Bone Mineral Density Efficacy Analysis Subset

The hip BMD analysis subset will include all randomized subjects who have a baseline hip DXA BMD measurement and at least 1 post-baseline hip DXA BMD measurement. Data from subjects in this subset will be analyzed according to randomized treatment groups, regardless of treatment received.

10.2.1.4 Safety Analysis Subset

The safety analysis subset will include all randomized subjects who receive at least 1 dose of investigational product. These subjects will be analyzed according to their actual treatment received, such that subjects who received at least 1 dose of the romosozumab self-administration by AI/Pen will be analyzed in the romosozumab self-administration by AI/Pen treatment group, regardless of the randomized treatment.

10.2.1.5 Per Protocol Analysis Subset

A per protocol analysis for the primary efficacy endpoint will also be implemented and be considered supportive to the primary analysis based on the primary efficacy analysis subset. The per protocol analysis subset will include all subjects in the primary efficacy analysis subset who received 5 of the 6 planned doses and who had no important protocol deviations through Month 6. Subjects who received the incorrect treatment (compared to their randomized treatment) at any time point will be excluded from this subset. The important protocol deviations will be defined in the Statistical Analysis Plan and will be identified prior to the primary analysis. Subjects will be analyzed according to their randomized treatment group.

10.2.2 Covariates

All analyses assessing treatment effect of BMD will include randomized treatment, baseline BMD at the same body site as the endpoint, machine type, and interaction between baseline BMD and machine type as prognostic variables in the model.

10.2.3 Subgroups

No subgroups will be evaluated in this study.

10.2.4 Handling of Missing and Incomplete Data

Subjects may have missing specific data points for a variety of causes. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a specific clinical measurement at its planned clinical visit. Unless specified, no imputation will be used. The general procedures outlined below describe the procedures when a data point is missing.

10.2.4.1 DXA BMD Endpoints

Missing baseline values for endpoints by DXA at any anatomical site will not be imputed. Sensitivity analysis accounting for missing data will be described in the statistical analysis plan.

10.2.4.2 Bone Turnover Markers

Missing bone turnover maker (either baseline or post-baseline values) will not be imputed. Any values below the lower limit of quantification (LLOQ) will be imputed using the LLOQ for analysis.

10.2.4.3 Laboratory Parameters

Lab parameters with values below the LLOQ or above the upper limit of quantification (ULOQ) will be imputed as the LLOQ or ULOQ value, respectively

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following EOS, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Interim Analysis and Early Stopping Guidelines

No interim analyses or sample size re-estimation are planned for this study.

10.3.1.2 Primary Analysis

The primary analysis will be performed after all subjects have had the opportunity to complete the Month 6 visit. The primary objective of the primary analysis is to evaluate the noninferiority of the effect of self-administering 210 mg romosozumab QM via AI/Pen compared with the effect of 210 mg romosozumab QM administered by HCP via PFS in postmenopausal women with osteoporosis with respect to percent change from baseline in DXA BMD of lumbar spine at Month 6. Formal statistical testing will be conducted to evaluate the following hypothesis: the mean percent change from baseline in lumbar spine DXA BMD at Month 6 in subjects self-administering 210 mg romosozumab QM with AI/Pen is not inferior to that in subjects receiving 210 mg romosozumab QM by HCP administration with PFS using a margin of -2 percentage points. The lower bound of the one-sided 97.5% CI from mean treatment difference for the treatment arms will be compared with the noninferiority margin of -2% for assessing noninferiority.

Secondary objectives of the primary analysis include the evaluation of the efficacy of self-administration of 210 mg romosozumab QM by AI/Pen and HCP administration of 210 mg romosozumab QM by PFS on the following:

- percent change from baseline in DXA BMD of total hip and femoral neck at Month 6

[redacted]

Safety objectives of the primary analysis include the comparison of safety and tolerability of self-administration of 210 mg romosozumab QM by AI/Pen and HCP administration of 210 mg romosozumab QM by PFS on the following:

- subject incidence of treatment-emergent adverse events
- subject incidence of the formation of anti-romosozumab antibodies
- change from baseline in laboratory assessments and vital signs

The focus of the safety statistical analyses will be estimation. No formal statistical testing will be performed.

10.3.1.3 Final Analysis

The final analysis will be performed after all subjects have had the opportunity to complete the Month 9 visit, ie, after all subjects have had the opportunity to complete the 3-month follow-up study period. The 3-month follow-up period will provide the opportunity to monitor all subjects for adverse events and formation of anti-romosozumab antibodies.

The primary objective of the final analysis is the safety objective, ie, the comparison of the safety and tolerability of a 6-month treatment with 210 mg romosozumab at 90 mg/mL QM by HCP administration with PFS or by subject self-administration with AI/Pen.

The focus of the safety statistical analyses will be estimation. No formal statistical testing will be performed.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

For computation of change from baseline endpoints, baseline will be taken as the observation recorded just prior to first dose of investigational product. In the case in which the protocol specifies multiple baseline measurements to be taken, the mean of the baseline records will be used for analysis.

Continuous variables will be summarized descriptively using mean, median, standard deviation, 25th percentile, 75th percentile, minimum, maximum, and the number of nonmissing observations. Frequencies and percentages will be presented for nominal categorical variables.

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary analysis to assess the percent change from baseline in dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) at lumbar spine at Month 6 will employ an analysis of covariance (ANCOVA) model. The ANCOVA model will include randomized treatment, baseline value of BMD, machine type, and interaction of baseline BMD value and machine type as prognostic variables. Summaries for the results will include least-squares means point estimates of the percent change from baseline for each treatment arm. The variance structure will allow for heterogeneity between treatments. The 2-sided 95% CI and associated p-value will be provided for the difference between the least-squares means for HCP-administered 210 mg romosozumab by PFS and self-administered 210 mg romosozumab by AI/Pen. Conclusions for the primary efficacy hypothesis of efficacy of self-administration of romosozumab by AI/Pen compared with HCP-administered romosozumab by PFS at lumbar spine BMD at Month 6 will be made using a 1-sided test with type 1 error rate of 0.025 and noninferiority margin of -2.0%. The primary efficacy analysis set will be used to for the primary analysis. A sensitivity analysis using the per protocol analysis subset will be performed.

Secondary	For the secondary efficacy BMD endpoints (total hip and femoral neck at Month 6), the percent change from baseline in DXA BMD will employ an ANCOVA model. The ANCOVA model will include treatment group, baseline value of BMD, machine type, and interaction of baseline BMD value and machine type as prognostic variables. Summaries for the results will include least-squares means point estimates of the percent change from baseline for each treatment arm. The variance structure will allow for heterogeneity between treatments. The 2-sided 95% CI and associated p-value will be provided for the difference between the least-squares means for self-administration of romosozumab by AI/Pen and HCP-administered romosozumab by PFS. The hip BMD efficacy analysis subset will be used to for these analyses.

10.3.2.3 Safety Analyses

10.3.2.3.1 Adverse Events and Disease-related Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided. Subject incidence of disease-related events, fatal disease-related events, and adverse device effects, if applicable, will be tabulated by system organ class and preferred term. The subject incidence of treatment-emergent adverse events and adverse device effects will be summarized by actual treatment received.

10.3.2.3.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics (actual value and change or percent change from baseline for each laboratory parameter) over time by visit for the 6-month treatment period. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated. Graphical representation of aggregate data may also be presented.

10.3.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics over time by treatment group.

10.3.2.3.4 Physical Measurements

The analyses of physical measurements will include summary statistics over time by treatment group.

10.3.2.3.5 Antibody Formation

The incidence and percentage of subjects who develop anti-romosozumab antibodies (binding and, if positive, neutralizing) at any time will be tabulated by treatment group.

10.3.2.3.6 Exposure to Investigational Product

Compliance with investigational product will be summarized for each subject using descriptive statistics

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12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AI/Pen	Autoinjector/pen
ALN	alendronate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMD	bone mineral density
BTM	bone turnover marker
CI	confidence interval
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTX	collagen C-telopeptide
DILI	drug-induced liver injury
DXA	dual-energy x-ray absorptiometry
EDC	electronic data capture
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	end of study
ET	early termination
GCP	Good Clinical Practice
HCP	Healthcare provider
HepBcAb	total hepatitis B core antibody
HepBsAg	Hepatitis B Surface Antigen
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
INR	international normalized ratio

Abbreviation or Term	Definition/Explanation
IVRS	interactive voice response system, telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
IV	intravenous
LLOQ	lower limit of quantitation
P1NP	procollagen type 1 N-telopeptide
PCR	polymerase chain reaction
PK	pharmacokinetic
PFS	prefilled syringe
PTH	parathyroid hormone
QM	once a month
RRR	relative risk reduction
SC	subcutaneous
sCTX	serum type-1 collagen C-telopeptide
SERM	selective estrogen receptor modulator
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
TBL	total bilirubin
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

The tests for all applicable screening and all on-study blood samples detailed in Table 12-1 will be performed by the central laboratory. Depending on the assessment, the central laboratory will be responsible for either performing the assays or shipping samples to Amgen or a specialty laboratory for assay. The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all serum samples.

Blood samples for BTMs, romosozumab levels, and anti-romosozumab antibodies will either be processed by the central laboratory, sent to an appropriate secondary laboratory or sent to Amgen for analysis or further distribution to other laboratories.

All blood samples will be obtained by venipuncture before investigative product administration, when applicable, at the time points outlined in the Schedule of Activities (Table 2-1). Blood samples for the assessments of BTMs must be obtained from subjects in fasting state, as indicated in Section 9.2.4.3. The date and time of blood collection will be recorded in the subject's medical record.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Central Laboratory			
Serum Chemistry	Hematology	BTM	Other Labs
Sodium	Red blood cell	P1NP	Romosozumab levels
Potassium	Hemoglobin	CTX	25 (OH) vitamin D
Chloride	Platelets		Anti-romosozumab antibody
Bicarbonate	White blood cell		HepBsAg
Total protein	Differential		HepBcAb
Albumin	• Neutrophils		Hepatitis C virus antibody
Calcium	• Eosinophils		PCR for hepatitis B[a]
Albumin-adjusted calcium	• Basophils		PCR for hepatitis C[b]
Magnesium	• Lymphocytes		Serum protein electrophoresis
Phosphorus	• Monocytes		
Glucose			
Blood urea nitrogen			
Creatinine			
TBL			
ALP			
ALT (SGPT)			
AST (SGOT)			

ALP = alkaline phosphatase; ALT (SGOT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BTM = bone turnover marker; CTX = serum type-I collagen C-telopeptide; HepBsAg = hepatitis B surface antigen; HepBcAb = total hepatitis B core antibody; PCR = polymerase chain reaction; P1NP = procollagen type 1 N-telopeptide; TBL = total bilirubin

[a] Hepatitis B Virus DNA Real-Time PCR will be only performed if total HepBcAb is positive and HepBsAg is negative.
[b] Hepatitis C Virus RNA Real-Time PCR will be only performed if hepatitis C virus antibody is positive.

Appendix 3. Study Governance Considerations

Independent Adjudication Committee(s) for Osteonecrosis of the Jaw, Atypical Femoral Fracture, and Serious Cardiovascular Events

The Osteonecrosis of the Jaw Adjudication Committee and the Atypical Femur Fracture Adjudication Committee will independently adjudicate potential osteonecrosis of the jaw (ONJ) and atypical femur fracture (AFF) events identified in this clinical trial. The respective processes are described in the ONJ and AFF Manuals of Operations.

The Duke Clinical Research Institute Clinical Events Classification (CEC) group will independently adjudicate potential serious cardiovascular adverse events identified in this clinical trial. The processes are described in the CEC Charter for romosozumab protocol 20150120.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative, defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study, will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such

notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened for vitamin D is not required to sign another informed consent form if the rescreening occurs within 35 days from the previous informed consent form signature date. Rescreening for any other reason is not permitted.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of signing of informed consent.

For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities. These include:

- Subject files containing informed consent forms and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence, including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Disease-related Event

Disease-related Event Definition

• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See Section 9.2.3.1.1.1 for the list of disease-related events.
• Disease-related events that would qualify as an adverse event or serious adverse event:
  ○ An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.
• Disease-related events that do not qualify as adverse events or serious adverse events:
  ○ An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an

adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:

Results in death (fatal)

Immediately life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires in-patient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices or combination products provided for use in the study (see Section 7.1.2 for the list of Amgen medical devices).

Adverse Device Effect Definition
An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording

• When an adverse event, disease-related event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
• The investigator will then record all relevant adverse event/disease-related event/serious adverse event information in the Event CRF.
  o Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.
• The investigator must assign the following adverse event attributes:
  o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  o Dates of onset and resolution (if resolved);
  o Severity (or toxicity defined below);
  o Assessment of relatedness to investigational product, other protocol-required therapies, or devices; and
  o Action taken.
• If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF.
• It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the Event CRF page.
• If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the sponsor.
• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The **Common Terminology Criteria for Adverse Events (CTCAE)**, version 3.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, device(s), and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • Relatedness must also be assessed between the combination product device and any event • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the EDC system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an Electronic Serious Adverse Event (eSAE) Contingency Form (paper form; see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on an Electronic Serious Adverse Event Contingency Form (paper form; see Figure 12-1).

Adverse Device Effects: Recording, Evaluating, and Reporting

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event CRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study # 20150120 Romosozumab	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? <PRIMARY> No ☐ Yes ☐ <PRIMARY> No ☐ Yes ☐ <PRIMARY> No ☐ Yes ☐ <PRIMARY> No ☐ Yes ☐	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

Serious Criteria:
01 Fatal
02 Immediately life-threatening
03 Required/prolonged hospitalization
04 Persistent or significant disability /incapacity
05 Congenital anomaly / birth defect
06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20150120 Romosozumab	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test / Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20150120 Romosozumab	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)

- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of investigational product of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 3 months after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 227.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 3 months after the last dose of investigational product after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20150120

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax** (____) _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm____ / dd____ / yyyy____ ☐ Unknown

Estimated date of delivery mm____ / dd____ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm____ / dd____ / yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm____ / dd____ / yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix 6. Sample Storage and Destruction

Any blood, pharmacokinetic (PK), anti-drug antibody, or biomarker sample collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the osteoporosis, the dose response and/or prediction of response to romosozumab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Appendix 3 for subject confidentiality.

Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-1 antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible DILI according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then romosozumab is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3x upper limit of normal (ULN) are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 to 48 hours
- In cases of TBL > 2x ULN or AST/ALT much greater than 3x ULN, retesting should be performed within 24 hours; subjects should be monitored at least twice weekly.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- PT/INR, fractionated bilirubin, and any other potentially relevant laboratory evaluations of liver function or disease
- Complete blood count (CBC) with differential to assess for eosinophilia

- A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
    - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr Virus, Herpes Simplex Virus, etc.); evaluate for other potential causes of DILI, including but not limited to: Nonalcoholic Steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease
- Creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
- Appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation that require permanent withholding of investigational product
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Gastroenterology or hepatology consult

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.